WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 9, 412-423. Review Article ISSN 2277–7105

ROSACEA: A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY, DIAGNOSIS, AND MANAGEMENT

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Article Received on
07 March 2025,

Revised on 28 March 2025,
Accepted on 18 April 2025

DOI: 10.20959/wjpr20259-36419

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ABSTRACT

Rosacea is a prevalent inflammatory dermatological illness that primarily affects the central area of the face and is chronic and prone to relapse. It can manifest as a variety of clinical symptoms, including telangiectasia, papules, pustules, ocular signs, and temporary or chronic face erythema. Although the precise pathophysiology is still complex and poorly understood, deregulation of the innate and adaptive immune systems, neurovascular instability, changes in the skin microbiota (particularly Demodex mites), and hereditary susceptibility are all contributory factors. Additionally, recent research highlights the connection between rosacea and systemic conditions such gastrointestinal dysfunction and cardiovascular disease. The majority of the diagnostic evaluation is clinical, with non-invasive imaging methods and occasionally histological evaluation as supplements. Topical and systemic medicines, laser therapy, and lifestyle changes are some examples of management techniques.[1–5]

KEYWORDS: Rosacea, Pathophysiology, Demodex, Inflammation, Treatment, Topical Therapy, Systemic Therapy.

1. INTRODUCTION

The visual symptoms and accompanying discomfort of rosacea, a chronic, relapsing inflammatory dermatosis of the central face, greatly impair patients' quality of life. Known historically as the "curse of the Celts," rosacea was originally believed to primarily affect people with light skin, although it is now known to affect people of all skin types. However, patients with darker skin tones may have subtler and harder-to-detect erythema and telangiectasias, which could result in underdiagnosis.[6]

Though men frequently have more severe phymatous forms, the ailment usually manifests between the ages of 30 and 60, peaking around age 40. Its incidence is higher in women. Its erratic course, which is characterized by flare-ups and remissions, exacerbates patient annoyance and may cause them to put off seeking medical help.[7]

The classification and treatment of rosacea have undergone significant changes in recent years. A phenotype-based classification has replaced a conventional subtype system, enabling customized, symptom-focused treatment. Similar to this, improved diagnostic and treatment techniques, such as targeted pharmaceutical drugs and laser therapy, have been made possible by developments in our understanding of neurovascular signaling, skin immunological function, and microbiome interactions.[8–10] Key results and updates from the fields of epidemiology, pathophysiology, diagnosis, treatment, and new therapeutics are summarized in this review.

2. EPIDEMIOLOGY

Global prevalence estimates of rosacea range from 5% to 10%, differing based on geography, study design, and diagnostic criteria. Fitzpatrick skin types I and II, especially those of Northern or Eastern European ancestry, are more likely to have the disorder. But rather than reflecting actual epidemiologic disparities, this probably reflects diagnostic bias.[11] Although men frequently suffer from more severe versions, women between the ages of 30 and 50 are disproportionately affected. Geographic variations in occurrence may be partially explained by occupational and environmental exposures, such as hot climes, air pollution, and sun exposure, which can worsen symptoms. A higher incidence is seen in urban populations, which may be related to environmental and lifestyle factors.[12]

With a peak incidence around age 40, the condition usually manifests between the ages of 30 and 60. Men often appear with more severe types, including phymatous rosacea, while women are diagnosed more often. Up to 40% of patients have a positive family history, suggesting a possible genetic predisposition.

Several environmental and lifestyle risk factors have been implicated, including:

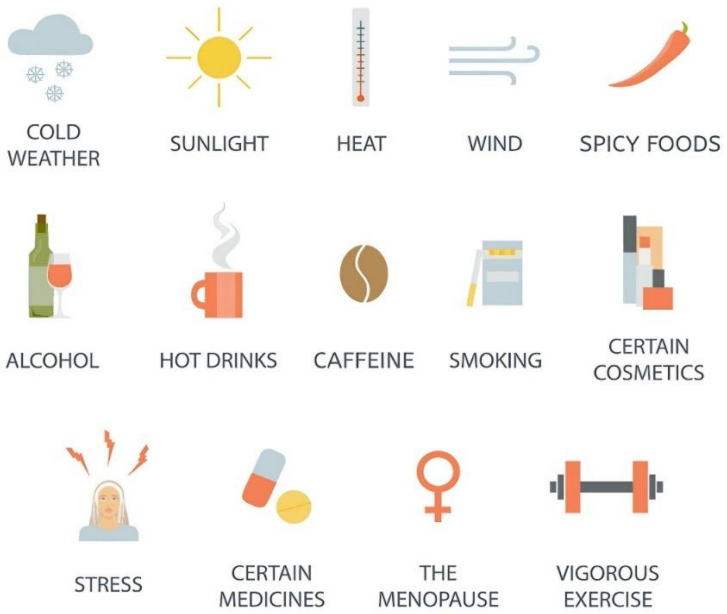

Fig. No. 1: Risk Factors.

