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REVIEW ARTICLE

# Recent trends in fungal infection management

**Gurmeet Singh[1,2], Amandeep Singh[2], Raj Kumar Narang[2]**

[1]Department of Pharmaceutics, IK Gujral Punjab Technical University, Jalandhar, Punjab, India, [2]Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India.

## ABSTRACT

This article provides an overview of the present state of medication therapy for invasive fungal illnesses, as well as research goals for the future new chemical development. Production of orally accessible medicines for the treatment of Candida infections is a key opportunity for novel drugs. In some cases, antifungal resistance is a problem, but it is normally less of a problem than bacterial infections. Improved results will come from earlier and more thorough mycological diagnosis, as well as improvements in underlying risk estimate.

**KEY WORDS:** Dermatophytes, Dermis, Fungal, Infection

## INTRODUCTION

The two most frequent forms of fungus are yeasts and moulds. Mould colonies consist of filamentous strands called hyphae, whereas yeasts are often single, small, and oval cells. Some fungi are dimorphic, meaning that depending on their environment, they may exist as yeasts or moulds (e.g., temperature). Invasive fungal infections are still a problem for clinicians, especially in critically ill patients and those who are immunocompromised due to sickness or immunosuppressive medicines. There are an estimated 1.5–5 million fungal species on the planet, with at least 300 of them associated to human sickness.[1]

As new dangerous fungi arise and our grasp of fungal taxonomy improves due to advances in molecular technology and phylogenetic studies, the number of fungi linked to illnesses in people, animals, and plants grows. In addition, resistance to therapeutically available antifungals has increased in a number of well-known pathogens, and there is a rising recognition of the importance of fungal coinfections with other microbes, such as respiratory pathogens, which frequently result in poor patient outcomes.[2]

The majority of fungi are ubiquitous, capable of reproducing without the assistance of human or animal substrates in their natural environments. In humans, certain species, on the other hand, are adventitious pathogens that cause infection through the skin, subcutaneously, or systemically. The majority of fungi that cause systemic (or deep-seated) infection do so by infecting a wound site or breathing straight into the lungs. Others, like as *Candida albicans*, are common residents of the gastrointestinal tract and skin, but they can develop and spread throughout the body under certain conditions, such as when injected into the body through medical devices such as vascular catheters.[3]

**Address for Correspondence:**
Dr. Raj Kumar Narang,
E-mail: drrknisf@gmail.com

## PATHOPHYSIOLOGY OF FUNGAL INFECTION

Only a few human-pathogenic fungi are vigorous enough to infect a healthy host. Most are harmless until they come into touch with an immunocompromised patient, in which case they can enter the body due to a weakened immune system. The intact epithelial surfaces of the gastrointestinal system and the mucociliary barrier of the respiratory tract prevent aspiration of fungal cells and spores under normal

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circumstances, but dead or wounded tissue can serve as a breeding ground for infection. Invasive fungal diseases must thus be categorized as opportunistic illnesses.

Genetic diversity among critical innate or adaptive immune response genes has recently been proposed to enhance vulnerability to invasive fungal infections, resulting in failures in Toll-like receptor polymorphism, interleukin-10 production, plasminogen gene polymorphism, and other mechanisms.[4,5] Invasive fungal infections will develop in patients being treated for a hematological malignancy as a result of treatment-related damage to all natural defense mechanisms. Chemotherapeutic medicines used at high dosages affect the mucosal barrier, resulting in reduced saliva production, secretory IgA, mucus, and stomach acid, as well as malabsorption and impaired peristalsis.[6] Patients' integument is disrupted by significant mucosal injury and the frequent use of central venous catheters.

Although neutropenia plays a role in the course of fungal infections, long-term corticosteroid usage, even at low levels, is dangerous because it impairs T-cell function and alters glucose metabolism.[7,8] If these conditions are met, any infection that has invaded injured tissue will have easy access to the body and will spread swiftly. Patients with hematological malignancies who get non-myeloablative allogeneic "minitransplants" to minimize transplant-related damage are more likely to acquire an invasive fungal infection, according to new study.[9] Both mucosal barriers and cellular immunity can be harmed by cytotoxic T cells and immunosuppressive medicines used to treat graft-versus-host disease.

