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TREATMENT OF DEEP AND SUPERFICIAL INFECTIONS OF CANDIDA-WHAT WE KNOW AND WHAT IS NEW?

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ABSTRACT: *Candidiasis* or *moniliasis* is more common among the critically ill patients in Intensive Care Unit and in highly immunocompromised patients. This mini review explains the various risk factors for their acquirement and the various treatment options which were used in the past and the current new approaches used in the treatment of candidiasis in the different clinical settings.

INTRODUCTION: Candidiasis is a fungal infection caused by the organisms belonging to the genus *Candida.*

The infection may be superficial, invasive or disseminated. This is also known as *moniliasis*. It is the fourth leading infection in U.S.A. [1] and mostly the important infection of critically ill patients in intensive care unit [1] (ICU).

Superficial lesions involve nails; skin of mucous membrane especially the oropharynx, vagina, esophagus and remainder of gastrointestinal tract. *Candida* enters blood stream and invades the kidneys, lungs, endocardium, brain, eye etc.

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Causative organism: *Candida albicans* is the most common organism worldwide [2]. Other infective strains include *C. parapsilosis*, *C. tropicalis*, *C. gullermondi* and *Candida* non-albicans which are more resistant to conventional antifungals.

Risk Factors: The important risk factors are [2];

1. Diabetes Mellitus
2. Immunosuppressed state such as cancer chemotheraphy, leukemia, renal transplantation etc.
3. Human immunodeficiency virus (HIV)
4. Drug abuse
5. Urinary catheters in ICU
6. Hyperalimentation / surgery
7. Pregnancy
8. Infant of mother with vaginal *moniliasis*
9. Aging
10. Radiation
11. Long duration of broad spectrum antibiotics

Signs and symptoms: It depends upon the anatomic sites involved shown in **table 1**.

TABLE 1: ANATOMIC SITES AND THEIR SIGNS AND SYMPTOMS

ANATOMIC SITE	SIGNS AND SYMPTOMS
Superficial lesions:	
Skin	Scaly, erythematous, papular rash
Nails	Red, swollen, darkened nail
Oropharyngeal mucosa	White patches of exudate of tongue, mouth and pharynx
Oesophageal mucosa	Dysphagia, pain in retrosternum.
Vaginal mucosa	White / yellow colored discharge with pruritus and local excoraition and dyspareunia
Deep lesions:	
Pulmonary	Haemoptysis, cough
Renal	Flank pain, haematuria, fever
CNS	Seizures, coma, focal neurological deficits.
Cvs	Endocarditis, arrthymia, conduction deficits
Eye	Opthalmitis, retinal involvement with blurring of vision

Systemic infection is associated with chills, high grade fever, hypotension, prostration and symptoms related to systems involved.

Diagnosis: Diagnosis [3] of various yeast infections are done by microscopic examination by gram staining and visualizing pseudohyphae or culturing of blood and tissue sample but the best way is obtaining the fungal components in blood.

The treatment modality depends on following factors like personal hygiene, control of risk factors like avoiding long term antibiotics and DM.

The mainstays are the antifungals like polyenes, echinocandins, azoles, allylamines. Among these the echinocandins and liposomal formulations of Amphotericin B are effective against broad spectrum of fungus.

Treatment and medication:

Medical care: The treatment used to manage Candida infections vary substantially and based on anatomic location, patients underlying disease and immune status, patients risk factors, specific species of Candida, susceptibility of Candida species to specific antifungal groups (**Table 2**).

Classes of antifungals in Candidiasis:

TABLE 2: ANTIFUNGAL DRUGS UNDER VARIOUS CLASSES

Polyenes	Amphotericin B, Liposomal Amphotericin B, Nystatin
Azole	**Imidazoles**: Ketaconazole, Clotrimazole, Miconazole **Triazoles**: Fluconazole, Itraconazole, Voriconazole, Posaconazole
Echinocandins	Caspofungin, *Anidula fungin*, Micafungin
Antimetabolite	Flucytosine
Allylamines	Terbinafine, Naftifine

Treatment of cutaneous *Candidiasis*: Cutaneous Candidiasis is treated by number of topical antifungal agents like clotrimazole, micanazole, ketaconazole, and nystatin. In paronychia drainage of abscess is done and antifungal therapy with fluconazole/itraconazole is given. In case of extensive cutaneous infections in immuno compromised patients, systemic antifungal therapy is recommended. In case of Candida Onychomycosis Oral itraconazole is most efficacious. For this, two treatment regimens are used. One is daily dose of itraconazole for 3-6 months; another regimen is pulsed dose of higher daily dose for 7 days followed by 3 weeks of no drug administration. This cycle is repeated every month for 3-6 months.

