"Fungal Infections : An Overview of Pathogenesis , and Clinical Manifestation ,and Treatment Stratergies"

Vishakha B Gurav, Vasim Aparadh, Samina Mujawar, Saniya Mullani, Neha Gaikwad
Y.D.Mane Institute Of Pharmacy, Kagal.

Abstract:

Fungal infections pose a significant threat to human health, with approximately 300 of the 250,000 known fungal species capable of causing illness in humans. Opportunistic pathogens, such as Aspergillus, Candida, and Cryptococcus species, are responsible for the majority of infections, disproportionately affecting immunocompromised individuals, including those with HIV/AIDS, cancer, and diabetes. The weakened immune systems of these patients, often compromised by underlying illnesses or medical treatments, render them more susceptible to fungal infections. Despite the availability of antifungal medications, the development of treatment resistance and high frequencies of adverse effects, including toxicity, hinder effective management. This highlights the need for continued research and development of novel therapeutic strategies to combat the growing burden of fungal infections, which pose a significant risk of morbidity and mortality worldwide.

KeyWords – Aspergillus , Candida spp, Cryptococcus Species ,PCR,

I.INTRODUCTION-

In general, out of the 250,000 fungal species found worldwide, about 300 are thought to be actual or prospective pathogens that could infect humans and cause superficial or even fatal illnesses. [1] However, opportunistic pathogens including Aspergillus, Candida, and Cryptococcus species are responsible for the majority of fungal infections. In other words, compared to healthy people, immunocompromised patients are more susceptible to fungal infections because their immune systems may be weakened by illnesses or controlled by medications. HIV/AIDS, TB, cancer, diabetes, organ transplantation, trauma, and even long-term usage of corticosteroids or antibiotics are a few examples.[1]

Significant rates of morbidity and mortality are caused by fungal infections. Although there are medications that can effectively treat fungal infections, the development of treatment resistance and the high frequency of adverse effects—particularly toxicity from the antifungal agents—present difficulties. Since there aren't many antifungal medications on the market, their potential side effects will restrict dosage and frequency of usage, which could lead to reduced effectiveness or even treatment failure.[2] Amphotericin B, for instance, is the recommended medication for systemic mycoses; nevertheless, its usage is restricted due to the moderate to severe nephrotoxicity it can cause.

Certain antifungal medications that are applied topically in gel or cream formulations may also irritate, swell, and redden the area where they are applied. Antifungals are medications that prevent the growth of fungi that cause infections. Another name for antifungals is antimycotic agents. Terbinafines, miconazole, econazole, and clotrimazole Common names for antifungal medications include amphotericin, nystatin, fluconazole, and ketoconazole. Fungal infections can be treated using antifungal creams, liquids, or sprays. The classes of antifungal medications include echinocandins, polyenes, azoles, and allylamines. The first antifungal, amphotericin B deoxycholate, was initially made available in 1958. Flucytosine, a pyrimidine analogue that is effective against Candida and Cryptococcus, was first presented in 1973. The first generation of azole medicines, which have good action against yeast infections and the benefit of oral administration, were made accessible in 1990. the azole's second generation in the 2000s. The commercial, which features the medication voriconazole, is presented as isovucanazole Posaconazole's broad range of action against filamentous fungus is an advantage of this medication. Hair loss, crusty areas, and itchy red spots are signs of fungal infections. Over 200 polyenes with antifungal properties were found in the 1950s. The circulation may be impacted by a fungal infection. Polyenes, azoles, allylamines, and echinocandins are the four primary classes of antifungal medications. The Food and Drug Administration has approved ten antifungal medications to treat systemic fungal infections. Antifungal medications can have both beneficial and detrimental effects, such as on the liver and heart. Failure Every four to six weeks, they must be tested. Using antifungal medications for damage to the kidneys, liver, and heart After therapy, infections might occasionally return. Fluconazole is frequently used to treat nail infections and nystatin is used for oral thrush.(3,4,5)

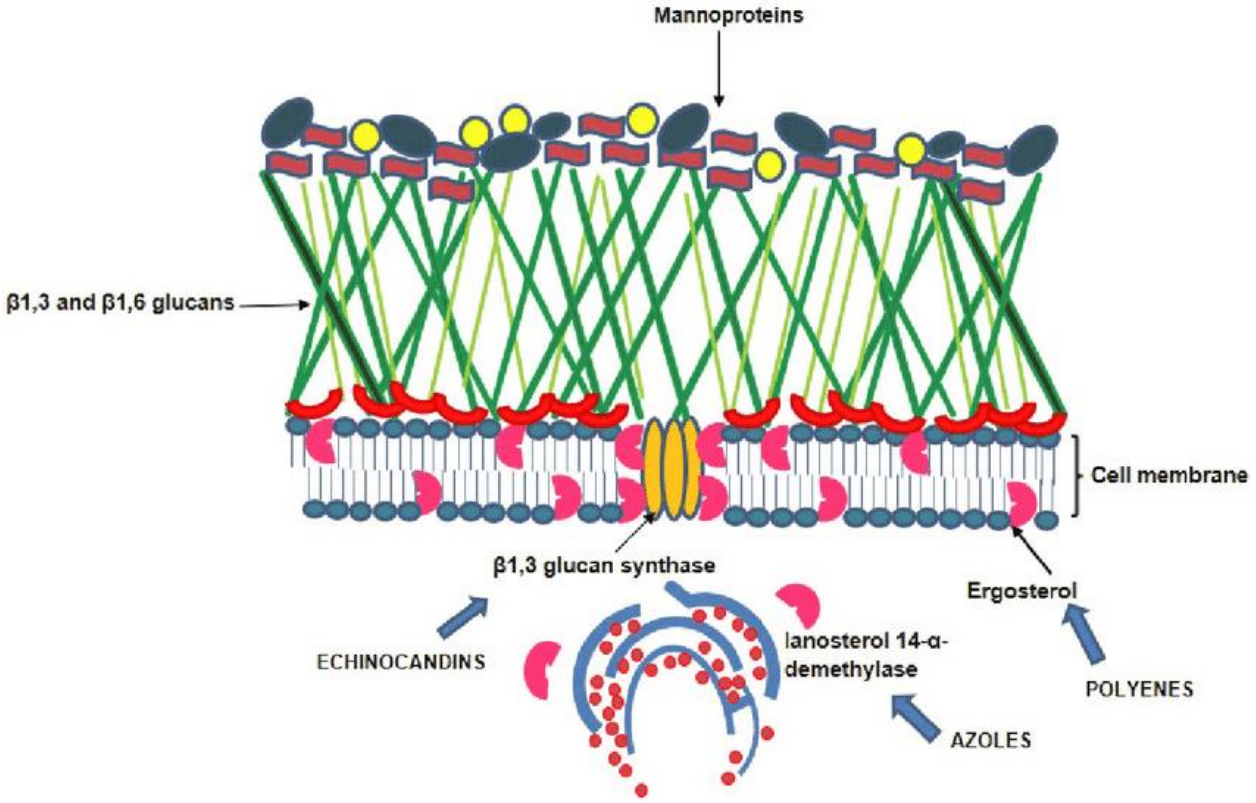

Fig. Traditionally antifungal drug

II.PATHOPHYSIOLOGY OF FUNGAL INFECTION –

The phylum Dikarya is the sub-kingdom of fungus. All human fungal infections and pathogens are mostly caused by Ascomycota and Basidiomycota. Oropharyngeal, otolaryngeal, dermatological, ophthalmic, neurological, genitourinary, cardiac, pulmonary, and systemic infections are all known to be caused by Ascomycota species (Fig. 1). Malassezia and Cryptococcus, two members of the Basidiomycota, are widely known for causing superficial skin infections and invasive meningitis, respectively. Fungal pathogens primarily use direct contact and/or inhalation.

route for transmission. Dermatophytic fungi belonging to the genera of Microsporum, Epidermophyton, Trichophyton, Sporothrix, and Malassezia spp. infect the damaged skin by direct contact.They produce various proteolytic enzymes to cause superficial mycoses in keratinized tissues

The other predominant route for transmission is by inhalation of spores/conidia that instigates pulmonary infections. Blastomyces dermatitidis (Blastomycosis), Paracoccidioides brasiliensis, and P. lutzii (Paracoccidiodomycosis), Histoplasma capsulatum (Histoplasmosis), Pneumocystis jirovecii (Pneumocystis pneumonia), Aspergillus fumigatus and A. flavus (Aspergillosis), Coccidioides immitis and C. posadasii (Coccidioidomycosis), C. neoformans and C. gattii (Cryptococcosis) are mainly transmitted through inhalation. While, Talaromyces marneffei (talaromycosis) uses both direct contact and the inhalation route for transmission.

III.EPIDEMIOLOGY OF FUNGAL INFECTION:

Organisms-

1. *Candida spp.*

A mortality rate of over 25% is linked to disseminated candidiasis (7).Candida is a common occurrence in the gastrointestinal, genitourinary, and skin systems. Although Candida albicans is the most commonly isolated species from clinical specimens, nonalbicans Candida, or NAC, is becoming more and more common. Because some NAC are extremely aggressive and linked to treatment failure because of decreased susceptibility to antifungal drugs, they are particularly concerning. Despite the technical difficulty of species-level identification and susceptibility testing, it is advised that these procedures be carried out on all fungi isolated from sterile areas and critical care unit urine.and transplant patient (8).The 1980s saw a sharp rise in the prevalence of candidemia, making Candida species the fourth most prevalent cause of bloodstream infections (BSI) in the United States (9). However, it has been observed that a notable decline in the frequency of C. albicans BSI in the late 1990s caused this rising trend to reverse (10).With the exception of those caused by Candida glabrata, which sharply increased, the incidence of NAC BSI stayed constant. Two prospective studies from Italy also reported an increase in C. glabrata (11,12).This shift in epidemiology could be explained by prophylactic use of azole antifungal medications. Only 37.5% of candidemias in haematology patients were caused by Candida albicans, compared to 79.4% in acute care patients (7).A prospective pan-European investigation found similar outcomes (13).

While past antifungals were protective, prior surgery, acute renal failure, prior yeast colonization, neutropenia, antibacterial drugs, parenteral feeding, and central venous catheters were linked to an elevated risk of invasive candidiasis (14).

Numerous Pdiseases can be brought on by Candida. Clinical diagnosis of invasive candida infection is difficult since cultures may only test positive late in the infection, most symptoms are nonspecific, and early clinical manifestations are sepsis-like. In cases with invasive candidiasis, delayed or nonexistent treatment is an independent predictor of death (8).

2] *Cryptococcus spp.*

The most frequent cause of cryptococcosis, Cryptococcus neoformans, is typically contracted by inhalation. Symptoms of pulmonary cryptococcosis can range from none at all togenerally with pleural, fever, or cough symptoms. Meningitis is a common infection symptom, particularly in solid organ transplant recipients and people with HIV seropositive status. The non-specific clinical symptoms necessitate a high index of suspicion for cryptococcal infection. Since treating cryptococcal meningitis necessitates more intensive and protracted therapy, a positive serum cryptococcal antigen is dependable for the diagnosis of disseminated disease and should result in a lumbar puncture to rule out central nervous system disease (15).All cerebrospinal fluid (CSF) specimens from patients with sarcoidosis, HIV-seropositive patients, and transplant recipients that exhibit abnormal biochemical parameters or elevated leukocytes without sufficient justification should be examined for cryptococcal antigen and cultures incubated for an extended length of time to promote organism isolation (e.g., fungal cultures for 21 days and bacterial cultures for at least 5 days) (8).

