MICROBIAL ECOLOGY OF INTERDIGITAL INFECTION OF TOE WEB SPACES AND THEIR MANAGEMENT

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Introduction

Interdigital infection of toe web spaces is a common health problem in dermatologic practice.[1] This infection may present as a relatively asymptomatic, mild scaling or a painful, exudative, macerated, inflammatory process accompanied by a foul odour.[2,3] Some authors refer to this condition as tinea pedis or "foot ringworm"[2] and consider it to be purely dermatophytes induced. However, toe web infection can be best viewed as an ecological interplay between dermatophytes, various bacterial species and candida species. [3]

A number of studies have demonstrated that recovery of dermatophytes from macerated interspecies is low,[3,4] it range from 7.5% to 61%. [1,2]

Therapeutic approaches shouldn't concentrate solely on antifungal therapy, but should concentrate on preventive measures, broad spectrum antibacterial agent and topical and systemic antifungal agents. [2,3]

Microbiology of the skin resident flora

Normal skin is colonized by large number of microorganisms that lives harmlessly as commensals on its surface. Relatively few are found consistently on the skin those organisms that are found regularly on the skin constitute its normal flora.

Those grew on skin and relatively stable in number and composition are called resident flora (Table 1). But those lie free on the skin surface are transiet flora. [5]

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Table 1 Resident skin flora

Micrococcaceae
Coagulase-negative staphylococci
Peptococcus
Micrococcus species
Coryneform organisms
Corynebacteria
Brevibacterium
Propionibacterium
Acinetobacter
Pityrosporum

Micrococcaceae

Staphylococci – human have a high degree of natural resistance to skin colonization by S. aureus. Staph. Can be found in intertriginous areas, particularly the perineum of up to 20% of persons.[6] In addition, persistent nasal carriage of the organisms is present in 20% - 40% of normal adults.[7] From when it can cause persistent skin colonization and recurrent infections. Patients with certain skin diseases tend to harbor S, aureus. In psoriasis[8] and atopic dermatitis[9] S. aureus may be found widely in both diseased and normal skin often contributing up to 80% of the flora.

Coagulase negative staphylococci are the most frequently found organisms of the normal flora. At least 18 different species have been isolated from normal skin.[10]

Coryneform organisms:

Gram positive rods – some times called diphteroids in medical literature. It compose a significant portion of the normal flora mainly in moist Intertriginous areas especially toe web spaces with hyperhidrosis.[2] (minutissimum once thought to be a single organism distinguished by the ability to produce porphyrin, is actually a complex of as many as eight different species.[11]

Brevibacterium

Also known as large colony corybeforms. They are penicillin resistant and probably the most rapidly growing of the coryneforms.[12] They are frequently isolated from the toe webs, especially in patients with tinea pedis and have been implicated in foot odor (B).

Propionibacteria

They are nonspore forming, anaerobic, gram positive bacterial that are normal inhabituals of hair follicles and

sebaceous glands. They are the most prevalent anaerobes of the normal flora and are known as anaerobic corybeforms.[14]

Gm negative Rods

Unknown components of the resident flora of the skin. They become occasional Resident flora in most intertriginous areas and mucosal surfaces such as perineum, axilla, toe webs or nasal mucosa of some persons. Escherichia coli, Klebsiella, Enterobacter and prospecies are the predominant organisms.[15]

Acinetobacter species are gram negative rods widely dispersed in nature found in 25% of persons as normal flora.[15] Increase in colonization during the summer.

Pityrosporum

Lipophilic yeasts which require lipids for growth. P. ovale and P. orbiculare are probably identical organisms that are prominent in sebaceous areas. They are most numerous on the back and chest.

Candida

It is normally found up to 40% of the oral macosa. Candida SPP other than c.albicans was found in 10% of normal interdigital space in one study done[2] found up to 40% of the oral mucous membranes, seldom colonize the normal skin. At present C. albicans is the most common species found existing in the blastospore form. Increase colonization of the skin by candida species is seen in immunosuppressed and diabetic patients and in patients with psoriasis or atopic dermatitis.[16]

Dermatophytes

In case of zoophilic dermatophytes e.g. microsporum canis a significant number of dermatophytes may reside on the skin of the appropriate hosts without visible skin lesions.[17] Dermatophytes can frequently found in clinically normal interdigital spaces.

Factors modifying the normal Flora

Although the resident flora remains relatively constant, several factors can change the quantity of organisms and the relative percentage of each organisms in the normal flora.

Effect of Climate

Increased temperature and humidity increase the density of bacterial colonization and alter the relative ratios of organisms.[15] These environmental changes have been experimentally reproduced by application of occlusive material on forearm skin.[17] After 24 hours of occlusion, bacterial counts increases 10, 1000 fold and the relative numbers of gm –ve rods and coryneform bacterial are increased over coccal forms.

Once the occlusive material is removed the numbers of bacteria decrease towards normal but only very slowly.[18]

The increase heat and humidity provided by occlusion are environmental factors that favor the growth of not only bacteria but fungal organisms as well.

