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Factors Contributing to Rising Fungal Infections & Burden of Acne in daily life

Date: 9th October, 2024 I Time: 1:30 PM I Venue: 57/E, Panthapath Dhaka, 1205

Chairperson

Prof. Dr. M.U. Kabir Chowdhury

MBBS (Dhaka), DDV (Vienna) AFICA (USA), FRCP (Glasgow, UK)

Powered by | NULIZA® Luliconazole 1% Cream | NuvaCare® White Soft Paraffin BP 14.5% + Light Liquid Paraffin BP 12.6% + Anhydrous Lanolin BP 1% Cream | Nulevi® Clascoterone 1% Cream

Dermatophytosis

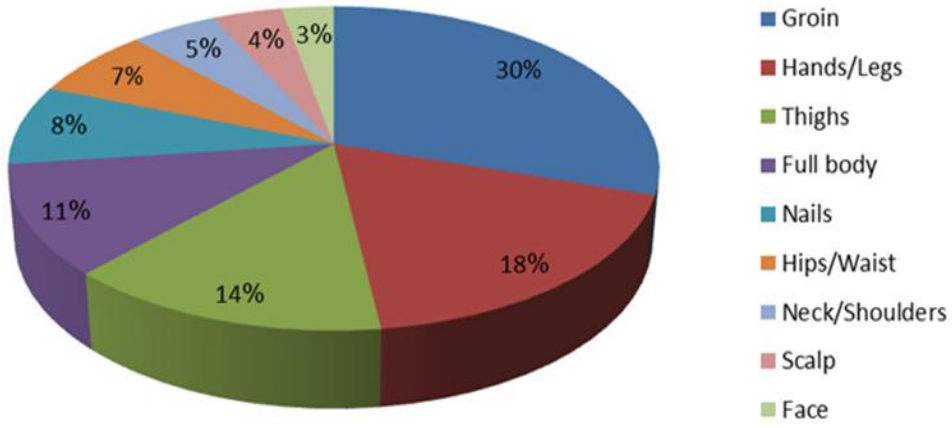
- Dermatophytosis is a term used to describe mycotic infections caused by a group of fungi that usually remain localized to the superficial layers of the skin, hair, or nails.
- Dermatophytosis is also known as
- About 40 types of fungus can cause ringworm. They are typically grouped into 3 types-
    - *Trichophyton*
    - *Microsporum*
    - *Epidermophyton*

Ref:Havlickova B, Czaika VA, Friedrich M. Epidemiological trends in skin mycoses worldwideexternal icon. Mycoses. 2008 Sep;51 Suppl 4:2-15.

Types of Dermatophytosis

The different types of ringworm are usually named for the location of the infection on the body. Areas of the body that can be affected by ringworm include:

Type	Site
Tinea pedis	Feet
Tinea cruris	Groin, inner thighs, or buttocks
Tinea capitis	Scalp
Tinea barbae	Beard
Tinea manuum	Hands
Tinea unguium	Toenails or fingernails
Tinea corporis	Other parts of the body



Mohammed Hussein Mushrif. Common Diseases of Dermatophytic Infection and Sensitivity Determining of Diagnostic Procedures. *American Journal of Medical Sciences and Medicine*. 2016; 4(4):87-91. doi: 10.12691/ajmsm-4-4-4.

Epidemiology

Globally, approximately **20–25%** of the population is affected by dermatophytosis.

61–67% patients with dermatophyte infections are from lower socioeconomic groups.

>60% patients suffer from Chronic dermatophytosis (disease for more than 6 months with or without recurrence despite being treated)

9-80% cases has the trend of recurrent and relapsing dermatophytosis.

Ref: The unprecedented epidemic-like scenario of dermatophytosis in India: I. Epidemiology, risk factors and clinical features,Indian Journal of Dermatology, Venereology and Leprology @March, 2021,

Causes of Rising Prevalence of Dermatophytosis

The current face of dermatophytosis has possibly been an outcome of a complex and intrigued interplay between host, fungus, drug and environment contributed by multiple factors like-

- ✓More humid and warmer climate
- ✓Irrational use of topical corticosteroid-based combinations and broad spectrum antibiotics.
- ✓Increasing burden of immune-compromised population
- ✓Widespread use of antifungals in the agricultural industry
- ✓The questionable role of antifungal drug resistance

Ref-Expert Consensus on The Management of Dermatophytosis in India (ECTODERM India):Rajagopalan et al. BMC Dermatology (2018) 18:6

Reason behind recurrence & resistance of antifungal

1. Incomplete eradication of hidden fungus:

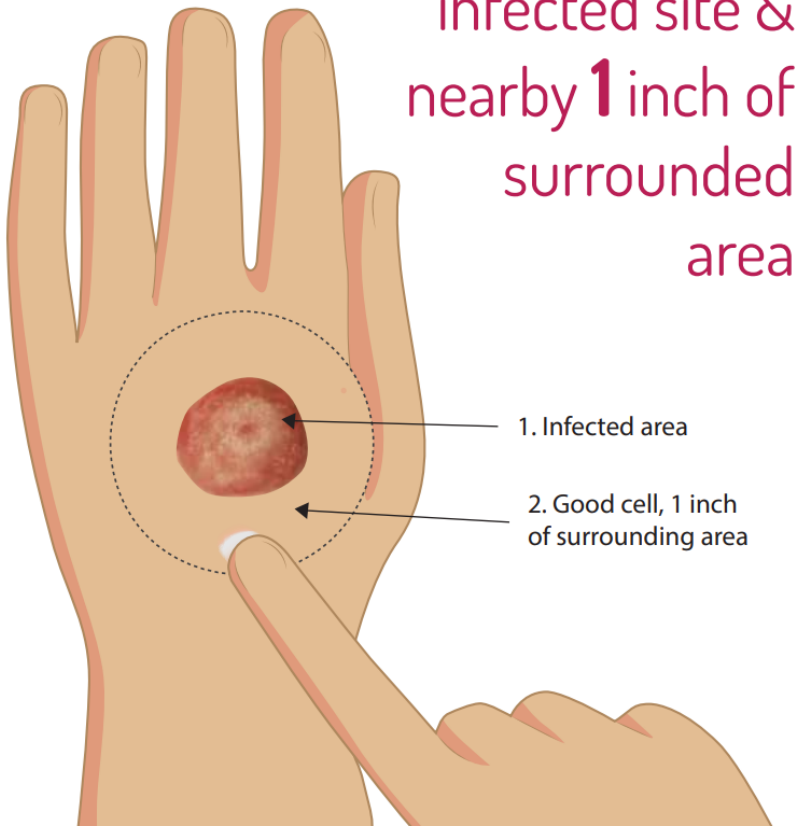
As most of the patients don't know to use the medication on infected site & nearby 1 inch surrounded area. Conventional treatment can not eradicate fungus from deep stratum corneum

2. Incomplete therapy:

Patients use substandard dosages (too low) or treatment courses that are not long enough as per recommended by originator brand.

US FDA approved product insert of Luliconazole states that

Application on infected site & nearby **1** inch of surrounded area



Mode of Transmission

- Anthropophilic –transmitted human to human, e.g., *T. verrucosum.*
- Zoophilic fungi- transmitted from animal to human *(e.g., M. canis, T. verrucosum).*
- Geophilic- transmitted from soil to man (e.g., M. gypseum, T. ajelloi).