3] *Aspergillus spp.*

The most often isolated invasive molds are Aspergillus species (16).Of the approximately 200 species, only a small number—mostly Aspergillus fumigatus, Aspergillus flavus, and Aspergillus niger—are harmful to humans.Although A. fumigatus is still the most commonly isolated mold, the epidemiology seems to be shifting. According to a fumigatus was responsible for 82% of invasive aspergillosis infections in 1985 and 66% in 1999 among patients receiving stem cell transplants.(17).Aspergillus terreus is becoming more widely acknowledged as a pathogen; according to one study, it accounted for 15% of isolates in 2001 as opposed to less than 2% in 1996 (18).

Although colonization without infection is possible, Aspergillus species can cause invasive aspergillosis, tracheobronchitis, aspergilloma, and chronic necrotizing aspergillosis.

Prolonged neutropenia (especially if >3 weeks) or neutrophil dysfunction, steroid therapy, hematological malignancy, cytotoxic medications, AIDS, and transplantation (especially when a mismatch exists) are risk factors for invasive aspergillosis. Invasive aspergillosis is known to occur in up to 13% of allograft and autograft recipients, making the risk particularly high in bone marrow transplantation (17).Recently, the immunosuppressive monoclonal antibody to TNF-a infliximab was identified as a risk factor (19).

Lung and heart-lung transplant recipients are most vulnerable to infection among solid-organ transplant recipients, affecting 14–18% of patients (20).. Because the respiratory tract is the main point of entrance and the lung is denervated below the anastomosis, which results in a loss of cough reflexes and mucociliary clearance, the transplanted lung is most at risk. Other factors that are linked include

cytomegalovirus (CMV) infection, inadequate blood supply, and rejection events. Invasive aspergillosis can strike up to 7% of liver transplant recipients (20).

Usually diagnosed two to four weeks following transplantation, it is linked to poor allograft function and increasing immunosuppression/postoperative dialysis. However, in relation to CMV infection, more episodes (55%) now happen after three months (21). Less than 1% of kidney transplant recipients develop invasive aspergillosis (20).

IV.TYPES OF FUNGAL INFECTIONS:-

Fungi are extremely important to the environment and medicine, and they are among the most extensively spread creatures on the planet. Many fungi live freely in soil or water, while others coexist with plants or animals as parasites or symbiotic partners. The kingdom Fungi is sometimes known by the alternate scientific term Mycota. Although they are not the most common or economically important fungus, mushrooms and toadstools (poisonous mushrooms) are the easiest to identify. Fungus (plural fungi), the Latin word for mushrooms, has evolved to refer to the entire group. Similarly, mycology—a broad application of the Greek word for mushroom, mykēs—is the study of fungi. Although this phrase is better limited to fungi of the type represented by bread mold, fungi other than mushrooms are occasionally referred to as molds(22).

Classification of fungal organisms based upon the reproductive method is illustrated in TabLE

Division MYCOTA		
Subdivision MYXOMYCOTINA [slimemolds]	**Subdivision EUMYCOTINA**	
Class MYXOMYCETES	**LOWER FUNGI[aseptate fungi]**	**HIGHER FUNGI**
	Class1 CHYTRIDIOMYCETES	**Class 7** ASCOMYCETES **Sub class:** HEMIASCOMYCETIDAE EUASCOMYCETIDAE LOCULOASCOMYCETIDAE
	Class 2 HYPOCHYRIDIOMYCETES	
	Class 3 OOMYCETES	**Class 8** BASIDIOMYCETES **Subclass:** HETEROBASIDIOMYCETIDAE HOMOBASIDIOMYCETIDAE
	Class 4 PLASMODIOPHOROMYCETES	
	Class 5 ZYGOMYCETES	**Class 9** DEUTEROMYCETES
	Class 6 TRICHOMYCETES	

le 1.

Table No. 2: Classification of fungi by Alexopolous.(22)

General classification: MYCOTA
Kingdom: PLANTAE
Division: MYCOTA
Sub-division: MYCOTINA
Class: MYCETES
Sub-class: MYCETIDAE
Order: ALES
Family: ACEA

V.Symptoms of Fungal Infection:

A fungal skin infection might cause(23):

- Irritation
- Scaly skin
- Redness
- Itching
- Swelling
- Blisters

Who is prone to fungal infection?

Those who are prone to fungal infections include:

- People with weakened immune systems such as children, elderly people, people suffering AIDS, HIV infection, cancer, diabetes.
- People with a genetic predisposition toward fungal infections.
- People who sweat a lot since sweaty clothes and shoes can enhance fungus growth on the skin.
- People who come in contact with a person suffering from a fungal infection.
- People who frequent communal areas with moisture, such as locker rooms and showers, since fungi require moisture to grow and reproduce.
- People who are obese as they have excessive skin folds.
- People with weak immune systems are very prone to fungal infections.

Examples of common fungal infections include(24) :

- Tinea pedis (athlete's foot)
- Tinea corporis (ringworms)
- Yeast infection
- Onychomycosis (fungal infection of the toenails)
- Tinea versicolor (fungal infection of the skin)
- Tinea cruris (jock itch)

Table No. 3: Signs and symptoms associated with common fungal infections24

Tinea Pedis	Tinea Corporis	Yeast infection	Onychomycosis	Tinea versicolor	Tinea cruris
Peeling, craking and scalinf of feet	Itchy red ring shaped patch that can be scaly	Itching, swelling around vagina	Nail discolouration	Affected area is lighter or darker than surrounding area	Redness in gron or buttocks
Redness, blistering/softening, breaking down of skin		Burning sensation/pain during urination or sexual intercourse	Nail flaking	Dry, itchy, scaly skin	Chafing, irritation or burning in infected area
Itching, burning or both		Redness, soreness in and around vagina	Nail thickening		Red rash with circular shape and rough edges
		Unusual vaginal discharge			

VI.Diagnosis of fungal infection :-

Advances in seriology based diagnosis-

Serological testing facilitates the diagnostic decision-making process by providing a faster means of identifying the causative fungi. These tests are performed to determine whether serum or bodily fluids from a suspected fungal infection include an antigen or antibody. Serology-based tests have the benefit of producing data quickly, in contrast to culture procedures, and using a non-invasive sample (such as blood, urine, sputum, etc.) that may serve as a prognostic marker [25].Serology tests can yield positive results even if culture tests are negative, the fungus species is nonculturable, or the patient's sample is difficult to obtain due to underlying conditions[26,27].

Antibody-based testing has limitations in immunocompromised or immunosuppressive patients, who may not produce enough antibodies, leading to false negative results [28]. However, detecting fungal antigens in these patients provides a remedy. Fungal antigens, which are released during fungus growth, can be detected in body fluids and serve as disease markers in both immunocompetent and immunocompromised individuals [26].Serology-based testing includes limitations and areas for development, as stated in each chapter.

The assay detects (1,3)-β-d-glucan (BDG), a polymer found in fungal cell walls. BDG is a pan-fungal antigen found in Candida spp., Pneumocystis jivoveci, Aspergillus spp., Acremonium spp., and Fusarium spp. (except for Cryptococcus spp., Microrales, and the yeast phase of Blastomyces dematitis us) [29]. The Fungitell Assay (Associates of Cape Cod, MA, USA) is the only FDA-approved test for BDG. It can diagnose intra-abdominal candidiasis and blood culture-negative instances of pneumophila pneumonia [30].A meta-analysis found that serum BDG has 75-80% sensitivity and 60-80% specificity for IC (30-31). For deep-seated candidiasis, the sensitivity and specificity were 65% and 75%, respectively [32-34].The EORTC-MSG definition of fungal infection includes the BDG assay, which can be performed colorimetrically or turbidimetrically [35]. Various BDG assays, including Fungitec-G, Beta Glucan-BGStar, and Beta-Glucan test (Mauha, Japan), have different cutoff values, sensitivity, and specificity based on the fungal strain, patient population, and assay platform.

The Fungitell assay shows sensitivity and specificity values of 69.9-100% and 73-97.3% for IC and IA, respectively, with a sensitivity of 81-93% and specificity of 77.2-99.5% (36-37). The Fungitell assay has been used as a diagnostic tool for IFIs for over 20 years [38]. The test is provided in a quick microtiter plate format, allowing for batch testing of 21 samples in one go. While major institutions and reference labs may benefit from a high sample volume, a low batch format is also necessary [39].Fungitell STAT™ is a modification of the original kit that allows for fast classification of serum BDG levels as positive, negative, or indeterminate. The innovative Fungitell assay uses LAL-based reagents to measure the rate of para-nitroaniline (pNA) release caused by activated BDG-sensitive protease zymogens, similar to the traditional method.

BDG has the disadvantage of being a non-specific pan-fungal biomarker with limited sensitivity and large false positive rates due to cross-reactivity. Racil, et al. [40]. reported 75% false positive values seen in patients attributed to concurrent bacteraemia, Treatment options include haemodialysis or human immunoglobulin. In 2018, a commercial assay for detecting BDG in plasma samples was released. The Wako-glucan test (GT) [Fujifilm Wako Pure Chemical Corporation, Osaka, Japan] was introduced as an alternative to Fungitell in the European market. In a research by Friedrich et al. [41].Serum samples were used to compare GT test performance with Fungitell in individuals with IC and Pneumocystis jivoreci pneumonia (PJP). The GT assay was more specific for candidemia (98% vs 85%), but the Fungitell assay had a higher sensitivity (86.7% vs 42.5%) for patients with IC and pneumonia (100%) compared to the GT assay (88.9%). De Carolis and crew conducted a separate investigation [42].A large cohort study comparing sera from patients with IA (n = 40), IC (n = 78), and PJP (n = 17) against sera from control patients (n = 187) found that decreasing the cutoff value for the Wako test increased sensitivity while maintaining specificity (97.3%). Lowering the GT limit to 7.0 pg/mL resulted in increased sensitivity and specificity for IA, IC, and PJP diagnoses, respectively.After adjusting the GT cutoff value for positivity, the Wako-glucan test was nearly as effective as the Fungitell in clinical settings. The researchers found GT to be easier to use and interpret than the Fungitell, with the ability to test single or several samples simultaneous.