Treatment of Gastrointestinal *Candidiasis*: In oropharyngeal *Candidiasis*, topical antifungal agents (nystatin, clotrimazole, amphotericin B oral suspension) and systemic oral azoles (fluconazole, itraconazole / posaconazole) are used. In HIV [4] patients HAART with high doses of fluconazole (up to 800 mg/d) or itraconazole (600 mg/d) is used. Additionally caspofungin 50 mg/d i.v. and anidulafungin 100 mg/d i.v. also yield excellent results. In oesophagitis fluconazole for 14-21 days in dosage of 100-200 mg/d is used. Other alternatives which were used in clinical settings include itraconazole, Voriconazole, caspofungin, mica-fungin, anidulafungin and amphotericin B.

Oral fluconazole is always preferred. For patients unable to tolerate an oral agent, IV fluconazole, an echinocandins or AmB-d is appropriate. For patients with refractory disease, the alternative therapy or AmB-d or any echinocandins is recommended,

Treatment of Genitourinary tract *Candidiasis*: In vulvovaginal *Candidiasis* [5] either topical antifungal agents or a single dose of oral fluconazole 150mg in acute episode and in chronic fluconazole 150 mg every other day for 3 doses weekly 150 – 200 mg for 6 months is given [6]. In asymptomatic aciduria change of catheter is must.

In patients with *Candida cystitis* who are noncatherized, fluconazole of 200 mg/d for 10 – 14 days is used and in catherized patients, catheter is removed and treated with 200 mg/d of fluconazole for 14 days. Other alternative is amphotericin B bladder irrigation. For renal *Candidiasis,* Oral / i.v. fluconazole of 40 mg/d for 2 weeks and amphotericin B 0.5 – 0.7 mg/kg i.v. for 4-6 weeks are used.

Treatment of Candidemia: In Candidemia, choice of drugs dosage depends on presence / absence of neutropenia[7] which were shown in **Table 3**.

TABLE 3: VARIOUS TREATMENT REGIMEN IN NEUTROPENIC AND NON NEUTROPENIC PATIENTS

Condition or Treatment group	Primary therapy	Alternative therapy
Candidemia, Nonneutropenic adults	Fluconazole 800-mg (12mg/kg) loading dose, then 400 mg (6 mg/kg) daily or an echinocandins.	LFAmB 3–5 mg/kg daily; or AmB-d 0.5–1 mg/kg daily; or Voriconazole 400 mg (6 mg/kg) bid for 2 doses, then 200 mg (3 mg/kg) bid.
Neutropenic patients	An echinocandina or LFAmB 3–5 mg/kg daily.	Fluconazole 800-mg (12mg/kg) loading dose, then 400 mg (6 mg/kg) daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses then 200 mg (3 mg/kg) bid

Empirical treatment of suspected disseminated candidiasis in febrile non-neutropenic patients: In patients without neutropenia intravenous Amphotericin- B or oral/intravenous fluconazole are recommended as empirical. But fluconazole is the drug of choice over amphotericin B as definitive treatment .It is given in the dosage of 400 mg/d .It has several advantages of lower nephrotoxicity, high degree of bioavailability and long half life[8]. Few clinical studies have carefully examined the impact of empirical or pre-emptive treatment strategies. In such one study, pre-emptive therapy with fluconazole was associated with reduced incidence of nephrotoxicity. In a more recent study of ICU patients at risk of invasive candidiasis and with unexplained fever, empirical fluconazole (800 mg daily for 14 days) was not associated with better outcomes [10].

