TINEA TIMES

4. In vitro evaluation of antifungal susceptibility and keratinase, elastase, lipase and DNase activities of different dermatophyte species isolated from clinical specimens in Iran. Sharifzadeh A, Shokri H, Khosravi AR.Mycoses. 2016;59(11):710-719.

The pathophysiology of dermatophytic infection includes several stages (i.e. fungal adhesion, germination, invasion and penetration) associated with the secretion of enzymes degrading the infected tissue components. The pattern of hydrolytic enzymes secreted by dermatophytes could underlie fungal survival on the host and the clinical evolution of the infection, not only by providing nutrients to the detriment of keratinised barrier but also by triggering and modulating the immune response. Dermatophytes are capable of producing different enzymes, such as keratinase, elastase, deoxyribonuclease (DNase), collagenase and lipase. It has been demonstrated that keratinase represents the most important virulence factor for dermatophytes in invading the host tissues and elastase in inducing human skin lesions. The high level of DNase is correlated with inflammatory intensity of dermatophyte infections in humans. Lipase plays a role in the initial stage of dermatophyte invasion of the stratum corneum. In the present scenario of difficult to treat dermatophytoses and possible resistance to previously effective drugs, early identification of dermatophyte species, attention to dermatophyte virulence factors and their antifungal susceptibility profiles has assumed importance. No comparative studies are available on the enzymatic activities of anthropophilic, zoophilic and geophilic dermatophytes. This study aimed to evaluate the potential of *Trichophyton mentagrophytes, T rubrum, Microsporum canis and M gypseum* in producing different enzymes, such as keratinase, lipase, elastase and DNase and to determine their antifungal susceptibility profiles. A total of 60 dermatophyte isolates, of the mentioned species, were examined. Dermatophyte isolates had higher keratinolytic activity than other enzymes. *Trichophyton mentagrophytes, M canis and M gypseum* isolates were capable of producing keratinase, lipase, elastase and DNase, while *T. rubrum* isolates were elastase negative. These elastase producing dermatophytes produce clinically more virulent skin infections than the elastase negative *T rubrum*.The greatest enzymatic activity was observed in *M. gypseum* isolates for keratinase and elastase, *M. canis* isolates for lipase and *T. mentagrophytes* isolates for DNase. Itraconazole was the most effective antifungal drug and fluconazole had the poorest activity.

Clinical Relevance

This work is a marvelous piece that is relevant as it looks beyond the conventional and usually clinically irrelevant MIC story. It focuses on what our meetings keep talking about. Why has X fungus become so aggressive. A part of the answer lies in its production of pathogenic enzymes. These are the parts of the fungal host story which is to be understood beyond just the antifungal drugs. Importantly *T. mentagrophytes*, which is the commonest causative species in India produces keratinase, lipase, elastase and DNase. Samples isolated from chronic dermatophytosis lesions express high DNase activity, while samples isolated from acute dermatophytosis lesions express low DNase activity. *T. mentagrophytes* expressed the highest DNase activity in this study. . So here we have the answer as to why it is so difficult to treat this infection .Part 2 is the MIC story, where itraconazole had the highest antifungal activity against dermatophytes when compared to the other tested antifungal drugs. Note the number 2, ketoconazole and the absence of terbinafine . So the lesson learnt is combine the virulence potential and the MIC and you have quality research , one reason why it is published in Mycoses . More work for our mycologists!

QUIZ

Q1. The mechanism of action of terbinafine is:
a) Inhibition of squalene epoxidase
b) Inhibition of 14 alpha lanosterol demethylase
c) Inhibition of mitosis
d) Inhibtion of glucan in fungal cell wall

Q.2. Antifungal approved by FDA in 2015 is
a) Cresemba (isavuconazonium sulfate)
b)Cosentyx (Secukinumab)
c)Savaysa
d)Kybella (Deoxycholic acid)

Q.3. The following is not true of Moccasin type of Tinea pedis
a) Trichophytom rubrum is the most common cause
b) It can involve hands and feet
c) It present with fine white scales
d) It has an excellent response to treatment

Q.4. The following is not true of Tinea incognito
a) Bruise like pigmentation may be seen
b) Scaling is very prominent
c) Ill defined margins may be present
d) Pustules are present