**Advances in molecular-based diagnostic methods:-*

Mycology has made significant progress in using molecular approaches to detect and diagnose fungi. Molecular procedures provide faster and more accurate answers than culture tests due to their low variability and great performance. Furthermore, they are the primary method for identifying antifungal medication resistance and detecting non-culturable organisms.ishows that fungal PCR tests have been extensively developed, verified, and standardized. This section will cover recent advancements in molecular-based methods for identifying fungal pathogens, including PCR assays, DNA metabarcoding, sequencing, and bioinformatics.T2 Candida can quickly diagnose candidemia in whole blood. Candidaemia is the fourth most cause of hospital-related bloodstream infections, with a mortality rate of 25-40%. [43]Although blood cultures are the gold standard for diagnosing candidemia, they may only be positive in 50% of cases [44].. Traditional blood cultures have poor performance because to prolonged positive and antifungal resistance. Candida albicans, Candida tropicalis, and Candida parapsilosis can be found within 36 hours, but Candida glabrata, a slow-growing organism, can take up to 80 hours [45]A new technique has been developed to speed up invasive candidiasis detection, taking into account the risk of sepsis from delayed diagnosis and the importance of time during sepsis. In 2014, the US FDA authorized T2Candida, a qualitative, non-culture-based platform for diagnosing candidemia.

This test may quickly identify the five most common Candida species in whole blood within 5 hours. According to Joshi and Shenoy [46], T2 Candida is a game changer in diagnosing invasive fungal infections due to its early detection and ability to reduce mortality rates. The test uses both magnetic resonance and molecular procedures (e.g., PCR), and this section focuses on the latter.To perform T2 Candida testing, the following steps are taken: (a) collect whole blood from the patient in the presence of EDTA, (b) insert whole blood tubes into the fully automated T2Dx instrument (T2Biosystems, Inc., Wilmington, MA, USA), (c) mechanically lyse the Candida cells, (d) amplify the Candida ribosomal DNA using thermostable polymerase and primers, and (d) detect the amplified Candida DNA product.The test results are positive or negative for identifying the five most prevalent Candida species (C. albicans, C. tropicalis, C. parapsilosis, C. krusei, and C. glabrata), which account for almost 95% of candidemia cases [47,48,49]. The test requires only 2-4 mL of whole blood, making it suitable for paediatric use.The average turnaround time is less than 5 hours, and the detection limit is as low as 1-3 CFU/mL of whole blood, compared to the 100-1000 CFU/mL required by traditional PCR procedures. A multi-center experiment found that T2 Candida has 91.1% sensitivity, 99.4% specificity, and an NPV of 99.4% in a general hospital/ICU context with a candidemia prevalence of 5% (50). T2 Candida's remarkable features make it a game changer, accelerating the start of antifungal therapy before the patient and physician experience negative outcomes. T2MR covers all five Candida species.This method may quickly detect six prevalent bacteria, known as "ESKAPE" pathogens (Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and Enterococcus faecium) [51].Bilir et al. [52] found that the T2 candida panel has a significant economic impact using a 1-year decision-tree model. A hospital with 5100 high-risk patients annually might save $26,887 per patient with candidemia, resulting in a 48.8% reduction in hospital expenses. While avoiding 60.6% of mortality caused by candidemia.Rapid Candida identification can save over 30 lives each year in hospitals, resulting in a 60.6% reduction in mortality rates. T2 Biosystems' new T2 C.auris panel marks a significant advancement.The CDC has identified C. auris as a significant worldwide health issue due to its resistance to multiple antifungal medications. The T2Cauris panel has a time advantage of 5 hours and can detect tiny quantities of C. auris, unlike traditional culture methods that take 14 days. The T2Cauris panel outperforms previous molecular diagnostic assays for C. auris by over 100-fold, detecting levels as low as 5 CFU/mL [52,53,54].T2-MR is a breakthrough tool for

detecting candidemia, leading to significant reductions in patient mortality, morbidity, hospital stays, and expenses. T2Candida is highly recommended for use in diagnostic algorithms and guidelines alongside blood cultures to manage patients with suspected invasive candidiasis, particularly in high-prevalence settings such as ICUs.The high NPV allows practitioners to safely discontinue antifungal therapy and transition to other treatment options. Positive T2MR data should be interpreted in relation to the expected illness prevalence in the specific clinical context. More research is needed to determine if T2Candida can be used as a monitoring tool to ensure complete candidemia clearance, as previous studies have indicated that it can remain positive even after blood cultures are clear [50].Deep-seated infections can be caused by hematogenous seeding or non-hematogenous introduction of Candida into sterile areas, such as the abdominal cavity after GI tract disruption or through an infected peritoneal catheter [44].However, blood cultures may fail to detect candida and yield negative results. This could be owing to insufficient viable candida cell concentrations in a sample, sporadic or transitory release into the bloodstream, or mismatched culturing timings [56]. T2 Candida has been shown to give promising results in detecting deep-seated invasive candidiasis (IC) in patients whose blood cultures wereInitially negative, but later proved positive through tissue biopsy [48]. More research is needed to assess the effectiveness of T2MR in diagnosing invasive candidiasis without candidemia.

Advances in PCR tests for fungal diagnosis PCR was the first nucleic acid amplification technology developed. PCR techniques have evolved to include nested PCR, real-time PCR, and multiplex PCR. Advancements in PCR-based approaches have improved mycological testing and identification platforms. Fungus-specific primers and quantitative real-time PCR have been used to diagnose infections such as Aspergillus, Candida, Mucorales, and Pneumocystis jirovecii [57].A PCR assay for detecting fungal nucleic acids may be the best diagnostic strategy because it is more sensitive than culture-based methods, takes less time, can be applied to various clinical sample types (e.g. blood, body fluids, BAL, CSF), and can detect nonculturable species or when culture tests are negative due to early antifungal treatment.This section will focus on current improvements in diagnosing invasive fungal diseases from 2015 forward, as it is impossible to cover all PCR variants.

Multiplex PCR advancements. The concept of multiplex PCR (m-PCR) is not new. To address the high cost and enhance diagnostic capacity of PCR, a version known as multiplex PCR was devised.A m-PCR detects multiple targets simultaneously in a single reaction well, using unique primer pairs for each target. This saves cost, time, and labor without compromising test utility. Real-time multiplex PCR can detect two to five pathogenic species utilizing species-specific primers and probes labeled with fluorescent dyes [58,59,60]. m-PCR may detect many diseases with high specificity, resulting in significant cost savings.While there are numerous commercial m-PCR kits available for detecting common fungal infections, only a few stand out for their effectiveness. Our kits, such as SeptiFast (Roche Diagnostics) and MycAssay Aspergillus, eliminate the need for prior fungal culture and allow for direct DNA amplification from clinical samples, eliminating an extra step.The SeptiFast m-PCR kit has a high sensitivity (90.5%) for detecting pathogens in as little as 100 µL of blood, making it useful for diagnosing fungal neonatal sepsis in cases where higher blood volumes from neonates and preterm infants are limited [61].The AsperGenius PCR assay (PathoNostics, Maastricht, the Netherlands) combines two real-time PCRs: one to identify clinical Aspergillus species and a second to detect azole resistance mutations in A. fumigaetus's CYP51A gene.AsperGenius is a unique approach that uses the patient's BAL sample to diagnose both the underlying cause and treatment resistance. The kit has an overall sensitivity, specificity, PPV, and NPV of 84.2%, 91.4%, 76.2%, and 94.6% [62].The FilmArray Meningitis/Encephalitis (ME) panel (BioFire Diagnostics, Salt Lake City, UT) is the first to achieve FDA approval in October 2015. The FilmAr ray Meningitis/Encephalitis panel identifies Cryptococcus neoformans/Cryptococcus gattii, a fungal target, with bacterial and viral targets in CSF [63].MucorGenius (Patho Nostics) is a new commercial PCR assay designed to identify invasive mucormycosis (IMM). The kit detects the 28S multi-copy gene in therapeutically relevant species, including pan-Mucorales DNA, Rhizopus spp., Mucor spp., Lichtheimia spp., Cunninghamella spp., and Rhizomucor spp. The kit detects directly in BAL samples and provides results in less than 3 hours [64,65].The technique detected IMM in serum and tissue samples with 91% sensitivity [64].. Mucorales DNA was found in serum of patients with probable/proven IMM (100%) and 29% of potential cases. In a multicenter retrospective research [66], MucorGenius was evaluated on 106 blood samples from 16 patients with culture-positive invasive mucormycosis and demonstrated 75% overall sensitivity.The kit's positive results occurred 81 days before a positive culture, indicating that Mucorales DNA can be detected in patients with suspected IMM at an early stage of infection. This allows for better control over the fungal infection in the host system, unlike traditional tests.
The MucorGenius® assay can run alongside an Aspergillus-specific AsperGenius® assay from the same manufacturer, providing a unique benefit.. In a single run, the BAL sample can be tested for the presence of both molds simultaneously utilizing four separate detection channels (green, yellow, orange, and red).

AsperGenius®, yellow, and red for MucorGenius®).

This method could be useful in clinical settings to detect coinfections and guide optimal treatment options. Multiple mold infections can lead to poor treatment outcomes.Mixed infections have occurred.SARS CoV-2 has been identified in immunocompromised patients [67,68]. Accurate diagnostic assays covering a wider range of suspected fungal strains are crucial for achieving high precision. Carvalho-Pereira and team [69] created a novel multiplex PCR with two panels: Candida (to identify C. albicans, C. parapsilosis, C. glabrata, C. krusei, C. tropicalis) and Filamentous Fungi (to identify A. fumigatus, A. flavus, A. terreus, A. niger, and R. arrhizus) using species-specific primers.This one-of-a-kind m-PCR identifies ten clinically relevant fungus species that cause invasive infections from positive blood cultures, tissue specimens from biopsy, or sterile areas. This innovative technique uses species-specific primers outside

mitochondrial or ribosomal DNA, reducing cross-amplification from non-target species.The test detected fungal DNA from spiking human serum with no interference from human DNA. It had a limit of detection of 10 to 1 pg of DNA and demonstrated encouraging results. This dual panel m-PCR allows for simple visualization of final results based on accurate fragment size and fluorescent color, preventing unspecific amplification.Future possibilities include customizing the assay to incorporate new species based on the epidemiology of a certain geographical region.

* *Advances in biosensor-based fungal diagnostic tests:-*

The International Union of Pure and Applied Chemistry (IUPAC) defines biosensors as "integrated receptor-transducer devices that provide quantitative or semi-quantitative analytical information utilizing a biological recognition element" [69].A biosensor consists of three major components: a recognition element that separates an analyte or set of analytes, a transducer that generates a signal, and a signal processor. The biosensor's recognition and transducer components work together to generate a quantitative signal. Biosensors have significantly improved healthcare and diagnostics since their development.Biosensor technology enables low-cost, disposable point-of-care devices and continuous monitoring of biomarkers in less intrusive ways [70,71].Advancements in biosensor technology have improved invasive fungal diagnosis, as discussed in this section. Biosensors can be electrochemical, optical, piezoelectric, or thermometric, depending on the signal generation method or transducer used. We will describe innovative methods for identifying invasive fungus species.Electrochemical biosensors analyze biological samples by converting them into measurable electronic signals, such as impedance (electrochemical impedance spectroscopy), current (amperometric), or potential difference (potentiometric) [72].. However, few articles have explored their potential for diagnosing fungus. Kwansy et al. [73] developed an electrochemical impedance-based biosensor for detecting C. albicans. The biosensor detected yeast cells on electrodes functionalized with anti-Candida antibodies, resulting in changes in electrochemical impedance spectroscopy.Using a biosensor can identify yeast cells in test specimens in about an hour, saving time when deciding on antifungal therapy. Increasing yeast cell concentration resulted in higher transfer charge resistance (Rct values of 350, 500, and 578 Ohms for 10, 100, and 1000 CFU/mL, respectively), with a linearity fit of $R2 = 0.916$ and sensitivity to capture as low as 10 CFU/mL in PBS samples. The team is working on improving and testing the biosensor in clinical samples. In another study, a team developed an electrochemical biosensor to detect the pathogenic glip target gene and diagnose IA [74].