Cutaneous candidiasis, tinea versicolor and Trichophyton rubrum infection can be experimentally reproduced on human skin only if applied under occlusion. The raised carbon dioxide tension produced by occlusion may also favor the conversion of yeasts and dermatophytes to a more infectious stage.[19]

The effect of body location

The composition of the normal flora varies depending on body location. The face, neck and hands represent exposed areas of the body and as a result may have a higher proportion of transiet organisms and a higher bacterial density. The head and upper trunk have more sebaceous glands and a great number of lipophilic organism, with propionibacterium. The dominant organisms, the axilla, perineum and toe webs are areas under partial occlusion with an increased temperature and moisture level. These areas are colonized more heavily with all organisms, but particularly gram negative rods or coryneform that need moisture for survival. Coryneform organisms are frequently reported to be the predominant organisms in these areas.[20]

The effect of hospitalization

Hospitalized patient have increased colonization with pathogenic and antibiotic-resistant organisms such as group JK coryneforms, increase in total gram –ve organisms favoring especially proteus and pseudomonas species and in C. albicans. One study showed that the frequency of nasal carriage of S. aureus in neonates or in patients with eczema increases with the number of days hospitalized.[21]

The effect of disease

The presence of systemic disease may predispose to colonization or infection with different organisms, which may be due to an associated immunologic abnormality or

to changes in bacterial adherence.[22] In diabetes mellitus another possible factor affecting colonization is an increase in skin glucose concentrate. An increase in the nasal carriage of S-aurea occurs in diabetic children and insulin dependent diabetic adult compared with either non insulin dependent or control subjects. The prevalence of candidal infections, particularly in females is increased in diabetic persons.[22]

The effect of age

The age of the person has a profound influence on the microflora.[23] The flora is most varied in young children, who carry micrococci, coryneform bacteria and grow –ve organisms more frequently and larger number than older children and adults.[23] Infants also carry a higher proportion of pathogens or potential pathogens on their skin.[24]

Pityrosporum and propionibacterium species are present at much lower levels before puberty.[25] These organisms require higher skin lipid levels and their appearance parallels age related changes in sebum production. Elderly patients have a decrease in sebum production and infection with these organisms are rare.

The effect of sex

Evidence exists that men carry higher absolute number of organisms and more biotypes.[23] has been related to a higher sweating rate in men as well as a tendency to wear more occlusive clothing.[22] Other possible factors include increased sebum production in men and hormonal differences between the sexes.[23]

The effect of occupation

Occupation to some extend may also influence the pattern of resident flora. Those who work in environments with high temperature and humidity, for example, might develop microflora favored by these factors, such as candida, gram –ve organisms and coryneforms.[22] Hospital workers have also been shown to harbor more pathogenic organisms as transiet organisms, which may become established as resident flora if continually exposed.[22]

The effects of soaps and disinfectants

Repeated washing with soap makes the skin more alkaline than washing with medicated disinfectants.[25] Propionibacteria were markedly increased when soap was used and depressed with medicated disinfectant.

Of all exogenous influences, drugs are capable of making the most rapid and radical changes in the normal flora. Antibiotics may suppress the normal flora and increase colonization by other organisms. In addition, they may impair bacterial adherence to epithelial cells and allow the natural selection of organisms, such as gm negative rods, candida or pityrosporum.[26] Oral steroid and hormones are associated with changes in normal flora. Corticosteroid suppress the immune system and increase susceptibility to various bacterial, fungal, viral and parasitic infections.[22] Women on estrogen therapy may experience an increase in vaginal as well as cutaneous candidiasis. The use of topical antibiotic may induce resistant strains to appear. However, topical steroids have little effect on the numbers of types of cutaneous microflora.[22]

The effect of ultraviolet light

UVB has been shown to inhibit growth of certain organisms. Pityrosporum and candida species were more sensitive than staphylococci.

Natural Resistance of the skin

Various factors that determine the natural resistance of the skin include:

Host defense:

Normal skin is resistant to colonization and invasion by most bacteria. Many factors exist which prevent colonization and invasion by pathogenic organisms.

1- Intact stratum corneum:

Overlapping cells, joined by modified desmosomes, function as an armor against organisms. In addition, the relative dryness of intact skin limits the growth of organisms that require moisture, such as candida species. Experimental production of localized infection with pathogenic organisms is difficult if the skin is intact,[27] and a break in the stratum corneum was an absolute requirement for the induction of streptococcal infection. S.aureus can infrequently cause infection on intact skin, but the presence of a single silk suture through the skin increase the infectiousness of S. aureus by a factor of 10.000.[28]

2- Rapid Cell turn over:

Another feature of the stratum corneum that offers protection from invasion is its rapid turnover, the transit time is only 14 days. If pathogenic organisms adhere, they have a limited time to invade. The resident flora are better suited for reattachment after

desquamation than the weekly adhering transiet organisms.[29]

3- Lipid Layer:

Many components of the resident microflora have lipase activity and liberal fatty acids, such as oleic, stearic or palmitic acid from the triglyceride of sebum. These free fatty acids create an acid mantle on the surface of the skin, which has a potent antimicrobial effect, on S.aureus and streptococcus organism,[30] and a simulating effect on some other organisms such as propionibacterium species which produce propionic acid with antimicrobial effect on many organisms.

