Fungal Infections in Children: A Simplified Approach

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ABSTRACT

Fungal infections in pediatric practice are too common and yet often not discussed. Superficial fungal infections are primarily due to a poor personal hygiene. They are easy to treat provided a prompt diagnosis is made and prolonged topical antifungals are used, occasionally requiring oral antifungals. Systemic fungal infections are assuming great importance because of rampant antibiotic use, increasing intensive care centers and a big subsection of survivors in oncology, primary, and acquired immunodeficient states. The key to a successful management rests on a high index of suspicion in the vulnerable population, laboratory evidence and selecting the appropriate antifungal drug based on the local epidemiology.

Keywords: Antifungal agents, Aspergillosis, Candidemia, Invasive fungal infections, Neonatal sepsis, Ringworm, Tinea.

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INTRODUCTION

Fungal infections in pediatric practice are too common and yet often not discussed. While superficial fungal infections are primarily due to a poor personal hygiene, systemic fungal infections are assuming great importance because of rampant antibiotic use, increasing intensive care centers and a big subsection of survivors in oncology, primary and acquired immunodeficient states.

SUPERFICIAL FUNGAL INFECTIONS IN CHILDREN

Superficial fungal infections (mycoses) are some of the most common skin lesions affecting children. Three most common types are dermatophytosis, pityriasis versicolor, and candidiasis. Superficial mycoses involve keratin-containing layers of the hair, skin, and nails and do not usually penetrate deeper. They can even occur in healthy children without underlying immunodeficiency and causes significant morbidity because of associated symptoms and concern for transmission. These are often missed due to a widespread and erratic use of over-the-counter medicines.

Dermatophytosis

Dermatophytosis (tinea or ringworm) refers to skin infection by a group of aerobic fungi, which are generally classified on the basis of area affected: tinea capitis—scalp, tinea pedis—feet, tinea corporis—trunk and limbs, tinea cruris—groin, and tinea unguium—nails.

Tinea Capitis

Lesions are seen on scalp with multiple patchy, scaly, alopecic areas of different sizes and shapes, often associated with broken hair shaft near scalp surface (Fig. 1A). Lesions may have erythema, scaling, pustules, “black dots,” pruritus, tenderness, and lymphadenopathy (postauricular, suboccipital, or cervical). It spreads through direct contact with animals, humans, and fomites. Fomite transmission occurs via sharing of combs, caps, helmets, pillows, and other objects which may have fungal spores. Various clinical patterns are described with tinea capitis.¹

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- “Black dot”—After broken off hair shafts close to the scalp, the left-over hair follicles are seen as prominent black dots (Fig. 1B).
- “Gray patch”—Prominent scales in patchy alopecia with or without erythema (Fig. 1C).
- “Diffuse pustular”—Scattered pustules with scale, alopecia, and lymphadenopathy (Fig. 1D).
- “Diffuse scale”—Large areas of scaling of scalp with or without erythema (Fig. 1E).
- “Kerion”—Well-defined bald area with red, boggy, pus-filled tender plaque, and lymphadenopathy (Fig. 1F).

Treatment

Systemic therapy with griseofulvin is the gold-standard therapy. Alternative systemic agents include terbinafine, fluconazole, and itraconazole. Therapy must be given for 6–8 weeks, may be longer for resistant cases. Adjunctive topical treatment with antifungal shampoos such as ketoconazole (2%) or selenium sulfide (1%), povidone-iodine (2.5%), ciclopirox (1%) shampoo is sometimes recommended. They are sporocidal and help in removal of scales. All shampoos should be applied for 5 minutes thrice weekly for 2–4 weeks.