## DISEASES CAUSED BY INVASIVE FUNGAL INFECTIONS ARE AS FOLLOWS

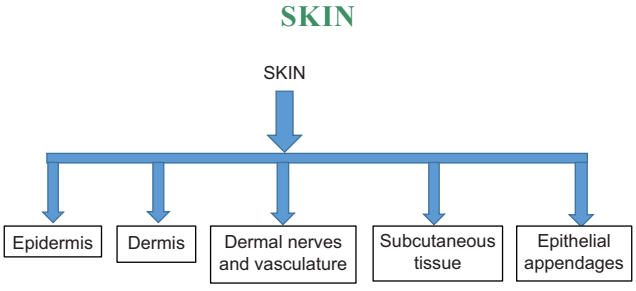
These are of following types:

1. Opportunistic pathogens (As shown in Table 1)
2. Endemic pathogens (As shown in Table 2).

## SKIN ANATOMY

The biggest organ in the human body is the skin. It serves as a dynamic barrier for the underlying organism, providing protection, thermoregulation, and sensory, metabolic, and immunological functions. The epidermis, or outermost layer, and the dermis, which are separated by the basement membrane (BM) yet mutually reliant on each other for skin integrity, are the two principal layers of the skin. The hypodermis is the subcutaneous tissue underneath the dermis that contains adipose cells, fibroblasts, and macrophages and feeds blood and nerve supply to the trunks. Embryonic tissue that develops into eccrine and apocrine glands, hair follicles, and nails gives birth to skin appendages in the dermis and hypodermis (Figure 1).

Wounding the skin can result in fluid loss, infection, scarring, hypothermia, or weakened immunity.[1] A rudimentary grasp of skin anatomy can aid in determining the amount of harm and guiding wound therapy and healing.




### Epidermis

The stratum corneum (SC) is composed of keratinized and dead cells that are surrounded by keratinocytes or squames with a cornified membrane. This layer sheds continuously, with replacement cells from the bottom layer migrating outward at nearly the same rate as dead cells from the outermost layer are sloughed off. PH variations, temperature swings, and dryness have little effect on this layer. The stratum lucidum, which lies underneath the SC, is a remodeling zone. This is a relatively thin layer that may be missing or uneven on electron microscopy of thin skin. The stratum granulosum (SG), commonly known as the granular layer, is made up of flat cells with active metabolism that reside underneath the lucidum.

The epidermis develops from the ectoderm. It is a stratified epithelial layer with a thickness ranging from 0.05 mm to 0.75 mm, depending on sex and anatomic location. The historically recognized layers of this avascular layer are the SC, stratum lucidum, SG, stratum spinosum, and stratum basale.

Keratin is made by keratinocytes, which are the most common cells in the epidermis. Interspersed among the keratinocytes are Langerhans cells, antigen-processing dendritic cells derived from the bone marrow and part of the reticuloendothelial system. Melanocytes are cells that arise from the neural crest and produce melanin, the primary pigment of the skin. The mechanism by which melanocytes transmit pigment to neighboring keratinocytes is known as pinocytosis. Merkel cells may also be found in the basal layer, which are important in afferent nerve conduction and mechanoreception.

### Dermis

Collagenous connective tissue makes up this layer of the skin. It is further separated into a papillary layer, which is connected to the epidermal ridges by dermal ridges and secondary dermal papillae, and a reticular layer, which is

connected to the epidermal ridges by dermal ridges and secondary dermal papillae. The reticular layer's blood supply penetrates the papillary layer's dermal ridges, supplying blood to the epidermis above. A vascular plexus nourished by the underlying hypodermis is supported by the reticular layer. This stratum contains hair follicles, sebaceous and eccrine glands, and Pacinian corpuscles.

