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REVIEW ARTICLE

A Review on Pathophysiology and Current Treatment Trends of Rosacea

Madan Attimarad*[1], Rajashree Masareddy[2], Archana Patil[3]

[1] *Research Scholar, Department of Pharmaceutics, KLE College of Pharmacy, Belagavi, Karnataka, India*
[2] *Professor, Department of Pharmaceutics, KLE College of Pharmacy, Belagavi, Karnataka, India*
[3] *Associate Professor, Department of Pharmaceutics, KLE College of Pharmacy, Belagavi, Karnataka, India*

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Abstract: Rosacea is a chronic inflammatory erythematous condition characterized by recurrent flushing, telangiectasia, papules, pustules, and potential progression to rhinophyma in advanced stages. The condition affects approximately 5.46% of the global population, predominantly individuals of northern European descent and those with fair skin. Rosacea's impact extends beyond physical manifestations, often leading to significant psychosocial complications including anxiety, depression, and social isolation. The pathophysiology of Rosacea involves vascular dysfunction, immune dysregulation, microbiome alterations, and environmental triggers. Management strategies vary based on disease subtype and severity, with topical agents such as metronidazole, azelaic acid, and ivermectin serving as first-line treatments for mild to moderate cases. Systemic therapies, including oral antibiotics and retinoids, are reserved for moderate to severe presentations. Laser and light-based treatments have shown considerable efficacy in addressing vascular manifestations. Recent treatment trends include using probiotics, microbiome modulation, and targeted biologics, including interleukin-17 inhibitors, interleukin-23 inhibitors, and CGRP antagonists. Despite the therapeutic advances, challenges persist regarding drug resistance and treatment limitations.

Keywords: Rosacea; Inflammation; Demodex mites; Vascular dysfunction; Immunomodulation.

1. Introduction

Rosacea manifests as a chronic inflammatory cutaneous disorder predominantly affecting facial skin, characterized by persistent erythema, flushing, telangiectasia, papules, pustules, and in advanced cases, rhinophyma. Global epidemiological data indicates a prevalence rate of 5.46%, though significant regional and ethnic variations exist. The condition demonstrates higher prevalence among individuals of northern European descent, particularly those with fair skin, where rates can reach 10% [1, 2].

The age of onset typically occurs between 30-50 years, with women showing higher incidence rates. However, men often present with more severe manifestations, particularly rhinophyma, attributed to hormonal influences, sebaceous gland activity, and vascular factors [3]. The condition's impact extends far beyond its physical manifestations, significantly affecting patients' quality of life through psychological distress, social anxiety, and diminished self-esteem [4].

Despite its prevalence and impact, rosacea remains frequently underdiagnosed and sub-optimally managed, partly due to limited awareness among healthcare providers and patients alike. The condition's presentation in darker skin tones poses particular diagnostic challenges, as the characteristic erythema may be less apparent, leading to potential underreporting in these populations [5, 6]. Recent molecular and clinical investigations have illuminated complex pathophysiological mechanisms underlying rosacea. These include alterations in both innate and adaptive immune responses, aberrant mast cell activity, and neurovascular dysfunction [7]. A crucial pathological feature involves compromised cutaneous barrier function, manifesting as increased transepidermal water loss, altered pH balance, disrupted microbiome homeostasis, and modified molecular architecture. These changes collectively enhance skin sensitivity and susceptibility to inflammatory responses [8].

The condition's multifactorial nature necessitates comprehensive therapeutic approaches. Various triggers, both endogenous and environmental, can initiate or exacerbate symptoms, highlighting the importance of trigger identification and avoidance in management strategies [9]. Advancing our knowledge of these underlying mechanisms continues to drive the development of more effective therapeutic interventions [10]

* Corresponding author: Madan Attimarad

2. Clinical Classification of Rosacea

2.1. Erythematotelangiectatic Rosacea (ETR)

Erythematotelangiectatic rosacea represents the most prevalent subtype, characterized by persistent central facial erythema and visible telangiectasia. Patients typically experience heightened cutaneous sensitivity and frequent flushing episodes triggered by various environmental and lifestyle factors including UV exposure, thermal changes, alcohol consumption, spicy foods, and emotional stress [11]. The pathophysiological basis involves significant neurovascular dysregulation, leading to prolonged vasodilation and eventual structural modifications in superficial blood vessels [12].

Recent investigations have revealed impaired barrier function in ETR patients, evidenced by increased transepidermal water loss and altered stratum corneum integrity. These modifications enhance skin susceptibility to external irritants and perpetuate inflammatory cascades [13]. The chronic nature of vascular dysfunction eventually leads to permanent telangiectasia formation through repetitive vessel dilation and endothelial damage [14].