Figs 1A to F: (A) Tinea capitis; (B) Black dot variant, showing broken hairs in areas of hair loss; (C) Gray patch variant; (D) Diffuse pustular variant; (E) Diffuse scale variant; (F) Kerion

Tinea Corporis (Ring Worm)

It consists of well-demarcated, irregular ring-like lesions on (nonhairy) skin of the face, trunk, and extremities. Lesions typically have erythematous raised borders (which can be papular, vesicular, or pustular) with scaling, central relative clearing and are itchy (Fig. 2A). Treatment with topical antifungal agents (such as allylamines, imidazole, tolnaftate, terbinafine, butenafine, and ciclopirox) for 2–4 weeks is standard therapy. Combination of topical antifungals with corticosteroids is not recommended because of inferior efficacy and higher risk of side effects.²

Tinea Pedis

It is dermatophytosis of feet, seen mostly in adolescents and adults but rare in prepubertal children. Lesions in-between and around digits are scaly, macerated skin, with variable inflammation and vesicobullous changes (Fig. 2B). Moist skin (caused by sweat) and maceration are important predisposing factors. Conditions that may mimic tinea pedis in children include contact and allergic dermatitis and occasionally atopic dermatitis, unlike tinea pedis, dermatitis generally spares the intertriginous areas.

Tinea Cruris

Superficial infection of the groin characterized by well-demarcated erythematous and scaly lesions with some central clearing (Fig. 2C). It occurs predominantly in adolescent and young adults and commonly associated with tinea pedis. Close mimics are *Candida* intertrigo and erythrasma. *Candida* intertrigo is more uniformly red with satellite lesion and absence of central clearing, whereas erythrasma is a bacterial infection caused by *Corynebacterium* that is more uniformly brown with fine scaling and superficial fissures.

Pityriasis Versicolor (Previously Known as Tinea Versicolor)

It is a superficial mycosis caused by yeast form of *Malassezia furfur*, a dimorphic fungus which is a skin commensal. Lesions are characterized by multiple monomorphic, round to oval, sharply demarcated macules, or plaques, with scaling and variable pigmentation (Fig. 2D). It is usually seen on upper trunk and shoulders. It is most common in tropical weather conditions (hot and humid) affecting adolescents and young adults. Diagnosis is mainly clinical. Potassium hydroxide (KOH) preparation of scrapings from affected skin shows short fungal hyphae and spores in clusters resembling spaghetti and meatballs.

Treatment

Topical ketoconazole cream (2%) or shampoo (2%), daily application at bedtime for 3 days; selenium sulfide (2.5%) shampoo, daily application for 10 minutes for 1–2 weeks.

Candidal Diaper Dermatitis

Groin area smeared with beefy red plaques with fine white scale, with typical involvement of intertriginous folds. Satellite papules and pustules are noted on the inner thigh and abdomen and help them differentiate candidiasis from other eruptions in the diaper area (Fig. 3).

Some important points are:

- In irritant dermatitis rash is distributed over convex skin surfaces with characteristic sparing of skin creases. After 72 hours, it may get colonized with *Candida albicans*.
- Suspect diaper candidiasis when rash does not improve with application of barrier creams such as zinc oxide paste, petrolatum, etc.

Figs 2A to D: (A) Tinea corporis over arm; (B) Tinea pedis; (C) Tinea cruris over groin and inner thigh; (D) Pityriasis versicolor over back

Figs 3A and B: Diaper dermatitis: (A) Irritant dermatitis; (B) Candidal diaper dermatitis. Note the characteristic sparing of skin creases in irritant dermatitis (arrow) and satellite lesion in candidiasis (arrow head)

- KOH preparation and fungal culture from lesions will help in confirming the diagnosis in doubtful cases.
- Wet and dirty diapers that are not changed on a regular basis predispose to diaper dermatitis.
- Urease enzymes present in feces release ammonia from the urine, causing an acute irritant effect leading to a disruption of the epidermal barrier. This allows the entry of *Candida* which is present in feces.
- Refractory diaper dermatitis may be a marker of an underlying serious metabolic or immunologic disease (e.g., zinc deficiency,

human immunodeficiency virus (HIV), and Langerhans cell histiocytosis)

Treatment

Topical application of antifungal creams (such as clotrimazole, miconazole, and nystatin) twice a day for 7–10 days. Keeping the groin area dry will help in faster healing. Topical low potency steroids can be used for short duration only in severe inflammation.