Q. 5. The following is not true of Moccasin type of Tinea corporis gladiatorum
a) It spreads due to skin contact
b) It presents in wrestlers
c) It present predominantly over legs
d) It responds well to standard treatment

Q. 6. The following drugs are fungistatic except
a) Azoles
b) Allylamines
c) Griseofulvin
d) Echinocandins

Q.7. The following antifungal drug is Pregnancy Category B
a) Griseofulvin
b) Itraconazole
c) Terbinafine
d) Fluconazole

Q. 8. The following are special stains for diagnosis of dermatophytic fungi except
a) Calcofluor white
b) Mucicarmine
c) Parkers blue ink
d) Chicago sky blue stain

Q. 9. The following investigation could simultaneously detect multiple strains of dermatophytic fungi
a) Real Time PCR
b) Culture
c) MALDI-TOF
d) Histopathology

Q.10. Chronic Dermatophytosis syndrome-All are true except
a) Culture grows Trichophyton rubrum
b) At least 2 sites are affected
c) Steroids predispose
d) KOH is positive in all sites involved

Answer Key:
Q.1-a, Q2-a, Q3-d, Q4-b, Q5-c, Q6 -b, Q7-c, Q8-b, Q9-c, Q10-b

Dr. Deepika Pandhi,
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Univeristy College of Medical Sciences & GTBH,
New Delhi

TINEA TIMES
Bulletin of "IADVL Task-force Against Recalcitrant Tinea" (ITART)
ISSUE 1 OCT' 17

EDITORIAL

Dermatophytosis has been a new challenge to the fraternity of dermatology. ITART has been given a task of scientific approach towards dermatophyte menace in India and to disseminate knowledge pertaining to the current situation and management of dermatophytosis. This bulletin is an effort to meet these objectives. We shall update the activities of the ITART, publish articles of practical use, and other useful materials in this bulletin. We wish you a wonderful reading and request you to mail your feedback at itart2017@gmail.com

CONTENTS

From the desk of National President, IADVL Dermatophytosis has assumed an epidemic proportion and it is challenging to treat chronic, recalcitrant and recurrent tinea. Dermatologists have risen to the occasion to fight this scourge. IADVL Task Force against Tinea was initiated in current year to offer consorted response to this menace and to consolidate efforts of many dermatologists in diagnostic, therapeutic and research area.

I am happy that many zonal seminars were already held and planned to disseminate latest information and share the experience gained. A user's manual on tinea is under preparation and will be supplied to every dermatologist so that it can be used as a ready reference. Any efforts from our side will be incomplete if we do not address the issue of topical steroid abuse. Various steps are being taken for the same including filing public interest litigation in the Supreme court of India, creating awareness in general practitioners.

At our level, we have planned to go to general practitioners in massive way by conducting series of lectures throughout the country. A standardized ready to use power point presentation was prepared by ITART group and is available to anyone interested .

Dynamic convener of ITART, Dr. Manjunath Shenoy has planned to come out with this news letter on tinea to include recent information and to share views. I am privileged that the first issue will be released during my tenure. My appreciation to editorial team. Keep strengthening IADVL

Best wishes,
Dr. Yogesh S Marfatia,President, IADVL

Message from Honorary Secretary General, IADVL It is a matter of great pleasure that the IADVL Taskforce Against Recalcitrant Tinea (ITART) is coming out with the inaugural issue of its news bulletin aptly titled – TINEA TIME.

I extend my congratulations and best wishes to the Chairperson – Dr. Madhu Rengarajan, the Convener-cum-Editor – Dr. Manjunath Shenoy and all members of the Taskforce for their dedicated efforts.

I hope that the various initiatives drawn up by ITART for the coming days are crowned with overwhelming success. May this news bulletin serve to light the way in the crusade against dermatophytosis!

Best wishes
Dr. Shyamanta Barua Honorary Secretary General, IADVL

Message from Chairperson's Desk

Dear all,

Greetings from IADVL Task force against Recalcitrant Tinea (ITART) !