Optical biosensors These are the most widely used biosensors. An optical biosensor combines a biorecognition component with an optical transducer system. The biosensor recognizes a variety of biomolecules, including enzymes, antibodies, antigens, receptors, nucleic acids, and entire cells.The transducer system can utilize surface plasmon resonance (SPR), evanescent wave fluorescence, or dynamic lightscattering, refractometry, etc. [75].These approaches provide advantages over conventional analytical methods by allowing for label-free analyte detection and real-time observation. Cai and colleagues [76] employed a photonic crystal (PC) with protein-carbohydrate specific recognition to identify C. albicans. The analyte reaction involved a particular interaction between Concanavalin A (Con A) and mannan on fungus cell walls.. To do this, pure ConA protein hydrogels were crosslinked with glutaraldehyde to form monodisperse 2D PC arrays. The blue shift in 2D array diffraction was proportional to fungal load due to cross-linking caused by hydrogel Con A proteins recognizing multiple mannose groups. The final phase was decreasing the spacing of 2D array particles. The sensor accurately detected C. albicans at 32 CFU/mL and distinguished it from other microbes. The team aims to improve sensitivity and detection times by using thinner, less crosslinked hydrogels.This study demonstrates that interactions between lectins and carbohydrate antigens can be used to create efficient and cost-effective biosensors. In addition to ConA, dendritic cell-associated lectin-2 (dectin-2) has been shown to bind fungal mannan [76]. Dectin-2 attaches to high-mannose structures and triggers inflammatory reactions. Another option is to use dectin-2's characteristics to create biosensors [77].

In a 2022 study, scientists developed an optical nano-biosensor using dynamic light scattering (DLS) to diagnose IA by detecting Aspergillus galactomannan in biological fluids. This technology is appropriate for fast point-of-care diagnosis. Biosensors use nanoparticles with receptors to detect the presence of an analyte in solution. In a work by [78], gold nanoparticles were functionalized with high-affinity antibodies to galactomannan (GM) and employed as probes.The researchers analyzed the hydrodynamic diameter of functionalized nanoparticles and the count rate of scattered light pulses separately. This was done to enhance the accuracy and dependability of DLS-based nanosensors. Data regarding hydrodynamic diameter and count rate showed a strong association.

Express point-of-care diagnostics In addition to the aforementioned biosensors, piezoelectric and thermal biosensors have significant potential for fungus detection. A piezoelectric biosensor contains a piezoelectric crystal. The oscillations of the piezoelectric crystal surface change when an analyte attaches to it [79,80]. The analytical signal is measured based on the shift in oscillatory frequency, which is proportional to the crystal's mass. Mass detection could enable real-time label-free operation and monitoring of fungal growth [81].Thermal biosensors monitor heat changes caused by biological reactions in a media [77-83]. There are no reports of using piezoelectric or thermal biosensors to detect invasive fungal species. In 2005, Nugaeva and colleagues [84] developed a micromechanical cantilever biosensor for detecting Saccharomyces cerevisiae and Aspergillus niger.. More study is needed to prove the effectiveness of these biosensors in detecting fungal pathogens. Previous research has explored the use of nano-sized materials (e.g., carbon dots, carbon nanotubes, nanowires, liposomes) to create novel biosensors that can detect invasive fungal strains with greater precision and speed. [84-86].

microfluidic-based detection Microfluidic methods are increasingly used for fungal diagnosis [87,88]. Microfluidics processes small amounts of fluids using tiny forces at the microscale. This approach involves precisely controlling and manipulating fluids on a microscopic scale. At this size, surface forces take precedence over volumetric forces, as fluid characteristics change.The microfluidic chip has several holes of varying sizes that connect the microchannel network to the surrounding environment. This technology offers benefits such as faster reaction times, improved temperature control, mobility, integration of lab procedures (lab-on-a-chip), automation, and high precision analytical capabilities [9,90,91].Asghar and crew [92] investigated how microfluidic chips can detect fungal infections. The researchers developed an immuno-based microfluidic system to quickly identify C. albicans in PBS and whole human blood. The microfluidic chip is constructed of PMMA, double-sided adhesive (DSA), and a laser-cut glass cover with three microfluidic channels and inlets.Anti-Candida antibodies were immobilized on the surface using protein G chemistry. The team tested the effectiveness of monoclonal and polyclonal antibodies in collecting C. albicans from spiked samples using microfluidic channels. Polyclonal anti-Candida antibodies had greater values (77.4 ± 4.4%) compared to monoclonal anti-Candida antibodies (48.6 ± 2.8%). As fungal load grew from 103 to 105 CFU/mL, capture efficiencies rose to 61 ± 12.7%, 70 ± 13.2%, and 77.4 ± 4.4%, respectively.Initially, capture efficacy dropped at 102 CFU/mL. However, increasing the sample amount from 50 µL to 1 mL resulted in higher capture efficiencies.

CFU/mL: 102 (78 ± 13.2%) and 10 (75 ± 21.1%). The capture efficiency of spiked whole blood was 40.5 ± 4.7%, presumably due to the high number of blood cells preventing Candida-antibody interactions. After lysing the spiked blood sample, the capture efficiency increased to 74.6 ± 6.8%.The process takes an average of 1-5 to 2 hours. The microfluidic technique captures and isolates complete Candida cells without lysing them, potentially allowing for drug resistance and susceptibility testing. Microchip approaches can be linked with smartphone images [93] for point-of-care diagnostics and remote patient care. In a similar study, Bras et al. [94] used a microfluidic technique to identify fungal plant diseases infecting grape varieties at multiple points of need.The data covered in this part highlights the potential for biosensor-based fungal diagnosis to transform the field of fungal diagnosis. Integrating various recognition elements on a multiplexed biosensor platform can improve sensitivity, specificity, and reproducibility. Biosensors accelerate analysis, reduce sample preparation time, and provide a cost-effective diagnostic tool for recording data. This allows for biosensor-based point-of-care diagnostics. Routine screening can eliminate the need for costly and time-consuming testing such as culture tests, PCR, immunoassays, ELISA, etc.Advances in biosensor research, point-of-care testing, and real-time monitoring of fungal growth can help detect fungal pathogens early and initiate relevant interventions.

**Artificial intelligence and machine learning: a new era in fungal diagnostics and patient care:*

Artificial intelligence (AI) simulates human intelligence through machine learning, reasoning, and self-correction. Machine learning (ML) is an area of AI and computer science that uses data and algorithms to improve software's accuracy in predicting outcomes, similar to human performance. Machine learning algorithms employ historical data to accurately predict fresh output values. Deep learning is a subset of machine learning that teaches computers to learn by example and massive datasets, similar to how humans learn [95].

AI approaches, including machine learning and deep learning, have significantly accelerated healthcare digitization during the past decade. Digitized health care reduces human errors, improves therapeutic outcomes, and enables real-time tracking of patient data [96,97].AI and machine learning models help physicians make faster and more accurate decisions by processing and analyzing large amounts of complex data. A doctor uses CT scans or magnetic resonance imaging for analysis, but an AI model may detect unhealthy areas in a fraction of a second. AI and machine learning can help physicians make better decisions by assisting with diagnosis and offering exact results.AI-based detection helps discover patients with undiagnosed, latent, or subclinical infectious illnesses. A study found that cutaneous deep-seated fungal infections can develop months or yearslaterTransplantation in healed areas indicates the presence of fungal organisms in a latent condition [98].Fungi can become active only when immune defenses are compromised by neutropenia or immunosuppressive drugs, resulting in fungal multiplication. AI-based disease identification can lead to earlier diagnosis and treatment for those in need [99].This section explains how AI and ML-based models can increase the accuracy and speed of detecting IFIs. We utilize simple terms to accommodate readers who may not have a strong background in computer science. This article does not go into detail into the algorithms, neural networks, image analysis, and classifiers utilized for data interpretation.

A brief understanding of how machine learning works. Classical machine learning relies on step-by-step techniques to improve prediction accuracy. These ML algorithms can process massive volumes of data and extract valuable insights. They improve on prior iterations by learning from available data (100,101).There are four main approaches: supervised learning, unsupervised learning, semi-supervised learning, and reinforcement learning. In supervised learning (task-driven), data scientists offer algorithms with labeled training data and a smaller dataset to train on. The dataset already includes defined variables that the algorithm must evaluate for correlation. The algorithm's input and output are specified. After training, the algorithm understands the data and its link with input and output.The algorithm is evaluated on the final dataset. Algorithms continuously improve by learning from new data and identifying new patterns and relationships [102].

VII.Treatment of fungal infection:-

Classfication of antifungal drug [103-107]

Antifungal drugs classified into 5 types-

1. Antibiotics

2. Antimetabolites

3. Azole

4. Allylamine

5. Topical Agents

1. Antibiotics Antibiotics also classified into 3 types.

A. Polyenes

B. Echinocandins

C. Heterocyclic benzofuran

A. Polyenes

♣ Amphotericin B

♣ Nystatin

♣ Hamycin B. Echinocondins

♣ Caspofungin

♣ Micafungin

♣ Anidulafungin

C. Heterocyclic Benzofuran

♣ Griseofulvin

2. Antimetabolites

♣ Flucytosine

3. Azoles Azoles having 2 types

A. Imidazoles

B. Triazoles

C. Imidazoles

Having 2 Subtype

a. Topical

♣ Clotrimazole

♣ Econazole

♣ Miconazole

♣ oxiconazole

b. Systemic

♣ Ketoconazole

B. Triazoles

♣ Fluconazole

♣ Itraconazole

♣ voriconazole

♣ posaconazole

4. Allylamine

♣ Terbinafine

5. Topical Agents

♣ Tolnaftate

♣ Undecylenic acid

♣ Benzoic acid

♣ Cicloplrox olamine

♣ Butenafine

♣ Quiniodochlor

♣ Sod. Thiosulfate

Antifungal therapy:-

Early commencement of antifungal medication is crucial for controlling systemic Candida infections and lowering mortality rates [108,109,110]. Treatment with antifungal drugs is recommended for all patients with candidaemia, defined as the presence of Candida in at least one blood culture, according to management recommendations [111,112,113].

