The Pharma Innovation Journal 2020; 9(6): 45-51

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2020; 9(6): 45-51

www.thepharmajournal.com
Received: 24-04-2020
Accepted: 26-05-2020

Banhishikha KAR
(a) Department of Pharmaceutics, Calcutta Institute of Pharmaceutical Technology & AHS, Banitabla, Uluberia, Howrah, West Bengal, India
(b) Department of Pharmaceutics, School of Pharmacy, Techno India University, Salt Lake, Kolkata, West Bengal, India

Ayan Kumar KAR
Department of Pharmaceutics, Calcutta Institute of Pharmaceutical Technology & AHS, Banitabla, Uluberia, Howrah, West Bengal, India

Subhabrota Majumdar
Department of Pharmaceutics, Calcutta Institute of Pharmaceutical Technology & AHS, Banitabla, Uluberia, Howrah, West Bengal, India

Beduin Mahanti
Department of Pharmaceutics, School of Pharmacy, Techno India University, Salt Lake, Kolkata, West Bengal, India

Corresponding Author:
Banhishikha KAR
(a) Department of Pharmaceutics, Calcutta Institute of Pharmaceutical Technology & AHS, Banitabla, Uluberia, Howrah, West Bengal, India
(b) Department of Pharmaceutics, School of Pharmacy, Techno India University, Salt Lake, Kolkata, West Bengal, India

A clinical overview on acuteness of rosacea

Banhishikha KAR, Ayan Kumar KAR, Subhabrota Majumdar and Beduin Mahanti

Abstract
Rosacea is a chronic inflammatory condition of the central facial skin affecting the blood vessels and pilosebaceous units. It is a common skin state that causes redness and visible blood vessels particularly in facial region. Generally, there are two types of rosacea based on either "performed" clinical or patient adopted analysis of rosacea. The etiology and pathophysiology are poorly understood. It may also produce small, red pus-filled bumps. These signs and symptoms may flare up for weeks to months and then go away for a while. In some circumstances it can be mistaken for acne, other skin problems or natural rosiness. Rosacea has a variety of triggers: lead to deliver of diverse mediators like endothelial cells, keratinocytes, macrophages, T1 and T17 cells. In addition, these trigger factors directly spread to the nurvous system, lead to the reflection of rosacea injury. Rosacea can affect anyone but it is most common in middle-aged women who have light skin. There is no permanent cure for rosacea, but treatment can control and reduce the signs and symptoms. Patients generally complaints of flushing and blushing and sensitive skin, and their skin may be especially irritated by any kind of topical preparations. Rosacea has a variety of triggers; however, they may be unnoticed by the patient. Validated treatments and drugs approved by the FDA which includes ivermectin, oxymetazoline hydrochloride, azelaic acid, topical metronidazole, and oral tetracyclines, in particular minocycline and doxycycline, brimonidine etc. Here, the aim of present strategies to sum up the modern concept along with diagnosis and address a symptom-based approach in the management of patients with rosacea.

Keywords: Rosacea, topical inflammation, flushing, classification, treatment.

Introduction
Rosacea is an acute inflammatory facial skin condition which is normally a manifest in adult people or in the people with pale skin and light eyes with a reported prevalence of between 0.5% and 10%.It is a chronic relapsing skin disease with a reported variable prevalence of 2.2%, 10% and 22% depending on the study population and setting [1, 4]. It is commonly estimated to affect about one in 10 people in the general population. In 1923-2010 US National Ambulatory Medical Care Survey on patients with rosacea, it was found that the skin colour has varied and rates up to 10% shown in Fig. 1 [5, 7]. The rosacea commonly has a definite characteristic pattern targeting mainly on the face including cheeks, nose, chin and central forehead but rosacea is generally under diagnosed and often overlooked [4, 8, 9]. It is more commonly noticed in United States and in the European countries. It is approximately estimated that from 10 to 20 million Americans have the condition. People in the age group of 20s manifests it as flushing in the facial region then it became severe to patients in their 30s [1]. A common inflammatory condition, Rosacea is a skin disease in adults with a preference for highly recognizable areas of the skin such as the face. It is distinguished by persistent facial erythema, telangiectasia, flushing, redness, inflammatory papules and pustules, pimples, dilated blood vessels and eye symptoms [10]. Combination of symptoms and signs focused around the central face can be divided in primary and secondary features. Although rosacea can occur in anyone, it most commonly affects middle-aged women with fair skin, blue eyes and blonde hair [11].