It gives me immense pleasure to address you all through this inaugural issue of, "TINEA TIMES". ITART, brain child of our President, Dr. Yogesh Marfatia was started in February 2017 with the main aim to work for the cause of recalcitrant tinea in terms of dissemination of knowledge about the correct principles of management of dermatophytosis, creation of awareness among the non-dermatology practitioners and public about the rampant, indiscriminate abuse of topical steroid/ antifungal combinations and judicious use of antifungal agents

ITART started its activity profile with "DERMATOFIGHT" organized by Dr. Manjunath Shenoy, Convener, ITART on 12th February 2017 followed by lectures and panel discussions by our members in various dermatology and non-dermatology forums over the last 5 months. We are in the process of preparing posters to be displayed in the clinics and pamphlets for the public, to be distributed across the country. Most important of all, we plan to bring out a user manual on dermatophytosis which would be a ready reckoner and to undertake a multi centric study on the clinic-epidemiological aspects of chronic/recurrent dermatophytosis in institutions across the nation.

At this juncture, I would like to express my sincere thanks to our President, Dr. Yogesh Marfatia and Dr. Shyamanta Barua, Hon. Secretary General, IADVL for their constant support and encouragement in all our activities. I would be failing in my duty if I do not express my heartfelt thanks to my friends in ITART, for their valuable time amidst their hectic schedule, enthusiasm, commitment and kind cooperation.

Miles to go .....
Wishing "Tinea Times" the very best in this journey of fight against superficial dermatophytosis!

Dr. Madhu Rengarajan, Chairperson, ITART,
Department of Dermatology (Mycology), Madras Medical College, Chennai

From Chairperson's Desk
Dr. Madhu Rengarajan

NEWS UPDATE

Dermatofight- Yenepoya medical college, Mangalore
Dr. Jyothi Jayaraman

Department of Dermatology, Yenepoya Medical College,Yenepoya University" in association with Karnataka branch of Indian Association of Dermatologists, Venereologists & Leprologists (IADVL), Karavali Dermatology Society (KDS) and IADVL Taskforce Against Recalcitrant Tinea (ITART) organized a symposium on Dermatophytosis titled "DERMATOFIGHT" Mangalore.

The program was inaugurated by the Hon. Chancellor of Yenepoya University Mr. Yenepoya Abdulla Kunhi .The guest faculties for this programme included Dr. Yogesh Marfatia (President, IADVL- National and Professor, Vadodra Medical college), Dr Sunil Dogra (Professor of Dermatology, PGI Chandigarh), Dr. Shivaprakash Rudramurthy (Professor and Mycology division incharge, PGI Chandigarh), Dr. Shital Amin Poojary (Professor and Head, K J Somaiya Medical College & Research Centre), Dr. Madhu Rengarajan (Senior Assistant Professor, Madras Medical College), Dr. Arun Inamadar (President IADVL-KN, Professor and Head, BLDEA Institute), Dr. Shashikumar BM (Hon Secretary, IADVL-KN) and Dr. Manjunath Shenoy M (Professor and Head, Department of Dermatology, Yenepoya Medical College).

The event was attended by 137 delegates from various parts of India. Interesting and informative topics such as steroids and dermatophytosis, dermatophytosis in special population, role of laboratory diagnosis and new developments in diagnostics, drug resistance as well as therapeutics and onychomycosis were covered to keep us abreast with the recent advances in this field.

Live streaming of the entire program was also arranged. An E-poster session, award paper presentation and postgraduate quiz program were other features of this symposium as conducted for residents.

Dr. Jyothi Jayaraman ,
Department of Dermatology,
Father Muller medical College, Mangalore

Practitioner's programme -at IMA Meets Mangalore & Surathkal
Dr. Manjunath Shenoy

ITART in association with the Indian Medical Association (IMA) branches conducted two activities for the general practitioners. First one was conducted on 07th April 2017 at Mangalore, Karnataka with IMA and Karavali Dermatology Society. Drs Ganesh Pai, Ramesh Bhat, Manjunath Shenoy, Jerome Pinto, Narendra Kamath K, Nadakishore B, Sukumar D and Vinma Shetty participated in this meeting and about 125 IMA members attended in the meeting. Second one was held at a small town Suratkal at Karnataka on 30th June 2017. Dr Manjunath Shenoy conducted the presentation and it was an interactive session well attended by 245 family physicians.