1.*Polyenes*-

Amphotericin B deoxycholate, a broad-spectrum antifungal drug that targets ergosterol in fungal cell membranes, has long been the preferred treatment for invasive candidiasis. It is typically administered intravenously at a dose of 0.6–1 mg/kg/day.Unfortunately, amphotericin B deoxycholate is poorly tolerated and can cause infusion-related acute responses such as chills, fever, hypoxaemia, and hypotension, particularly when given. Over a short period of time (4-6 hours) and with nephrotoxicity (lower glomerular filtrate). Potassium, magnesium, and bicarbonate squandering in the tubules.Recent studies indicate that administering amphotericin B deoxycholate as a continuous infusion over 24 hours with saline loading can reduce infusion-related reactions and renal impairment, particularly in allogenic stem cell transplant patients receiving cyclosporin A [114-117].A multivariate analysis of 494 patients receiving amphotericin B deoxycholate revealed that male gender, body weight 090 kg, chronic renal disease, treatment with aminoglycosides or cyclosporin, and amphotericin B doses 035 mg/day were independent risk factors for nephrotoxicity. The incidence of nephrotoxicity increased with the number of risk factors, indicating that alternate medication may be acceptable for patients with two or more risk factors (118119).

Lipid formulations of amphotericin B-

Colloid dispersion, lipid-complex, and liposomal amphotericin B are more well-tolerated than amphotericin B deoxycholate. They are mostly employed in individuals who are intolerant to traditional amphotericin B or have impaired renal function (120-123).In Switzerland, the only available amphotericin B is liposomal (AmBisome®). Few studies have examined the effectiveness of amphotericin B deoxycholate against lipid formulations for treating invasive candidiasis. Small non-comparative investigations show that lipid formulations of amphotericin B are equally effective as standard amphotericin B [124-127].Lipid formulations are typically utilized as a second-line therapy for refractory invasive candidiasis due to high prices, limited clinical data, and availability of alternative antifungal medications such as azoles and echinocandins [111,113].

2. *Azoles*-

In the late 1980s, triazoles became the standard treatment for invasive candidiasis. Azoles inhibit the formation of ergosterol in fungal cell membrane. These chemicals show antifungal activity against Candida species in vitro. Several clinical trials have evaluated the effectiveness and safety of azoles.While amphotericin B deoxycholate has been used to treat candidaemia in non-neutropenic patients, there is limited data on its effectiveness in neutropenic individuals.

3. *Fluconazole*-

It is offered in both intravenous and oral forms. Fluconazole is effectively absorbed orally and is not affected by H2 blocking drugs. For individuals with creatinine clearance of less than 50 ml/min or less than 20 ml/min, the daily dose should be lowered by 50% and 75%, respectively. A loading dosage of twice the daily amount is advised. A trial of 206 non-neutropenic individuals with candidaemia

revealed fluconazole to be equally effective (72% vs 79%, respectively) and better tolerated than amphotericin B deoxycholate [128].Fluconazole's widespread use has led to an increase in infections caused by non-albicans Candida species with reduced azole sensitivity (C. glabrata) or intrinsic resistance (C. krusei) in the late 1990s [129,130,131]. There is limited evidence on the effectiveness of high dosages (800 to 1200 mg) of fluconazole in treating suspected azole-resistant Candida bloodstream infections.

4.*Itraconazole*-

Itraconazole is available in oral and intravenous forms. However, the low bioavailability of the initial oral formulation (increased by food) has limited its use, and no clinical investigations have been conducted on candidaemia patients. Although an intravenous version of itraconazole is now available, clinical evidence on its efficacy and safety remain limited. Itraconazole blood levels should be monitored during therapy due to variations in bioavailability and potential medication interactions (e.g., with rifampicin, anticonvulsants, protease inhibitors, macrolides).

5.*Vorivonazole*-

Voriconazole is available in oral (60-100% bioavailability) and intravenous forms [132]. The P-450 system (CYP2C9, CYP3A4, and CYP2C19) metabolizes it in the liver, leading to possible medication interactions with rifampicin, anticonvulsants, sirolimus, tacrolimus, cyclosporin, oral anticoagulants, statins, omeprazole, protease inhibitors, and NNRTIs.Patients with renal impairment receiving the oral version of voriconazole do not require any adjustments to their dosage. In patients with mild renal impairment (creatinine clearance < 50 ml/min), intravenous voriconazole therapy may cause buildup of the b-cyclodextrin used to solubilize the drug. Adverse effects may include reversible, non-threatening vision problems (30-40%), rash, hepatitis, and hallucinations. Voriconazole is highly effective against Candida species, both in vitro and in vivo [133]. Clinical data from immunocompromised (mainly HIV-positive) patients with oropharyngeal and/or oesophageal candidiasis suggest that voriconazole has excellent activity against fluconazole-suscepti ble and fluconazole-resistant Candida infections:Voriconazole had a 98% success rate compared to 95% for fluconazole [134]. Voriconazole salvage therapy achieved a 55% success rate in treating resistant systemic candidiasis [135].. Voriconazole was found to be as effective as amphotericin B deoxycholate followed by intravenous or oral fluconazole in a non-inferiority trial of 422 patients with invasive Candida infections (over 95% of whom had candiaemia) [136]. Voriconazole was found to be more effective than amphotericin B/fluconazole for treating C. tropicalis infections (P = 0.03).

6. *Posaconazole*-

Posaconazole is a novel azole that has wide antifungal action against Candida, Aspergillus, Fusarium, and zygomycetes. Posaconazole's hepatic metabolism differs from other azoles, with glucuronation playing a large role and CYP450 enzymes playing a secondary function. This may reduce the possibility of clinically significant drug-drug interactions [137].The drug's oral version has varied bioavailability, which can be greatly improved (up to 90%) with food intake [138]. Posaconazole 400 mg twice daily was clinically effective in 75% of 199 HIV-positive patients with azole-resistant oropharyngeal or oesophageal candidiasis (modified ITT analysis) and 81.6% (evaluable population) [139].Posaconazole was successful as salvage therapy in 47.8% of patients with invasive candidiasis, according to a clinical research [140]. In a long-term safety study of 102 patients treated with posaconazole for invasive mycoses, 12 (12%) experienced serious side effects. However, only one patient discontinued posaconazole therapy [141]. Posaconazole will shortly be licensed for refractory mycoses, but more clinical data on first-line candidiasis treatment is needed.

Conclusion:-

To summarize, fungal infections are a worldwide problem that can be fatal for immunocompromised patients. Because our medical system has been overly reliant on antibiotics to combat fungal infections for so long, many other medications have lost their effectiveness in treating fungal infections.various antifungal drugs are used to treat the fungal infection .

References :-

1. Mahendra P. Morbidity and Mortality Due to Fungal Infections. J Appl Microbiol Biochem. 2017; 1(1):1-2.
2. Sawant B, Khan T. Recent advances in delivery of antifungal agents for therapeutic management of candidiasis. Biomed Pharmacother. 2017;96:1478 90.
3. Nett JE, Andes D. Spectrum of activity pharmacology and clinical indication. Antifungal agent.,2015:10:1 13
4. Houst J, Spizek J, Havlicek V. Review antifungal drug. Metabolites.,2020:10:1-16.
5. Kaur N, Bains A, Kaushik R, Dhull SB, Melinda F, Chawla P. A review on antifungal efficiency of plant extract entrenched polysaccharide Based Nanohydrogel. Nutrient 2021:13:2-26.
6. journal homepage: www.sciencedirect.com/journal/current-research-in-microbial-sciences.(Lee, P.P., Lau, Y.-.L., 2017)
7. Kibbler, C. C., Seaton, S., Barnes, R. A., Gransden, W. R., Holliman, R. E., Johnson, E. M., Perry, J. D., Sullivan, D. J. & Wilson, J. A. (2003). Management and outcome of bloodstream infections due to Candida species in England and Wales. J Hosp Infect 54, 18–24. Denning, D. W., Kibbler, C. C. & Barnes, R. A., and on behalf of the British Society for Medical Mycology (2003).

British Society for Medical Mycology proposed standards of care for patients with invasive fungal infections. Lancet Infect Dis 3, 230–240.
8. Denning, D. W. (2003). Echinocandin antifungal drugs. Lancet 362, 1142–1151.Denning, D. W., Kibbler, C. C. & Barnes, R. A., and on behalf of the British Society for Medical Mycology (2003). British Society for Medical Mycology proposed standards of care for patients with invasive fungal infections. Lancet Infect Dis 3, 230–240.
9. Edmond, M. B., Wallace, S. E., McClish, D. K., Pfaller, M. A., Jones, R. N. & Wenzel, R. P. (1999). Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis 29, 239–244.
10. Trick, W. E., Fridkin, S. K., Edwards, J. R., Hajjeh, R. A. & Gaynes, R. P., and the National Nosocomial Infections Surveillance System Hospitals (2002). Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989–1999. Clin Infect Dis 35, 627–630.
11. Tortorano, A. M., Biraghi, E., Astolfi, A. & 8 other authors, and the FIMUA Candidemia Study Group (2002). European Confederation of Medical Mycology (ECMM) prospective survey of candidaemia: report from one Italian region. J Hosp Infect 51, 297–304.
12. Tortorano, A. M., Caspani, L., Rigoni, A. L., Biraghi, E., Sicignano, A. & Viviani, M. A. (2004a). Candidosis in the intensive care unit: a 20-year survey. J Hosp Infect 57, 8–13.
13. Tortorano, A. M., Peman, J., Bernhardt, H. & 8 other authors, and the ECMM Working Group on Candidaemia (2004b). Epidemiology of candidaemia in Europe: results of 28-month European Confederation of Medical Mycology (ECMM) hospital-based surveillance study. Eur J Clin Microbiol Infect Dis 23, 317–322.
14. Eggimann, P., Garbino, J. & Pittet, D. (2003). Epidemiology of Candida species infections in critically ill non-immunosuppressed patients. Lancet Infect Dis 3, 685–702.
15. Saag, M. S., Graybill, R. J., Larsen, R. A., Pappas, P. G., Perfect, J. R., Powderly, W. G., Sobel, J. D. & Dismukes, W. E., for the Mycoses Study Group Cryptococcal Subproject (2000). Practice guidelines for the management of cryptococcal disease. Clin Infect Dis 30, 710–718.
16. Denning, D. W. (1998). Invasive aspergillosis. Clin Infect Dis 26, 781–803 Denning, D. W., Marinus, A., Cohen, J. & 11 other authors (1998). An EORTC multicentre prospective survey of invasive aspergillosis in haematological patients: diagnosis and therapeutic outcome. EORTC Invasive Fungal Infections Cooperative Group. J Infect 37, 173–180.
17. Marr, K. A., Seidel, K., Slavin, M. A., Bowden, R. A., Schoch, H. G., Flowers, M. E., Corey, L. & Boeckh, M. (2000). Prolonged f luconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood 96, 2055–2061.
18. Baddley, J. W., Pappas, P. G., Smith, A. C. & Moser, S. A. (2003). Epidemiology of Aspergillus terreus at a university hospital. J Clin Microbiol 41, 5525–5529.
19. De Rosa, F. G., Shaz, D., Campagna, A. C., Dellaripa, P. E., Khettry, U. & Craven, D. E. (2003). Invasive pulmonary aspergillosis soon after therapy with infliximab, a tumor necrosis factor-alpha neutralizing antibody: a possible healthcare-associated case? Infect Control Hosp Epidemiol 24, 477–482.
20. Hagerty, J. A., Ortiz, J., Reich, D. & Manzarbeitia, C. (2003). Fungal infections in solid organ transplant patients. Surg Infect (Larchmont) 4, 263–271.
21. Singh, N., Avery, R. K., Munoz, P. & 10 other authors (2003). Trends in risk profiles for and mortality associated with invasive aspergillosis among liver transplant recipients. Clin Infect Dis 36, 46–52.
22. David Moore. Fungus. Britannica. Accessed on 11 September 2020. Available from: https://www.britannica.com/science/fungus.
23. Fungal infections. Webmd. Accessed on 11 September 2020. Available from: https://www.webmd.com/skin problems-and-treatments/guide/fungal-infections-skin#1-1. Fungal infection. Practo. Accessed on 11 September 2020. Available from: https://www.practo.com/health wiki/fungal-infection-symptomstypes-and-treatment/18/article.
24. Fungal infection. Practo. Accessed on 11 September 2020. Available from: https://www.practo.com/health wiki/fungal-infection-symptomstypes-and-treatment/18/article.
25. . Kozel TR, Wickes B. Fungal diagnostics. Cold Spring Harb Perspect Med. 2014;4(4):a019299. https:// doi. org/ 10. 1101/ cshpe rspect. a0192 99.
26. Richardson M, Page I. Role of serological tests in the diagnosis of mold infections. Curr Fungal Infect Rep. 2018;12(3):127–36. https:// doi. org/ 10. 1007/ s12281- 018- 0321-1.
27. Cota GF, de Sousa MR, Demarqui FN, Rabello A. The diagnostic accuracy of serologic and molecular methods for detecting visceral leishma niasis in HIV infected patients: meta-analysis. PLoS Negl Trop Dis. 2012;6(5):e1665. https:// doi. org/ 10. 1371/ journ al. pntd. 00016 65.
28. Theel ES, Doern CD. β-D-glucan testing is important for diagnosis of invasive fungal infections. J Clin Microbiol. 2013;51(11):3478–83. https:// doi. org/ 10. 1128/ JCM. 01737- 13.
29. Tissot F, Lamoth F, Hauser PM, Orasch C, Flückiger U, Siegemund M, Zimmerli S, Calandra T, Bille J, Eggimann P, Marchetti O, Fungal Infection Network of Switzerland (FUNGINOS). β-glucan antigenemia anticipates diagnosis of blood culture-negative intraabdominal candidiasis. Am J Respir Crit Care Med. 2013;188(9):1100–9. https:// doi. org/ 10. 1164/ rccm. 201211- 2069OC.
30. Onishi A, Sugiyama D, Kogata Y, Saegusa J, Sugimoto T, Kawano S, Morinobu A, Nishimura K, Kumagai S. Diagnostic accuracy of serum 1,3-β-D-glucan for pneumocystis jiroveci pneumonia, invasive candidi asis, and invasive aspergillosis: systematic review and meta-analysis. J Clin Microbiol. 2012;50(1):7–15. https:// doi. org/ 10. 1128/ JCM. 05267- 11.

31. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, Michalopoulos A, Rafailidis PI, Falagas ME. β-D-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. Clin Infect Dis. 2011;52(6):750–70. https:// doi. org/ 10. 1093/ cid/ ciq206.
32. Fortún J, Martín-Dávila P, Alvarez ME, Norman F, Sánchez-Sousa A, Gajate L, Bárcena R, Nuño SJ, Moreno S. False-positive results of Aspergillus galactomannan antigenemia in liver transplant recipients. Transplantation. 2009;87(2):256–60. https:// doi. org/ 10. 1097/ TP. 0b013 e3181 9288d5.
33. León C, Ostrosky-Zeichner L, Schuster M. What's new in the clinical and diagnostic management of invasive candidiasis in critically ill patients. Intensive Care Med. 2014;40(6):808–19. https:// doi. org/ 10. 1007/ s00134- 014- 3281-0.
34. León C, Ruiz-Santana S, Saavedra P, Castro C, Loza A, Zakariya I, Úbeda A, Parra M, Macías D, Tomás JI, Rezusta A, Rodríguez A, Gómez F, Martín Mazuelos E, Cava Trem Study Group. Contribution of Candida biomark ers and DNA detection for the diagnosis of invasive candidiasis in ICU patients with severe abdominal conditions. Crit Care. 2016;20(1):149. https:// doi. org/ 10. 1186/ s13054- 016- 1324-3.
35. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the european organization for research and treat ment of cancer and the mycoses study group education and research consortium. Clin Infect Dis. 2020;71(6):1367–76. https:// doi. org/ 10. 1093/ cid/ ciz10 08.
36. Pickering JW, Sant HW, Bowles CA, Roberts WL, Woods GL. Evaluation of a (1->3)-beta-D-glucan assay for diagnosis of invasive fungal infections. J Clin Microbiol. 2005;43(12):5957–62. https:// doi. org/ 10. 1128/ JCM. 43. 12. 5957- 5962. 2005.
37. Sulahian A, Porcher R, Bergeron A, Touratier S, Raffoux E, Menotti J, Derouin F, Ribaud P. Use and limits of (1–3)-β-d-glucan assay (Fungitell), compared to galactomannan determination (Platelia Aspergillus), for diagnosis of invasive aspergillosis. J Clin Microbiol. 2014;52(7):2328–33. https:// doi. org/ 10. 1128/ JCM. 03567- 13.
38. Odabasi Z, Mattiuzzi G, Estey E, Kantarjian H, Saeki F, Ridge RJ, Ketchum PA, Finkelman MA, Rex JH, Ostrosky-Zeichner L. Beta-D-glucan as a diagnostic adjunct for invasive fungal infections: validation, cut-off development, and performance in patients with acute myelog enous leukemia and myelodysplastic syndrome. Clin Infect Dis. 2004;39(2):199–205. https:// doi. org/ 10. 1086/ 421944.
39. D'Ordine RL, Garcia KA, Roy J, Zhang Y, Markley B. Finkelman MA performance characteristics of Fungitell STAT™, a rapid (1→3)-β-D glucan single patient sample in vitro diagnostic assay. Med Mycol. 2021;59(1):41–9.
40. Racil Z, Kocmanova I, Lengerova M, Weinbergerova B, Buresova L, Toskova M, Winterova J, Timilsina S, Rodriguez I, Mayer J. Difficulties in using 1,3-{beta}-D-glucan as the screening test for the early diagnosis of invasive fungal infections in patients with haematological malignan cies–high frequency of false-positive results and their analysis. J Med Microbiol. 2010;59(Pt 9):1016–22. https:// doi. org/ 10. 1099/ jmm.0. 019299-0.
41. Friedrich R, Rappold E, Bogdan C, Held J. Comparative analysis of the Wako β-glucan test and the fungitell assay for diagnosis of candidemia and Pneumocystis jirovecii pneumonia. J Clin Microbiol. 2018;56(9):e00464-e518. https:// doi. org/ 10. 1128/ JCM. 00464- 18.
42. De Carolis E, Marchionni F, Torelli R, Angela MG, Pagano L, Murri R, De Pascale G, De Angelis G, Sanguinetti M, Posteraro B. Comparative per formance evaluation of Wako β-glucan test and Fungitell assay for the diagnosis of invasive fungal diseases. PLoS ONE. 2020;15(7):e0236095. https:// doi. org/ 10. 1371/ journ al. pone. 02360 95.
43. Tsay SV, Mu Y, Williams S, Epson E, Nadle J, Bamberg WM, et al. Burden of Candidemia in the United States, 2017. Clin Infect Dis. 2020;71(9):e449 53. https:// doi. org/ 10. 1093/ cid/ ciaa1 93.
44. Clancy CJ, Nguyen MH. Non-culture diagnostics for invasive candidiasis: promise and unintended consequences. J Fungi (Basel). 2018;4(1):27. https:// doi. org/ 10. 3390/ jof40 10027.
45. Fernandez J, Erstad BL, Petty W, Nix DE. Time to positive culture and identification for Candida blood stream infections. Diagn Microbiol Infect Dis. 2009;64(4):402–7. https:// doi. org/ 10. 1016/j. diagm icrob io. 2009. 04. 002.
46. Joshi DN, Shenoy B. T2 Candida panel: a game changer in diagnosis of fungal infections. Pediatr Inf Dis. 2022;4(1):24–5. https:// doi. org/ 10. 5005/ jp- journ als- 10081- 1333.
47. Neely LA, Audeh M, Phung NA, Min M, Suchocki A, Plourde D, et al. T2 magnetic resonance enables nanoparticle-mediated rapid detection of candidemia in whole blood. Sci Transl Med. 2013;5(182):182ra54. https:// doi. org/ 10. 1126/ scitr anslm ed. 30053 77.
48. Pfaller MA, Wolk DM, Lowery TJ. T2MR and T2Candida: novel technology for the rapid diagnosis of candidemia and invasive candidiasis. Future Microbiol. 2016;11(1):103–17. https:// doi. org/ 10. 2217/ fmb. 15. 111.
49. Monday LM, Parraga Acosta T, Alangaden G. T2Candida for the diag nosis and management of invasive Candida infections. J Fungi (Basel). 2021;7(3):178. https:// doi. org/ 10. 3390/ jof70 30178.
50. Mylonakis E, Zacharioudakis IM, Clancy CJ, Nguyen MH, Pappas PG. Efficacy of T2 magnetic resonance assay in monitoring candidemia after initiation of antifungal therapy: the serial therapeutic and antifungal monitoring protocol (STAMP) trial. J Clin Microbiol. 2018;56(4):e01756-e1817. https:// doi. org/ 10. 1128/ JCM. 01756- 17.
51. Seitz T, Holbik J, Hind J, Gibas G, Karolyi M, Pawelka E, Traugott M, Wenisch C, Zoufaly A. Rapid detection of bacterial and fungal patho gens using the T2MR versus blood culture in patients with severe COVID-19. Microbiol Spectr. 2022;10(3):e0014022. https:// doi. org/ 10. 1128/ spect rum. 00140- 22.
52. Bilir SP, Ferrufino CP, Pfaller MA, Munakata J. The economic impact of rapid Candida species identification by T2Candida among high-risk patients. Future Microbiol. 2015;10(7):1133–44. https:// doi. org/ 10. 2217/ fmb. 15. 29.