According to new information, urbanization, pollution, and greater knowledge and reporting of rosacea may be contributing factors to the disease's rising global incidence. More cases are being found thanks to developments in digital teledermatology, especially in underserved and distant areas. As per 2015 comprehensive study, 1.5% to 10% of adults worldwide suffer from rosacea, and up to 40% of patients have a family history, indicating a heritable component. Alcohol, hot food, mental stress, UV radiation, and topical corticosteroid use are other risk factors.[13]

Moreover, rosacea is increasingly recognized to coexist with several systemic diseases:

- Cardiovascular disease (e.g., hypertension, dyslipidemia)
- Gastrointestinal disorders, such as *H. pylori* infection and small intestinal bacterial overgrowth
- Endocrine and metabolic conditions, including diabetes and obesity
- Neuropsychiatric conditions, notably depression, anxiety, and Parkinson's disease[14–16]

These associations suggest rosacea may reflect broader systemic dysregulation and support a multidisciplinary approach in management.

Symptoms of Rosacea

Cutaneous Symptoms

- Flushing: Intermittent, intense redness triggered by heat, stress, or certain foods.[17]
- Persistent Erythema: Chronic central facial redness due to vasodilation and vascular hyperreactivity.[18]
- Papules and Pustules: Inflammatory lesions resembling acne but without comedones.[19]
- Telangiectasia: Visible dilated blood vessels, particularly on the cheeks and nose.[20]
- Burning or Stinging Sensation: Often associated with facial sensitivity and skin barrier dysfunction.[21]
- Dryness and Rough Texture: Frequently reported due to impaired epidermal hydration.[22]
- Facial Edema: Soft tissue swelling, particularly in the periorbital area.[23]
- Phymatous Changes: Skin thickening, often localized to the nose (rhinophyma), more common in men.[18]

Ocular Symptoms

- Dry, Gritty Sensation in the Eyes: A hallmark of ocular rosacea.[24]
- Redness of the Conjunctiva and Eyelids: Reflects ongoing ocular inflammation.[25]
- Tearing, Burning, or Stinging Eyes: Due to meibomian gland dysfunction and surface irritation.[26]
- Foreign Body Sensation: A common complaint in moderate to severe ocular involvement.[27]
- Blepharitis and Meibomian Gland Dysfunction: Eyelid margin inflammation and oil gland dysfunction.[28]
- Photophobia: Light sensitivity, especially in advanced ocular rosacea.[29]

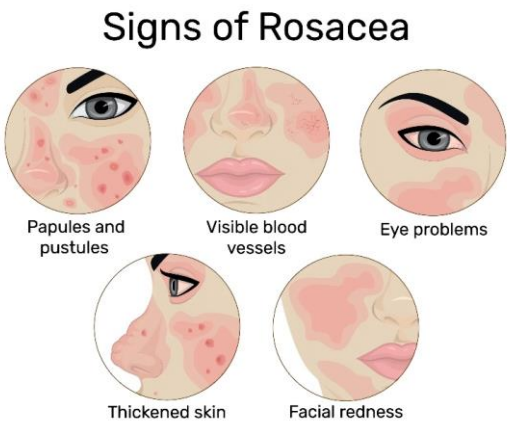

Fig. No. 2: Signs of Rosacea.

Causes and Contributing Factors of Rosacea

Rosacea is a multifactorial condition with no single definitive cause. However, several internal and external factors are known to contribute to its development:

1. Genetic Predisposition

- A family history of rosacea is seen in up to 40% of patients, suggesting a heritable component.[30]
- Genome-wide studies have identified potential susceptibility loci associated with immune and vascular regulation.[31]

2. Dysregulated Immune Response

- Upregulation of Toll-like receptor 2 (TLR2) and overproduction of cathelicidin (LL-37) promote inflammation and vascular changes.[32]
- Abnormal innate and adaptive immunity contribute to chronic inflammation.[33]

3. Neurovascular Dysregulation

- Flushing and persistent erythema are linked to increased expression of TRPV1 channels, which regulate vasodilation and sensory nerve activation.[34]
- This leads to hypersensitive blood vessels and heightened skin sensitivity.