### Dermal nerves and vasculature

The source is a single piece of the spinal cord known as the "dermatome." The blood supply to the skin runs parallel to the cutaneous nerve supply. The terminal nerve branches, as well as several specialized sensory structures such as Meissner corpuscles and Merkel cells for light touch, Pacinian corpuscles for pressure detection, Raffini corpuscles for heat detection, thermo receptors for heat and cold detection, and naked nerve endings for pain sensation, are all found in the dermis and basal layers of the epidermis.

Cutaneous vessels develop from underlying vessels like septocutaneous or fasciocutaneous perforator vessels, as well as musculocutaneous vascular terminal branches. The terminal branches give rise to the massive superficial and deep vascular plexuses, which are linked by vertical dermal arteries to form a continuous circulatory network within the skin. This vascular network is responsible for the skin's thermoregulatory capabilities. The hypothalamus is in charge of managing blood vessel constriction and dilation. Glomus cells are a type of vascular structure that, when open, function as an arteriovenous shunt between an arteriole and a venule, enabling more blood to flow through the area.

Lymphatics travel parallel to the blood flow to the skin in the reticuloendothelial system. As they migrate deeper into the dermis and subcutaneous tissue, their diameter increases, and they finally drain into the venous circulation, following the pattern of blood vessels.

### Subcutaneous tissue

The majority of the subcutaneous tissue is made up of mature subcutaneous fat. The arteries and lymphatics pass through the lobules of the subcutaneous layer, which are separated by thin fibrous septae. The septae provide a structural foundation for the compartmentalising, subcutis it, and linking the dermis' reticular layer to the fascial planes under the subcutaneous fat.[10] The thickness of this layer varies depending on anatomical location and person.

### Epithelial appendages

To restore the skin's barrier function after an injury, reepithelialization is essential. This includes epithelial cells moving from wound edge to wound edge, arising from epithelial appendages such as hair follicles and apocrine and eccrine glands.

## BARRIERS

### Interfollicular epidermis

#### *SC*

The SC is the first mechanical barrier between the environment and the outside world. It is critical for the passive diffusion for the absorption of the vast majority of pharmaceuticals. Keratinocytes that have completed their differentiation process are known as corneocytes. Corneocytes are linked together by intercellular lipids and corneodesmosomes.[11,12] The lack of cell nuclei and organelles, as well as an aggregation of cytokeratin filaments bundled by filaggrin and the presence of a rigid cornified membrane, distinguishes them (CE). Several proteins, including involucrin, loricrin, short proline-rich proteins, envoplakin, periplakin, filaggrin, and cysteine protease inhibitor A, are cross-linked by transglutaminases to form the CE (cystatin A).[11-13]

Desmoplakin, desmoglein 1, desmocollin 1, and corneodesmosin are all proteins found in corneodesmosomes. Corneodesmosin is transported to the extracellular space through the granular cell layer's lamellar bodies, where it is absorbed into desmosomes[14] before being progressively changed into corneodesmosomes. Corneodesmosome degradation is required for corneocyte desquamation and, as a result, an orderly epidermal turnover. Corneodesmosomes are broken down by proteases such Kallikrein-related peptidases and cathepsins. Protease inhibitors, such as lymphoepithelial-Kazal-type 5 inhibitor, cholesterol sulfate, and pH, control them. TJ remnants may block proteases from entering corneodesmosomes.[12,15]

Other SC components, such as filaggrin, CE-proteins, and corneodesmosin, have been identified to have a role in skin barrier function.

#### *Tight junctions*

TJs create a continuous barrier in the epidermis of SG. As molecules go from the outside to the inside of the cell, they must pass the second barrier. TJs in the epidermis act as a barrier to molecules of varying sizes, with Biotin-SH being the smallest, that is, 556 Da. TJs, particularly claudins, can impede the movement of molecules in a charge-selective manner depending on their composition. As a result, they inhibit chloride, sodium, and calcium ion transport outside the cell.[16,17]

TJs are made up of three groups of transmembrane proteins like TJ-associated MARVEL-proteins (including occludin and tricellulin), claudins, and junctional adhesion molecules. Claudins, in particular, are required for the barrier function of TJs to be established. It has been proven that claudin-1 and claudin-4 occur in the human epidermis. Claudins that help to keep the barrier in place.[18] TJs also

include plaque proteins such ZO-1, −2, cingulin, and atypical proteinkinase C, which are important for signaling, scafolding, and regulation, and contribute to create TJs as a signaling platform.[19]