53. Kordalewska M, Zhao Y, Lockhart SR, Chowdhary A, Berrio I, Perlin DS. Rapid and accurate molecular identification of the emerging multid rug-resistant pathogen Candida auris. J Clin Microbiol. 2017;55(8):2445 52. https:// doi. org/ 10. 1128/ JCM. 00630- 17.
54. Sexton DJ, Bentz ML, Welsh RM, Litvintseva AP. Evaluation of a new T2 Magnetic Resonance assay for rapid detection of emergent fungal pathogen Candida auris on clinical skin swab samples. Mycoses. 2018;61(10):786–90. https:// doi. org/ 10. 1111/ myc. 12817
55. Clancy CJ, Nguyen MH. T2 magnetic resonance for the diagnosis of bloodstream infections: charting a path forward. J Antimicrob Chem other. 2018;73(suppl_4):iv2–5. https:// doi. org/ 10. 1093/ jac/ dky050.
56. Mendonça A, Santos H, Franco-Duarte R, Sampaio P. Fungal infections diagnosis—past, present and future. Res Microbiol. 2022;173(3):103915. https:// doi. org/ 10. 1016/j. resmic. 2021. 103915.
57. Palka-Santini M, Cleven BE, Eichinger L, Krönke M, Krut O. Large scale multiplex PCR improves pathogen detection by DNA microarrays. BMC Microbiol. 2009;3(9):1. https:// doi. org/ 10. 1186/ 1471- 2180-9-1.
58. Tsuji S, Iguchi Y, Shibata N, Teramura I, Kitagawa T, Yamanaka H. Real time multiplex PCR for simultaneous detection of multiple species from environmental DNA: an application on two Japanese medaka species. Sci Rep. 2018;8(1):9138. https:// doi. org/ 10. 1038/ s41598- 018- 27434-w.
59. Arastehfar A, Fang W, Badali H, Vaezi A, Jiang W, Liao W, Pan W, Hagen F, Boekhout T. Low-cost tetraplex PCR for the global spreading multi-drug resistant fungus, candida auris and its phylogenetic relatives. Front Microbiol. 2018;29(9):1119. https:// doi. org/ 10. 3389/ fmicb. 2018. 01119.
60. Straub J, Paula H, Mayr M, Kasper D, Assadian O, Berger A, Ritten schober-Böhm J. Diagnostic accuracy of the ROCHE Septifast PCR system for the rapid detection of blood pathogens in neonatal sepsis-A prospective clinical trial. PLoS ONE. 2017;12(11):e0187688. https:// doi. org/ 10. 1371/ journ al. pone. 01876 88.
61. Chong GL, van de Sande WW, Dingemans GJ, Gaajetaan GR, Vonk AG, Hayette MP, et al. Validation of a new Aspergillus real-time PCR assay for direct detection of Aspergillus and azole resistance of Aspergillus fumiga tus on bronchoalveolar lavage fluid. J Clin Microbiol. 2015;53(3):868–74. https:// doi. org/ 10. 1128/ JCM. 03216- 14.
62. Radmard S, Reid S, Ciryam P, Boubour A, Ho N, Zucker J, et al. Clinical utilization of the filmarray meningitis/encephalitis (ME) multiplex polymerase chain reaction (PCR) assay. Front Neurol. 2019;26(10):281. https:// doi. org/ 10. 3389/ fneur. 2019. 00281.
63. Springer J, Goldenberger D, Schmidt F, Weisser M, Wehrle-Wieland E, Einsele H, Frei R, Löffler J. Development and application of two inde pendent real-time PCR assays to detect clinically relevant Mucorales species. J Med Microbiol. 2016;65(3):227–34. https:// doi. org/ 10. 1099/ jmm.0. 000218.
64. Guegan H, Iriart X, Bougnoux ME, Berry A, Robert-Gangneux F, Gangneux JP. Evaluation of MucorGenius® mucorales PCR assay for the diagnosis of pulmonary mucormycosis. J Infect. 2020;81(2):311–7. https:// doi. org/ 10. 1016/j. jinf. 2020. 05. 051
65. Mercier T, Reynders M, Beuselinck K, Guldentops E, Maertens J, Lagrou K. Serial detection of circulating mucorales DNA in invasive mucormycosis: a retrospective multicenter evaluation. J Fungi (Basel). 2019;5(4):113. https:// doi. org/ 10. 3390/ jof50 40113.
66. Bellanger AP, Navellou JC, Lepiller Q, Brion A, Brunel AS, Millon L, Ber ceanu A. Mixed mold infection with Aspergillus fumigatus and Rhizopus microsporus in a severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) patient. Infect Dis Now. 2021;51(7):633–5. https:// doi. org/ 10. 1016/j. idnow. 2021. 01. 010.
67. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 2021;15(4):102146. https:// doi. org/ 10. 1016/j. dsx. 2021. 05. 019.
68. Carvalho-Pereira J, Fernandes F, Araújo R, Springer J, Loeffler J, Buitrago MJ, Pais C, Sampaio P. Multiplex PCR based strategy for detection of fungal pathogen DNA in patients with suspected invasive fungal infec tions. J Fungi (Basel). 2020;6(4):308. https:// doi. org/ 10. 3390/ jof60 40308.
69. Thévenot DR, Toth K, Durst RA, Wilson GS. Electrochemical biosen sors: recommended definitions and classification. Biosens Bioelectron. 2001;16(1–2):121–31. https:// doi. org/ 10. 1016/ s0956- 5663(01) 00115-4.
70. Patel S, Nanda R, Sahoo S, Mohapatra E. Biosensors in health care: the milestones achieved in their development towards lab-on-chip-analy sis. Biochem Res Int. 2016;2016:3130469. https:// doi. org/ 10. 1155/ 2016/ 31304 69.
71. Omidfar K, Ahmadi A, Syedmoradi L, Khoshfetrat SM, Larijani B. Point of-care biosensors in medicine: a brief overview of our achievements in this field based on the conducted research in EMRI (endocrinology and metabolism research Institute of Tehran University of medical sciences) over the past fourteen years. J Diabetes Metab Disord. 2020;28:1–5. https:// doi. org/ 10. 1007/ s40200- 020- 00668-0.
72. Grieshaber D, MacKenzie R, Vörös J, Reimhult E. Electrochemical biosensors—sensor principles and architectures. Sensors (Basel). 2008;8(3):1400–58. https:// doi. org/ 10. 3390/ s8031 4000.
73. Kwasny D, Tehrani SE, Almeida C, Schjødt I, Dimaki M, Svendsen WE. Direct detection of Candida albicans with a membrane based electrochemical impedance spectroscopy sensor. Sensors (Basel). 2018;18(7):2214. https:// doi. org/ 10. 3390/ s1807 2214.
74. Bhatnagar I, Mahato K, Ealla KKR, Asthana A, Chandra P. Chitosan stabilized gold nanoparticle mediated self-assembled gliP nanobio sensor for diagnosis of Invasive Aspergillosis. Int J Biol Macromol. 2018;15(110):449–56. https:// doi. org/ 10. 1016/j. ijbio mac. 2017. 12. 084.
75. Damborský P, Švitel J, Katrlík J. Optical biosensors. Essays Biochem. 2016;60(1):91–100. https:// doi. org/ 10. 1042/ EBC20 150010.

76. Vendele I, Willment JA, Silva LM, Palma AS, Chai W, Liu Y, Feizi T, Spyrou M, Stappers MHT, Brown GD, Gow NAR. Mannan detecting C-type lectin receptor probes recognise immune epitopes with diverse chemical, spatial and phylogenetic heterogeneity in fungal cell walls. PLoS Pat hog. 2020;16(1):e1007927. https:// doi. org/ 10. 1371/ journ al. ppat. 10079 27.
77. Hussain K, Malavia D, Johnson EM, Littlechild J, Winlove CP, Vollmer F, Gow NAR. Biosensors and diagnostics for fungal detection. J Fungi (Basel). 2020;6(4):349. https:// doi. org/ 10. 3390/ jof60 40349.
78. Alenicheva MK, Levin AD, Yushinaa AA, Kostrikinab ES, Lebedin YS, Andreevac IP, et al. Nano-biosensor based on the combined use of the dynamic and static light scattering for Aspergillus galactomannan analysis. Sensing Bio-Sensing Res. 2022;35: 100475.
79. Pohanka M. Overview of piezoelectric biosensors, immunosensors and DNA sensors and their applications. Materials (Basel). 2018;11(3):448. https:// doi. org/ 10. 3390/ ma110 30448.
80. Chorsi MT, Curry EJ, Chorsi HT, Das R, Baroody J, Purohit PK, Ilies H, Nguyen TD. Piezoelectric biomaterials for sensors and actuators. Adv Mater. 2019;31(1):e1802084. https:// doi. org/ 10. 1002/ adma. 20180 2084.
81. Naresh V, Lee N. A review on biosensors and recent development of nanostructured materials-enabled biosensors. Sensors (Basel). 2021;21(4):1109. https:// doi. org/ 10. 3390/ s2104 1109.
82. Kopparthy VL, Tangutooru SM, Guilbeau EJ. Label free detection of l-glutamate using microfluidic based thermal biosensor. Bioengineer ing (Basel). 2015;2(1):2–14. https:// doi. org/ 10. 3390/ bioen ginee ring2 010002.
83. Nugaeva N, Gfeller KY, Backmann N, Lang HP, Düggelin M, Hegner M. Micromechanical cantilever array sensors for selective fungal immobili zation and fast growth detection. Biosens Bioelectron. 2005;21(6):849 56. https:// doi. org/ 10. 1016/j. bios. 2005. 02. 004.
84. Villamizar RQ, Maroto A, Rius FX. Improved detection of Candida albicans with carbon nanotube field-effect transistors. Sens Actuators, B Chem. 2009;136(2):451–7.
85. Yoo SM, Kang T, Kang H, Lee H, Kang M, Lee SY, Kim B. Combining a nanowire SERRS sensor and a target recycling reaction for ultra sensitive and multiplex identification of pathogenic fungi. Small. 2011;7(23):3371–6. https:// doi. org/ 10. 1002/ smll. 20110 0633.
86. Gaikwad A, Joshi M, Patil K, Patil, Sathaye S, Rode C. Fluorescent carbon dots thin film for fungal detection and bio-labeling applications. ACS Appl Bio Mater. 2019;2(12):5829–40.
87. Chin CD, Laksanasopin T, Cheung YK, Steinmiller D, Linder V, Parsa H, Wang J, Moore H, Rouse R, Umviligihozo G, Karita E, Mwambarangwe L, Braunstein SL, van de Wijgert J, Sahabo R, Justman JE, El-Sadr W, Sia SK. Microfluidics-based diagnostics of infectious diseases in the developing world. Nat Med. 2011;17(8):1015–9. https:// doi. org/ 10. 1038/ nm. 2408.
88. Campbell JM, Balhoff JB, Landwehr GM, Rahman SM, Vaithiyanathan M, Melvin AT. Microfluidic and paper-based devices for disease detection and diagnostic research. Int J Mol Sci. 2018;19(9):2731. https:// doi. org/ 10. 3390/ ijms1 90927 31.
89. Velve-Casquillas G, Costa J, Carlier-Grynkorn F, Mayeux A, Tran PT. A fast microfluidic temperature control device for studying microtubule dynamics in fission yeast. Methods Cell Biol. 2010;97:185–201. https:// doi. org/ 10. 1016/ S0091- 679X(10) 97011-8.
90. Saxena S, Joshi R. Microfluidic Devices: Applications and Role of Surface Wettability in Its Fabrication [Internet]. 21st Century Surface Science - a Handbook. IntechOpen; 2020. https:// doi. org/ 10. 5772/ intec hopen. 93480.
91. Shang Y, Sun J, Ye Y, Zhang J, Zhang Y, Sun X. Loop-mediated isothermal amplification-based microfluidic chip for pathogen detection. Crit Rev Food Sci Nutr. 2020;60(2):201–24. https:// doi. org/ 10. 1080/ 10408 398. 2018. 15188 97.
92. Asghar W, Sher M, Khan NS, Vyas JM, Demirci U. Microfluidic chip for detection of fungal infections. ACS Omega. 2019;4(4):7474–81. https:// doi. org/ 10. 1021/ acsom ega. 9b004 99.
93. Alawsi T, Bawi Z. A review of smartphone point-of-care adapter design. Eng Rep. 2019;1: e12039.
94. Bras EJS, Fortes AM, Esteves T, Chu V, Fernandes P, Conde JP. Microfluidic device for multiplexed detection of fungal infection biomarkers in grape cultivars. Analyst. 2021;145(24):7973–84. https:// doi. org/ 10. 1039/ d0an0 1753a.
95. Goldenberg SL, Nir G, Salcudean SE. A new era: artificial intelligence and machine learning in prostate cancer. Nat Rev Urol. 2019;16(7):391 403. https:// doi. org/ 10. 1038/ s41585- 019- 0193-3.
96. Alotaibi YK, Federico F. The impact of health information technology on patient safety. Saudi Med J. 2017;38(12):1173–80. https:// doi. org/ 10. 15537/ smj. 2017. 12. 20631.
97. Kumar Y, Koul A, Singla R, Ijaz MF. Artificial intelligence in disease diag nosis: a systematic literature review, synthesizing framework and future research agenda. J Ambient Intell Humaniz Comput. 2022;13:1–28. https:// doi. org/ 10. 1007/ s12652-021- 03612-z.
98. Shoham S, Marr KA. Invasive fungal infections in solid organ transplant recipients. Future Microbiol. 2012;7(5):639–55. https:// doi. org/ 10. 2217/ fmb. 12. 28.
99. Keenan TD, Dharssi S, Peng Y, Chen Q, Agrón E, Wong WT, Lu Z, Chew EY. A deep learning approach for automated detection of geographic atrophy from color fundus photographs. Ophthalmology. 2019;126(11):1533–40. https:// doi. org/ 10. 1016/j. ophtha. 2019. 06. 005.
100. Davenport T, Kalakota R. The potential for artificial intelligence in healthcare. Future Healthc J. 2019;6(2):94–8. https:// doi. org/ 10. 7861/ futur ehosp.6- 2- 94.
101. Nichols JA, Herbert Chan HW, Baker MAB. Machine learning: applica tions of artificial intelligence to imaging and diagnosis. Biophys Rev. 2019;11(1):111–8. https:// doi. org/ 10. 1007/ s12551- 018- 0449-9.

