



ROSACEA: A REVIEW

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Abstract: Rosacea is a facial skin condition causing inflammation and vascular dysfunction, influenced by microbiota. It affects individuals with diseases like Demodex folliculorum mites, Helicobacter pylori, Staphylococcus epidermidis, Chlamydia pneumoniae, and Bacillus oleronius. Treatment options include topical metronidazole and azelaic acid, while severe cases can be treated with oral metronidazole, tetracyclines, or isotretinoin. The condition negatively impacts quality of life, self-esteem, and well-being. Treatment options include topical and systemic treatments, as well as skin care and advanced scientific research.

Keywords: demodex folliculorum, nodularities, phyma, telangiectases.

I. Introduction

Rosacea is a distinctive, chronic skin condition primarily affecting the middle of the face [1]. Rosacea is a common cutaneous condition that accounts for 0.5% to 1% of all patients examined in a dermatology department [2]. Rosacea is a common cutaneous condition that accounts for 0.5% to 1% of all patients examined in a dermatology department [3]. Rosacea, a condition affecting the face, significantly impacts wellbeing, self-esteem, and quality of life. It can be effectively managed through various approved therapies and general skin care [4]. This condition is characterized by redness, flushing, acne, pustules, and dilated blood vessels, often affecting the eyes and causing skin thickening, especially in the nose [5]. Ocular symptoms such as dryness, photophobia, conjunctivitis, blepharitis, and, in rare instances, keratitis that could impair vision are experienced by more than half of rosacea patients. Rosacea can strike at any age, however it typically first manifests between the ages of 30 and 50. Topical brimonidine and oxymetazoline are approved treatments for erythema; topical ivermectin, metronidazole, azelaic acid, and oral doxycycline 40 mg modified release are approved treatments for papules/pustules. Erythema, phyma, and telangiectasia can all be treated using laser and light-based therapy. The latter might also need to be corrected surgically [6]. Rosacea is home to various microbes such as Bacillus oleronius, Demodex associated bacterium, Staphylococcus epidermidis, Helicobacter pylori, and Demodex folliculorum mites [7].

II. Epidemiology

Rosacea is prevalent in Caucasians with pale, sun-sensitive skin, with a lower diagnosis rate among darker skin tones. Possible causes include melanin's UV radiation protection and genetic variations in rosacea susceptibility [8]. Rosacea, a skin condition with a distinctive centro-facial composition, is difficult to link to a specific cause due to its dense concentration of sebaceous glands, neural and vascular networks, and Demodex mites. Symptoms are often described as searing or stinging pain, and eliminating Demodex infestation may help alleviate rosacea symptoms by stopping the production of pro-inflammatory cytokines [9].

III. Pathogenesis

Multiple evidence supports flushing in rosacea etiology, with face exhibiting flushing reactions more frequently and for longer duration [10]. Early stages of Rosacea involve flushing episodes, which eventually develop into persistent dark red erythema. Most individuals experience telangiectases and erythrosis in the same flushing regions, triggered by emotional stress, spicy food, wind, alcohol, and hot beverages, which often worsens in heat [11]. The association between rosacea and single nucleotide polymorphisms in major histocompatibility complex gene associations suggests genetic vulnerability with altered immune reactivity [12]. Microbes like Demodex species and bacteria like *Bacillus oleronius* and *Staphylococcus epidermidis* can trigger both innate and adaptive immune responses [13]. The study examined the potential impacts of rosacea [14].

i) vascular disease

Dermal edema can increase vascular permeability, with redness being common and the most annoying subtype. Non-transient erythema may be hidden by dry, irritated skin or inflammation from papules and pustules, affecting the neurovascular component.

ii) neurovascular component

The study found that individuals with rosacea have a lower heat pain threshold, increased sensitivity to noxious heat stimuli, and a higher subjective burning perception, particularly in areas with PPR vs ETR, compared to non-affected areas.

iii) inflammation: innate immunity

During the development of rosacea, both innate and adaptive immune systems play a role. T-cells and macrophages release chemicals that cause persistent vasodilation, erythema, and draw in neutrophils and other cells, resulting in pustules in clinical settings.

iv) demodex folliculorum

Humans have two species of Demodex mites: *D. brevis* and *D. folliculorum*, with a 0.1-0.4 mm length. Rosacea patients have a higher mean mite density and prevalence of *D. folliculorum* compared to controls and acne [15].



Figure 1: Demodex folliculorum in cluster obtained by the skin surface biopsy technique (original magnification, 3200) [16].