INVASIVE FUNGAL INFECTIONS (IFI)–RISING INCIDENCE AND CHANGING EPIDEMIOLOGY!

During the past several decades, there has been a 10-fold increase in incidence of invasive candidiasis and 20% increase in incidence of aspergillosis among critically ill patient.³ This can be attributed to rising cohort of patients on immunosuppressive medications across medical specialties (e.g., malignancies, organ transplants, autoimmune disorders), rise in number of pediatric intensive care units (ICUs) with more complex interventions, expanding population of extremely premature neonates in neonatal ICUs, increase in survival of children with primary immunodeficiency, better antibacterial therapy, and major advances in fungal diagnostic techniques. IFI in the ICU are associated with considerable morbidity and mortality even under optimal treatment conditions. In addition to being difficult to diagnose and treat, these infections are costly to treat and significantly prolong hospital stay. *Candida*, *Aspergillus*, *Pneumocystis* spp., and *Cryptococcus* are the most encountered pathogens responsible for invasive fungal disease in neonatal and pediatric population. Incidence of *Pneumocystis jirovecii* pneumonia has declined significantly with widespread use of trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis in oncology and HIV-infected children. The epidemiology of *Candida* species has changed dramatically from albicans to nonalbicans in the last few decades.

Insights into Fungal Isolates from tertiary Care Centers in Public and Private Sectors

Among 92 fungal isolates from blood in a large tertiary care public sector hospital in Delhi, *Candida* was the most common (91) with only one *Aspergillus*. Only 23% *Candida* were albicans with 77% being non-albicans, such as, *C. tropicalis*, *C. pelliculosa*, *C. parapsilosis*, *C. krusei*, and other non characterized, in that order. About 25% of *C. albicans* were azole resistant compared with 80 to 100% of non-albicans. *C. pelliculosa* exhibited emerging resistance to even caspofungin and amphotericin. The spectrum across other body fluid specimens had a similar distribution and sensitivity pattern. In a private sector tertiary care center, there were 21 isolates of *Candida* with no other fungus identified. Only 14% were albicans, while non-albicans were *C. tropicalis*, *C. krusei*, *C. parapsilosis*, *C. pelliculosa*, *C. glabrata*, and others in that order (Table 1).

In published literature by the International Pediatric Fungal Network, the spectrum of fungal isolates shows predominance of nonalbicans species in pediatric (56%) and neonatal population (52%).⁴

When to Suspect for Invasive Fungal Infection?

- Identify high-risk groups for fungal disease⁵
 - Premature neonates [requiring mechanical ventilation (MV), total parenteral nutrition (TPN), central lines, broad spectrum antibiotics, steroids]
 - Disruption of cutaneous/mucosal barriers (burns, surgical wounds, extensive dermatitis/mucositis)
 - Invasive lines, catheters, prolonged drains
 - Total parenteral nutrition
 - High-dose prolonged steroids, cytotoxic drugs, or immunosuppressive drugs
 - Prolonged use of broad-spectrum antibiotics
 - Hematological malignancy
 - Post-transplant patients
 - Primary and acquired immunodeficiency (especially defects of cell-mediated immunity)
 - Major surgery (especially gastrointestinal surgery) at admission
 - Severe pancreatitis, diabetes mellitus
 - Renal replacement therapy
 - Prolonged stay in ICU
 - Known *Candida* colonization at multiple sites
 - Prolonged neutropenia (absolute neutrophil count of <500 cells/L) or neutrophil dysfunction, HIV infection
- Look out for soft clinical signs:⁶

A high index of suspicion is the perquisite in especially in critical care units for diagnosis. IFI can either present as indolent infection or as severe sepsis. Depends on whether it is blood stream infection or a deep-seated infection. Blood stream infections are mostly associated with indwelling catheter as a risk factor. Nonspecific signs of infection (such as fever, organ dysfunction, and tachycardia) are seen. In premature neonates, it presents clinically as late onset sepsis, which is not improving on usual antibacterial agents. Soft clinical signs include new onset thrombocytopenia, hyperglycemia, and meningoencephalitis. Invasive candidiasis in neonates can involve kidneys leading to development of a fungal bezoar (fungal ball) and urinary tract obstruction.