Occluded areas of the body, such as intertriginous areas, have a natural or slightly alkaline PH because of the diluting effect of the skin's secretions and because more densely populated with microorganims.[29] Epidermal lipids also play a role. Free fatty acids, polar lipids and glycosphinogolipids derived exclusively from the stratum corneum have significant anti staphylococcal activity. These lipids provide a significant antimicrobial line of defense.[30]

4- Immune system:

The skin has hormonal and cellular immune system that can influence the composition of the microbial flora. In normal skin the hormonal mechanisms involve the secretion of primal original or most important IgA and IgG antibodies, brought to the surface through the eccrine system.[31] The secretory IgA in sweat may prevent infection by several possible mechanisms, and its presence may explain the absence of colonization in the eccrine duct. Elements of cellular immunity in the epidermis include antigens presentation by langerhans Cells and T-cell activation by epidermal thymocyte activating factor, a product of epidermal cells. The skin also plays a role in T-cell differentiation.[31] These interactions are vital in preventing cutaneous infection. Patients with defects in cellular immunity are more susceptible to infections.[30] These infections may include diseases with a narrow limited defect such as a patient with chronic mucocutaneous candidiasis with more widespread defects, such as patients with acquired immunodeficiency syndrome.

5- Role of the organism:

Antibacterial substances:

Many microorganisms produce protein or protein-complex antibiotics that have an antagonistic effect on other organisms but not on the producer bacterium.[31] Substances produced by gram negative bacteria generally have a wide range of antibacterial activity, whereas those produced by gram positive organisms are usually effective only against strains.[30] These latter substances are called bacteriocins.

Dermatophytes on the skin can also produce antibiotics, including penicillin and other substances with antibacterial and antifungal activity.[32] Penicillin production can suppress the bacterial flora in fungal lesions and tend to select a penicillin resistant flora,[33] such as brevi bacterium or penicillin resistant staphylococci.

6- Bacterial interference:

A resident bacterium sometimes prevents colonization by other strain of a similar species, which most likely occur by competitive inhibition of binding sites. The protective role of the resident staphylococcal flora is demonstrated by its absence in the newborn, when during the first week of life pathogenic organisms such as S.aureus frequently colonize the skin because of the absence of an established resident microflora.[37]

Other interactions:

Suppression of the gram positive organisms by topical antibiotics causes a corresponding proliferation of gram negative bacteria.[33] A reciprocal relationship between carriage of S.aureas and gram negative organisms in the nose has also been seen.[34] The development of candidiasis after suppression of the normal flora suggests that the inhibitory function of the normal flora has an influence on fungal organisms as well. Normal oral microflora were found to block the adherence of C.albicans to host epithelium in normal mice.[35] Similarly, when the normal flora is suppressed with oral antibiotics, C.albicans quickly colonizes.[36]

Interdigital toe web infection is a complex entity. Although it is a result of interaction of multiple factors including those of host, bacterium and flora, it is usually categorized or classified under the fungal infection of tinea pedis. Thus before we proceed with a detailed discussion of interdigital toe web-infection it is worthwhile to review in short about tinea pedis and exactly where interdigital toe web-infection been placed in classification.

Prevalence of Tinea Pedis

Tinea pedis is now the most common fungal infection, having surpassed tinea capitis, the most common infection of years gone by. The incidence worldwide of T.pedis has increased.[36]

This infection was unknown in early Roman and Greek times, and the first case was not described until the late nineteenth century.

The disorder is very common in males, but rare in females.[36,58] It is rare in children and most inflammatory disorders of the feet in prepubertal children result from other causes.[36]

T. pedis is the commonest form of dermatophytes infection in the UK and North America and probably through out the developed world.[58] Although it occurs in all parts of the world, it is more prevalent in tropical and temperate climates. It comprises 35 to 45% of all clinical manifestations in Western Europe.[38] Since Athlete's foot is not a reportable disease and primary disease is often not diagnosed by a physician, exact morbidity and figures are difficult to obtain.

Predisposing factors:

Factors that may predispose to infection in otherwise normal individuals include hot, humid climates which cause excessive moisture. Over-hydration which develops in a variety of ways, namely exercise, emotional hyperhidrosis, tight shoes, occlusive foot wear which increase the native micro flora.[2,18] T. pedis occurs most often in populations that wear shoes. The warmth and moisture provide by shoes are key factors in establishing and maintaining tinea pedis.[39] The incidence of tinea pedis is more frequent in persons who use communal baths such as, swimming pools, sports club, industrial baths.[4]

The single most important factor that regulates the incidence, prevalence and severity of tinea pedis is occlusion.[4] The occlusive effects of the army boot on the prevalence of tinea pedis in soldiers in tropical climates have been studied.[4] Those soldiers in high humidity areas developed tinea pedis more frequently than those in high temperature low humidity areas.

