Original Article

A Review on Anti Fungal Preparations, Indications, Adverse Reactions and Mechanism of Action

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Abstract

Fungal may cause infection in humans from skin to brain and other vital organs. The estimated cost of fungal infection is about $48 billion per year in the United States. Antifungal medications play a role in eradicating or limiting fungal infections. These drugs include a group of medications that are vital components in the new techniques of management of mycoses. Mainly there are 3 forms of antifungal as azoles, polyenes, and allylamine-thiocarbamates. These drugs work on ergosterol and either kill or limit the growth of fungus. In this review, brief discussion about fungus, infections and anti fungal with mechanism, adverse reactions and indications are aimed.

Key words: Fungus, antifungal, ergosterol, hypersensitivity reaction, candidiasis

INTRODUCTION:

The burden of fungal infection on societies is difficult to calculate since many types are still undiagnosed and there is not a national or international surveillance system for monitoring the condition. [1]
Some efforts to estimate cost of fungal infection states $6.7 to $7.5 billion direct costs and $4 billion indirect costs and total costs can be high as $48 billion. [2]
Fungal may cause infection in human from skin to brain and other vital organs. Risk of hosting Fungus may be increased in immune-deficient patients and immune-suppressed one or those which had surgical procedures. [3]
Mycoses can develop in immune-compromised patients due to host response to them. in some cases host response is not strong enough so pathogen causes infection while is some, very strong action of immune system leads damage and make environment susceptible for fungus.[4]
Antifungal medications play role in eradicating or limiting fungal infections. These drugs include a group of medication that are vital components in the new techniques of management of mycoses. High mortality rate of fungal infection especially in Covid pandemic has made the importance of these drugs more. Candida albicans by rate of 20 to 40%, Aspergillus fumigates by 50 to 90% and Cryptococcus neoformans by 20 to 70% are leading fungus as far as mortality rate is concerned. [5]

CLASSIFICATION OF FUNGAL INFECTION

Mycosis may be classified according to different aspects. Based on site of action they may be found on cutaneous, subcutaneous, deep, and systemic. Cutaneous infections include skin and nails which respond to local agents. Subcutaneous type of fungal infection commonly results from Sporothrix. Deep types are usually caused by infiltration of fungus into deep soft tissues. Systemic types may occur in either immune-compromised or immune-suppressed patients. [6]
According to route of acquisition, fungi may act by either exogenous routes or endogenous one. Exogenous routes can be exampled as airborne, cutaneous or percutaneous while infection which results from colonization normal flora is route for endogenous invasion. [7] Fungus can be categorised base on host. Some type can cause infections in normal hosts while some are opportunistic and taking advantage of deficiency in defence mechanisms of host. [3] Superficial mycosis also may infect stratum corneum. [7]

MECHANISM OF ACTION OF ANTIFUNGAL

As far as biochemistry is concerned, 3 types of anti fungal can be considered. They are azoles, polyenes, and allylamine-thiocarbamates. The centre concept in these three subclasses is they inhibit synthesis of ergosterol which is principle component of fungal cell wall. [8] Ergosterol regulates fluidity, asymmetry and integrity of membrane in fungal cells. [9]

Azole type antifungal

These antimycosis drugs include miconazole, econazole, ketoconazole, fluconazole, and itraconazole. In this class, fluconazole has been predominantly used. [10]

Main target of azoles is the heme protein, which accelerates de-methylation of lanosterol. It leads to evacuation of ergosterol and accumulation of its precursors. This action causes plasma membrane with different structure and function to be formed. [11]

Polyene type antifungal

Nystatin, amphotericin B and pimaricin are members of polyene anti fungal. These medications interact with ergosterol in fungal cells; cholesterol in human cells and makes a tunnel through the membrane. This action leads cell membrane becomes leaky. [12]