Classification of rosacea
For a diagnosis of rosacea, one or more prime features concentrated on the central areas of the face are required: flushing (transient erythema), nontransient erythema, papules and pustules, and telangiectasia. Subordinate features include burning or stinging, edema, plaques, a dry appearance, ocular manifestations, peripheral locations, and phymatous changes. Rosacea has a wide range of variety based on different factors, triggers shown in Table 1. However, many specialists suggested that rosacea can occur in various areas other than the central region of

face. According to its signs and symptoms, it has been classified into the following 4 subtypes that often occur together: erythematotelangiectatic, papulopustular, phymatous and ocular.

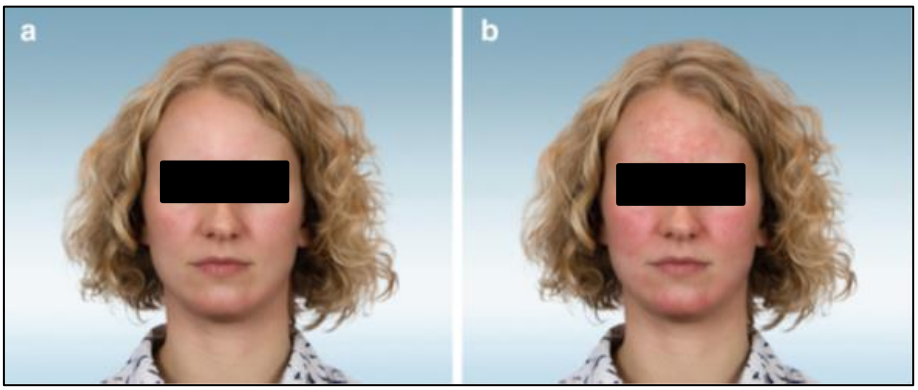

Fig 1: Examples of images shown to respondents (a) female image without facial erythema (b) female image with facial erythema.

Table 1: Characteristics of different types of rosacea [11, 16]

Subtype	Characteristics
Subtype I: Erythemato-telangiectatic rosacea (ETR)	1. Flushing and persistent redness of the central face, occurs before or at the same time as the bumps & pimples of subtype 2 rosacea. 2. Visible blood vessels may also be present. 3. Persistent erythema of the central aspects of the face. 4. People with these rosacea have very sensitive skin and may feel as if their skin stings or burns at times (Fig. 2A).
Subtype II: Papulopustular rosacea	1. May occur along with the facial redness and flushing of rosacea subtype 1 (Fig. 2B). 2. Symptoms include: papules and/or pustules that come and go, combined with transient or persistent facial redness, primarily on the central face; burning and stinging; small visible blood vessels (telangiectasia); raised, scaly red patches known as plaques. 3. This type of rosacea occurs most commonly in middle age and affects more commonly women than men.
Subtype III: Rhinophyma (Phymatous rosacea)	1. Affect nose (rhinophyma), chin (gnatophyma), forehead (metophyma),ears (otophyma) and eyelids (blepharophyma). 2. Most frequent location shows marked skin thickenings and irregular surface nodularities especially of the nose. 3. Telangiectasia can also be presented. 4. 4 histological types of rhinophyma that include glandular, fibrous, fibroangiomatous and actinic. 5. Problem is much more common in men than in women (Fig. 2C).
Subtype IV: Ocular rosacea	1. Ranges from minor irritation, foreign body sensation, dryness, and blurry vision to severe ocular surface disruption and inflammatory keratitis. 2. Other ocular findings include lid margin and conjunctival telangiectasias, eyelid thickening, eyelid crusts and scales, corneal infiltrates, corneal ulcers, corneal scars, and vascularization. 3. Problem is common in 20% of patients with rosacea. There is no correlation between the severity of ocular disease and severity of facial rosacea (Fig. 2D)