Serious public health problem may occur in high risk groups in which infections occur with great frequency, tend to be more chronic, may be resistant to treatment, may even disseminate and may ultimately be life threatening. These groups include the elderly in whom peripheral vascular diseases are common and in whom reported prevalence including tinea unguium approaches 70 to 100% in individual over 60 years of age, the institutionalized, especially in nursing homes for the elderly and in prisons where hygienic conditions may be poor, military personal, especially in tropical combat zones, patient with debilitating diseases such as AIDS, patients with diabetes, alcoholics and drug addicts, patients receiving long term treatment with broadspectrum antibiotics, corticosteroid, radiation or cytotoxic drugs, immunocompromized patients and patients with genetic predisposition including those with atopy.[40]

Clinical variants of T.pedis

The general term tinea pedis encompasses three clinically distinctive syndrome, viz, interdigital toe web infections, scaly hyperkeratotic moccasion type of infection of the sole of foot and a highly inflammatory vesicular/bullous variety. These three varieties have differences in terms of the site of infection, the causative organisms, host immune response and microbial ecological interactions which have important implications for therapy.[2,4]

Interdigital toe-web infection

The commonest form of T.pedis.[37] Historically interdigital toe web infections have usually been categorized as fungal diseases. They usually start as a dermatophyte infection with scaling, and when the bacterial proliferate maceration occurs. The inability to culture dermatophytes from symptomatic macerated interspaces is now understood in terms of the dynamic interplay between fungi and bacterial which we will speak later about them.

Plantar Moccasin – type

This type results in diffuse hyperkeratotic scaling of the plantar surface and is often associated with nail involvement,[2,4] many patients have an atopic history.[36,4] These patients appear to have a defect in their cell-mediated immune reactivity and are unable to mount a delayed type hypersensitivity to certain dermatophytes, although other antigens evoke normal response. Negative reaction to intradermal Trichophyton are common. Immediate wheal and flare responses indicate the presence of IgE antibodies.

This type of T.pedis is usually chronic and resistant to treatment, it affect soles, heels and side of feet. The affected area is pink and covered with fine silvery white scales. The dorsal surfaces of toes and feet not often affected. Because the plantar surface has such a thick stratum corneum, delivery of topical and systemic drugs in a sufficient quantity to have fungicidal effect is difficult.

Tr. rubrum appear to be less efficient in eliciting the T-cell, delayed type immune response which is the host machanism by which fungi are eliminated.[41] This inherent differences in inducing immediate response, coupled with the organism being relatively sequestered from the body in the thick plantar stratum corneum, accounts in part for the chronicity of T. rubrum Moccasian infection.[42]

Vesiculobullous tinea pedis

Acute highly inflammatory eruptions particularly on the arch and side of the foot occur with T. mentagrophytes infection. The intense inflammatory reaction represents T-cell immune host response[4] presumably, different environmental factors such as seasonal temperature, sweating from physical activities and type of shoe wear influence the growth of fungus and when sufficient proliferation and penetration of the stratum corneum occur, epidermis comes into contact with fungal antigens and a T-cell-mediated immune reaction occurs, that is an allergic contact dermatitis occur.[43] Between attacks of acute inflammation more or less low-grade scaling exists.

This type may be preceded for months or years by macerations or fissuring in the toe clefts.[37] It frequently goes on to apparent spontaneous cure but tend to recurs in warm weather. There is often associated hyper hidrosis.

Epidermophyton floccosum may occasionally cause a vesicular infection of the sole like T.menta grophytes with less toe nail involvement but chronicity of the skin infection may be just as troublesome.[37]

Compresses and topical or systemic cortocosteroids in conjunction with antifungal agents are used with acute attacks. The choice of topical or systemic agents depends on the extend and severity of the process. Steroid therapy is withdrawn once the cell mediated immune response is curtailed, but continued topical therapy is desirable in an attempt to eradicates residual fungus. The allylamines which are fungicidal, appear to be the best choice.[4]

Interdigital toe web infection

Interdigital toe web infections have been traditionally categorized as caused by invasion of the skin by dermatophytic fungi. This is a gross over-simplification that have adversely affected diagnosis and treatment.[4]

Inflammation begins in areas of moisture and maceration, the integrity of skin is lost and fungus begins to grow. An inflamed, irritated toe web is the result. T. mentagrophytes is a common cause with the var. mentagrophytes producing much more inflammation than the var. Interdigitale.[59] Epidermophyton floccosum and T.rubrum may also be isolated.

Dermatophytes can be isolated from clinically normal toe clefts in 21%[1] a contrary situation exists in which mildly abnormal toe clefts yields no dermatophytes.[58]

Dermatophytes are frequently absent from severe cases of interdigital infections and, in general, recovery of fungi from clinically abnormal interspaces ranges from 7.5% to 61%.[66] These interdigital infection respond poorly to purely antifungal agents such as tolnaftate.[66] Thus it is evident that the dermatophytes population can't be solely responsible for the clinical spectrum seen in interdigital infection.