### *BM (Basal lamina)*

The BM is located at the dermoepidermal interface on the basal side of the stratum basale. It consists of a variety of matrix proteins as well as carbohydrates. Laminins and collagens, as well as proteoglycans like perlecan and hyaluronic acid, are important components. They form a cross-linked mat-like structure with a variety of chemicals,[20,21] which is essential for appropriate epidermal synthesis and, as a result, barrier formation. Blistering pemphigoid disorders are caused by autoantibodies directed against laminin.[22,23] The thickness of the BM has been reported to be considerably decreased in atopic dermatitis.[24]

It is debatable whether the BM qualifies as a barrier. Material contact between the epidermis and the dermis is hindered by the mesh structure of the BM. However, inside-out barrier testing revealed that the expected transport of proteins up to 40 kDa (HRP) was not affected.[25] Nonetheless, the epidermis considerably decreased the absorption of particles with a diameter of roughly 8 nm.[26,27] The BM also stopped viral particles like the herpes simplex virus from spreading.[28] Furthermore, due to its substantial negative charge, it has been postulated that the BM acts as a charge-selective barrier for larger (approximately 450 kDa) molecules.[29]

**Table 1:** Opportunistic pathogens

| Disease type | Clinical signs and symptoms | Causative agent |
|---|---|---|
| Aspergillosis | Halo and air crescent sign on chest radiograph and CT scan. Unremitting fever and pulmonary infiltrates during antibiotic therapy. Chest pain, pleural rub, pleural effusion, and hemoptysis. Clinical and radiologic sinusitis. | *Aspergillus* spp |
| Zygomycosis | Like aspergillosis, more outspoken rhino-cerebral form with serosanguinous nasal discharge. | *Rhizopus* spp<br>*Absidia* spp<br>*Mucor* spp |
| Candidiasis | Acute disseminated: polyarthralgia, fever, chills, polymyalgia, not tender pinkish skin lesions, and retinal exudates.<br>Chronic: Complaints of the organ involved. | *Candida* spp |
| Cryptococcosis | Flu-like symptoms; skin lesions, headache without meningismus. | *Cryptococcus neoformans* |
| Others | Often catheter-associated; pneumonia<br>Skin and lung lesions<br>Often positive bloodcultures.<br>Skin lesions, severe myalgia.<br>Abscess formation with symptoms depending on organ involved.<br>Like aspergillosis; wound infections. | *Malassezia furfur*<br>*Trichosporon* spp<br>*Fusarium* spp<br>*Pseudallescheria boydii*<br>*Scedosporium* spp.<br>*Alternaria* spp. |

## Hair follicles

With the exception of glabrous skin, hair follicles (HFs) are complex structures found throughout the human body. Anagen (growth phase), catagen (regression phase), and telogen/exogen are all phases that HFs go through (resting phase).[30] Only a few HFs are in catagen or telogen, while the most are in anagen. Despite the fact that HF flow is mostly from the inside out, HFs have been used to demonstrate drug absorption, and pharmaceutical administration through the HF route is of significant interest (Figure 2).[31,32]

Human anagen HFs have two primary challenges. From the infundibulum to the lower central part of the HF's outer root sheath, TJs that create barriers may be detected.[33] A SC in the infundibulum that is continuous with the epidermis' SC covers these TJ-containing layers. On the other hand, the composition is a little different.[34] Barrier-forming TJs exist between Henle and Huxley's layers. The upper area