Candidal Score–An Important Bedside Clinical Tool⁷

It is a simple bedside scoring tool, formulated by Leon et al., which helps in predicting likelihood of invasive candidiasis in “non-neutropenic critically ill patients.” The score of more than 2.5 predicts invasive candidiasis with sensitivity of 81% and specificity of 74%.

Table 1: Fungal isolates in blood culture from NICU and PICU of two tertiary care centers

Organism	Public sector hospital		Private sector hospital	
	Blood (n = 92) (%)	Fluconazole resistance	Blood (n = 21) (%)	Fluconazole resistance
<i>C. albicans</i>	21 (23%)	25%	3 (14%)	0%
Nonalbicans				
<i>C. tropicalis</i>	18 (20%)	0%	6 (29%)	0%
<i>C. parapsilosis</i>	15 (16%)	0%	3 (14%)	0%
<i>C. krusei</i>	7 (8%)	100% (also flucytosine)	4 (19%)	100%
<i>C. pelliculosa</i>	18 (20%)	100% (Caspofungin & Amphotericin)	2 (9%)	100%
<i>C. glabrata</i>	0	–	2 (9%)	50%
Other candida	12 (13%)	–	1 (5%)	–
<i>Aspergillus</i>	1		–	

Candidal Score for Non-neutropenic Patients

- Multifocal colonization with *Candida** – 1
- Surgery on ICU admission – 1
- Total parenteral nutrition – 1
- Severe sepsis – 2

"Total score >2.5 has 7 times higher risk of invasive candidiasis".

*Defined as the detection of *Candida* species by KOH mount in samples/swabs obtained from 2 or more noncontiguous sites such as oropharynx, stomach, urine, rectum, or tracheal aspirates, even if two different *Candida* species were isolated.

DIAGNOSING INVASIVE FUNGAL DISEASE

Traditional methods of diagnosing fungal infection include combination of clinical evaluation, radiographic evidence, histopathology from body fluids or biopsy specimens and culture. However, the main challenge of early diagnosis is limited by nonspecific clinical signs, difficulties in obtaining samples from deep-seated infections from compromised hosts, and long time to culture the fungi. Classic radiographic findings of fungal infections are usually absent in immunosuppressed patients. Although culture is a reliable and gold-standard method of detecting fungemia, identification delays and poor sensitivity can prolong the time to appropriate antifungal treatment. Recent advances in molecular biomarkers and serological markers have overcome the limitations of culture.

IMAGING IN IFI

Often different imaging modalities provide an important clue but elude a definitive diagnosis. Radiologist should be given the full clinical history and effort should be made to discuss the findings and differentials.

Ultrasound

Space occupying lesions in renal pelvis, lungs may be the first evidence needing further evaluation.

Lung HRCT

High-resolution computed tomography with contrast is the best modality to look for evidence of invasive pulmonary fungal infections, especially invasive pulmonary aspergillosis (IPA) (Table 2). The classical CT findings in the angioinvasive form of IPA consist of dense and well-circumscribed lesions >1 cm, surrounded by a wide zone ground-glass attenuation (halo sign) at early stages.⁸

Table 2: Commonly described radiological patterns of invasive pulmonary aspergillosis on CT

Angio-invasive pulmonary aspergillosis	Macronodules, mass-shaped consolidations, infarct-shaped consolidations, or halo signs
Airway-invasive invasive pulmonary aspergillosis	Clusters of centrilobular nodules, peribronchial consolidation, ground-glass opacities, and smooth bronchial wall thickenings
Necrotizing pneumonia invasive pulmonary aspergillosis	Cavitary lesions, low internal attenuation compared with muscle, reverse halo signs, or bird's nest signs were diagnosed as necrotizing pneumonia invasive pulmonary aspergillosis.