Clinical Manifestations Of Ringworm

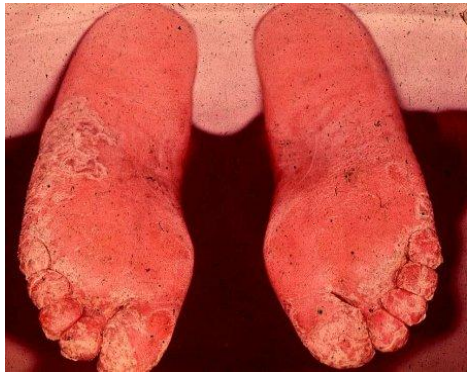
The symptoms often depend on which part of the body is infected, but they generally include:

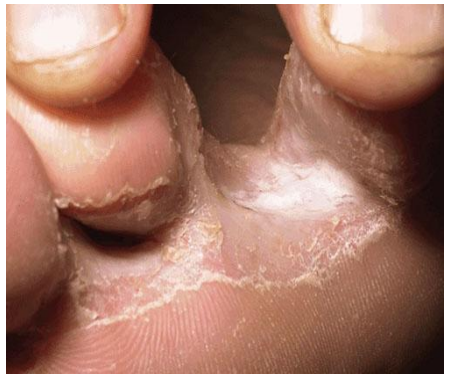
- Ring-shaped lesion
- Itchy skin
- Red, scaly, cracked skin
- Multifocal alopecia

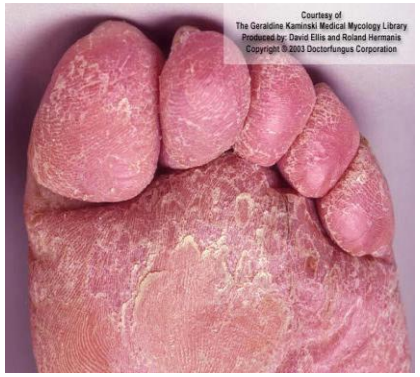
Tinea Pedis - Athletes' Foot

Features-

- Site- Between toes or toe webs (releasing of clear fluid) - 4th and 5th toes are most common.
- Soreness and itching of any part of the foot.

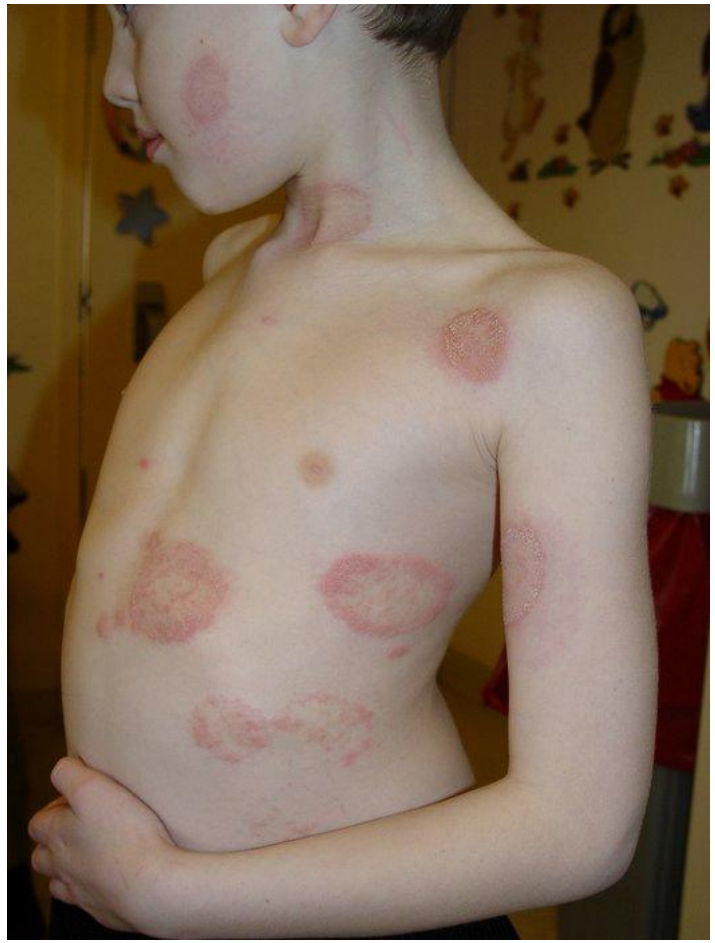






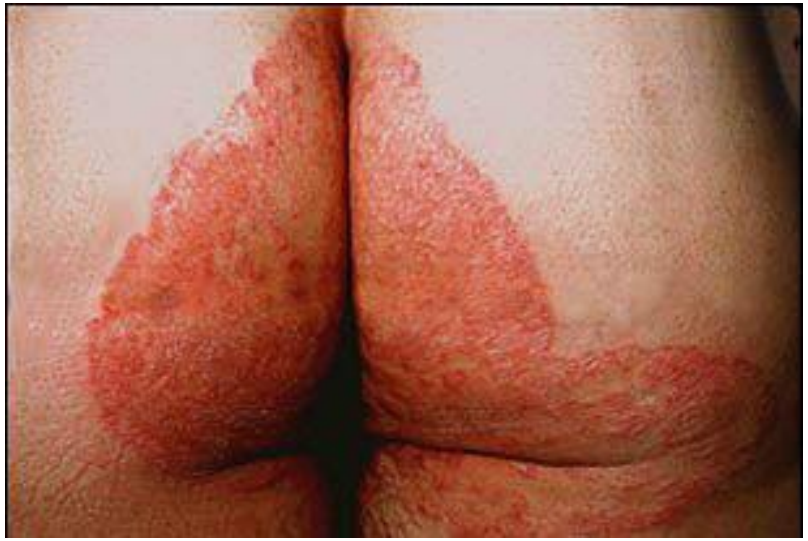
Tinea Corporis – Body ringworm

- Generally restricted to stratum corneum of the smooth skin.
- Produces concentric or ring-like lesions on skin
- In severe cases –Lesions are raised and inflamed.
- Normally resolves itself in several months.



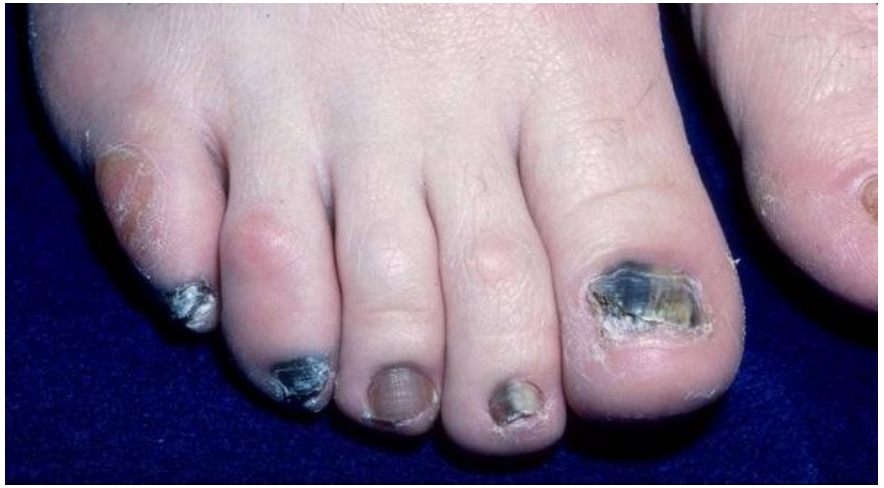
Tinea Cruris-Jock Itch

- Infection seen on scrotum and inner thigh, the penis is usually not infected.
- More common in men
- Epidemics associated with grouping of people into tight quarters - athletic teams, troops, ship crews, inmates of institutions.



Tinea Unguium or Onychomycosis

- Onychomycosis is a fungal infection of the nails that causes discoloration, thickening, and separation from the nail bed.
- Resistant to treatment, rarely resolves spontaneously.