Dr. Manjunath Shenoy,
Professor & Head, Department of Dermatology, Yenepoya Medical College, Mangalore

ITART has prepared a PPT for giving lectures on dermatophytosis to family physicians and other medical colleagues. We request dermatologists to conduct educative programs on dermatophytosis in your institutions or with organisations like IMA. You may send in your request for the PPT at itart2017@gmail.com

DERMATOPHYTOSIS: FIGHTING THE CHALLENGE ON 2nd AND 3rd SEPTEMBER 2017

Organized by: Department of Dermatology, Venereology & Leprology & Department of Medical Microbiology, PGIMER, Chandigarh
Dr. Tarun Narang, Organizng Secretary
Dr Sunil Dogra, Chairperson Scientific Committee

The department of Dermatology, Venereology and Leprology and Department of Medical Microbiology organized the conference Dermatophytosis: Fighting the Challenge on 2nd and 3rd September 2017 at PGIMER Chandigarh. The conference was attended by about 250 delegates from all over India. It was the first conference of its kind that was dedicated to dermatophytosis and eminent speakers from all over India deliberated on various issues and problems which are currently being faced by clinicians in the management of Dermatophytosis (Tinea). The conference had arranged special Mycology Workshop for practical lab experience starting from conventional to current techniques in the diagnosis of tinea and antifungal drug susceptibility tests in dermatophytes isolates. The conference started with lectures on the epidemiology and etiopathogenesis of Tinea. The key note address by Dr. Roderick J Hay from London, UK on the reasons for treatment failures in Dermatophytosis included agent, host and environmental factors specifically the emergence of drug resistance in tinea, tropical environmental conditions and the important role of recent lifestyle changes in the community. This was followed by the debate on different burning issues in the diagnosis and management of tinea. After deliberations by speakers it was concluded that resistant and the recalcitrant nature of dermatophytic infections was not due to mycological resistance alone but also as a result of poor compliance, OTC irrational steroid preparations abuse, transmission within the family members, sharing of the fomites within the family etc. All these factors play a significant role in decreasing the quality of life of the affected individuals while also proving to be a psychosocial burden for the society and economic burden on the healthcare system. The second day started with Dermatophytosis PG quiz , the team from PGIMER, Chandigarh stood first and the IGMC, Shimla team were runners up . The second plenary session had lectures on Chronic Dermatophyte infections. It was felt that recurrent and chronic dermatophyte infections have become more common and more difficult to treat requiring prolonged treatment. Dr. Ruth Ashbee from Leeds UK deliberated on the need to standardize the anti fungal susceptibility testing. The next few sessions were dedicated to therapeutics and management of tinea and there were deliberations on management of Dermatophytosis in special circumstances, in pregnant females and children.The second debate session on various management dilemmas concluded that we need to formulate national guidelines on the management of this new epidemic like wave of the recalcitrant dermatophytoses so that there is uniformity of management and this will also be helpful for the general practitioners and other medical specialists who manage the cases of Tinea .

GUEST ARTICLE

Could misuse of topical Antibiotics be a reason for recalcitrant dermatophytosis
Dr. Suchitra Shenoy (Associate Professor, Department of Microbiology, Kasturba Medical College, Mangalore.)

Having come across a wide variety of fungal infections with special reference to the recalcitrant tinea infections, a thought may be given towards the misuse or abuse of the topical and systemic antibiotics. In India, there are a number of combination of topical antifungal-steroid-antibiotic creams available which being misused due to over-the-counter availability and unjustified prescriptions. Discussions are often held about the adverse effects and a possible role of the steroid component in these "combo-creams" but the presence of antibiotics is often forgotten which may cause a serious damage to the barrier function of the skin.

Skin, largest organ in the body, provides enough niches for a large number of microbes to reside as normal flora.[1] The variable flora in different sites depends on the adnexa like the hair or nail, the seasonal changes, hormonal changes, food and the clothing habits of the individuals. In healthy, majority of the microbial ecology is largely represented by the bacteria like Corynebacterium, Propionibacterium, Staphylococcus, virus and fungi like Malassezia species, Candida.[2] The normal flora are known to protect the host from pathogenic microbes by competing for the receptors and the nutrition. They are also known to educate the human immune system against the pathogens. Elimination of resident bacterium's endogenous antimicrobial peptides may allow pathogenic organisms to colonize on skin.[2] These factors may contribute to the upsurge of tinea infections and recalcitrant nature of them in our country.