**Table 2:** Endemic pathogens

| Disease type | Clinical signs and symptoms | Causative agent |
|---|---|---|
| Penicilliosis | Splenomegaly, skin and subcutaneous lesions, lung, and lymphadenitis. | *Penicillium marneffei* |
| Coccidioidomycosis | Pulmonary infection. arthritis, dissemination with osteomyelitis, and meningitis | *Coccidioidis immitis* |
| Blastomyscosis | Ulcerative lesions; skin, urogenital tract<br>Central nervous system | *Blastomyces dermatitidis* |
| Para-coccidioidomycosis | Pulmonary infection. dissemination to lymphnodes, skin, and mucosa | *Paracoccidioidis brasiliensis* |
| Histoplasmosis | Pulmonary infiltrates; mucocutaneous ulcers hepatosplenomegaly | *Histoplasma capsulatum* |

of the HF is particularly accessible in terms of medicine distribution. As a result, SC and TJs in this area may play a key role in medication absorption. The importance of TJs between Henle and Huxley's layers for the outside-in barrier is a complex question that will require more investigation utilizing sophisticated microscopical tools.

TJs are located in the outermost living layer, which borders the environment, in catagen and telogen HFs. They are strewn around the hair of the club. A SC is also seen in the infundibulum. Drug delivery into and through hair follicles looks to be especially promising for nanocarrier-loaded medications.

### Glands

Skin glands, in general, create barriers. Because cutaneous glands have an inside-out flow direction, these routes are not suitable for drug administration; nevertheless, certain methods, such as iontophoresis, can be used to achieve absorption into glands.

TJ barrier altering enhancers, for example, may improve transepidermal medicine administration while reducing the barriers in glands caused by TJs. As a result, negative side effects including increased or decreased sweat flow or lipid release through the sebaceous glands may occur.

These are of two types:

a. Sebaceous glands
b. Sweat glands.

**Table 3:** Drugs with a high risk for inducing AGEP

| | |
|---|---|
| Anti-infective drugs | Antibacterial sulfonamides |
| Anti-infective drugs | (Hydroxy-) chloroquine |
| Anti-infective drugs | Terbinafine |
| Anti-infective drugs | Quinolones |
| Anti-infective drugs | Aminopenicillins |
| Anti-infective drugs | Macrolides |
| Others | Diltiazem |

### Blood vessels

The "last line of defence" is the skin's vasculature. The contact between the surrounding skin tissue and the human circulatory system is marked by a one-cell thick endothelial cell layer, which ends up in the papillary loops of the superficial arteriovenous plexus at the dermoepidermal junction in the upper dermis. In response to pressure, shear pressures, osmolarity, heat, chemokines, and cytokines, the endothelium in the skin controls permeability and causes vegetatively controlled vasodilation or constriction.[35]

Aside from the direct effect of inflammatory stimuli on permeability, the skin vasculature plays an important role in thermoregulation, opening up vascular loops that are ordinarily closed during rest. As a result, total skin

**Table 4:** Conventional treatment for fungal infection

| Drug | Brand name | Dose | Dosage form | Manufacturer |
|---|---|---|---|---|
| Amorolfine | Loceryl (5%) | Once daily | Nail lacquer | Roche lab |
| Cicloptroxamine | Nailon (8%)<br>Penlac (8%)<br>Onylac (8%) | Once daily<br>Once daily<br>Once daily | Nail lacquer<br>Nail lacquer<br>Nail lacquer | Protech- biosystem<br>Dermilk<br>Cipla |
| Natamycin | Natacyn (5%) | One drop instilled in conjuctival sac two hourly | Ophthalmic suspension | Alcon |
| Fluconazole | Zocon (0.3%)<br>Syscan (0.3%)<br>Flucomet (0.3%) | 3 times a day<br>3 times a day<br>3 times a day | Eye drops<br>Eye drops<br>Eye Drops | FDC<br>Torrent<br>Sun (milmet) |
| Terbinafine | Lamisil (1%) | Twice daily | Cream | Merz pharmaceuticals |
| Ciclopirox | Laprox (0.77%)<br>Laprox (0.77%) | Once daily<br>Twice daily | Gel<br>Cream | Aventis pharma<br>Hoechst-Marrion-Roussel |
| Sertaconazole | Ertaczo (2%) | Twice daily | Cream | Ortho neutrogena |
| Econazole | Econail (5%)<br>Spectazole (1%) | Once daily<br>Twice daily | Nail lacquer<br>Cream | Macrochem corporation<br>Ortho |
| Ketoconazole | Nizoral (2%)<br>Xolegel gel (2%) | Twice daily<br>Once daily | Cream<br>Gel | Janssen<br>Stiefel labs |
| Miconazole | Micatin (2%)<br>Manistat-ermD (2%) | Twice daily<br>Twice daily | Cream<br>Cream | Ortho-McNeil pharmaceutical<br>Pfizer |
| Clotrimazole | Mycelex-G (1%)<br>Gyne-Lotrimin (1%)<br>Lotrimin (1%) | Twice daily<br>Twice daily<br>Twice daily | Cream<br>Cream<br>Cream | Miles<br>Schering- plough<br>Schering |