The inability to culture dermatophytes from symptomatic, macerated interspaces is now understood in terms of the dynamic interplay between fungi and bacteria.[4]

Dermatophytosis simplex is a term given for uncomplicated, relatively asymptomatic fungal type of scaling, (dermatophytes recovered from 85% of patients).[2] Athletes foot and dermatophytosis complex for the macerated, symptomatic often malodorous process from which a variety of bacteria were recovered and dermatophytes were infrequently cultured (dermatophytes can be recovered in only one third of patients).(3)

In macerated interspaces, there is an increased prevalence of staphylococcus aureus, M. Sedantarium, B. epidermdis, C-minutissimum, the multiple antibiotic resistant cosyrebacterium Jei keium and pseudomonas and proteus species.[3]

The microbial flora of normal and macerated interdigital toe web spaces was qualitatively and quantitatively identified in 77 patients.[3] Dermatophyte fungi were recovered from 11% of normal patients compared with 31% from macerated interspaces. Macerated interspaces were characterized by a greater recovery of organisms with pathogenic potential with staphylococcus aureus recovered from 36% of patients, Micrococuss sedentarium in 37%, Brevibacterium epidermidis in 54%, Corynebacterium minutissimum in 69% and pseudomonas species in 26%. The bacterial flora of macerated interspaces showed a significant higher incidence of resistance to multiple antibiotics and the recovery of antibiotic resistant bacteria correlated with the recovery of dermatophytes that produce penicillin like substances. The result of this study support the hypothesis that over growth of the resident bacteria population determines the severity of interdigital toe-web infections.

In the setting of a weakened stratum corneum caused by dermatophytes invasion, these bacteria can produce tissue damage with maceration and leukokeratosis. Normal interspaces without dermatophytes invasion appear to resist damage from these bacteria, presumably because of the thickness of the stratum corneum and its barrier properties.

A probable mechanism by which dermatophyte positive interspaces can be converted into macerated interspaces from which fungi can't be recovered involves the production of a variety of sulfur compounds such as methanethiol, ethanethiol, dimethyl sulfide and others.[68] Those sulfur compounds are potent antifungal agents and are produced by M.sedantarius and B-epidermidis. Dermatophytes promote the selection of antibiotic-resistant bacteria through the protection of penicillin and streptomycin like antibiotics and that these bacterial damage the interspace producing symptomatic, macerated condition while also suppressing dermatophytes through the production of a variety of sulfur compound.

Prophylaxis in Tinea Pedis

In general, proper hygiene will help to prevent infections in the otherwise normal individual and will help to control infections in high risk groups. Recommendations for prophylaxis include bathing daily and drying feet well between the toes, wearing absorbent socks, change daily or twice daily if the patient is susceptible to hyperhidrosis, wearing shoes that "breath", changing shoes daily and wearing different shoes for sports, and using drying agent or antifungals for prophylaxis.[44]

Some authors stated,[37] if individuals avoid exposing others to their infection by not walking on the floors of communal changing rooms and by avoiding swimming baths, the level of infection in the community would fall. Because such large numbers of people are involved, many of whom are completely asymptomatic, this is usually not feasible. More over, eradication of these fungi from the toe clefts is often a long and tedious process, and elimination of the organism may never be achieved.

Frequent hosing of the floors of shower rooms and the sides of swimming baths does reduce the prevalence of dermatophytes on these surfaces and probably would lead to a reduction of infection in time. This should certainly be encouraged.

Satisfactory antifungal powder is readily available and encouragement of its use has been demonstrated to be effective in the long term reduction of tinea pedis at one swimming bath.[37]

Topical Antifungal Drugs

The challenge in antifungal drug development has been to discover away to block crucial steps in the metabolism of fungi, which are themselves eukaryotes, without adversely affecting the cellular function of their eukaryotic hosts.[45]

Newer antifungal drugs have increased specificity toward fungal cell membranes synthesis yet preserve biosynthetic pathways of the host cell membrane (Table II)

1. Castillani's paint (carbol fuchsin).

It is a mixture of fuchsin, phenol, resorcinol, paint, acetone, and alcohol. It has an antifungal and antibacterial actions besides drying effect.[46] It has been used to treat seborrheic eczema and interdigital athlete's foot[47] eliminating the fuchsin makes it colorless without loss of activity.[48]

Side effects include irritant and toxic reactions to phenol, its elimination has not led to decreased efficacy.[46]

2. Aluminum chloride 30% solution:

Has the same efficacy as Castillani's paint in tinea pedis and may be cosmetically more acceptable.[49]