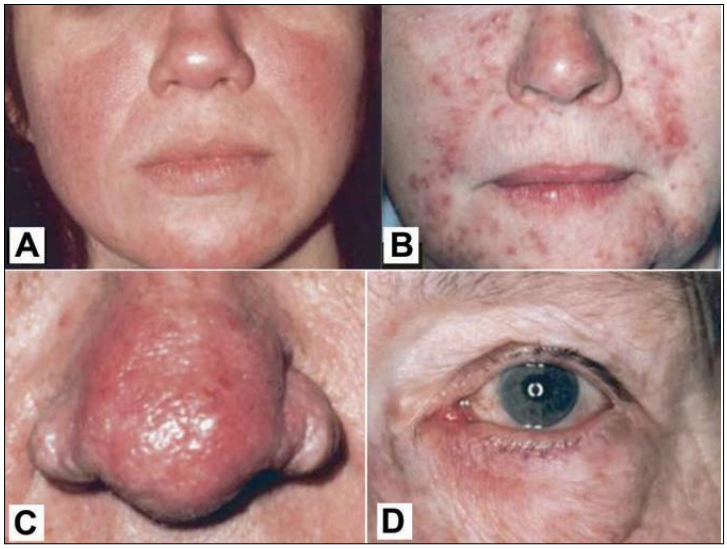

Fig. 2 The four types of rosacea: (A) erythematotelangiectatic rosacea; (B) papulopustular rosacea; (C) rhinophyma (phymatous rosacea) and (D) ocular rosacea [11].

The newly introduced classification of rosacea highlights the importance of each rosacea reflections and distinguishes diagnostic signs from major and secondary symptoms (Table 2). Briefly, phymatous changes and persistent centro-facial erythema are considered the only diagnostic features of rosacea, whereas flushing, and inflammatory papules/pustules are considered crucial symptoms and only in combination can recommended the diagnosis of rosacea. Stinging or burning pain, edema, and dry sensation are defined as secondary quality of rosacea [17].

Table 2. Classification of rosacea on the basis of diagnostic and secondary features of rosacea [19].

Diagnostic features	Major features	Secondary features
Persistent centro-facial erythema associated with aggravation by trigger factors	Flushing/transient erythema	Burning sensation
Phymatous changes	Inflammatory papules and pustules	Stinging sensation
	Telangiectasia	Edema
	Ocular manifestations Lid margin telangiectasia Blepharitis, keratitis, conjunctivitis, and sclerokeratitis	Dry sensation of the skin

Pathophysiology of rosacea

Genetic factors

A patient's particular genes may donate to his or her growth of rosacea as an adult; 10-20% reports a family history of rosacea. In Northern European descents, the higher occurrence of rosacea also recommended a feasible genetic component. Still, some genomic studies have failed to find a causative gene[18]. The genetic predisposition, together with trigger factors leads to the clinical occurrence of transient flushing due to the overstimulation of the sensory and/or autonomic nervous system in the skin and initiation of innate immune responses.

Innate immune response

The innate immune system along with adaptive immune system might play an important role in the pathophysiology of rosacea. The innate immune system serves as the body's nonspecific, acute defense mechanism against contaminations. When triggered, it guides to the controlled release of numerous cytokines and antimicrobial peptides in the skin. The innate immune system may be disrupted in patients with rosacea [19]. One of the pathogen that has been proposed to be involved in the pathophysiology of rosacea is *H. pylori*. However, a recent meta-analysis found between *H. pylori* infection and rosacea and between successful removal of *H. pylori* and improvement of rosacea manifestations [20].

Microorganisms

Outcome of microbes can be acknowledge by cells of the innate immune system and activate, for example, Toll-like receptors (TLRs) and the G-protein-coupled receptor proteinase-activated receptor 2 (PAR2) that are communicated by keratinocytes and can bring up inflammatory processes. TLR-2 and probably PAR2 are unregulated in patients with rosacea, and *in vitro* activation of both receptors encourages the activation of cathelicidin, an anti-microbial peptide that is overexpressed in patients with rosacea (Figure 3)[19,21].