**Table 5:** Dermatophytes: topical treatment[71]

| Agent | Dose | Formulation |
|---|---|---|
| Imidazoles | Once or twice daily | 1% cream or lotion |
| Sulconazole (exelderm) | Once or twice daily | 1% cream or lotion |
| Oxiconazole (oxistat) | Twice daily | 2% cream, spray, lotion or powder |
| Miconazole (micatin) | Once daily | 1% cream |
| Ketoconazole (nizoral) | Twice weekly | 1% shampoo |
| Econazole (spectazole) | Once daily | 1% cream |
| Clotrimazole (lotrimin) | Twice daily | 1% cream, solution, or lotion |
| Benzylamine butenafine (Mentax) | Once or twice daily | 1% cream |
| Allylamines | Once or twice daily | 1% cream or solution |
| Terbinafine (lamisil) | Once or twice daily | 1% gel |
| Naftifine (naftin) | Once Daily | 1% cream |
| Miscellaneous | Twice daily | 1% cream, solution, or powder |
| Tolnaftate (tinactin) | Twice daily | 1% cream or lotion |
| Ciclopirox (loprox) | | |

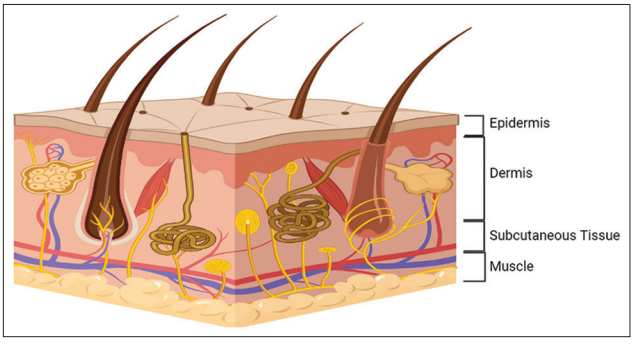



**Figure 1:** Structure of skin anatomy.

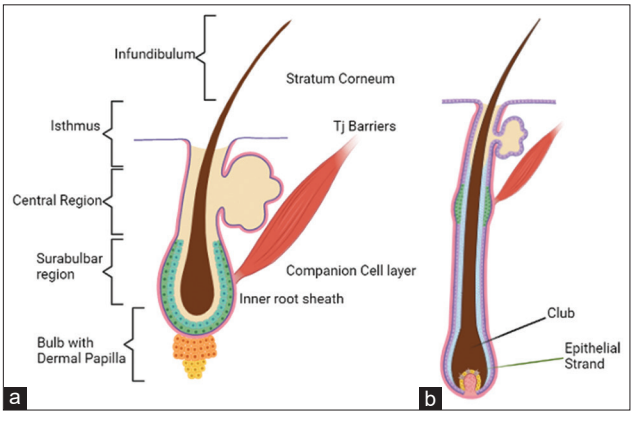



**Figure 2:** Schematic diagram of a hair follicle in anagen (a) and catagen (b).

perfusion varies from 0.05 L/min under cold stress to more than 5.00 L/min under hyperthermia.[36] In addition to the thermoregulatory function of the skin, this considerable variation in local perfusion rates affects the flow rate of substances outside-in and inside-out, and hence the barrier function of the skin.[35,37] A number of clinical trials focusing on the heat-induced rise in systemic plasma concentrations of topically applied medicines such as fentanyl, clonidine, testosterone, or nicotine have previously been successfully conducted for transdermal pharmaceutical delivery.[38]