Allylamines

Terbinafine and naftifine are functionally and chemically different from the other ergosterol-inhibiting antifungal agents. [13] Terbinafine can be administered both orally and topically but naftifine acts only topically. [14] Terbinafine with high effect against dermatophytes can be used in some azole-resistant C. albicans type.[15] This class acts by blocking synthesis of ergosterol. The inhibition happens while squalene epoxidation occurs. Here squalene epoxidase is the target for allylamine. [16] Different mechanism of this class from other is cell death happens due to action of accumulated squalene since it leads membrane permeability. [17]

There is other mechanism like griseofulvin acts as mitotic inhibitors, flucytosine by antimetabolite activity play role anti fungal. [18]

TYPE OF ANTIFUNGAL

There are different types of antifungal. Base on mechanism they are categorized as [19]:

- Anti fungal act on cell membrane integrity: Polyenes: amphotericin B, nystatin. Azoles: ketoconazole, miconazole, clotrimazole, itraconazole, isavuconazonium sulfate (isavuconazole), fluconazole, voriconazole, posaconazol, Allylamines: terbinafine
- Anti fungal act on cell wall integrity: Echinocandins: anidulafungin, caspofungin, micafungin
- Quinoline Derivatives: iodoquinol, clioquinol
- Potassium Iodide: in form of saturated solution
- Zinc pyrithione
- Mitotic Inhibitors: griseofulvin
- Antimetabolites: flucytosine
- Ciclopirox

Indication

Antifungal are widely used for treating different condition. Hereby Food and Drug Administration approved indications are listed.

Table 1: FDA approved indications of antifungal

S.N	Indication	Antifungal name
1	American mucocutaneous leishmaniasis	Amphotericin B [20]
2	Aspergillosis, Invasive:	Amphotericin B[20], Itraconazole [21], Voriconazole[22], Isavuconazole[23], Posaconazole[24], Caspofungin[25]
3	Blastomycosis:	Amphotericin B[20]
4	Candidiasis:	• Amphotericin B [20] • Nystatin[26] (Candidal vulvovaginitis, Candidiasis of skin, Gastrointestinal candidiasis, Oropharyngeal candidiasis), • Ketokonazole, [27] • Miconazole (Candidal vulvovaginitis) [28], • Clotrimazole(Candidal vulvovaginitis, Candidiasis, Topical,Oropharyngeal candidiasis) [29,30] • Itraconazole (Candidiasis of the esophagus, Oropharyngeal candidiasis)[21] • Fluconazole (Bone marrow transplant - Candidiasis; Prophylaxis, Candidal vulvovaginitis, Candidemia Candidiasis, Candidiasis of the esophagus, Candidiasis of urogenital site, Oropharyngeal candidiasis) [31] • Voriconazole (Candidiasis of the esophagus, Invasive candidiasis, Of the skin and infections in abdomen, kidney, bladder wall, and wounds).[22] • Posaconazole (HIV infection - Oropharyngeal candidiasis, Invasive candidiasis, Severely immunocompromised patients; Prophylaxis, Oropharyngeal candidiasis)[24] • Anidulafungin [32] (Candidiasis of the esophagus, Candidiasis of the esophagus - HIV infection, Invasive candidiasis, Intra-abdominal and peritonitis)