Table 1. Classification and Clinical Features of Rosacea Subtypes

Subtype	Primary Features	Secondary Features	Common Triggers
Erythematotelangiectatic	Persistent central facial erythema Flushing Telangiectasia	Burning/stinging Edema Roughness/scaling	Sun exposure Heat Emotional stress Spicy foods
Papulopustular	Papules Pustules Central facial erythema	Burning/stinging Edema Plaques	Microorganisms UV radiation Stress Diet
Phymatous	Skin thickening Irregular nodularities Area enlargement	Visible pores Telangiectasia Sebaceous hyperplasia	Chronic inflammation Genetic factors Environmental factors
Ocular	Eye irritation Burning/stinging Bloodshot appearance	Blepharitis Keratitis Light sensitivity	Screen time Wind Environmental irritants

2.2. Papulopustular Rosacea (PPR)

Papulopustular rosacea manifests through inflammatory papules and pustules predominantly affecting the central facial region. Unlike acne vulgaris, PPR lacks comedonal formation, serving as a crucial diagnostic differentiator. The inflammatory process stems from dysregulation of innate immunity, particularly involving antimicrobial peptide expression, notably cathelicidin LL-37 [15].

The pathogenesis involves activation of innate immune responses, leading to neutrophil recruitment and pro-inflammatory mediator release. This subtype frequently coexists with ETR features, creating complex clinical presentations requiring carefully tailored therapeutic approaches [16].

2.3. Phymatous Rosacea

Phymatous changes represent advanced manifestations of rosacea, characterized by tissue hyperplasia and fibrosis, most commonly affecting the nose (rhinophyma). The condition demonstrates marked gender disparity, predominantly affecting male patients, suggesting androgenic influence in its pathogenesis [17].

Histopathological examination reveals sebaceous gland hyperplasia, fibrosis, and extensive connective tissue remodeling. The progressive nature of tissue changes results from chronic inflammation-induced matrix metalloproteinase activation and subsequent collagen degradation [18].

2.4. Ocular Rosacea

Ocular involvement occurs in approximately 50-70% of rosacea patients, often preceding cutaneous manifestations. Clinical features include blepharitis, meibomian gland dysfunction, conjunctival hyperemia, and in severe cases, corneal complications [19]. The condition significantly impacts visual function and quality of life, necessitating early recognition and intervention.

The pathological process involves inflammatory mediator release affecting ocular surface homeostasis, tear film stability, and meibomian gland function. Chronic inflammation may lead to corneal neovascularization and potential vision impairment without appropriate management [20].

3. Pathophysiology

3.1. Genetic and Environmental Factors

Genetic predisposition plays a significant role in rosacea development, evidenced by familial clustering patterns and higher prevalence among specific ethnic groups. Several genetic polymorphisms affecting vascular regulation, immune response, and barrier function have been identified [21]. Environmental factors, including UV radiation, temperature extremes, and atmospheric pollution, interact with genetic susceptibility to trigger or exacerbate symptoms. This gene-environment interaction modulates disease expression and severity [22].

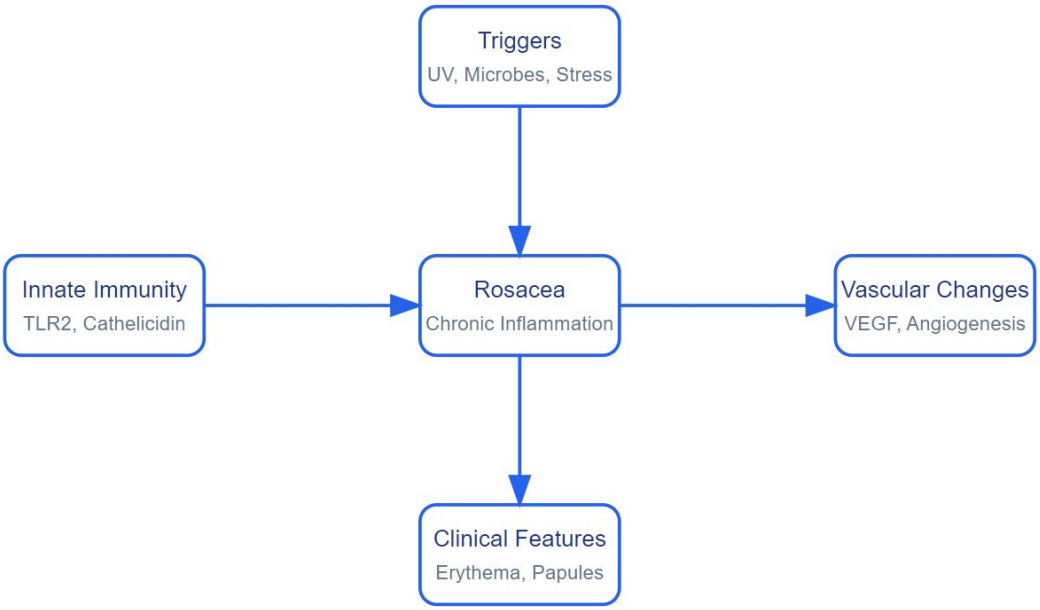

Figure 1. Pathophysiological Mechanisms in Rosacea

3.2. Vascular Dysfunction

3.2.1. Neurovascular Dysregulation

Aberrant neurovascular signaling represents a central pathogenic mechanism in rosacea. Enhanced expression of vasoactive neuropeptides, particularly calcitonin gene-related peptide (CGRP) and substance P, leads to persistent vasodilation and neurogenic inflammation [23]. These alterations result in increased blood flow, vessel permeability, and inflammatory cell recruitment to affected areas [24].