4. Microbial Involvement

- Demodex folliculorum mites are more abundant on rosacea skin and trigger inflammation through their bacterial symbionts, such as *Bacillus oleronius*.[35]
- Helicobacter pylori infection has been associated with systemic inflammation and may exacerbate rosacea symptoms in some individuals.[36]

5. Environmental and Lifestyle Triggers

Certain triggers can exacerbate rosacea symptoms, including:

- UV radiation – increases oxidative stress and inflammation.[37]
- Hot or spicy foods and beverages
- Alcohol consumption – especially red wine.[38]
- Temperature extremes – both hot and cold weather
- Emotional stress – linked to vasomotor instability
- Strenuous exercise
- Topical corticosteroids or irritants – can induce rosacea-like dermatitis.[39]

6. Skin Barrier Dysfunction

- Increased transepidermal water loss (TEWL) and reduced skin hydration compromise the barrier, making the skin more reactive to irritants and microbes.[40]

7. Hormonal and Metabolic Factors

- Fluctuations in sex hormones (e.g., during menopause) may influence vascular reactivity and inflammation.[41]
- Associations with metabolic syndrome and insulin resistance have also been reported.[42]

4. Classification and Subtypes

The traditional classification included four subtypes:

1. **Erythematotelangiectatic Rosacea (ETR)** – Persistent central facial redness and telangiectasias
2. **Papulopustular Rosacea (PPR)** – Inflammatory papules and pustules on erythematous skin
3. **Phymatous Rosacea** – Tissue hypertrophy and sebaceous hyperplasia, especially on the nose (rhinophyma)
4. **Ocular Rosacea** – Red, dry, irritated eyes and lids (blepharitis, conjunctivitis)[43]

   In 2017, a phenotype-based classification was introduced to address the limitations of subtype definitions. This modern approach assesses individual clinical features such as flushing, inflammation, phymatous changes, and ocular involvement to guide treatment decisions more effectively.[44]

5. Pathophysiology

Rosacea's pathogenesis is complex, involving multiple overlapping mechanisms:

- **Immune System Dysregulation**: Kallikrein-5, which cleaves cathelicidin into LL-37, a pro-inflammatory peptide that causes chemotaxis and vascular alterations, is expressed more when Toll-like receptor 2 (TLR2) is overactivated. An inflammatory cascade is supported by elevated levels of TNF-α, interleukin-1β, and other cytokines.[45, 46]
- **Neurovascular Dysregulation**: Vasodilation and flushing are brought on by abnormal activation of transient receptor potential (TRP) channels, particularly TRPV1. Erythema and edema are also caused by neurogenic inflammation, which is mediated by neuropeptides such as substance P.[47]
- **Microbial Involvement**: Immune activation is triggered by increased colonization by Demodex folliculorum and its related bacteria, Bacillus oleronius. Skin lesions are made

worse by inflammatory reactions to these microorganisms. Furthermore, infection with Helicobacter pylori has been suggested as a possible systemic cause.[48,49]

- **Skin Barrier Dysfunction:** Rosacea patients have higher skin pH, a disturbed lipid composition, and increased transepidermal water loss (TEWL), all of which increase sensitivity and irritation susceptibility.[50]
- **Genetics and Matrix Remodeling**: Numerous susceptibility loci have been found by genome-wide association studies (GWAS). Increased matrix metalloproteinase (MMP) activity, particularly MMP-9, deteriorates inflammation and destroys skin structures. These interrelated pathways result in the phenotypic variability seen in rosacea, including facial flushing, persistent erythema, inflammatory lesions, and phymatous changes.[51]

6. Diagnosis

The main method of diagnosing rosacea is clinical assessment. Diagnostic criteria include the appearance of persistent central facial erythema accompanied by one or more secondary symptoms, such as ocular signs, papules, pustules, telangiectasias, or flushing.[52] Disease assessment is aided by dermoscopy, digital photography, and non-invasive imaging techniques like laser Doppler flowmetry. Referral to an ophthalmologist is required when ocular involvement is suspected.[53]

Differential diagnoses include

- Acne vulgaris
- Seborrheic dermatitis
- Perioral dermatitis
- Lupus erythematosus

Histopathology may be employed in ambiguous cases, revealing perivascular and perifollicular lymphohistiocytic infiltrates and dermal telangiectasia.