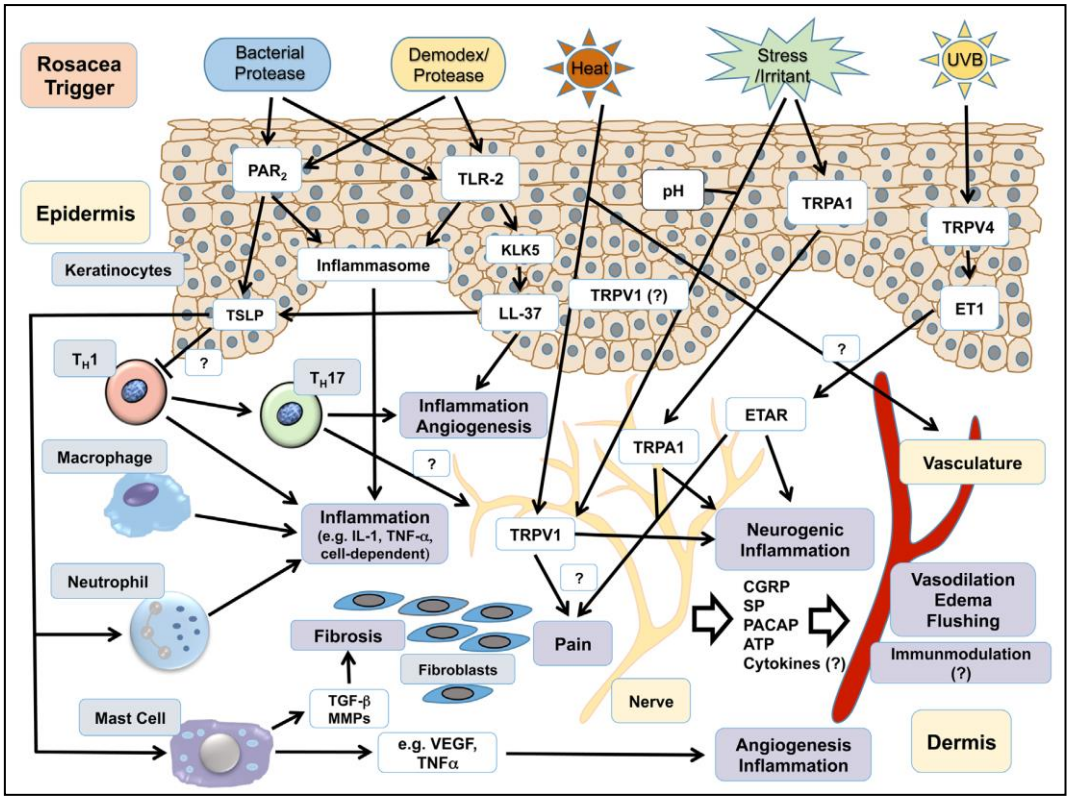

Fig 3: Current understanding of the pathomechanisms in rosacea [21].

Vascular hypersensitivity

An acute, temporary intensifying of facial erythema, known as flushing, can take place after subjection to various triggers. For example, patients with rosacea were started to flush readily after subjection of heat. Other feasible triggers include spicy foods or alcohol, but require mechanism of how these dietary factors play a role in the pathogenesis has yet to be explained. Various medications, like amiodarone, topical or nasal steroids, and high doses of vitamins B6 or B12, are described potential rosacea triggers (See Table 3) [22, 23].