Diagnosis & Different diagnosis

- ✓ Diagnosis mostly depends on clinical examination.
- ✓ Confirmatory Laboratory investigations are-
- Nail clipping or SKIN SCRAPING TEST WITH 10% KOH- Skin scrapings should be collected from the edge of the lesions
- CULTURE- Sabouraud's dextrose agar.
- Wood's lamp test

- ❖ Allergic contact Dermatitis
- ❖ Psoriasis
- ❖ Eczema
- ❖ Cutaneous candidiasis
- ❖ Acanthosis nigricans

K. Neena, Illustrated synopsis of Dermatology & Sexually Transmitted Diseases. 3rd Edition. New Delhi: Elsevier Health INR publication; 2012.

Treatment

Effectiveness of dermatophytosis treatment depends on 3 factors-

- Fungal Characteristics
- Host immunity
- Drug competency

Treatment options-

- Azoles
  - Clotrimazole
  - Econazole
  - Ketoconazole
  - Miconazole
  - Itraconazole
  - Tioconazole
  - Fluconazole
  - Luliconazole.
- Allylamines-Terbinafine
- Griseofulvin

Challenges in the treatment of dermatophytosis

Topical Antifungal Agent

Most of the currently used antifungals requires prolonged treatment for complete clearance of the fungal elements.

⬇

patient nonadherence

⬇

- The high rate of relapse
- Antifungal resistance

Systemic antifungals

- Risk of hepatotoxicity
- Possible drug-drug interactions with other systemic medications.

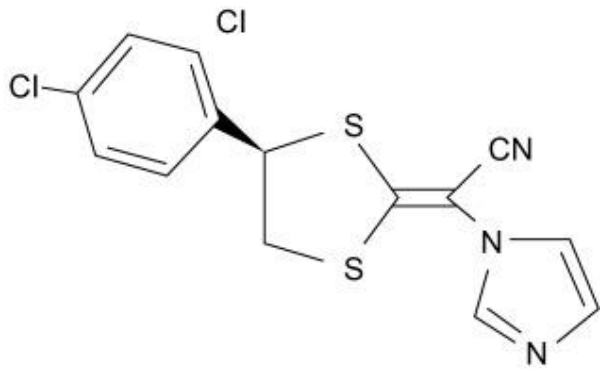
So, there is a substantial Unmet Need for an Ideal topical antifungal agent with……

- Broad-spectrum activity
- Convenient dosing schedules
- Efficacy at low concentrations
- High mycologic and clinical cure rates
- Low relapse rates
- A reservoir effect in the stratum corneum
- Lack of development of resistance
- A low cost.

The Potent power Antifungal- Luliconazole

Luliconazole is **The Potent power Antifungal** because-

- Unique ketene dithioacetate structure incorporated with imidazole moiety exerts strong fungicidal effect by weaking fungal cell wall
- Has broad spectrum antifungal activity with lowest concentration
- Less chance of recurrence of fungal infection
- Patient compliance with convenient dosing schedules and cost.



Luliconazole

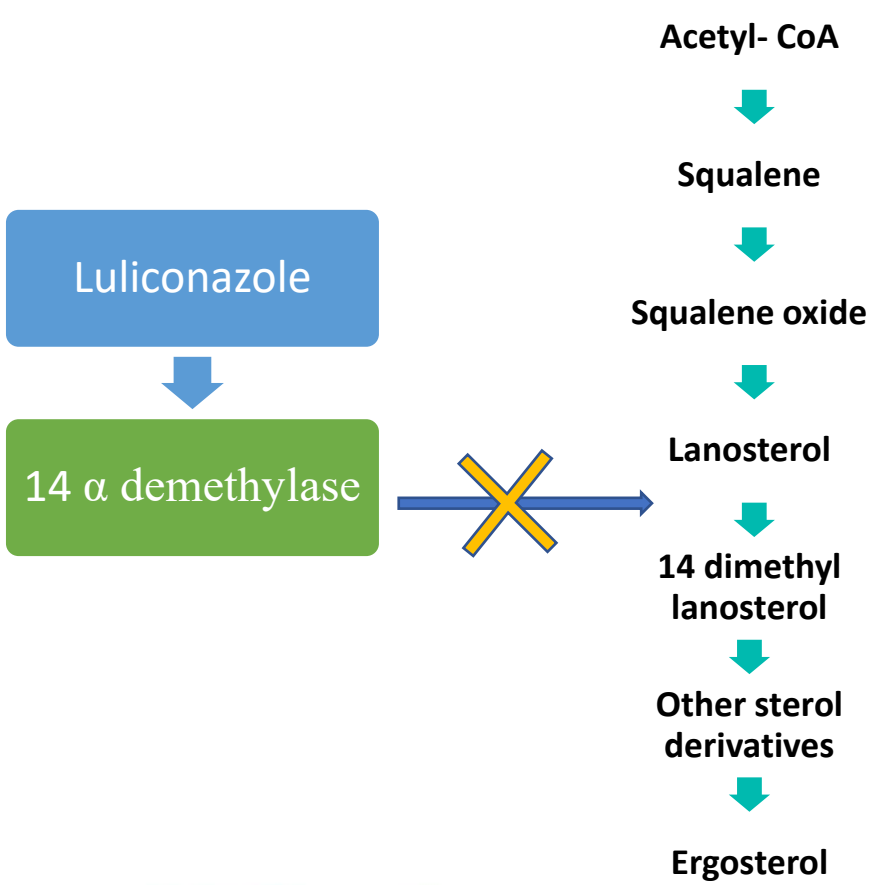
Ref: Luliconazole for the treatment of fungal infections: an evidence-based review, Core Evidence 2014:9

Luliconazole is the antifungal with Superpower

- **S**horter duration of therapy
- Excellent **S**pread-ability
- **S**uperior potency
- **S**uperior Efficacy
- **S**tratum Corneum Reservoir effect

Luliconazole exert both fungistatic and fungicidal action

Fungistatic Role



Fungicidal Role

Luliconazole

↓

Alteration in triglyceride & phospholipid synthesis

↓

Accumulation of toxic levels of H2O within fungal walls

↓

Deterioration of cell

↓

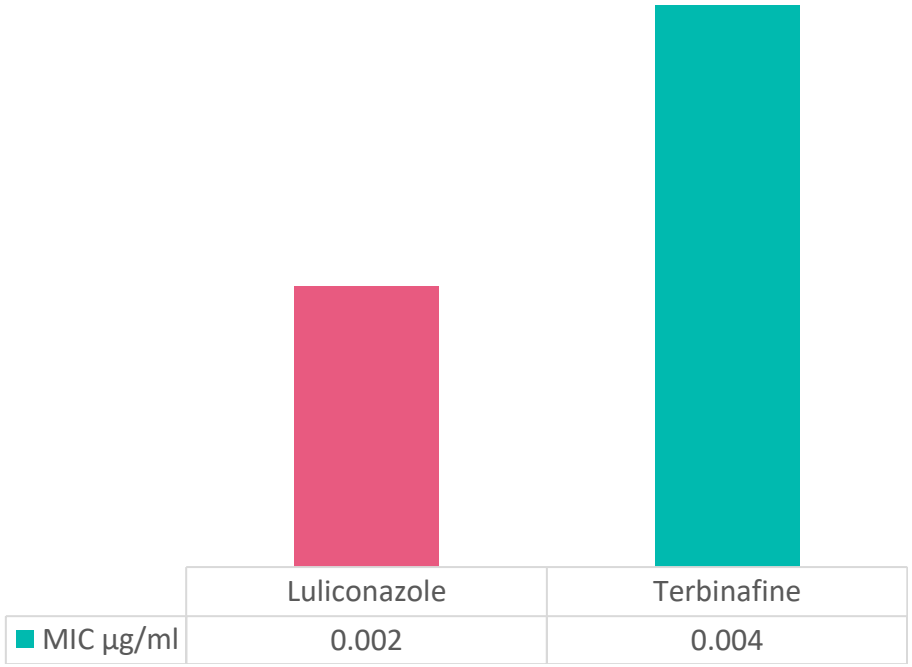
Cell death

MIC comparison

Minimum Inhibitory Concentration (MIC) of Luliconazole has been shown to be 2–4 times lower than that of lanoconazole, and the lowest amongst a wide variety of antifungal drugs.