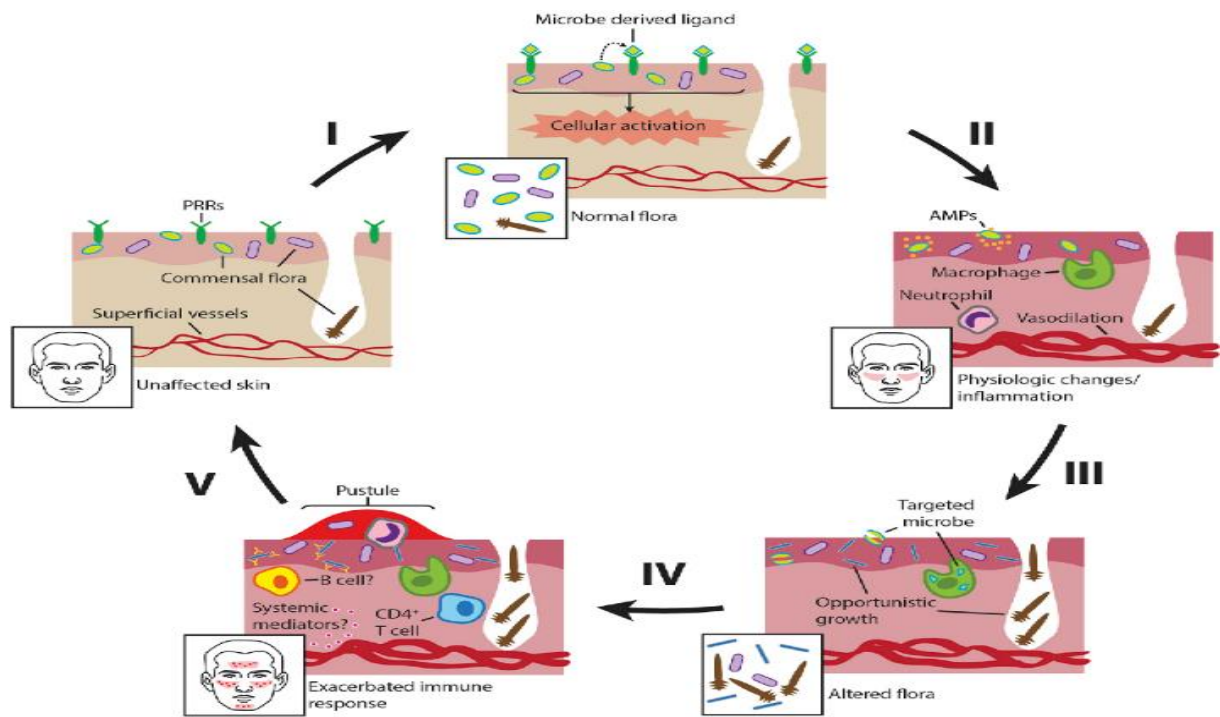


Figure 2: The study suggests that microbes play a significant role in rosacea, with normal flora and microbe-sensing machinery being more expressed in rosacea-prone skin than non-afflicted skin. Commensal substances can trigger inflammation by activating pattern recognition receptors or changing tolerance. The skin's physiological and inflammatory alterations may create a favourable microenvironment for modified microbial species' proliferation or metabolism. Modifications to commensal flora or non-commensal substances may aggravate the disease or cause unique symptoms. The immune system's ability to eliminate aggravating substances may provide temporary relief and restore microbial balance [17].

IV. Variants

1. Granulomatous Rosacea

Granulomatous rosacea is a type of rosacea with brown-red papules or nodules, often affecting the lower eyelids and cheeks. It has a chronic course and may not always require the presence of other rosacea symptoms, despite the common features of the two conditions. 15% of individuals have additional facial lesions.

2. Rosacea fulminans

In 1940, O'Leary and Kierland first described pyoderma facial, later named Rosa fulminans. This condition, primarily affecting young women, can cause sudden deep abscesses, confluent sinuses, papules, pustules, and massive coalescent nodules. Typically affecting the forehead, cheeks, and chin, it can also affect the entire face in more severe cases [18].

V. SUBTYPES

1. Erythematotelangiectatic type (ETR)

Rosacea patients experience persistent flushing, while others experience transient flushing due to social situations, physical activity, or hot weather. Topical treatments can worsen these symptoms, including itching due to makeup, sunscreen, and redness-reducing medications. Treatment options include brimonidine, azelaic acid, and metronidazole, which can be used separately or in combination to reduce inflammation by modifying neutrophil chemotaxis [19].

2. Papulopustular rosacea (PPR)

PPR, also known as classic rosacea, pink papular rosacea, and typologic center illness, is a condition characterized by a prominently red central region of the face and continuous or intermittent inflammation [20]. Patients with a central facial distribution of papules or pustules are classified as having the papulopustular rosacea subtype, which can lead to long-term facial oedema [21].

3. Phymatous rosacea

Phymatous rosacea, one of four rosacea subtypes, affects the nose, chin, forehead, ears, and eyelids, characterized by noticeable skin thickening and irregular surface nodularities, according to an expert committee.

4. Ocular rosacea

Rosacea patients often experience ocular symptoms like blepharitis and conjunctivitis, with potential for chalazion on the lids and irritation of the meibomian gland. This condition can lead to interpalpebral conjunctival hyperemia, conjunctival telangiectases, dry, itchy, or watery eyes, and may also involve meibomian glands [22].