The presence of a reversed halo sign or a bird's nest sign, along with multiple nodular lesions or pleural effusion should raise suspicion for mucormycosis. Lung nodules are also seen in chronic disseminated candidiasis, in addition to hepatosplenic involvement.

CECT Nasopharynx and Sinuses

Rhino-sinusal disease caused by invasive aspergillosis or mucormycosis is suggested by maxillary and/or ethmoid sinuses showing mucosal thickening, fluid level, with or without bone erosion and soft-tissue infiltration. Magnetic resonance imaging has higher sensitivity and specificity to visualize the extent of the lesions into soft tissues, optic nerve, and brain involvement.

IDENTIFICATION BY DIRECT MICROSCOPY, HISTOPATHOLOGY, AND CULTURE

Conventional, yet gold-standard methods to identify and isolate fungi include direct microscopic examination and the culture of samples in the mycology laboratory. Pathological examination and direct smears of samples with KOH is the most rapid, cost-effective, and sensitive method for the diagnosis of fungal infections. Calcofluor white stains chitin present in fungal cell wall, so that they fluoresce bright white under ultraviolet light in a fluorescent microscope (useful for *Candida* and *Pneumocystis*). Visualization of fungi by direct microscopy in tissue specimen helps to rule out contamination. Direct microscopy with standard and specialized stains can identify some genera of etiologic agents such as yeasts or molds (with septated or nonseptated hyphae) within hours and thus give important clues to the physician for prompt initiation of antifungal therapy. Special stains (such as Giemsa, crystal violet, diff-quick, and methenamine silver) on respiratory samples can rapidly identify *Pneumocystis* species.

Isolation by culturing clinical specimens (such as blood, urine, or tissue) remains the gold standard for the diagnosis of IFI, provided that the samples are from sterile sites such as blood, tissue, or cerebrospinal fluid. Although blood cultures remain the cornerstone of diagnosis, they have poor sensitivity (<50%) and need long incubation time.⁵ Yield is very low in deep-seated infections or in patients under antifungal prophylaxis. Newer culture methods have decreased the incubation time and raised the sensitivity of *Candida* detection to almost 70%. The use of latest techniques such as peptide nucleic acid fluorescent *in situ* hybridization) and matrix-assisted laser desorption ionization time of flight can rapidly identify *Candida* species (after blood culture becomes positive for *Candida*).⁵ Prior information to the microbiologist regarding a suspected fungal infection/separate requisition for fungal culture often yields good results.

BIOMARKERS AND RAPID DIAGNOSTIC TESTS

To overcome the major limitations of culture techniques, various biomarkers have been developed and validated in many studies, and their utilization as a part of screening in high-risk groups with risk factors have become part of standard recommendations to enable clinicians in taking appropriate therapeutic decisions.

Galactomannan

Galactomannan (GM) is a water-soluble cell wall polysaccharide that is a major constituent of *Aspergillus* cell walls. It is released by hyphae of *Aspergillus* spp. during active fungal growth in tissue, thus

becomes useful in differentiating contamination by conidia (which can grow in culture) from invasive aspergillosis. A commercially available double sandwich enzyme immunoassay that detects GM by use of a rat monoclonal antibody has been validated and approved for testing in serum and bronchoalveolar lavage (BAL). Circulating GM may be detected in serum several days before clinical manifestation of aspergillosis and also in other body fluids (especially BAL), also the levels may correlate with the burden of infection and decrease on appropriate treatment. However, a wide variation in sensitivity (30–100%) and specificity (38–98%) has been reported, limiting its clinical usage. While prior antifungal may render it false-negative, few commonly used antibiotics such as beta-lactams (piperacillin–tazobactam and amoxicillin) with or without clavulanate yield a false-positive report due to the presence of cross-reactive antigens.