Luliconazole showed excellent in vitro activity with

Two times lower MIC than that of Terbinafine which ensures its excellent efficacy at lowest concentrations.



Ref: 1. Luliconazole for the treatment of fungal infections: an evidence-based review, Core Evidence 2014:9
2.Therapeutic efficacy of topically used luliconazole vs. terbinafine 1% creams, Mycoses. 2021;00:1–9.

In Tinea pedis, Tinea cruris and Tinea corporis,

redefining the fight against fungal infections with advanced state-of-the-art intelligent formulation of luliconazole

Rx NULIZA®

Luliconazole 1% Cream

Intelligence applied. Benefits multiplied

NULIZA® is optimally micronized formulation

MICRONIZED LULICONAZOLE

Nuliza®
Particle size ~ **20** microns

NULIZA® is formulated with nanostructured lipid carrier[1]

enhances skin penetration
& skin retention

NULIZA® has potent power in antifungals[2]

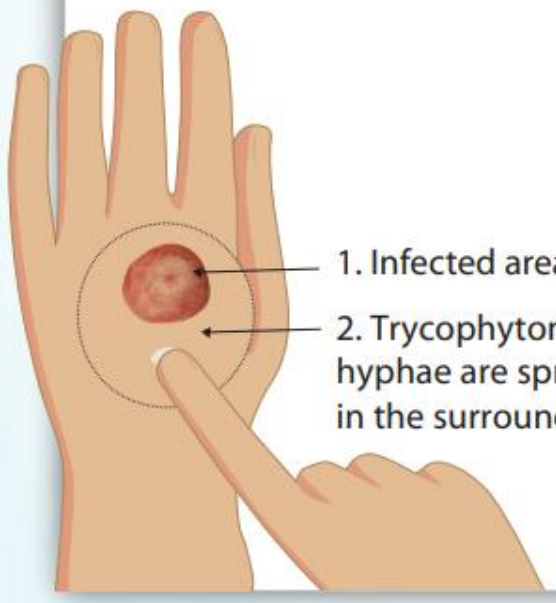
32x Stronger than Terbinafine

5x Lower Relapse rate than Clotrimazole

NULIZA® has superior stratum corneum reservoir effect[3]

71 µg/g reserved in startum corneum after single application

5x more drug release than Terbinafine



NULIZA® is optimal pack sizes of 30 gm & 50 gm

According to Pharmaceutical guideline

Application on infected site & nearby 1 inch of surrounding area

Avoids incomplete therapy due to small pack of 10 gm

...gives assurance of complete cure minimizing the risk of recurrence in Tinea infections

Importance of moisturizers

Xerosis or Dry Skin or Asteatosis

ICD 10 :The condition is characterized by *decreased quantity and/ or quality* of lipids and/or hydrophilic substances (the latter is referred to as natural moisturizing factor).

ICD 11 : Defines xerosis cutis/asteatosis (code ED 54) as a condition usually caused by a *lack in epidermal lipids* (as of May 2018).

Disease subgroups listed in the ICD 11 include *atopic xeroderma, asymptomatic or pruritic xerosis cutis, asteatosis and senile xerosis.*

How does it manifest?

- Decreased elasticity
- Coarsening of its texture
- Wrinkling
- Erythema
- Fissures
- A feel of tightness and pruritus
- Perceived as pain or a burning sensation by some patients

Dry Skin Condition

Eczema

- Atopic Dermatitis
- Hand Eczema

Disorder of Keratinisation

- Ichthyosis
- Psoriasis
- Palmoplantar Keratoderma
- Lichen planus

Dermatosis secondary to an underlying disorders

- Diabetes
- Thyroid disorders
- Pruritus of pregnancy

Damaged skin integrity in special populations

- Elderly
- Neonates & infants
- Amputee & bed ridden patients

Other Dermatologic disorders

- Acne Vulgaris
- Rosacea
- Xerosis
- Contact dermatitis

Indian J Oermatol. 2016 Moy-Jun, 61(3): 279—287.

Pathophysiology

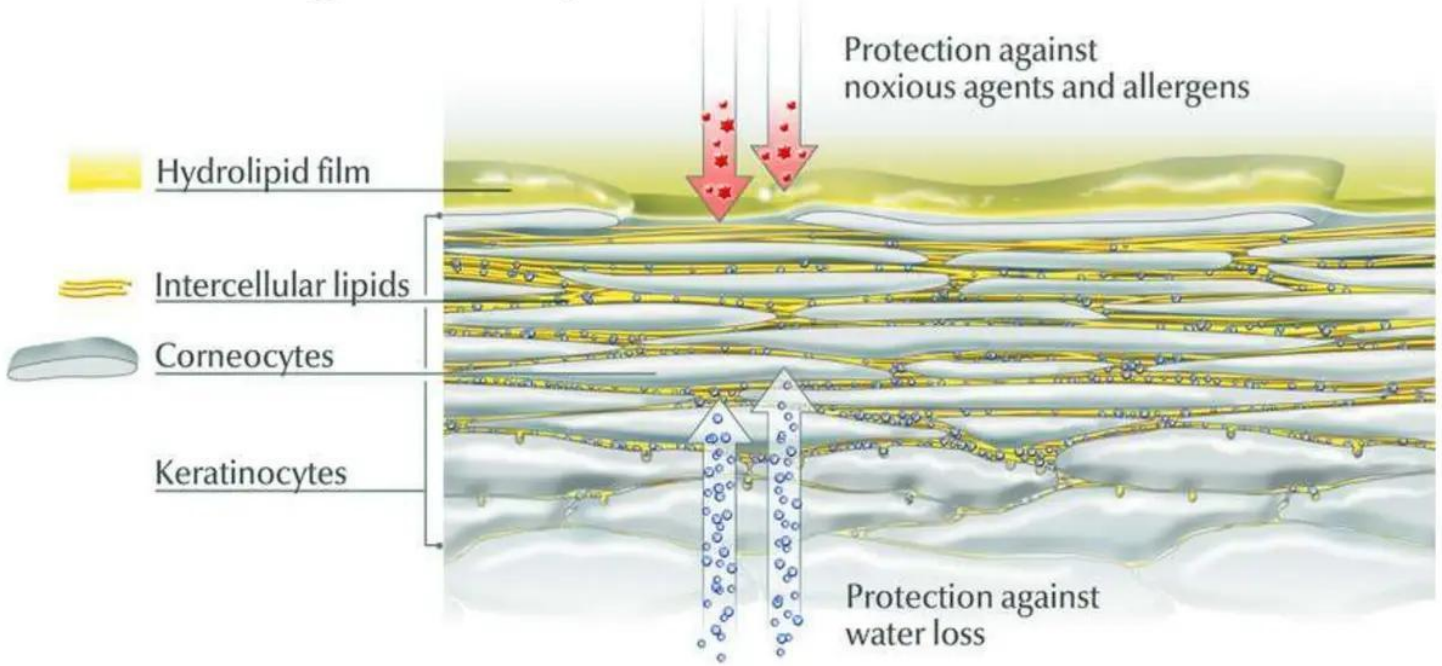
- Altered composition of the intercellular lipid bilayer, e.g., caused external or endogenous factors .

- Abnormal keratinocyte differentiation or desmolysis, e.g., in psoriasis,
  ichthyosis and others.

- Decreased content of moisturizing factors in the skin e.g., caused by environmental factors , fluid deficiency or by decreased endogenous production (e.g., inherited filaggrin deficiency) or poor distribution (e.g., aquaporin 3 deficiency).