7. Treatment Strategies

Treatment is guided by clinical phenotype and disease severity:

- **Topical agents**

Topical agents are generally first-line treatments for mild to moderate rosacea, especially the papulopustular and erythematotelangiectatic phenotypes:

- **Metronidazole (0.75–1%)**: A well-established agent with anti-inflammatory and antioxidant properties. It is well-tolerated and effective for reducing inflammatory lesions.
- **Azelaic Acid (15–20%)**: Exhibits anti-inflammatory and keratolytic effects, and helps reduce erythema and papules.
- **Ivermectin (1%)**: Targets inflammatory lesions and has anti-parasitic effects on *Demodex folliculorum*, thought to play a role in rosacea pathogenesis.
- **Brimonidine and Oxymetazoline**: Alpha-adrenergic agonists that cause vasoconstriction to reduce persistent facial erythema.[54]

- **Systemic agents**

Systemic therapies are preferred in moderate to severe cases or when topical treatments are insufficient:

- **Doxycycline (40 mg modified-release)**: Offers anti-inflammatory benefits at sub-antimicrobial doses, with minimal risk of bacterial resistance
- **Tetracyclines (doxycycline, minocycline)**: Commonly used in standard doses (100 mg) for short-term control of papulopustular rosacea
- **Isotretinoin**: Reserved for refractory rosacea or phymatous subtypes. It reduces sebaceous gland activity and inflammation.[55]

- **Laser and light therapy**

Used primarily for **persistent erythema and telangiectasias**:

- **Pulsed Dye Laser (PDL)** and **Intense Pulsed Light (IPL)**: Effective in reducing vascular lesions by targeting hemoglobin
- **Nd:YAG Laser**: Can treat deeper and more prominent vessels.[56]

- **Ocular rosacea management**
- **Oral doxycycline or tetracycline**: Reduces ocular inflammation and blepharitis.
- **Lid hygiene and artificial tears**: Improve symptoms of dry eyes and irritation.[57]

- **Lifestyle and skincare**
- Use of non-irritating, fragrance-free cleansers and moisturizers.
- Daily broad-spectrum sunscreen with SPF ≥ 30 to prevent UV-triggered flares. Avoidance of known triggers: hot beverages, alcohol, spicy foods, extreme temperatures, and emotional stress.[58]

8. Antibiotic Resistance and Challenges

Concerns about antimicrobial resistance have been raised by the long-term use of antibiotics in rosacea, especially those containing macrolides (like erythromycin) and tetracyclines (like doxycycline and minocycline). Even while these substances aren't used mainly for their ability to kill bacteria in rosacea, long-term use can nevertheless put commensal skin and gut microbiota under selective pressure, which can lead to the development of resistant bacterial strains. This issue has led to a move toward sub-antimicrobial dosing regimens and is particularly pertinent in an era of rising antibiotic resistance worldwide.

Low-dose doxycycline (40 mg/day), which maintains strong anti-inflammatory qualities without having clinically meaningful antibacterial effects, is one of the most commonly used remedies.

With a decreased chance of selecting for resistant organisms, this sub-antimicrobial regimen has shown effectiveness in decreasing inflammatory lesions including papules and pustules. It provides a safer long-term approach for chronic therapy by modifying inflammatory mediators, such as matrix metalloproteinases (MMPs), as opposed to preventing bacterial growth.

However, because rosacea is a chronic and recurrent condition, controlling it is still difficult. Patients often have recurrence after stopping medication, even with adequate therapy.

In light of these factors, there is growing emphasis on minimizing unnecessary antibiotic exposure, promoting topical alternatives (e.g., ivermectin, azelaic acid), and incorporating adjunctive skincare, trigger avoidance, and patient counseling into a comprehensive rosacea management plan.[59]

9. Emerging Therapies

Promising therapeutic approaches include:

- **Minocycline foam**: Topical anti-inflammatory with low systemic absorption
- **TRPV1 antagonists**: Block neurogenic inflammation and reduce flushing
- **Botulinum toxin A**: May modulate neurovascular activity
- **Probiotics and microbiome-targeted treatments**: Aim to restore microbial balance.[60,61,62]

10. CONCLUSION

Rosacea is a complex condition that is impacted by vascular, immunological, genetic, and microbiological variables. Diagnostic precision is being improved by advances in imaging and biomarker discoveries, even though diagnosis is still clinical. There is potential for more individualized and efficient care thanks to phenotype-driven treatment approaches and new medicines. Addressing the unmet needs of rosacea patients worldwide will require ongoing research and clinical education.

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