Table 3: Potential Triggers for Facial Flushing

Rosacea triggers	Patients affected
Sun exposure	81%
Stress	79%
Heat	75%
Wind	57%
Strenous activity	56%
Alcohol consumption	52%
Cold weather	46%
Spicy foods	45%
Certain skin care products	41%
Hot beverages	36%
Medications	15%

Ultraviolet radiation

Ultraviolet (UV) exposure and photodamage play an important role in the pathophysiology of rosacea. Most patients with rosacea reported worsening of their rosacea along with flushing in presence of sunlight. UVA radiation increases the expression of matrix metalloproteinase's (MMPs) and denatured collagen in the skin [24]. MMPs are zinc-containing proteases broken down various components of the extracellular matrix, resulting the damage to blood vessels and the dermal matrix. In general, UV radiation produces reactive oxygen species (ROS) that have a pro-inflammatory effect on the skin. ROS bind to toll-like receptor 2 (TLR2) on keratinocytes, which further propagates the inflammatory cascade occurring in rosacea [25].

Diagnosis of rosacea

Rosacea typically appears consistently in the central face with gender and ages specific predilection with regard to lesion qualities. Typical centre facial presence of rosacea, a causative association with the unique facial skin composition that is characterized by a heavy existence of sebaceous glands, nerve and vascular networks. Despite of that *Demodex* mites cannot be drawn conclusively as of yet. However, *Demodex* infection is increased in some patients with rosacea, and suppression seems to alleviate rosacea symptoms probably by preventing the formation of pro-inflammatory cytokines [19, 26, 27]. Rosacea can be particularly suffer for self perception as flare-ups can be triggered or enhance by emotional stress with the visible redness creating further distress. The condition has been associated with anxiety, avoidance of social settings and emotional suffering.

Patients usually have complaints of flushing, blushing and sensitive skin. Various Signs and symptoms of rosacea include-

1. **Facial redness.** Rosacea usually causes a persistent redness in the central part of your face. Small blood vessels on your nose and cheeks often swell and become visible.
2. **Swollen, red bumps.** Many people with rosacea also develop pimples on their face that resemble acne. These bumps sometimes contain pus. Your skin may feel hot and tender.
3. **Eye problems.** Many people with rosacea also experience dry, irritated, swollen eyes and red, swollen eyelids. This is known as ocular rosacea. In some people, the eye symptoms precede the skin symptoms.
4. **Enlarged nose.** Over time, rosacea can thicken the skin on the nose, causing the nose to appear bulbous (rhinophyma). This occurs more often in men than in women.

Sometimes patients may be unaware of these symptoms prior to diagnosis, but a variety of triggers, or factors that induce or intensify rosacea which is shown in Table-4. The diagnosis of rosacea is usually made on history
and clinical features which must be considered and ruled out shown in Table 5.

Table 4: Triggers of Rosacea [1]

Ingested	Environmental
Foods and drinks	**Temperature**
Cheese	Sauna heat
Chocolate	Overheating
Spicy food	Sun lamp
Soy sauce	Humidity
Vanilla	Hot baths
Dairy products Liver	
Beverages	**Weather**
Red wine	Sun
Hot drinks	Heat
Alcohol (beer, bourbon, gin, vodka)	Strong wind Cold
Drugs	**Emotion**
Niacin	Anger
Nitroglycerin	Stress
Tobacco	Rage Embarrassment
Topical agents	**Activity**
Topical corticosteroids	Exercise
Retinoids	Menopause
Cosmetics (sometimes)	Caffeine withdrawal
Acetones	Chronic cough
Alcohol	Straining

Table 5: Differential diagnoses of rosacea [28]

Common	Uncommon
Acne vulgaris	
Seborrhoeic dermatitis	Lupus erythematosus
Tinea faciei	Dermatomyositis
Periorificial dermatitis	Drug reaction, e.g. isoniazid
Contact dermatitis (irritant or allergic)	Sarcoidosis
Steroid-induced acneiform eruption	Demodicosis (mange)
Folliculitis	

Table 6 exhibits distinctive diagnoses to assistance in recognizing conditions commonly mistaken for rosacea in skin of color. In patients with facial erythema, collagen vascular diseases, including lupus erythematosus may be considered. A skin biopsy can be used to test for common comorbidities, such as demodicidosis. Note that granulomatous rosacea is more common in patients of African ancestry. Rosacea can also look alike to a skin condition that influenced primarily black children, facial Afro-Caribbean childhood explosion. (Table 6).