Empirical antifungal treatment of neutropenic patients with prolonged fever: In patients with neutropenia Liposomal formulated AmB, caspofungin, fluconazole, voriconazole are recommended as empirical treatment [10]. But the definite treatments are echinocandins. They are caspofungin [9] in dose of 70mg as loading dose followed by 50 mg/d i.v. For 2 weeks, anidulafungin 200 mg loading dose followed by 100 mg i.v for 2 weeks and micafungin in dose of 100 mg/d i.v. For 2 weeks. The standard recommended dose for fluconazole is 800 mg as the loading dose followed by 400 mg/d for 2 weeks. Other options are voriconazole 6 mg/kg i.v. / orally twice / day (or) 3 mg / kg orally twice / day (or) 200 mg/kg orally twice / day and amphotericin B deoxycholate 0.7 mg/kg/d for 4-6 weeks.

Treatment of Hepatosplenic *Candidiasis*: In Induction therapy amphotericin B deoxycholate for 2 weeks is used followed by consolidation phase in which fluconazole of 400 mg/d for 4-12 weeks is used. Respiratory *Candidiasis* is treated as disseminated *Candidiasis*.

Disseminated *Candidiasis* with end organ Involvement: The standard recommended dose is fluconazole 800 mg as loading dose followed by fluconazole 400 mg either iv / orally for 2 weeks. The other treatments are using echinocandins namely caspofungin as 70 mg loading dose followed by 50mg/d for 2 weeks, anidulafungin as 200 mg/loading dose followed by 100 mg i.v. for 2 weeks and micafungin as 100 mg/d i.v. for 2 weeks. Alternate theraphy with voriconazole, amphotericin B, liposomal preparation of amphotericin B is used.

Alternative Antifungals: This is used when conventional regimen is refractory. They have combination of Amphotericin B and flucytosine and human recommended monoclonal antibody against heat shock protein 90 is used. Apart from this surgical care and consultations for appropriate organ involvement is done.

Medication: The Success of treatment for serious systemic Candida infections requires initiation of antifungal therapy as early as possible as soon as the adequate culture results are obtained.

Azoles Antifungals: They are the synthetic compounds comprising 2 groups Imidazoles and Triazoles. The Imidazoles include miconazole, Itraconazole and clotrimazole and the triazole include fluconazole, Itraconazole, econazole, terconazole, voriconazole, posaconazole, ravuconazole.

- **Mechanism of action**: It Inhibits lanosterol 14-alpha demethylase, an enzyme required for synthesis of ergosterol, the main component of fungal cell membrane there by disrupting the fungal cytoplasmic membrane.

Fluconazole: It is used in oropharyngeal candidiasis, candidemia, and invasive Candidiasis. In Oropharyngeal disease in adults 100 mg/d po/iv for 7-14 days is given. In Candidemia and Invasive Candidiasis 800 mg loading dose followed by 400 mg/d po/iv for 7-14 days is given. In special situation like renal insufficiency there is reduction of dosage by 50% when Creatinine clearance of 25-49 ml/min and 75% when creatinine clearance of <25ml/min and in bone marrow transplantation dose of 200 – 400 mg/d po/i.v is given. In pediatrics of <2 weeks administer q 72hour i.v and >2 weeks 3mg/kg/d po/i.v for superficial and 6-12mg/kg/d for systemic infections used.

- **Interactions:** It Inhibits CYP P450 so it increases levels of many drugs like theophylline, tacrolimus, clarithromycin.
- **Adverse effect:** Hypersensitivity, precautions is needed in pregnancy with fetal risk revealed; minor GI upset is also seen.

Itraconazole: It has fungistatic activity.

- **Mechanism of action**: It slows fungal cell growth by inhibiting CYP 450 dependent synthesis of ergosterol, a vital component of fungal cell membranes.
- **Uses**: It is effective against broad range of fungi and is indicated for treatment of cutaneous, oral, esophageal and disseminated Candidiasis.
- **Dosing:** In Adults, dose for Cutaneous Candidiasis is 200 mg po/i.v. bd for 7 days per month for 3-6 months. In oropharyngeal and esophageal Candidiasis dose of 200 mg/d po/i.v. for 7-14 days is given. In case of Candidemia and invasive Candidiasis 200 mg po/i.v. tds for 3 days followed by 200 mg po/i.v. bd for 14-21 days. In pediatrics for Cutaneous Candidiasis a dose 3-5 mg/kg/d po/iv for 30 days is used.
- **Interactions:** Antacids decrease its absorption, rhabdomyolysis occurs with co administration of HMG-CoA reductase inhibitors; edema with Ca^{2+} channel blocker occurs. It inhibits CYP 450.
- **Adverse effects**: Hypersensitivity and GIT upset is seen. Precautions in pregnancy with fetal risk and in hepatic insufficiency.