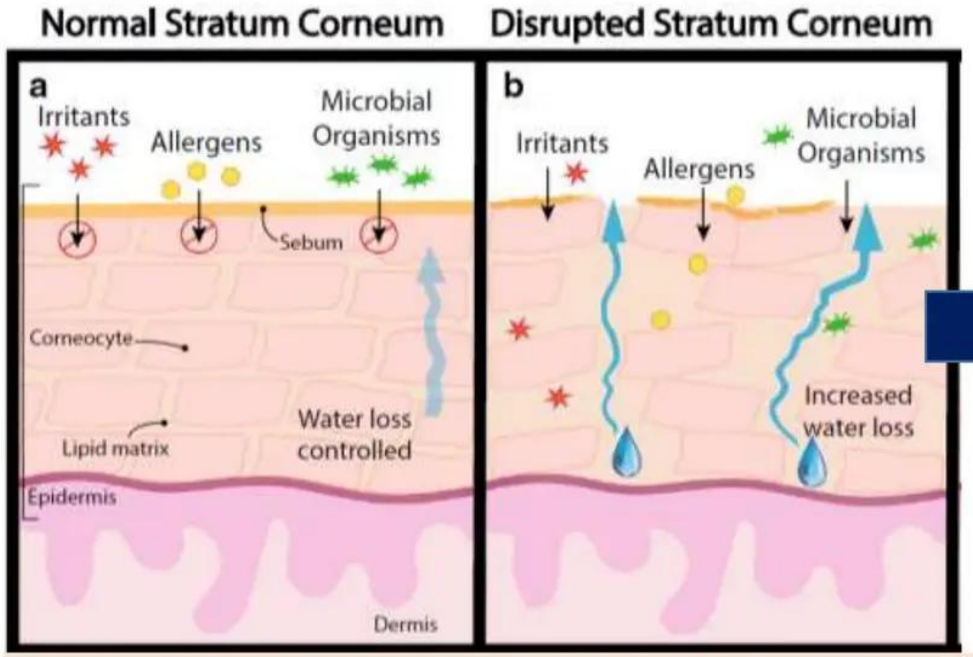
Impaired Skin Barrier

Keratinisation abnormalities ± change to lipids



JDDG. 2018; 16 (Suppl. 4): 3-35.

Skin Barrier Dysfunction & Skin Diseases



Normal SC **Disrupted SC**

Skin barrier dysfunction leads to trans epidermal water loss (TEWL)

Diseases	*Ceramides missing in the skin*
Psoriasis	Ceramide 1↓, Ceramide 3↓, Ceramide 6↓ *(Motta S et al., Arch. Dermatol. **130**, 452 - 456 (1994))*
Ichthyosis	Ceramide 1↓, Ceramide 6↓ *(Paige DG et al., Proc. Br. Ass. Dermatol. **25** (1993))*
Acne (vulgaris)	Linoleate in Ceramide 1↓ (Ceramide 1 through 6↓) *(Pershho K et al., J. Invest. Dermatol. **90**, 350 - 353 (1988))*
Atopic dermatitis	Ceramide 3 and 6↓ *(Di Nardo A et al., Acta Dermatol. Venereol. **78**, 27 - 30 (1998))*
Surfactant-induced dermatitis	Ceramide 3↓ *(Di Nardo A et al., Contact Dermatitis **35**, 86 - 91 (1996))*

Diseases that cause Disrupted SC

Am J Clin Dermatol . 2018 Feb;19(1):103-117

Management

- Basic skin care in the treatment of xerosis cutis is intended
- to improve skin hydration.
- compensate the lack in barrier lipids.
- improve the skin's barrier function.
- Thus, a combination of hydrophilic and lipophilic components is preferable.
- Lipophilic (lipid-replenishing, film-forming) and hydrophilic (remoisturizing) ingredients.

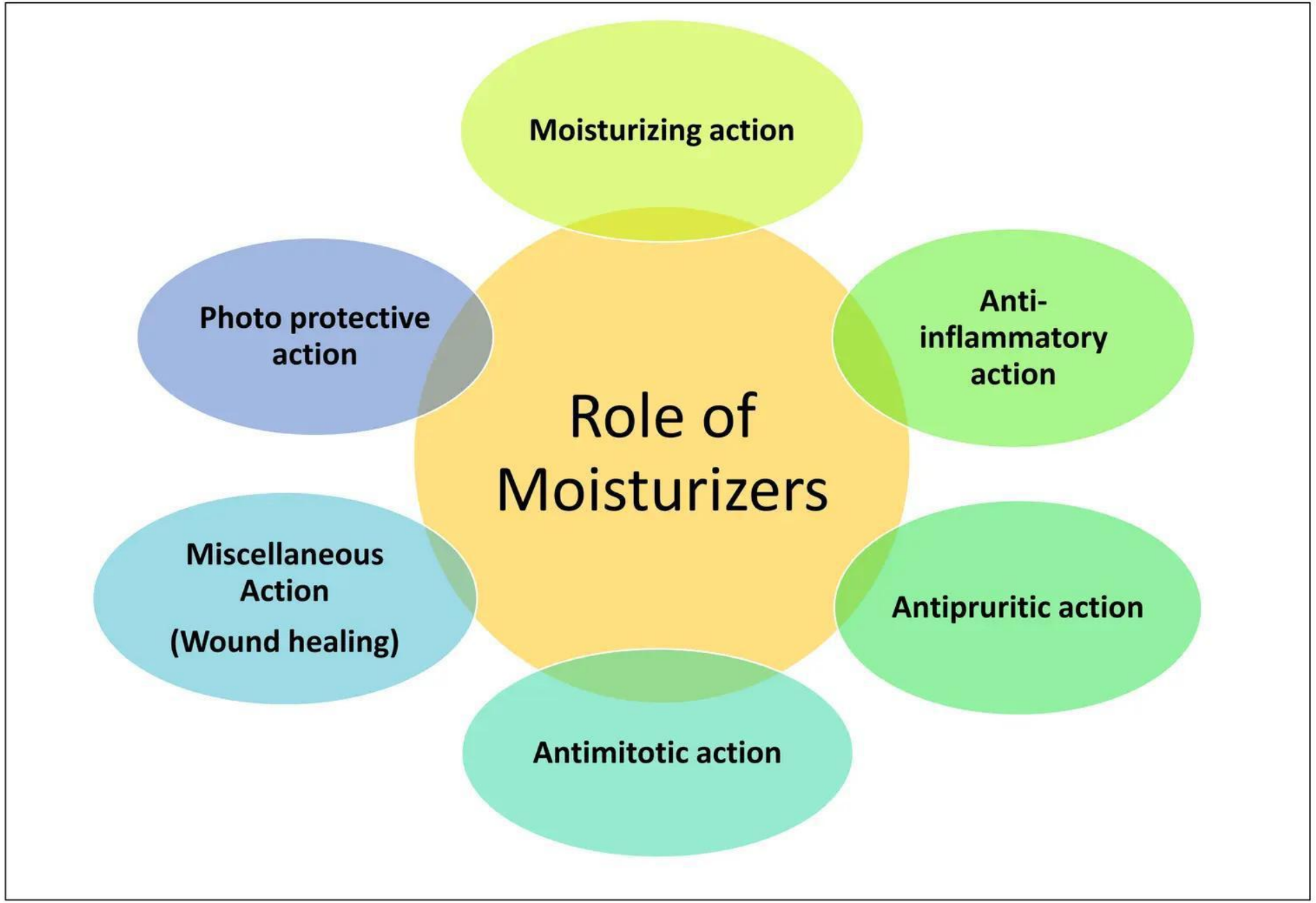
Characteristics of Moisturizers

The IDEAL Topical Moisturisers

- **Cosmetic Benefits**
- **Therapeutic benefits**

1. Provides immediate skin hydration and prevents TEWL
2. Contains no soap, fragrance, colours or common irritants
3. Affordable, cosmetically elegant and acceptable
4. Rapid absorption, non-comedogenic, long-lasting and pH balanced
5. Eases itching and inflammation and relieves irritation and soreness
6. Soften dry and cracked skin, and reduces scaling
7. Protects the skin and restores lipid barrier

http://dx.doi.org/10.5772/intechopen.101964



Clin Med Res. 2017 Dec; 15(3-4): 75–87.