Table 6: Differential diagnoses for rosacea in patients with skin color [7, 29, 31]'

Diagnosis	Features
Acne vulgaris	Pustules and erythematous papules on face and upper trunk, usually accompanied by open and closed comedones and no telangiectasia, typically occurring in adolescence and young adulthood.
Contact dermatitis	Skin inflammation or rash that is normally itchy; condition connected with exposure to chemical or physical allergens or irritants; condition might involve erythema, scaling, blistering, thickening, or cracking of skin, sometimes with pain, burning, or stinging.
Seborrheic dermatitis	Skin inflammation occurring near eyebrows, ears, nose, and glabellar site.
Periorificial dermatitis	Self-limiting eruption of erythematous papules and pustules near mouth, nose, and eyes, primarily in young women.
Facial Afro-Caribbean childhood eruption	Self-limiting, monomorphic flesh-colored or hypopigmented papules, around mouth, ears, and eyelids, primarily in black children, usually male.
Keratosis pilaris rubra	Marked erythema and keratotic follicular papules covering cheeks and proximal arms.
Dermatomyositis	Red or purplish rash along with edema usually showing on eyelids, knuckles or fingers along with scaly, red papules on neck, shoulders, or on trunk, scalp or face; often accompanied by muscle weakness; commonly found in female patients.
Lupus erythematous	Erythematous rash spanning cheeks and nasal bridge in butterfly pattern.
Sarcoidosis	Granulomatous disorder usually involving multiple organs and affecting middle-aged and older patients with comorbid hypertension, thyroid disease, type 2 diabetes mellitus, hearing loss, or eye disease.
Steroid acne	Acne vulgaris induced by steroid-containing topical agents; patient will have history of using this type of products.

Treatment of rosacea

Educating patient on rosacea is the prime factor in the treatment of this acute disease and showing the appropriate path of the therapy is an important aspect in helping patients succeed with therapy. Treatment should be done by monitoring the various symptoms and individual aspects. In the treatment of rosacea a wide range of topical formulations has developed which was showing a promising result to the patients. Based on the existing evidence for the treatment of rosacea in patients of colour is major. To treat darker skin successfully, clinicians must pay special attention to the presence or potential development of pigment alteration. The treatment plan is generally being adapted by knowing type as well as stages of the disease. This ensures that the patients will get better therapy and maximum efficacy. Among all of the steps of treatment skin care is major for this case, like avoidance of sun. Skin care also includes a gentle facial cleanser and a moisturiser, as this can consecutively improve therapeutic outcomes and reduce skin irritation in patients undergoing medical therapy. Also another important step is avoiding triggers such as extreme temperatures (hot or cold), ultraviolet radiation exposure, spicy foods, hot or alcoholic beverages, wind, exercise and stress, should be maintained by all patients [28].

The treatment approach for rosacea in skin color is near to that in lighter skin types necessitate the same topical, oral, laser, light-based, or surgical treatments targeted to the patient's individual signs of rosacea. Patients with skin color might have distinctive clinical characteristics that need to be super scribe during rosacea treatment which might be included cultural and geographic variations in skin care that might affect skin condition. For example, patients with skin color problem might be habituated to using abrasive skin care products, astringent or occlusive moisturizers like cocoa butter [7]. The selection of Laser and light-based therapies which may be considered for lowering the capillary network of the skin or for reemerging of phymatous changes must be based on suitability for Fitzpatrick skin phototypes. Another key measurement of the rosacea treatment for patients with skin color is admonishing on appropriate skin care (Table 7). A censorious component is the use of sunscreen. Additionally, patients should be advised on rosacea trigger identification, management and avoidance including nutritional therapy, environmental, and lifestyle triggers [7, 32].