The antibiotic usage may result in a selection of drug resistant bacteria and also contribute to disruption of the normal flora.[3] Antibiotics are effective in many of the dermatological conditions such as acne without any convincing evidence of a specific microbe. Clindamycin and macrolides are commonly used topical broad spectrum antibiotics effective against a large group of bacteria.[3] Therefore the question arises, whether the use of broad spectrum antibiotics change the normal flora of humans predisposing to the recalcitrant dermatophyte infections. Studies are necessary to confirm this hypothesis.

References:
1. Nina N. Schommer and Richard L. GalloStructure and function of the human skin microbiome. Trends Microbiol. 2013; 21(12): 660–668
2. Cogen AL, Nizet V, Gallo RL. Skin microbiota: a source of disease or defence? Br J Dermatol. 2008 March ; 158(3): 442–455
3. Elizabeth A. Grice The skin microbiome: potential for novel diagnostic and therapeutic approaches to cutaneous disease Semin Cutan Med Surg. 2014; 33(2): 98–103.
4. David N. Fredricks. Microbial Ecology of Human Skin in Health and Disease. JID Symposium Proceedings. 2001: 6-167 - 169
Dr. Suchitra Shenoy M. Associate Professor, Department of Microbiology, Kasturba Medical College, Mangalore.

User's manual on management of dermatophytosis: This is an upcoming publication of IADVL & ITART which will be coming soon under the editorship of Dr. Kabir Sardana. This will be a useful ready reckoner for the practicing dermatologists.

DRUG CORNER

ITRACONAZOLE

Dr. Madhu Rengarajan Professor, Department of Dermatology, Madras Medical College, Chennai

Intoduction: Itraconazole, a broad spectrum synthetic triazole, fungistatic drug discovered in 1992 is highly keratinophilic and lipophilic.

Mechanism of action : Damages the fungal cell membrane by inhibiting enzyme Lanosterol 14 alpha demethylase. Itraconazole has 3 nitrogen atoms in its azole ring which improves tissue penetration, prolongs half life and drug specificity for fungal enzymes .

Pharmacokinetics: Oral absorption of itraconazole is variable, is enhanced by food and gastric acid. Hence it should be taken immediately after a full meal. Bio availability is 55%. Oral solution has increased bioavailability.
- Highly lipid soluble - Well distributed to sebum, sputum, adipose tissue
- Metabolized in liver extensively by cytochrome CYP3A4
- Stable tissue concentration higher than plasma concentration
- Persists in the Stratum corneum for 3 to 4 wks after discontinuation of therapy; In nails – after 2 pulse for 9 months; after 3 pulses for 11 months

Therapeutic effect
In Skin: achieved by
- Passive diffusion into the basal keratinocytes
- High concentration in sebum (10 fold higher than in plasma, decreased in sweat)

In Hair – Drug is incorporated into the hair via matrix cells and sebum
In Nail - Drug reaches the free end of the nail plate via nail matrix & nail bed. Does not distribute back to the plasma, but remains in the nail until it is shed through normal growth. Hence ,can be used as pulse therapy.

FDA Indications:
Dermatophyte onychomycosis of the toenails and/or fingernails in immunocompetent adults -1995
Immunocompromised//immunocompetent patients for systemic mycoses – Blastomycosis, histoplasmosis, aspergillosis in patients who are intolerant of or refractory to amphotericin B

Off label indications :
1.Superficial Mycoses
Dermatophytosis, Majocchi's granuloma, Tinea imbricata ,Pityriasis versicolor, Pityriasporum folliculitis, Seborrhoeic dermatitis, Candidiasis – Oral, Vulvovaginal
2. Subcutaneous Mycoses
Mycetoma , Phaeohyphomycosis ,Chromoblastomycosis, Sporotrichosis, Paracoccidioidomycosis
3. Systemic mycoses : Candidiasis, Cryptococcosis , Paracoccidioidomycosis
Recommended drug dosage
Duration is best individualized. End point to decide on treatment should be the clinical cure
- Tinea corporis – Cap Itraconazole – 100 mg od x 4 weeks
  - Most often used is 100 mg bd x 2- 4weeks
- Tinea pedis – 100 mg bd x 4-6 weeks
- Onychomycosis – pulse therapy – 200 mg bd x 1week / month
  - Finger nails – 2 pulses
  - Toe nails – 3-4 mpulses
- Subcutaneous and deep mycoses – 200 mg bd for long periods. Periodic Liver function tests to be done