## Etiology of skin infection

It is now impossible to quantify the incidence exactly due to a lack of population-based statistics and varying nomenclature. The incidence was estimated to be 1–5 cases/1,000,000 per year using the EuroSCAR research. Acute generalized exanthematous pustulosis (AGEP) affects people of all ages; however, it is more common in women.[39,40] The current death rate is estimated to be 5%; however, it might be far lower.[41] Drugs are responsible for more than 90% of AGEP cases (Table 3).[42]

Antibiotics, (hydroxy-)chloroquine, and diltiazem were identified as major triggers in the EuroSCAR experiment. A number of case reports have been published, with some citing systemic, topical, and herbal medications, as well as viral infections, as possible causes.[43] Aminopenicillins have a high chance of generating AGEP in Germany. The time between starting a medicine and experiencing a cutanous response varies depending on the causative substance. Other triggers have an 11-day median, whereas antimicrobial drugs have a 1-day median.[44]

As evidenced by its ability to grow in distilled water using just dissolved carbon dioxide and residual ions as growth substrates, *Pseudomonas aeruginosa* can thrive in low-nutrient settings.[45] It is a highly effective opportunistic pathogen in instances when the host's defenses have already been compromised due to its resilience.[46] It is also hydrophilic, which means it likes to be wet. *P. aeruginosa* infections have traditionally been linked to water-related reservoirs such as swimming pools, hot tubs, and contact lens solution.

Because it can be collected from almost any source of water in the environment, these two characteristics combine to make the bacteria more prevalent. Despite its broad distribution in the environment, *P. aeruginosa* colonizes therefore only a small percentage of healthy human hosts[47] nonetheless, colonization has been observed in persons

who have received many antibiotic treatments, as well as in the respiratory tracts of mechanically ventilated patients.[43] During the past 60 years, *P. aeruginosa* has evolved from a little-known pathogen to one of the most common microorganisms linked to hospital-acquired infections.

It was the most common Gram-negative species isolated from bronchopulmonary infection sites of patients hospitalized in 1417 critical care units throughout 17 Western European nations, according to data from the EPIC (European Prevalence of Infection in Intensive Care) research (28.7%).[48] According to the 1999 SENTRY Antimicrobial Surveillance Program, it was the third most prevalent pathogen (10.6%) detected in 4267 bloodstream isolates from Canada, the United States, and Latin America.[49] *P. aeruginosa* has been shown to be very successful in contaminating hospital-based water reservoir systems, and carrying the bacteria on the hands of health-care personnel can make transmission even easier.[50]

## PREVALENCE OF SKIN INFECTION

A fungal infection was the most common skin ailment. This must be handled since it has the potential to cause acute bacterial cellulitis, which affected as many as 61.4% of our patients.[51-53] Over half of the study participants had onychomycosis, the most common condition in this group. Dermatitis was the second most frequent skin disease.

Wu *et al*.,(2014) discovered that persons with schizophrenia had a significant frequency of skin issues. Patients who received non-clozapine atypical antipsychotics (NCAAs) had a fourfold higher incidence of pilosebaceous illness than those who just receivedtypical antipsychotics(TAs). On the other hand, clozapine users appeared to have a lower chance of acquiring a fungal infection. Patients with higher PANSS levels had a lower risk of developing hyperkeratotic diseases. In individuals with diabetes and a high BMI, bacterial and fungal infections were shown to be more prevalent. The significant frequency of skin disorders in the study population (97.6%) exceeded all of our expectations.[54]

Even when Wu *et al*.,(2014) limited their research to dermatitis and infectious skin illnesses, which have a significant influence on a patient's quality of life and can lead to problems, the number of people impacted remained at 83.7%. Only 21.2% of those with skin diseases were aware of their condition. This gap might be attributed to cognitive deficiencies in schizophrenia patients, which could influence symptom identification.[55] Patients with schizophrenia, according to previous research, have greater pain thresholds, thus they may be less likely to report physical symptoms until they become severe.[56]

This is the region's first research of its sort, and it found that socioeconomic and environmental factors had a major impact in the onset and duration of the disease. 23.6% was found to be the prevalence. Eczema, acne, allergies, skin irritation, and lichen planus were the top five skin illnesses in the region. This percentage is comparable to those in other parts of the Kingdom, such as 27.2% in Al-Hassa and 19.23% in Jeddah.[57,58] Eczematous dermatosis, allergies, infectious dermatosis, and other skin conditions such pigmentary diseases and acne were among them.