Voriconazole: It is used against esophageal candidiasis, invasive Candida infections which are resistant to treatment with fluconazole

- **Dosing**: It is given in a loading dose of 6 mg/kg i.v. q12h over 2 hours for 2 doses followed by maintenance dose of 4 mg/kg i.v. q12h over 2 hours. In adults, the recommended oral dosing regimen includes a loading dose of 400 mg twice daily, followed by 200 mg twice daily. Oral voriconazole does not require dosage adjustment for renal insufficiency.
- **Interactions**: They are CYP450 inducers.
- **Adverse effects:** The most important is the visual disturbances, followed by photosensitivity dermatitis and hypersensitivity. Precautions to be taken in pregnancy, hepatic insufficiency.

Posaconazole is used in treatment of oropharyngeal Candidiasis refractory to itraconazole or fluconazole, in hematological malignancy, in stem cell transplantation prophylaxis

- **Dosing**: For oropharyngeal candidiasis in adult a suspension of 100mg qid is used. For refractory cases 400mg po twice a day is used.
- **Interactions**: CYP3A4 inhibitor, UDP-G induers
- **Adverse effect**: hypersensitivity, precautions in pregnancy, minor gi upset.

Glucan Synthesis Inhibitors (Echinocandins):

- **Mechanism of action:** Echinocandins act at the level of the fungal cell wall by the inhibition of the synthesis of (1–3) glucan. This results in the disruption of fungal cell wall and causing cell death (**Table 4**).

TABLE 4: VARIOUS ECHINOCANDINS DRUGS, INDICATION, DOSAGE, INTRACTION AND CAUTIONS

Caspofungin	Candidemia, invasive candidiasis and esophageal candidiasis	70 mg in over 1 hr on day 1 followed by 50 mg i.v. qid thereafter	Co-administration with cyclosporine increases hepatotoxicity.	Hypersensitivity, precautions in pregnancy, hepatobiliary dysfunction, mild gastrointestinal upset.
Micafungin	Esophageal, candidemia, as prophylaxis	50 mg i.v. qid infused over 1 hr – prophylaxis for stemcell transplant 150 mg i.v. qid Esophageal 100 mg qid i.v. – candidemia and candidiasis	Coadministration with cyclosporine increases hepatotoxicity.	Hypersensitivity, precautions in pregnancy, hepatobiliary dysfunction, mild gastrointestinal upset.
Anidulafungin	Esophageal candidiasis, candidemia and other candidal interactions.	Candidemia – 200 mg i.v. on day 1 then100 mg Esophageal – 100 mg i.v.on day 1then 50 mg	Coadministration with cyclosporine increases hepatotoxicity.	Hypersensitivity, precautions in pregnancy, hepatobiliary dysfunction, mild gastrointestinal upset.

Polyenes: Polyenes are broad spectrum fungicidal agents which act by inserting into fungal cytoplasmic membranes causing increase in permeability by making pores. The following drugs are used

Amphotericin B: It is one of the oldest antifungals used as broad spectrum antifungal. It is used in the dose of 0.3 – 1.5 mg/kg/d i.v. infused in 5% dextrose over 2-4 hrs in adults. They are used for candiduria by bladder irrigation at concentration Of 50 mg/L for 3 consecutive days. In paediatric same dose is used.They have Interactions with other nephrotoxic drugs increasing its toxicity, enhances the effect of neuromuscular blocking drugs and increases toxicity of digitalis, hypersensitivity is documented.

These drugs are cautiously used in pregnancy. The most common adverse effects of amphotericin b are renal dysfunction and infusion related toxicities. These toxicities have been decreased in the various lipoidal formulations.