Pityriasis versicolor – 200 mg for 5-7 days

Side effects
Nausea, vomiting, abdominal pain, hypertriglyceridemia, hypokalaemia, Increased aminotransferase, hepatotoxicity, Edema, fatigue, fever, malaise, somnolence, Hypertension, albuminuria ,impotence
Rare – Peripheral neuropathy, transient taste disturbance

Contraindications
- Known hypersensitivity to Itraconazole
- Pregnancy (Category C drug) – Effective contraception throughout therapy & until 2 months after cessation, Lactation (until 6 months)
- Ventricular dysfunction, Cardiac failure
- Terfenadine , astemizole, cisapride can cause VT-Torsades de pointes

Drug Interactions
Decreased levels of Itraconazole
Decreased absorption - Antacids , H2 receptor antagonists, Proton pump inhibitors, Didanosine
Due to metabolism- Rifampicin, Rifabutin, Phenytoin , Carbamazepine, INH, Nevirapine

Increased levels of Co-administered drugs
- Erythromycin, Clarithromycin, Ciprofloxacin, Indinavir, Ritonavir
- Increased levels of Co administered drugs
- Warfarin, Sulfonylureas
- Ritonavir, Indinavir, Saquinavir, Zidovudine
- Cyclosporin, Tacrolimus, Sirolimus
- Atorvastatin, Alprazolam, Pimozide, Fluoxetine
- Verapamil, Digoxin, Calcium channel antagonists
- Busulfan, Docetaxel, Vinca alkaloids, Buspirone,
- Dexamethasone, Methylpredinosolne, Budesonide
- Colchicine in patients with renal or hepatic impairment

Used with Caution
Coumarins, ebastine, domperidone ; Antineoplastics – erlotinib, lapatinib
Antipsychotics/ anxiolytics – alprazolam, haloperidol, quetiapine, risperidone
Urological drugs – sildenafil, imidafenacin
Drugs that may be decreased in activity – Oral contraceptives, Antipyrine

References :
• Gupta AK, Systemic antifungal agents. In: Wolverton SE, editor. Comprehensive dermatologic drug therapy. 3rd ed. Edinburgh: Elsevier Saunders; 2013.pp:99-120. • Jacob R, Kanekiyo N. Oral antifungal agents. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick's Dermatology in General Medicine 8th ed. New York: Mc Graw Hill Companies, 2012.pp.2776–2804 • Sigurgeirsson B, Hay R. The antifungal drugs used in skin disease.In: Olahsson JH, Hay R J editors.Antibiotic and antifungal therapies in dermatology.New Delhi:Springer(India).2017:141–156

LITERATURE REVIEW

Dr. (Prof) Kabir Sardana, Dr. (Assoc Prof) Ananta Khurana
PGIMER & Dr. RML Hospital, New Delhi

Introduction
The aim of this section is to pick up cutting edge research, related to dermatophytoses, from across the world and apply it to India. There are many factors that may play a role in the present recalcitrant nature of dermatophytic infections in India. Apart from steroid abuse, the strain of fungi, compliance and the quality of drugs (especially in the case of Itraconazole) may be responsible for the same. We have seen numerous cases of Tinea responding dramatically to a standard brand of itraconzole while failing the umpteen generic variants.
All the presented articles are followed by a brief clinical relevance summary aiming at sensitising the practitioners regarding the current scenario of dermatophytosis.