Around half of the trial participants had eczema. When compared to the general US population, the proportionate morbidity ratio of contact dermatitis and other eczema among mental patients was 2.9, according to a research based on data from the National Hospital Discharge Survey.[59] According to Taiwan's NHIRD, atopic dermatitis and asthma have a significant comorbidity rate, with evidence of both illnesses in 20.2% of persons with schizophrenia.[60] Despite the lack of a direct relationship between schizophrenia and dermatitis, both disorders are likely to aggravate one another, creating a vicious cycle.

### Conventional treatment[61]

Conventional treatment: It is typically found that even for deeply seated fungal infections, standard formulations like cream, powder, gels, etc. (as shown in table 4 & table 5) are utilized to treat skin fungal infections. However, the application site of these formulations exhibits a variety of adverse effects, including burning, redness, and swelling. Additionally, because the medications are released instantly from these formulations, they might activate the immune system of the body and cause severe allergic reactions (Tables 4 and 5).

## DRAWBACKS

Traditional topical treatments have several disadvantages.

Skin irritation with antifungal lotions, gels, and ointments can include burning, stinging, erythema, and redness.[62] Traditional topical antifungal treatment for ocular infections has several limitations, including poor ocular penetration, local bioavailability, and drug toxicity.[63]

When compared to topical antifungals, oral antifungals have higher side effects. Some are prohibitively expensive, while others may induce organ damage and have more evident interactions with other medications.[64,65] Grifofulvin is one of the most regularly prescribed antifungals. When used to treat onychomychosis over an extended length of time, it may cause hepatotoxicity.[66] Headaches, photosensitivity, nausea, and vomiting are some of the other negative effects. It can detect unfavorable medication interactions with barbiturates, alcohol, oral contraceptives, and warfarin, among other pharmaceuticals.[67]

Hepatotoxicity has also been associated to ketoconazole. Hepatotoxicity with ketoconazole affects one out of every 10,000 to 12,000 people. Other side effects of this medicine include hemolytic anemia, impotence, and stomach pain.[66] When taken with antihistaminic medications like triazolam, this antifungal medication is usually contraindicated.[65] Itraconazole causes adverse effects that are similar to ketoconazole; however, hepatotoxicity is uncommon. Side effects with fluconazole are more prevalent in HIV-positive people.[62]

Among the symptoms include dyspepsia, confusion, stomach pain, exfoliative skin problems, and anaphylaxis.[65] Terbinafine is an orally active antifungal medicine that has a number of unpleasant side effects when used as a standard formulation. Among them include neutropenia, vision difficulties, urticaria, and dyspepsia. In rare situations, it might lead to cholestatic liver disease or fulminant hepatic failure.[68-70]

## RECENT TRENDS IN PRESCRIPTION OF DERMATOPHYTES

Recent Trends in Prescription of dermatophytes: A illness that spreads throughout the world is dermatophytosis. A significant field of management and research has been dedicated to the treatment of dermatophytosis. Resistance to routinely used antifungal medications is another factor contributing to the rise in dermatophytosis. Very few strains of fungi were resistant to the antifungal medication before 2000. But there have been numerous reports of novel resistant strains in recent years. Dermatophytosis can be treated naturally with substances like natural plant extract and various essential oils. Numerous studies have demonstrated the anti-microbial characteristics of essential oils, which have led to their widespread use as medications to treat fungus infections.[69-71]

## CONCLUSION

On the basis of the analysis, we can draw the conclusion that dermatophytosis is a disease that spreads around the world and offers a summary of current medical treatment for invasive fungal infections as well as research objectives for the creation of novel chemicals. An important chance to talk about current trends in the treatment of dermatophytosis with the new trend.

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