		• Caspofungin(Candidiasis of the esophagus, Invasive candidiasis, Intra-abdominal abscesses, peritonitis, or pleural space infections)[25] • Micafungin(Candidiasis of the esophagus, Invasive candidiasis, Hematopoietic Stem Cell Transplantation; Prophylaxis, Invasive candidiasis, Peritonitis or abscess) [33] • Flucytosine [34] (Candidal endocarditis, Candidiasis, Candidiasis of urogenital site)
5	Candidemia	Voriconazole[22], Anidulafungin[32], Caspofungin[25], Micafungin[33]
6	Coccidioidomycosis	Amphotericin B [20], Ketokonazole[27]
7	Cryptococcal meningitis - HIV infection:	Amphotericin B [20], Fluconazole[31]
8	Cryptococcosis:	Amphotericin B[20], Flucytosine [34]
9	Fungal infection of central nervous system (Severe)	Amphotericin B[20]
10	Fungal infection of lung (Severe)	Amphotericin B[20]
11	Histoplasmosis	Amphotericin B[20], Ketokonazole[27], Itraconazole[21]
12	Histoplasmosis - HIV infection	Amphotericin B[20]
13	HIV infection - Pulmonary cryptococcosis	Amphotericin B[20]
14	Infection by Basidiobolus	Amphotericin B[20]
15	Infection by Conidiobolus	Amphotericin B[20]
16	Mucormycosis	Amphotericin B[20], Isavuconazole [23]
17	Sporotrichosis	Amphotericin B[20]
18	Urinary tract mycosis (Severe)	Amphotericin B[20]
19	Blastomycosis	Ketokonazole[27], Itraconazole [21]
20	Dandruff	Ketokonazole[27]
21	Pityriasis versicolor	Ketokonazole[27], clotrimazole [35]
22	Seborrheic dermatitis	Ketokonazole[27], Ciclopirox [36]
23	Systemic chromomycosis	Ketokonazole[27]
24	Pulmonary histoplasmosis	Itraconazole[21]
25	Onychomycosis due to dermatophyte	Itraconazole[21], Terbinafine [37], Griseofulvin [38], Ciclopirox [36]
26	Tinea corporis	Ketokonazole[27] , Terbinafine[37], Griseofulvin [38]
27	Tinea, Superficial	Miconazole[28], Ciclopirox [36]
28	Tinea barbae, capitis, cruris, pedis	Griseofulvin[38], Clioquinol [39]
29	Dermal mycosis	Terbinafine[37]
30	Febrile neutropenia:	Caspofungin(Empiric antifungal therapy) [25]

Potassium iodide [40] and zinc pyrithione [18] are not categorized as antifungal but have some off label indication in sporotrichosis and mycoses leading to hyperkeratotic skin respectively.

ADMINISTRATION

Amphotericin B is not formulated for oral and intra muscular routes. [41] It is formulated for intravenous and topical use. Recently New lipid formulations with fewer nephrotoxicity have been marketed. [42]Terbinafine is taken topically or orally. [43] Nystatin is available in oral solution, cream, powder, troches as well as topical form. [44] Griseofulvin is available in form of tablet or suspension for oral use and needs to be taken with fatty food. [45] Ketoconazole is marketed in tablet form, cream, foam and shampoos. [46] Fluconazole is given in oral either suspension or tablet form and intravenous formulation. [47]

ADVERSE REACTION

There are different adverse reaction which can be listed for anti fungal. Here we review some commonly used antifungal. Amphotericin B may lead to hypotension, thrombophlebitis, anemia, tachypnea, potassium imbalance, hypocalcemia, hypomagnesemia, nephrotoxicity, asystole, cardiac arrest. [48]

Nystatin which is approved for topical administration rarely may cause Stevens-Johnson syndrome. [49]

Ketoconazole may lead to severe adverse reaction such as cardiac dysrhythmia, torsades de pointes, hepatotoxicity and anaphylaxis. [50] Dermatological effects like acne, erythema, erythroderma, facial swelling, nail discoloration, photosensitivity, pyogenic granuloma, skin irritation also can be mentioned. [51]

Clotrimazole can cause common adverse reaction like nausea and vomiting. [52] It rarely may result renal impairement. [53]

Fluconazole by13% may lead to headache. [31] It has about to 5% chance of miscarriage. [54] Agranulocytosis also has been reported. [31]

Terbinafine use may cause headache by about 12.9%. Nasopharyngitis has been reported in 10% of cases. Hearing loss and tinnitus and abnormal colour vision also reported during post-marketing studies. [55, 56]

Griseofulvin may cause blurred vision, leukopenia, and increased estrogen level. [57] Erythema multiforme, hepatotoxicity also are other possible reactions. [58]

CONCLUSION

Anti fungal medications are one the common group of drugs which are being used for treating fungal or bacterial infection. These drugs mainly work on ergosterol and destroy fungus structure. Different dosage forms and route of administration make them drug of choice for infectious from skin to deep tissue. Nephrotoxicity, dermatological effect, hypersensitivity reactions and headache are common adverse reaction of antifungal.

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