Application of moisturizer to neonates prevents development of atopic dermatitis

- A prospective, randomized controlled trial to investigate whether protecting the skin barrier with a moisturizer during the neonatal period prevents development of AD and allergic sensitization

- Intensive use of a moisturizer was reported to increase hydration of the stratum corneum in neonatal skin

Daily application of emollient reduces the risk of AD/eczema by 32 weeks. Also able to reduce the prevalence of allergic sensitization by preventing the development of AD/eczema.

J Allergy Clin Immunal . 2014 Oc ;1 4(4 .'B24-B30

Emollient enhancement of the skin barrier

- A multicenter, multinational, 2-arm parallel-group, assessor-blind, randomized (1:1) controlled pilot trial of 6 months' duration. The intervention started within 3 weeks of birth.

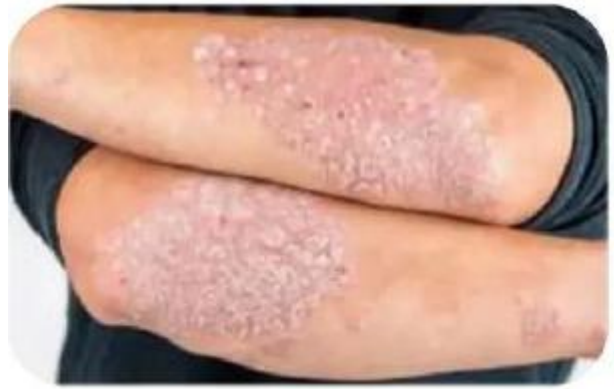
- Emollients provide a safe and effective method of skin barrier enhancement because they provide the skin with a source of exogenous lipids, improving its barrier properties.

- The results of the trial suggest the use of bland emollients from birth might protect against the onset of skin inflammation in neonates.

A statistically significant protective effect was found with the use of daily emollient on the cumulative incidence of atopic dermatitis with a relative risk reduction of 50%

Simpson EL, et. al. J Allergy Clin Immunol2014;134:818-23

In psoriasis



- Morphologic findings are consistent with biochemical studies that show a decrease in relative free fatty acid content and a different pattern in ceramide distribution in psoriatic plaques compared with normal control skin
- In psoriatic skin, the phytosphingosine-carrying ceramides (Cer 3 [NP] and Cer 7 [AP]) show a statistically significant decrease versus normal stratum corneum
- According to various studies the results suggest, ceramide I, III, IV, V, and VI reduced TEWL increased in all psoriatic scales
- Emollients form the backbone of therapy for psoriasis
- Moisturizers help in normalizing hyper-proliferation, differentiation, and apoptosis. They have anti-inflammatory effects in addition improving barrier function
- Keratolytics, such as salicylic acid and urea, are typically used on areas with thick scaling

Medicina 2022, S8, 8BB.

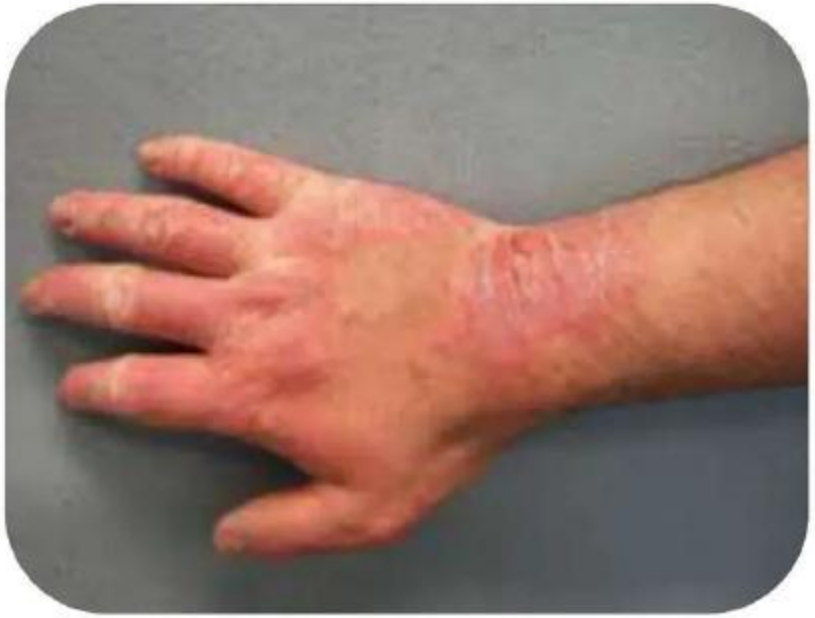
Therapeutic moisturizers as adjuvant therapy for psoriasis patients

- At any point in time, psoriasis affects 2-3ᵒoof the world's population and has one of the biggest impacts on quality of life of any dermatological disorder.
- Treatment is extremely costly and prevention of disease progression in severity and extent is crucial.
- Moisturizers have been shown to significantly improve skin conditions and quality of life for psoriasis patients. They are a valuable first-line treatment.

Am J Clin Dermatol . 2009;10 Suppl 1: -12

In Contact Dermatitis

- Common skin inflammation characterized by pruritic and erythematous skin lesions induced by contact with foreign substances. It is divided into two major groups: irritant and allergic.



- Moisturizer application provides protection and strengthens skin barrier function.

- Lipid-rich moisturizers are particularly recommended to be routinely used in all contact dermatitis patients.

- Restoration of damaged epidermal barrier and adequate skin hydration is extremely important for prevention of chronic contact dermatitis

Medicina 2022, 58, 888.

In Ichthysosis

- A well constructed moisturizers should contain key factors for hydration which include
- Ceramides- Stimulates barrier
- NMF
- Urea- reduces TEWL
- Lactate
- Aquaporins

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Caring for your skin

Triple action therapeutic moisturizer with Lanolin

In dry skin, eczema and psoriasis

NuvaCare®

1ST Time in Bangladesh

White Soft Paraffin BP 14.5% + Light Liquid Paraffin BP 12.6%
+ Anhydrous Lanolin BP 1% Cream

Optimum Hydrating care to break the itch-scratch cycle

Triple action therapeutic moisturizer with Lanolin

In dry skin, eczema and psoriasis

NuvaCare®

1ST Time in Bangladesh

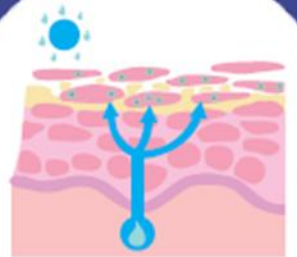
White Soft Paraffin BP 14.5% + Light Liquid Paraffin BP 12.6%
+ Anhydrous Lanolin BP 1% Cream

Optimum Hydrating care to break the itch-scratch cycle

Triple action to relieve dry skin

1

NuvaCare is a humectant[1,2]

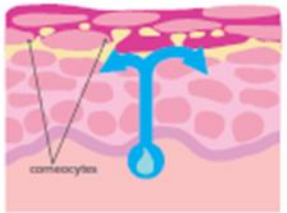


Helps stratum corneum to absorbs water from dermis & humid environment

...softens the skin

2

NuvaCare is an emollient[3]

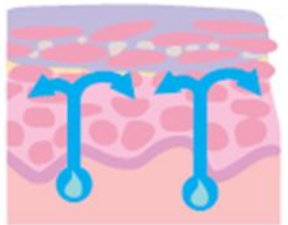


Fill the Intercorneocytes gap

...ensures skin hydration

3

NuvaCare has occlusive properties[3]



Creating hydrophobic barrier

...enhances water holding capacity of skin

Acne vulgaris

Acne vulgaris is a chronic inflammatory dermatosis of the face and torso, characterized by open or closed comedones and inflammatory lesions including papules and pustules.