1,3-beta-D-glucan

The beta-D-glucan test is a nonspecific diagnostic test that detects the presence of many types of fungi (*Candida*, *Aspergillus*, *P. jirovecii*, *Fusarium*, *Trichosporum*, and *Saccharomyces*) by targeting a component of the fungal cell wall. However, it is not useful for *Cryptococcus* or *Zygomycetes*. The test has high sensitivity, but ubiquitous environmental sources of beta-glucan limit its specificity. At best it can be used as a screening tool for serial monitoring in high-risk groups.

T2 Candida Panel

It is a novel qualitative rapid nanodiagnostic panel, performed on the fully automated machine, which can amplify and detect *Candida* DNA directly in whole blood, with detection limit of 1 CFU/mL. It delivers result in 3–5 hours (10-fold decrease in time to result when compared with blood cultures).⁹

MANAGEMENT OF IFI

Given the delay in the microbiological evidence of fungal infections, clinicians usually resort to preemptive and empirical treatment in high-risk groups, pending isolation of fungi. Factors that should always be taken into account when choosing antifungal agent for empirical therapy include local epidemiological data of prevalent strains and resistant rates, prior exposure to antifungal therapy, presence and duration of neutropenia, severity of clinical presentation, and the presence of underlying organ dysfunctions that may affect the drug metabolism and further increase the risk of drug related toxicities. In a suspected catheter-associated infection, the invasive device should be removed as soon as possible. The various strategies for treatment are:⁵

Prophylactic Treatment

Starting antifungal agents in high-risk groups, who have not yet developed any symptom/signs of infection, in an order to prevent the development of fungal infections, is termed as prophylactic treatment. However, routine use of this strategy in critically sick ICU patients is discouraged, owing to increase in incidence of colonization with resistant strains. Prophylactic antifungals are recommended in certain special high-risk groups (such as extreme prematurity, hematopoietic stem-cell transplants recipients, solid organ transplantation, on chemotherapy for leukemia, and fulminant hepatic failure with encephalopathy).

Empirical Treatment

When antifungal treatment is given to a patient with clinical signs of infection (e.g., persistent fever not responding to antimicrobials) and several risk factors for IFI, without proof in the form of biomarkers or radiological evidence.

Pre-emptive Treatment

When antifungal treatment in high-risk patient with multiple risk factors, and biomarkers or radiological evidence is supportive of fungal infection, even though clinical signs may be absent, it is termed as pre-emptive treatment.

Definitive/targeted Treatment

When definitive proof of fungal infection is given by direct microscopy, histopathology, polymerase chain reaction, or culture (Fig. 4).

Fig. 4: Treatment strategies for invasive fungal infections

Antifungal Agents for Invasive Candidiasis (Flowchart 1)

Flowchart 1: Choice of antifungal agent for invasive candidiasis

When Species Identification is Available for *Candida*

Candida albicans, *C. tropicalis*, and *C. parapsilosis* are invariably sensitive to azoles, hence fluconazole can be used. *C. glabrata* is often resistant to azoles; hence, the first-line therapy is amphotericin-B or caspofungin. *C. kruzei* and *C. auris* are inherently resistant to azoles; hence, echinocandins such as caspofungin is the drug of choice.

Duration of Treatment

Treat for 2 weeks after the last negative culture report. In neonates, however, treat for 3 weeks after last negative culture report. Always get fundoscopic examination to rule eye involvement.

Invasive Aspergillosis

Voriconazole is the drug of choice for invasive aspergillosis. Liposomal amphotericin-B can be used as an alternative. In refractory disease, combining with caspofungin can be used as salvage therapy. Duration of treatment should continue till resolution of all clinical and radiological signs of infection. Surgical intervention may be required for angioinvasive aspergillosis.

CONCLUSION

Fungal infections are assuming great importance in the present scenario. While superficial fungal infections are ubiquitous, a simple clinical diagnosis, can get complicated because of delayed medical seeking behavior, secondarily infected, may still be amenable to treatment that must be prolonged. On the contrary, IFI are difficult to diagnose, life-threatening have emerging antimicrobial resistance and need urgent intervention warranting a high index of suspicion.

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