Various aluminum salts were evaluated for invitro and invivo antimicrobial activity and ability to bind with serum proteins (astrigency) with the object of finding a colorless substance to substitute for carbol-fuchsin solution (castallani paint) in the treatment of symptomatic interdigital athlete's foot.[49] Aluminum chloride showed pronounced astringency and bring about rapid resolution of the signs and symptoms of athlete's foot in open-ended clinical trials.[49] It promptly controls odor, pruritis, and macerations. The beneficial effect depends largely on drying the surface. A solution of 30% aluminum chloride was found to be equivalent to castillani paint.[46]

It exerts its antibacterial effects in two ways: by directly killing bacteria and by making the interspace inhospitable through drying.[49]

3. Whitfield's ointment

Contains 12% benzoic acid and 6% salicylic acid. This fungistatic compound, used to treat superficial fungal infections, has a nonspecific activity, acting as a keratolytic causing desquamation of keratinized epidermis containing fungal organisams. If applied over a large surface area or occluded areas it may be irritating. Systemic absorpation may occur, leading to salicylic acid toxicity especially in those with impaired renal function.[46]

4. Compound undecylenic acid

Contains undecylenic acid and its zinc, calcium or sodium salts.[50] This compound is fungistatic with an astringent action. It is available as cream, aerosol, powder or solution.[50]

5. Potassium permanganate

It has nonspecific antifungal activity. A 1:5000 dilution has been of benefit in inflammatory candidiasis in intertriginous areas.[51]

6. Tolnaflate

It is a synthetic fungicidal thiocarbamate derivative introduced in 1962,[52] active against growing dermatophytes but weak against candida species. The mode of action involves squalene epoxidase inhibition with accumulation of squalene in the target cells, with same manner as the allylamines.[52] It is effective in tinea cruris and pedis but not the "dry type" of Trichophyton rubrum infection.

7. Haloprogin (Iodinated trichlorophenol)

It is a systemic topical antifungal agent for dermatophyte, yeast infections and erythrasma. Haloprogin 1% is available as a cream and solution. Possible side effects include irritation, pruritus and rarely vesicle formation or an allergic contact dermatitis.[46]

8. Ajoene

It is an organosulfur compound originally isolated from garlic, has been shows to be effective in short term treatment of Tinea apedis.[53] It is an inhibitor of phospholipid biosynthesis in human dermatophytosis.

9. Butenafine hydrochloride

It is a potent new benzyl amine with fungicidal activity. It has a similar structure and mode of action as allylamine antifungals.[54] It is active against dermatophytes, Aspergilli and dimorphic fungi. It has a low relapse rate and has been commercially introduced in Japan 1992 as 1% cream applied once daily for 4 weeks.[54]

10. Azole Compounds

Most of the broad-spectrum antifungals that are available for the treatment of superficial fungal infections belong to the azole class. These include the imidazoles and more recently the triazoles. (Azole preparations are cheap and effective in up to 30 days).[58]

Imidazoles: Inhibits the growth of fungi by interfering with cell membrane ergosterol biosynthesis. They act primarily by preventing 14 – demethylation of lanosterol to ergosterol. The demethylation step has been shown to be dependent on cytochrome P450 activation. Imidazoles bind cytochrome P450 thereby inhibiting its activation and enzyme function. They may also inhibit cytochrome oxidative and peroxidative enzymes, resulting in increased intracellular peroxide generation.[55]

Currently available imidazole of importance include clotrimazole, miconazole, econazole and ketoconazole.

Econazole nitrate is a member of the imidazole class of antifungal drugs. Although econazole is primarily considered an antifungal agent, there are reports of in vitro antibacterial activity.[56] This antibacterial activity is due to destruction of bacterial cell wall membranes. However, it has far less activity against gram-negative than against gram-positive bacteria.

More recently some of the newer imidazole antifungal agents such as sulconazole, oxiconazole, tioconazole and ketoconazole have been approved for once daily application.[57]

Tioconazole has a fungicidal activity and leads to more rapid clearing of infection compared with other imidazole. The formation's advantages may be its penetration into nail plate.[58]

Triazoles

The mechanism of action of the triazoles appears to be similar to that of the imidazole. However, the triazoles may be more selective for fungal P450 enzymes.

Little information is available concerning topical use of the newer triazoles.

11. Allylamines

Naftifine and Terbinafine:

Are the first of a new class of antifungal agents, the allylamines – syntethic antimycotic agents.[60]

Terbinafine exerts a primary fungicidal action against dermatophytes and a number of yeasts and moulds.[61] Clinically both oral and topical formation have been shown to be highly effective against superficial dermatophyte infections and less active against candida species and pitrosporum ovale.[61]

Results have been obtained similar to some imidazole derivatives (clotrimazole and econazole) in the treatment of superficial mycotic infection.[62]

The tolerance is good, although contact allergy may rarely be a problem. Treatment time is as short as one week.

The mechanism of action of the allylamine is similar to that of thiocarbomate, namely, the inhibition of squalene epoxydation. In the sterol synthetic pathway interference occurs earlier, that is, at the transition from squalene to squalene epoxide. Cytochrome P450 are not involved in this step.