Pathogenesis

Acne vulgaris is a multifactorial condition characterized by-

- Overproduction and changes in the composition of sebum
- Epithelial hyper-keratinization of pilosebaceous duct with sebaceous obstruction
- *Cutibacterium acnes* over-colonization and inflammation.

Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74:945–973.

Epidemiology

- Acne is the eighth most prevalent disease in the world affecting 10% of the world population[1]
- Affects approximately 85% of adolescents and young adults aged 12 to 25 years[2]
- Prevalence of acne is higher in females than males
- about 48–52% of facial acne patients also have truncal acne.[3]

1.Adelaide Hebert, MD; Diane Thiboutot, MD; Linda Stein Gold, MD; Martina Cartwright, PhD;Mara Gerloni, PhD; Enrico Fragasso, MS; Alessandro Mazzetti, MD: Ecacy and Safety of Topical Clascoterone Cream, 1%, for Treatment in Patients With Facial Acne, JAMA Dermatology June 2020 Volume 156, Number 6
2.Anna Hwee Sing Heng & Fook Tim Chew, Systematic review of the epidemiology of acne vulgaris, Scientic Reports (2020) 10:5754
3.Yu Ri Woo and Hei Sung Kim, Truncal Acne: An Overview, J. Clin. Med. 2022, 11, 3660

Contributing factors

- Genetic predisposition
- Diet-High glycemic diet
- Cosmetics-Long term use of oil based cosmetics, Facial massage
- Menstrual cycle
- Psychological factor-Stress

Varieties of acne lesion

- Acne vulgaris can be divided into
- non- inflammatory (open and closed comedones)
- and inflammatory (papules, pustules and nodules) lesions

Types of acne

- Acne Conglobata
- Occupational acne
- Cosmetic acne
- Drug-induced acne
- Infantile acne
- Late onset acne
- Acne excoriee
- Acne fulminans
- Post-facial massage acne

Differential diagnosis & Management

- Rosacea
- Perioral dermatitis
- Folliculitis
- Hidradenitis suppurativa

General measures

- Maintain local hygiene
- Avoid high glycemic food
- Reduce stress

Management

Acne vulgaris can be treated either topically or systemically

Topical Therapy

Anti Comedonal Agents

- Topical Retinoids
- Azelaic acid
- Salicylic acid

Anti Inflammatory Agents

Benzoyl Peroxide

Topical antibiotics

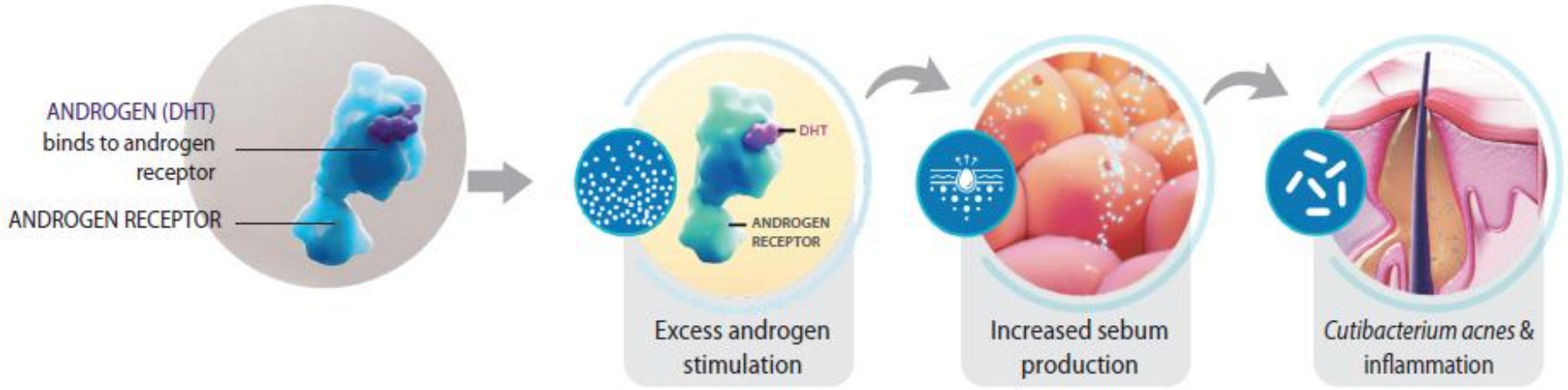
Systemic Therapy

- Oral Antibiotics-Tetracycline, Doxycycline , Minocycline& Erythromycin
- Isotretinoin
- Hormonal Therapy -Oral contraceptives pill, Spironolactone

Challenges in the management of Acne vulguris

- Benzoyl peroxide -> has an irritant effect on skin-> Poor adherence
- Retionoids-> associated with adverse effects like local irritation, erythema and must be used with caution in females of childbearing age owing to known teratogenicity.
- Topical and oral antibiotics->Raising antibiotic resistance leads to poor therapeutic outcome
- Hormonal therapy->associated with a relative increase in certain cardiovascular risk factors & contraindicated in males and in pregnancy.

Androgen receptor pathway



Androgen hormones play a key role in pathogenesis of Acne in both sexes.

nuvista | introduces

The novel, first-in-class, topical androgen receptor inhibitor to treat Acne differently

Nulevi

Clascoterone 1% Cream

First-in-class in 40 years approved by FDA

Help your patients feel the difference in Acne

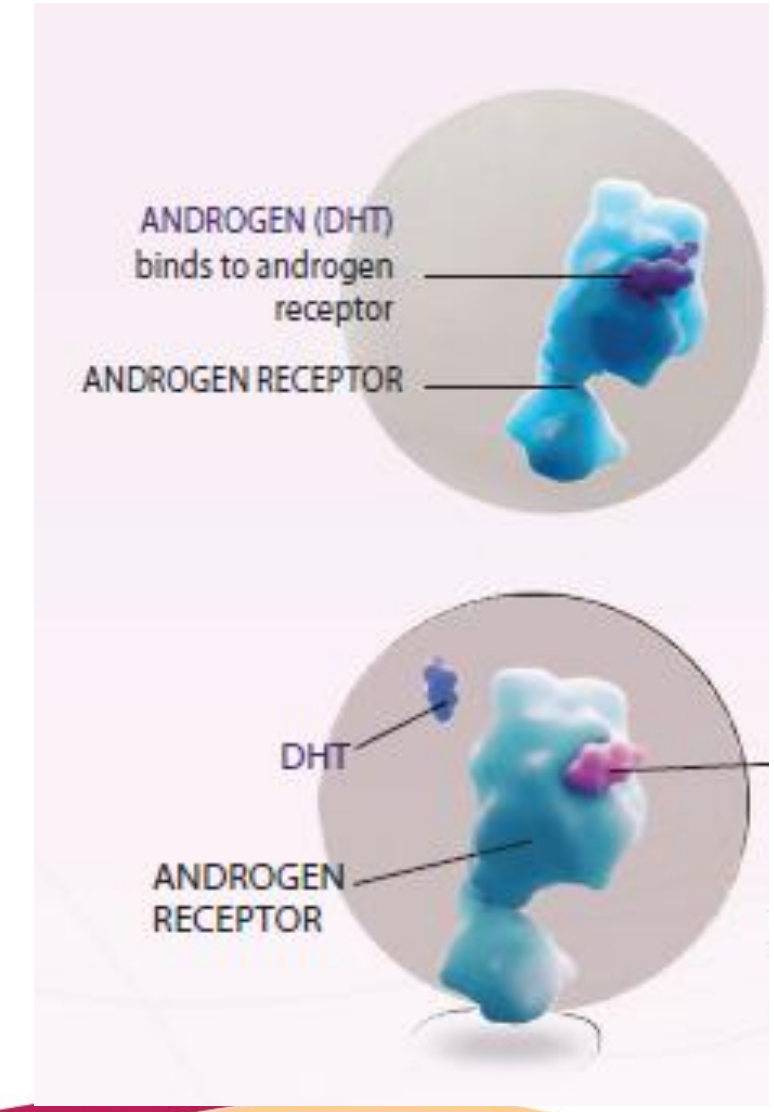
#1 prescribed topical treatment of Acne in the USA