Amphotericin B, lipid formulations: They are the novel lipid formulations that deliver higher concentration of drug with increase in therapeutic potential and decrease nephrotoxicity. There are 3 types of amphotericin preparation shown in Table 5 namely Amphotericin B lipid complex (ABLC), Amphotericin B colloidal dispersion (ABCD), Liposomal Amphotericin B (L-AmB*).*

Fungisome: The gold standard for treatment for systemic candidiasis which is safe in paediatric, neonates is fungisome, liposomal Amphothericin B available as i.v. in dosage of 10 mg,25 mg,50 mg.

Nystatin: It is used as fungicidal and fungistatic antifungals.

- **Uses:** Vaginal candidiasis, oropharyngeal candidiasis.
- **Dosing**: 1, 00, 000U vaginal tablets for14 days in case of vaginosis. 2, 00, 000U QID for 7-14days in case of oropharyngeal *candidiasis*.
- **Adverse effects**: Hypersensitivity, precautions in pregnancy to be taken (**Table 5**).

TABLE 5: VARIOUS PREPARATION OF AMPHOTERICIN B

ABCD, ABLC	ABCD – Treating adults and children intolerent to conventional Amphotericin B	ABLC as 5 mg/kg/d i.v. over 1-2 hr- ABCD as 3-6 mg/kg/d i.v.over 1-2hr	With Antineoplastic it Increases renal toxicities, bronchospasm and hypotension. With Corticosteroids, digoxin, thiazides it causes hypokalemia.	Hypersensitivity Precautions in Pregnancy, Renal toxicity.so monitor BUN, Sr. Creatine, K^{+}, and Mg^{++}. Infusion related toxicities
L-AMB	Candidiasis and neutropenic patients with fever	L-AMB as 1-7 mg/kg/d i.v.over 1-2hr	With Antineoplastic it Increases renal toxicities, bronchospasm and hypotension. With Corticosteroids, digoxin, thiazides it causes hypokalemia.	Hypersensitivity Precautions in Pregnancy, Infusion related toxicities

Antimetabolite, Flucytosine: They are deaminated to 5FU in fungal cell by an enzyme and inhibits RNA and protein synthesis and used in invasive candiasis in the dose of 100-150 mg/kg/d po divided 6 h in adults.With AmphotericinB its increase its toxicity.

Hypersensitivity is seen,caution taken in case of pregnancy. Myelosuppression is most common adverse side effect.

Topical Azoles: Topical azoles are used for cutaneous and mucosal involvement.The drugs used are:

Clotrimazole: It alters cell membrane permeability used in oropharyngeal, cutaneous, vaginal candidiasis. In oropharyngeal 10mg troche to be dissolved in mouth 5 times per day for 7 days is used. For cutaneous lesions apply 1% lotion and for vaginal use 100mg qid for 6 days. Care should be taken in pregnancy

Allylamines: It causes deficiency of ergosterol within fungal cell wall, causing cell death. Topical terbinafine is used in dosage of 250mg po qid for 12 weeks in case of paronychia in adults. For paediatric < 12 kg not used. It is given in dosage of 62.5 mg/d in 12-20kg, 125 mg/d in25-40kg, 250 mg/d in >40kg.

- **Interactions**: It decreases cyclosporine effects. Toxicity of terbinafine increase with rifampin and cimetidine
- **Adverse effect**: Hypersensitivity, upper and lower gastrointestinal upset, headache, hepatotoxicity, Stevens Johnson syndrome, precautions in pregnancy, hepatobiliary dysfunction.

CONCLUSION: All patients with Candidemia should undergo opthalmological evaluation to exclude candida endophthalmitis .This procedure has direct therapeutic implications, because patients with endophthalmitis may require surgery and local therapy, and patients with disseminated disease require longer courses of systemic therapy. We suggest that this be performed at a time when the candidemia appears to be controlled and when new spread to the eye is unlikely. Neutropenic patients may not manifest visible endophthalmitis until recovery from neutropenia; therefore, ophthalmo-logical examination in neutropenic patients should be performed after recovery of the neutrophil count.

Antifungal therapy should be started on all candidemic patients within 24 h after a blood culture positive for yeast. Recent studies stress the importance of addressing a positive blood culture result with prompt initiation of systemic antifungal therapy, because delays are associated with increased mortality. Follow-up blood cultures should be obtained for all patients with candidemia to ensure clearance of *Candida* from the bloodstream. The Expert Panel recommends that blood cultures be performed daily or every other day until they no longer yeast in blood.

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