In a double blind study comparing terbinafine 1% cream with clotrimazole 1% (canesten),[60] in the treatment of tinea pedis over a 4 weeks period, patients treated with terbinafine fungal cultures became negative significant sooner than in those treated with clotrimazole.

More recently - placebo controlled study of 14 days treatment of tinea pedis have shown terbinafine to be highly effective when used for short duration.[63]

Topical naftifine and terbinafine are lipophilic, bind well to the stratum corneum, and penetrate into hair follicles.[64] At therapeutic concentrations, in addition to having broad spectrum antifungal activity, terbinafine also has invitro antibacterial activity against some gram positive and gram negative bacterial such as staphylococcus aureus, streptococcus faecalis, propionibacterium, acne, scherichiacoli, and pseudomonas aeruginosa.[65]

Systemic antifungal treatment

Interdigital toe web infection may require systemic antifungal treatment. The safety profile of these drugs and the excellent results possible with short-term or pulse regimens may also allow treatment of non-extensive lesions.[62]

Three points should be considered when choosing the best possible regimen with oral antifungals:

1- The spectrum of activity of the antifungal
2- Pharmacokinetic profile of the agent
3- The clinical type of infection

4- Others including safety, compliance and cost.

When evaluating the pharmacokinetic profile, the following points are important:

1- How does the antimycotic reach the site of infection?
2- How fast does it reach the site of infection?
3- How much of the drug gets to the site of infection
4- How long does an effective concentration of the drug remain at the site of infection?

Because dermatophytes are the primary inciting factor, the use of a fungicidal agent is preferable to minimize survival of dermatophyte spores that can subsequently germinate, penetrate, the stratum corneum and select growth of bacteria that damage tissue.[62] Likewise any other reservoir of fungi (e.g. toe nails) must be addressed.

When inflammation is present, many health care professionals suggests the use of a steroid to reduce the inflammation. However, this may also result in less efficious clearing of the original infection because, while topical corticosteroids reduce the signs of inflammation, they may also inhibit the cellular response to infection, which is important to the patient's defense mechanism and to clearing of the fungal infection.[63] A low level of anti-inflammatory action, as is present in some of the available antifungal agents, may be all that is needed to help to reduce the signs and symptoms that cause the patient distress, while allowing the natural body defenses to function fully.[64]

(1) Azole

(a) imidazoles

In vitro studies have demonstrated that the imidazoles have inhibitory activity towards inflammatory cells, the polymorphonuclear leukocytes.[64] The ability of these agents to inhibit polymorphonuclear leukocytre migration i.e. neutrophil chemotaxis, may account for their efficacy in inflammatory fungal skin diseases.[64]

Of the famous imidazoles known Miconazole and Ketoconazole.

Ketoconazole was the first orally active imidazole derivative, available for systemic therapy since 1980.[62] It has broad spectrum activity against dermatophytes, yeasts and some systemic mycoses.[64]

Sweat is the most important delivery route by which ketoconazole reaches the skin and also has strong keratin adherence.[64] It is indicated for plantar type of tinea pedis, tinea cruris and T.corporis.

It is effective in Trichophyton rubrum infections.[46] The use of ketoconazole has been restricted by the rare but serious side effect of hepatotoxicity.[64,46]

With the introduction of the newer antifungal agents such as terbinafine, intraconazole, fluconazole and amorofine the therapy for superficial and deep mycoses is likely to change significantly.[46]

(b) Triazoles

Itraconazole has the breadest in vitro spectrum of activity which includes activity against dermatophytes, candida species and M. furfur as well as some molds.[46]

It is a highly lipophilic drug with a high affinity for keratinous tissues, in which the concentration is several

times greater than the obtained in plasma.[46] In Tinea pedis itraconazole is given as 200mg daily for two weeks or 200mg twice daily for one week, which result in mycologic cure rate of 85% and a corresponding clinical response in 95% of patients at 4 weeks after treatmenty.[65]

2) Allylamines

Terbinafine is the first orally active compound in the allylamine family to be studied extensive it has in vitro activity that includes dermatophytes and some molds. It is less active against candida and no effect in malassasifurfur.

It is lipophilic and keratophilic compound which is delivered to the horny layer by positive diffusion from the blood stream.[66]

It act by inhibition of squalene epoxidase in the formation of cell membrane. This enzyme acts at an early stage in membrane biosynthesis.[58] (table 2)

The drug is fungicidal rather than fungistatic.[50] When given orally it is rapidly taken up into the stratum corneum and persists in nails at high concentrations for several months.[58] It bounds strongly to plasma proteins, but the binding is not specific and elimination from plasma is slow.[67] Relatively short term oral treatment with terbinafine may be effective in the treatment of superficial dermatophytoses.

Terbinafine at a dose of 250mg once daily for 2 weeks is likely to be satisfactory in most cases of tinea pedis.[62] It has produced rapid and longlasting remissions in both nail diseases and persistent T.pedis[58]) the frequency of relapse is much lower than with griseofulvin.