Table 7: Recommended skin-care regimen for rosacea patients with skin of color [7]

Recommended types of products	Product types to avoid
Gentle, nonalkaline, fragrance-free, emollient cleanser once per day in the evening.	Alcohol-based cleansers, astringents, or abrasive exfoliating cleansers.
Silicone-based moisturizer daily	Nonsilicone-based moisturizers.
Light, water-based cosmetics (but powders are preferable to creams)	Cosmetics with iridescent effects
Physical sunblock (eg, zinc oxide)	Chemical sunscreens (if sensitivity reported)

FDA is approved several drugs for the treatment of rosacea which is normally formulated in topical or oral preparation. The efficacy of topical therapy for rosacea relates primarily to the reduction in inflammation (papules, pustules), a decreased intensity of erythema, a decrease in the number and intensity of flares. The list of topical drugs which used to treat rosacea is mention in the Table 8.

Table 8: FDA approved topical and oral therapy of rosacea [1, 33]

Type of drug		
Topical Antibiotics	**Non-antibiotics**	**Oral Antibiotics**
Metronidazole 0.25%, 0.75%, 1% cream, gel, lotion (e.g., MetroCream, MetroGel)	Azelaic acid 15% gel (Azelex)	Doxycycline, USP (Oracea Capsules), 40 mg once daily (30-mg immediate release and 10-mg delayed-release beads).
Oxymetazoline hydrochloride 1% gel.	Sodium sulfacetamide 10% and sulphur 5% combinations, lotion, cream, cleanser (Sulfacet).	
Ivermectin 1% gel.	Sodium sulfacetamide 10% lotion.	
Brimonidine 0.33% gel.	Sodium sulfacetamide 10%, sulfur 5%, sunblock lotion combination.	

Also few other drugs which are being used in the treatment of rosacea are Tetracycline 500 mg b.i.d., Doxycycline 50–100 mg b.i.d., Azithromycin 250 mg, Amoxicillin or ampicillin 100–500 mg q.d.–b.i.d., Dapsone 50–200 mg q.d., Clindamycin 1% lotion, gel, solution,pledget, Azelaic acid 20% cream Crotamiton 10% q.d.–t.i.d., Erythromycin 2% solution, ointment, pledget, Permethrin cream 5% q.d.–q.w. Lindane 1% cream q.d., Benzoyl peroxide 5%/ clindamycin 1% etc. The oral treatment of rosacea involves the use of tetracyclines. Tetracycline 500 mg twice a day is an effective treatment, but when it is taken with food it absorption may be decreased. Doxycycline and minocycline 50 -100 mg once daily to twice daily are the most currently used oral antibiotics by dermatologists for the treatment of rosacea [33, 34].

Duration of therapy

In case of rosacea it depends on how well treated the patients are. Like acne, rosacea the continuous use of therapy has advantages. Many acne and rosacea patients can continue with an antibiotic for more than a year without adverse effects. A suggested standard for diagnosing and treating rosacea in patients on the basis of our clinical experience appears in Fig 4.

A stepwise approach therefore includes: (i) getting the inflammatory lesions under control; (ii) using laser modality to get free of the blood vessels (under control), (iii) and finally use brimonidine to minimize the background erythema (Fig. 5) [11].