1. Azole Resistance in Dermatophytes: Prevalence and Mechanism of Action. Ghannoum M.J Am Podiatr Med Assoc. 2016 Jan-Feb;106(1):79-86
Azole antifungal agents (eg: fluconazole and itraconazole) have been widely used to treat superficial fungal infections caused by dermatophytes and, unlike the allylamines (such as terbinafine and naftifine), there are rampant reports of resistance to azoles.. Although resistance among yeast and molds is well described, reports describing resistance of dermatophytes are now starting to appear too. In this review, the author discusses the mode of action of azole antifungals and mechanisms underlying their resistance, compared with the allylamine class of compounds. Data from published and original studies are compared and summarized, and their clinical implications discussed. Azoles are static drugs only inhibiting the growth of the organism, thus permitting the occurrence of mutations in enzymes involved in ergosterol biosynthesis, which serve as the drug target .In contrast, the allylamines are fungicidals a consequence of accumulation of toxic ergosterol precursors and hence are unlikely to promote resistance in the exposed fungi. The prevalence of azole resistance in dermatophytes has been reported to be as high as 19% in certain areas worldwide. Resistance to azoles has been reported as an innate resistance in previously unexposed isolates as well as secondary resistance after repeated drug exposures. The efflux transporters are the most likely culprits in this regard. The implicated genes for azole resistance among dermatophytes are TruMDR1and TruMDR2 genes. In contrast, modification of the target enzyme squalene epoxidase by gene mutation (substitution of a single amino acid in the squalene epoxidase gene) is the likely mechanism in mediating Terbinafine resistance in dermatophytes.
Clinical relevance
The first aspect to understand is that the prevailing rampant use and updosing of itraconazole (ITR) has little clinical value as the skin levels achieved by ITR are high enough with 100 mg BD dose. Also ITR has a nonlinear kinetics (described for oral ITZ 100, 200, and 400 mg),, suggesting saturation of first-pass metabolism in the liver. Disproportionate increases in C max and area under curve (AUC) of both ITZ and the metabolite hydroxy-ITZ (OH-ITZ) are observed with an increasing dose.
Hence there is little use of increasing the dose beyond 100 mg BD. Pertinently, US FDA has not approved a dose →100 mg for dermatophytes. The fad of the day is the use of ITR but as this article shows it has a higher chance of developing resistance. This, with the use of topical azoles, this can soon lead to another drug class getting resistant. Hence probably the answer lies elsewhere.

2.Terbinafine resistance conferred by multiple copies of the salicylate 1-monooxygenase gene in Trichophyton rubrum. Santos HL, Lang EAS, Segato F, Rossi A, Martinez-Rossi NM. Med Mycol. 2017 Jun 2.
Resistance to antifungals is a leading concern in the treatment of human mycoses. The authors demonstrate that the salA gene, encoding salicylate 1-monooxygenase, is involved in resistance of the dermatophyte Trichophyton rubrum to terbinafine (TER). A strain with multiple copies of salA was constructed and exhibited elevated expression of salA and increased terbinafine resistance. This reflects a mechanism not yet reported in a pathogenic fungus.

Clinical relevance
This article is for those rare few who are pursuing extensive research work on drug resistance in the labs. It is true we have a high MIC to TER, but the proof lies in the mutation and this maybe the novel mutation which we are not looking for.

3. Natural Products: An Alternative to Conventional Therapy for Dermatophytosis? Lopes G, Pinto E2, Salgueiro L. Mycopathologia. 2017 ;182(1-2):143-167
Medicinal plants represent an endless source of bioactive molecules, and their volatile and non-volatile extracts are clearly recognized for being the historical basis of therapeutic health care. Because of this, the research on natural products with antifungal activity against dermatophytes has considerably increased in recent years. However, despite the recognized anti-dermatophytic potential of natural products, often advantageous face to commercial drugs, there is still a long way to go until their use in therapeutics.. The main classes of molecules studied so far include lignans, coumarins, flavanoids, quinones, tannins, alkaloids, saponins, phenolic compounds, alkaloids and volatile natural extracts (essential Oils and terpenes). Most of the available studies on these have been conducted on fungal isolates, making it difficult to extrapolate the results to real conditions. Concerning phenolic compounds, more studies are needed to confirm their absorption and bioavailability in humans, which remains controversial. Even though most of these compounds are intended for topical application, it is necessary to go further into chemical and biological terms, before that isolated compounds and crude extracts can reach the market. This review attempts to summarize the current status of anti-dermatophytic natural products, focusing on their mechanism of action, the developed pharmaceutical formulations and their effectiveness in human and animal models of infection

Clinical Relevance
They have a long way before they can match the conventional products. This is as they have never been compared in vivo vis-a- vis the basic antifungal drugs. For example in our experience, plain old ketaconazole (KTZ) works remarkably well even in today's times! So when these botanicals are compared with KTZ then maybe their virtuous advantages will translate into clinical uses