There are few drug interactions reported for terbinafine and side effects are uncommon.[58] Some patients describes abdominal fullness and nausea. Taste loss may occur occasionally but is reversible.[58] Hepatic reactions although reported are exceptionally rare. Skin rashes including erythema multiforme are also seen on occasion.

Conclusion

This study support the hypothesis that over growth of resident bacterial population correlates with the severity of interdigital toe web infections:

The therapeutic implication of these findings is that antifungal therapy alone will not be successful in the most severe forms of interdigital toe web infections. Therefore, appropriate therapy may require treatment either with antifungal agent alone or both antifungal, and antibacterial agents.

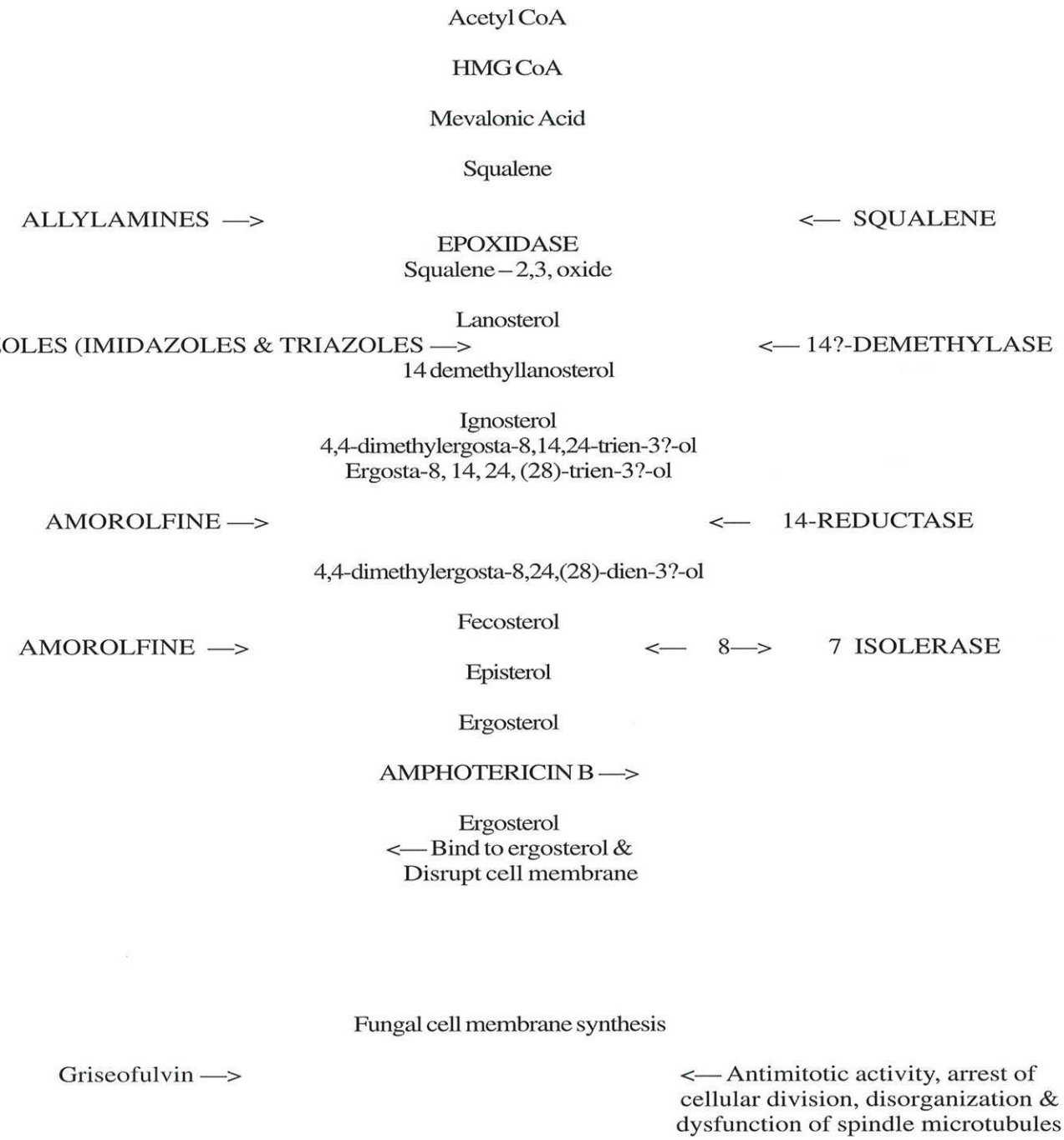

Fig. 1. Site of action of antifungal agents. (Adapted from Gupta AK, Shear NH, Sauder DN. Curr Opin Dermatol 1993; 2:200-6).

(1) Potassium hydroxide (KOH) positive mount for candida species
(2) Potassium hydroxide (KOH) positive mount for dermatophyte
(3) The macroscopic picture of candida colony (creamy color)
Clinical presentation of patient with interdigital toe web infection

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