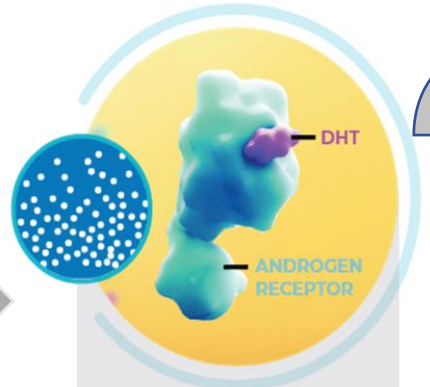
Indication & administration:
Acne Vulgaris, Twice daily 12 weeks

Guideline
Apply a thin layer approximately 1 gm to affected area twice daily

Mode of Action

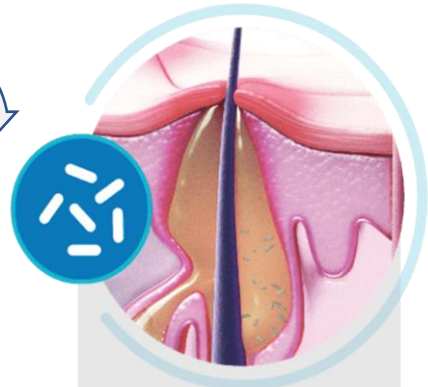
DHT (dihydrotestosterone) is active form of testosterone





Excess androgen stimulation

Increased sebum production



Cutibacterium acnes & inflammation

inhibits the action of androgen receptors on cells in the sebaceous gland, reducing sebum production

reducing sebum production

Significantly reduces inflammatory & non inflammatory lesion

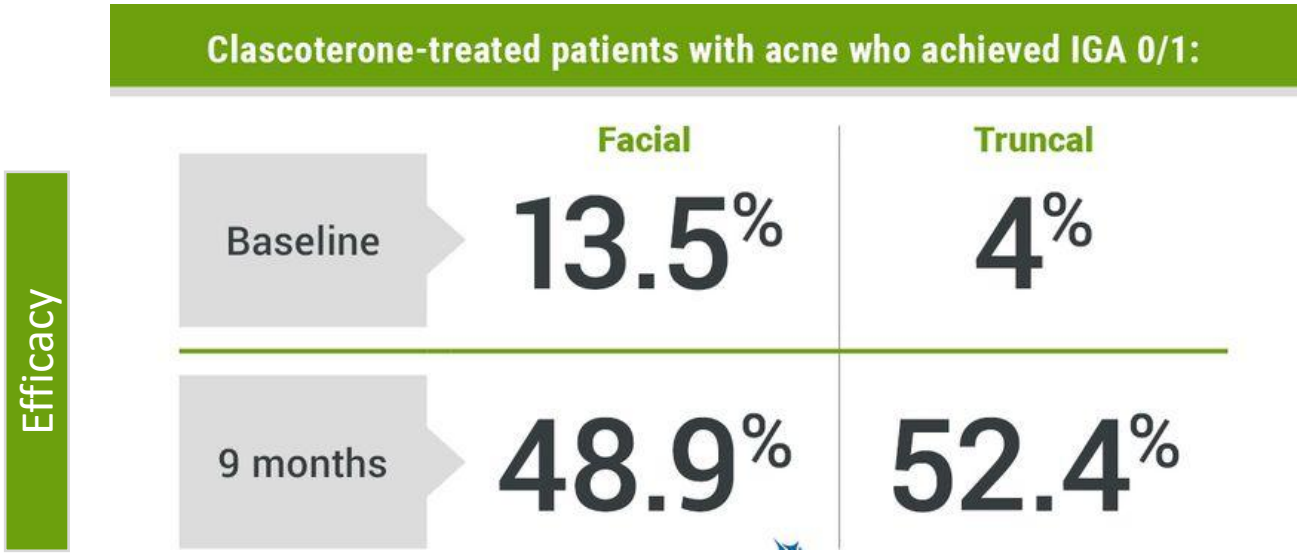
Nulevi®
Clascoterone 1% Cream

News

Clascoterone cream exhibits significant long-term improvement among children with acne

"Clascoterone safety was well maintained for up to an additional 9 months of treatment in patients [aged 9 years and older] with moderate to severe acne vulgaris,"

Lawrence F. Eichenfield, MD, chief of pediatric and adolescent dermatology at Rady Children's Hospital and professor of dermatology at UC San Diego School of Medicine

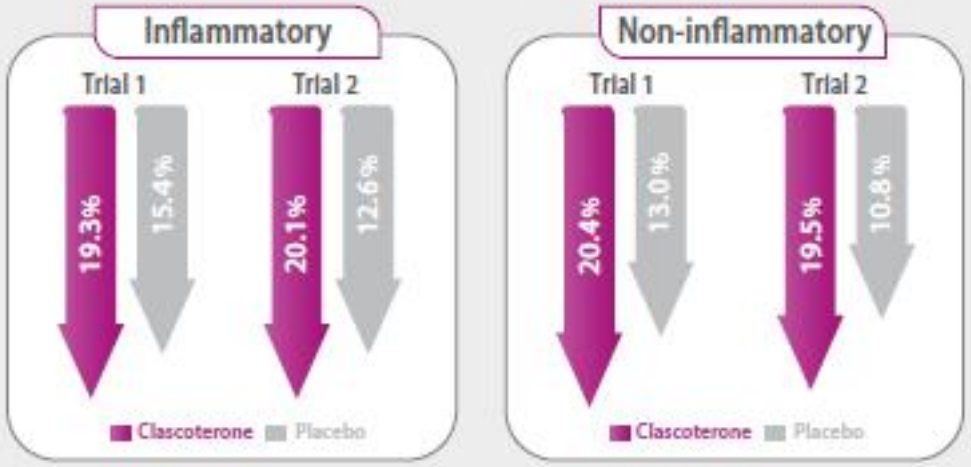


Ref:
https://www.healio.com/news/dermatology/20230815/clascoterone-cream-exhibits-significant-longterm-improvement-among-children-with-acne?utm_source=selligent&utm_medium=email&utm_campaign=news

Why Nulevi?

Clascoterone (Nulevi) demonstrates significant reduction in facial & truncal Acne in Investigator's Global Assessment (IGA) Score from ≥ 2 to ≤1 in just 12 weeks[6]

In clinical trials, clascoterone (Nulevi) showed significant reduction in Acne lesions vs placebo at weeks 12[7]



Clascoterone (Nulevi) showed significant reduction in Inflammatory & non-inflammatory lesions compared to Tretinoin[8]

...gives confidence of treatment success in facial & truncal Acne equally in women & men

USP

- Nulevi is the novel topical treatment of Acne to directly inhibit the androgen receptors in the skin
- Significantly reduces sebum production and inflammatory & non inflammatory lesions of Acne
- Superior efficacy and tolerability compared to topical tretinoin
- Equally e treating Acne in women & men aged 12 years & above
- Devoid of systemic anti androgenic effects in most patients