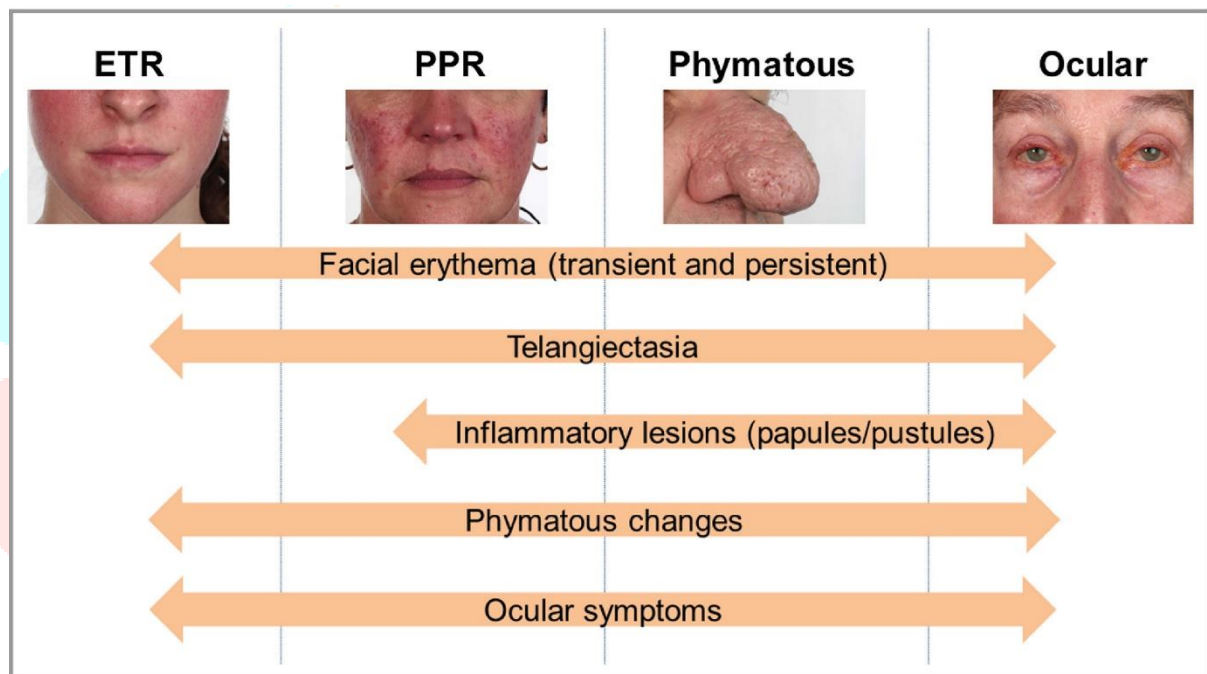


Figure 3: types of rosacea [23].

VI. Treatments

Combination therapy, a common treatment recommended by dermatologists, is only partially supported by available data on its effectiveness [24].

Table 1: New and emerging indications for already available medications for the treatment of rosacea, as well as agents under development or recently approved [25].

Agent	Manufacturer	Route of administration	Patients enrolled	Phase, status and reference
B244 spray	AOBiome LLC	Topical	140	Phase II, completed [50]
DMT210 5% gel	Dermata Therapeutics	Topical	104	Phase II, completed [58]
Encapsulated benzoyl peroxide cream (1% and 5%); brand name: Epsolay® (5%)	Sol-Gel technologies, Ltd.	Topical	733	Phase III, completed [41–46], under FDA review, and FDA assigned Prescription Drug User Fee Act for April 2021 [47]
Erenumab 140 mg 4-weekly; brand name Aimovig®	Novartis Pharmaceuticals Corporation	Subcutaneous	30	Phase II, recruiting [49]
Hydroxychloroquine 200 mg twice daily	Various manufacturers	Oral	6	Pilot study [59]
			66	Pilot study [60]
Minocycline				
Minocycline extended release capsules (DFD-29 20 and 40 mg)	Dr Reddy's Laboratories Ltd	Oral	205	Phase II, completed [40]
Minocycline foam (FMX103 1.5% and 3%); brand name: Zilxi™ (1.5%)	VYNE Therapeutics Inc.	Topical	1522	Phase III, completed, FDA approved [37, 38]
Minocycline gel 1% and 3%	Hovione Scientia, Ltd	Topical	270	Phase IIb, completed [39]
Omiganan gel	Maruho Co., Ltd	Topical	240	Phase II, completed [53]
			307	Phase III, completed [51]
			463	Phase III, completed [54]
			263	Phase III, completed [52]
Rifaximin; brand name Xifaxan®	Alfasigma S.p.A	Oral	236	Phase II, completed [57]
Secukinumab 300 mg weekly for 5 weeks then monthly; brand name Cosentyx®	Novartis Pharmaceuticals Corporation	Subcutaneous	24	Phase Ib, completed [48]

VII. Conclusion

Rosacea is an inflammatory condition affecting the face center, with or without eye involvement. Research on dysbiosis in the gastrointestinal and cutaneous systems is improving our understanding of rosacea. Treatment focuses on erythema and papules/pustules, but ocular rosacea and phyma have received limited attention. To maintain eye health, reduce oral therapy, switch to topical treatments, provide guidance on physical therapies like laser treatment, and provide detailed medical and physical care.

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