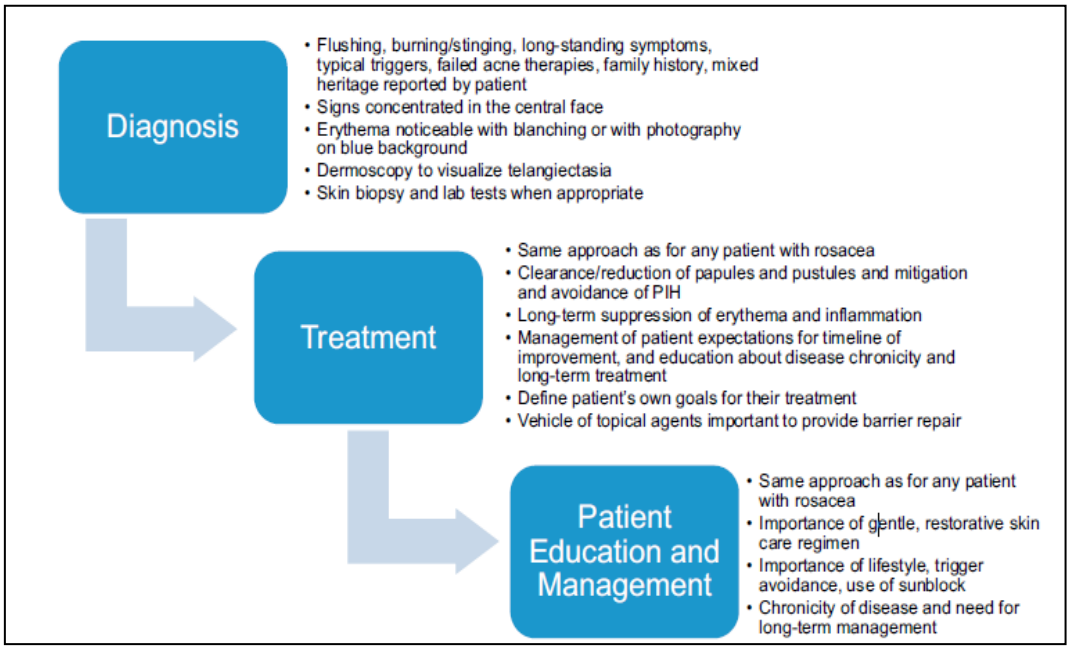

Fig 4: Different steps in Rosacea from diagnosis to treatment [7]

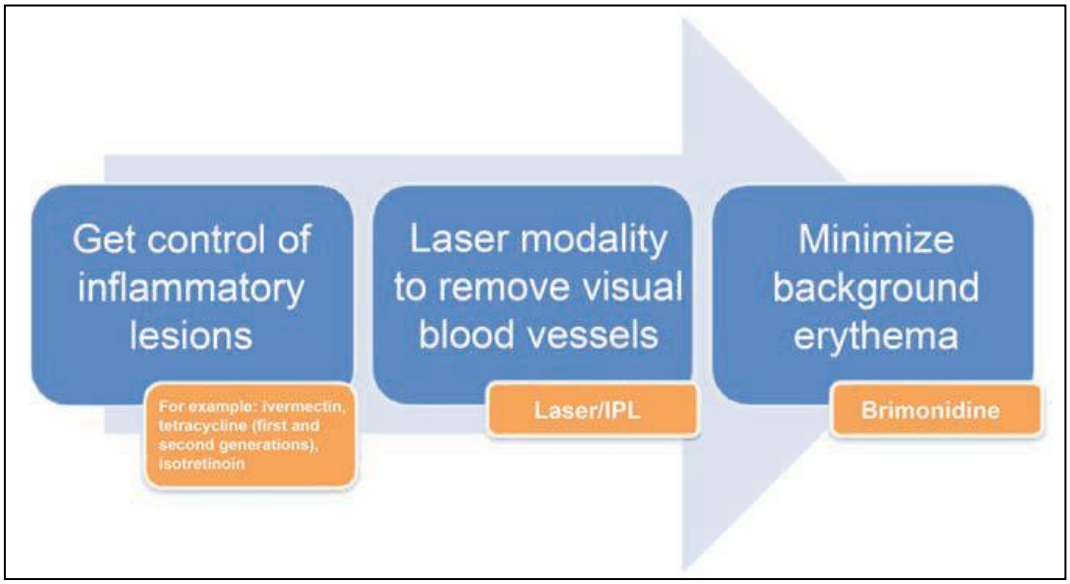

Fig 5: Step by step treatment of rosacea [11]

Conclusion

Rosacea is a unique anti in flammatory and anti-erythematous treatments. The pathophysiology of rosacea is still poorly understood. So to treat rosacea effectively, it is very important to know the factors, symptoms and also the triggers. Information about possible triggers of flushing can allow the patient to decide which are important for them. For patients with inflammatory papules or pustules and a significant erythematous component, topical therapy may be considered. Generally the most effective topical therapies seem to be

azelaic acid, brimonidine, ivermectin, and oxymetazoline hydrochloride. Combinations of topical and oral therapy may provide satisfactory results for individuals with mild-to-moderate rosacea or for those with both inflammatory and erythematous components.

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