102. Badillo S, Banfai B, Birzele F, Davydov II, Hutchinson L, Kam-Thong T, Siebourg-Polster J, Steiert B, Zhang JD. An introduction to machine learning. Clin Pharmacol Ther. 2020;107(4):871–85. https:// doi. org/ 10. 1002/ cpt. 1796.
103. Tripathi KD. Essentials of Medical pharmacology. New Delhi,2013:8:838-848.
104. Nett JE, Andes D. Spectrum of activity pharmacology and clinical indication. Antifungal agent.,2015:10:1 13.
105. Houst J, Spizek J, Havlicek V. Review antifungal drug. Metabolites.,2020:10:1-16.
106. Lewis RE. Current concept in antifungal pharmacology. Antifungal Pharmacology.,2011:8:805-817.
107. Kaur N, Bains A, Kaushik R, Dhull SB, Melinda F, Chawla P. A review on antifungal efficiency of plant extract entrenched polysaccharide Based Nanohydrogel. Nutrient 2021:13:2-26.
108. Nguyen MH, Peacock JE, Tanner DC, Morris AJ, Nguyen ML, Snydman DR, et al. Therapeutic approaches in patients with candidemia. Arch Intern Med 1995;155:2429–35.
109. Nolla-Salas J, Sitges-Serra AL-GC, Martinez-Gonzales J, Leonb-Regodir M, Ibanez-Lucia P, Torres-Rodriguez J, et al. Candidemia in non-neutropenic critically ill patients: analysis of prognostic factots and assessment of systemic antifungal therapy. Intensive Care Med 1997;23:23–30.
110. Morrell M, Fraser VJ, Kollef MH. Delaying the Empiric Treatment of Candida Bloodstream Infection until Positive Blood Culture Results Are Obtained: a Potential Risk Factor for Hospital Mortality. Antimicrob Agents Chemother 2005; 49:3640–5.
111. Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, et al. Guidelines for treatment of candidiasis. Clin Infect Dis 2004;38:161–89.
112. Edwards JE Jr, Bodey GP, Bowden RA, Buchner T, De Pauw BE, Filler SG, et al. International Conference for the Devel opment of a Consensus on the Management and Prevention of Severe Candidal Infections. Clin Infect Dis 1997;25:43–59.
113. Rex JH, Walsh TJ, Sobel J, Filler SG, Pappas PG, Dismukes WE, et al. Practice guidelines for the treatment of candidiasis. Clin Infect Dis 2000;30:662–78.
114. Eriksson U, Seifert B, Schaffner A. Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: ran domised controlled trial. BMJ 2001;322:579–82.
115. Furrer K, Schaffner A, Vavricka SR, Halter J, Imhof A, Schanz U. Nephrotoxicity of cyclosporine A and amphotericin B deoxycholate as continuous infusion in allogenic stem cell transplantation. Swiss Med Wkly 2002;132:316–20.
116. Imhof A, Walter RB, Schaffner A. Continuous infusion of escalated doses of amphotericin B deoxycholate: an open-label observational study. Clin Infect Dis 2003;36:943–51.
117. Peleg AY, Woods ML. Continuous and 4 h infusion of ampho tericin B: a comparative study involving high-risk haematol ogy patients. J Antimicrob Chemother 2004;54:803–8.
118. Harbarth S, Pestotnik SL, Lloyd JF, Burke JP, Samore MH. The epidemiology of nephrotoxicity associated with conven tional amphotericin B therapy. Am J Med 2001;111:528–34.
119. Bates DW, Su L, Yu DT, Chertow GM, Seger DL, Gomes DR, et al. Correlates of acute renal failure in patients receiving par enteral amphotericin B. Kidney Int 2001;60:1452–9.
120. Walsh TJ, Hiemenz JW, Seibel NL, Perfect JR, Horwith G, Lee L, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin In fect Dis 1998;26:1383–96.
121. Ostrosky-Zeichner L, Marr KA, Rex JH, Cohen SH. Ampho tericin B: time for a new “gold standard”. Clin Infect Dis 2003; 37:415–25.
122. Hiemenz JW, Walsh TJ. Lipid formulations of amphotericin B: recent progress and future directions. Clin Infect Dis 1996;22(Suppl 2):S133–S144.
123. Barrett JP, Vardulaki KA, Conlon C, Cooke J, za-Ramirez P, Evans EG, et al. A systematic review of the antifungal effec tiveness and tolerability of amphotericin B formulations. Clin Ther 2003;25:1295–320.
124. Bowden RA, Cays M, Gooley T, Mamelok RD, van Burik JA. Phase I study of amphotericin B colloidal dispersion for the treatment of invasive fungal infections after marrow trans plant. J Infect Dis 1996;173:1208–15.
125. Noskin GA, Pietrelli L, Coffey G, Gurwith M, Liang LJ. Am photericin B colloidal dispersion for treatment of candidemia in immunocompromised patients. Clin Infect Dis 1998;26: 461–7.
126. Juster-Reicher A, Leibovitz E, Linder N, Amitay M, Flidel Rimon O, Even-Tov S, et al. Liposomal amphotericin B (AmBisome) in the treatment of neonatal candidiasis in very low birth weight infants. Infection 2000;28:223–6.
127. Lopez Sastre JB, Coto Cotallo GD, Fernandez CB. Neonatal invasive candidiasis: a prospective multicenter study of 118 cases. Am J Perinatol 2003;20:153–63.
128. Rex JH, Bennett JE, Sugar AM, Pappas PG, van der Horst CM, Edwards JE Jr, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in pa tients without neutropenia. N Engl J Med 1994;331:1325–30
129. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hos pitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309–17.
130. Viscoli C, Girmenia C, Marinus A, Colette L, Martino P, Van dercam B, et al. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis 1999;28: 1071–9.
131. Nguyen MH, Peacock JE, Morris AJ, Tanner DC, Nguyen ML, Snydman DR, et al. The changing face of candidemia: emergence of non-Candida albicans species and antifungal resistance. Am J Med 1996;100:617–23.
132. Johnson LB, Kauffman CA. Voriconazole: a new triazole anti fungal agent. Clin Infect Dis 2003;36:630–7.

133. Ostrosky-Zeichner L, Rex JH, Pappas PG, Hamill RJ, Larsen RA, Horowitz HW, et al. Antifungal susceptibility survey of 2,000 bloodstream Candida isolates in the United States. An timicrob Agents Chemother 2003;47:3149–54.
134. Ally R, Schürmann D, Kreisel W, Carosi G, Aguirrebengoa K, Hodges M, et al. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treat ment of esophageal candidiasis in immunocompromised pa tients. Clin Infect Dis 2001;33:1447–54.
135. Perfect JR, Marr KA, Walsh TJ, Greenberg RN, Dupont B, Torre-Cisneros J, et al. Voriconazole treatment for less-com mon, emerging, or refractory fungal infections. Clin Infect Dis 2003;36:1122–31.
136. Kullberg BJ, Sobel JD, Ruhnke M, Pappas PG, Viscoli C, Rex JH, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet 2005;366: 1435–42.
137. Wexler D, Courtney R, Richards W, Banfield C, Lim J, Laugh lin M. Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study. Eur J Pharmaceutical Sciences 2004;21:645–53.
138. Courtney R, Wexler D, Radwanski E, Lim J, Laughlin M. Ef fect of food on the relative bioavailability of two oral formula tions of posaconazole in healthy adults. Br J Clin Pharmacol 2003;57:218–22.
139. Skiest DJ, Vazquez JA, Graybill JR, Reynes J, Ward D, Cor coran GR, et al. Open-label trial of posaconazole for azole refractory oropharyngeal ans oesophageal candidiasis in HIV/ AIDS subjects: final analysis. 44th ICAAC, Washington D C 2004;Abs # M-1027.
140. Raad I, Chapman SW, Bradsher R, Morrison VA, Goldman M, Graybill JR, et al. Posaconazole salvage therapy for invasive fun gal infections. 44th ICAAC, Washington D C 2004;Abs # 669.
141. Graybill JR, Raad I, Negroni R, Corcoran GR, Pedicone L. Posaconazole long-term safety in subjects with invasive fungal infections. 44th ICAAC, Washington D C 2004;Abs # M-1025.