3.2.2. Endothelial Dysfunction

Chronic vascular changes involve endothelial cell activation and dysfunction, promoting inflammatory mediator release and vessel remodeling. Repeated vasodilation episodes lead to permanent structural alterations in dermal vasculature, manifesting as persistent erythema and telangiectasia [25].

3.3. Immune System Dysregulation

3.3.1. Innate Immunity

Dysregulation of innate immune responses plays a pivotal role in rosacea pathogenesis. Elevated expression of toll-like receptor-2 (TLR-2) and antimicrobial peptides, particularly cathelicidin LL-37, triggers inflammatory cascades. These molecular alterations lead to increased production of pro-inflammatory cytokines and chemokines [26].

3.3.2. Inflammatory Mediators

The inflammatory microenvironment in rosacea involves multiple mediators including matrix metalloproteinases, reactive oxygen species, and pro-inflammatory cytokines. These factors contribute to tissue damage, vascular changes, and clinical manifestations of the disease [27].

3.4. Alterations of Microbiome

3.4.1. Cutaneous Microbiota

Dysbiosis of the skin microbiome, particularly involving Demodex folliculorum mites and associated bacteria, contributes to rosacea pathogenesis. Elevated Demodex density correlates with disease severity and inflammatory responses [28]. The mites and their associated microorganisms trigger immune responses through TLR activation and inflammatory mediator release [29].

3.4.2. Gut-Skin Axis

Recent evidence suggests a significant role of the gut-skin axis in rosacea pathophysiology. Alterations in intestinal microbiota composition may influence systemic inflammation and cutaneous immune responses. This connection provides rationale for therapeutic approaches targeting microbiome modulation [30].

Table 3. Trigger Factors and Management

Category	Common Triggers	Management Strategies
Environmental	UV exposure Temperature extremes Wind Humidity	Broad-spectrum SPF Climate control Protective clothing Air quality management
Dietary	Spicy foods Hot beverages Alcohol Dairy products	Food diary Temperature modification Dietary adjustments Trigger identification
Lifestyle	Emotional stress Exercise Sleep deprivation Screen time	Stress management Modified exercise Sleep hygiene Regular breaks

3.5. External Triggers

Multiple external factors can initiate or exacerbate rosacea symptoms. UV radiation induces oxidative stress and matrix metalloproteinase production, while thermal changes affect vascular reactivity. Dietary factors, including spicy foods and alcohol, trigger neurogenic inflammation through various molecular pathways [31, 32].

4. Treatment and Management

4.1. Topical Treatment

4.1.1. Metronidazole

Metronidazole remains a cornerstone in topical rosacea management, available in various concentrations and formulations. Its therapeutic efficacy stems from multiple mechanisms including anti-inflammatory properties, reactive oxygen species reduction, and modulation of neutrophil activity. Clinical studies demonstrate significant reduction in inflammatory lesions and erythema with sustained use [33]. Long-term safety data supports its role as a first-line agent, particularly in mild to moderate papulopustular rosacea [34].

Table 2. Current Therapeutic Options and Evidence Levels

Treatment Type	Agent	Primary Indication
Topical	Ivermectin 1% Metronidazole 0.75%/1% Azelaic acid 15%/20% Brimonidine 0.33%	Papulopustular Papulopustular Papulopustular Persistent erythema
Systemic	Doxycycline 40mg MR Isotretinoin Tetracycline	Moderate-severe Severe/refractory Moderate-severe
Physical	Pulsed dye laser Intense pulsed light CO2 laser	Telangiectasia Erythema Rhinophyma

4.1.2. Azelaic Acid

Azelaic acid exhibits multifaceted therapeutic effects through anti-inflammatory, antioxidant, and antimicrobial mechanisms. Its ability to normalize keratinization and inhibit reactive oxygen species production provides additional benefits. Clinical trials demonstrate efficacy in reducing inflammatory lesions and erythema, with minimal adverse effects. The agent shows particular efficacy in combination therapy approaches [35, 36].

4.1.3. Ivermectin

Topical ivermectin represents an important therapeutic advancement, particularly effective against Demodex-associated inflammation. Its dual antiparasitic and anti-inflammatory properties provide comprehensive symptom control. Clinical studies demonstrate superior efficacy compared to vehicle alone in reducing inflammatory lesions, with sustained benefits observed during maintenance therapy [37, 38].

4.1.4. Vasoconstrictors

Brimonidine tartrate and oxymetazoline hydrochloride target persistent facial erythema through selective α-adrenergic receptor activation. These agents provide rapid but temporary improvement in erythema severity. Optimal results often require careful timing of application and consideration of potential rebound effects [39].

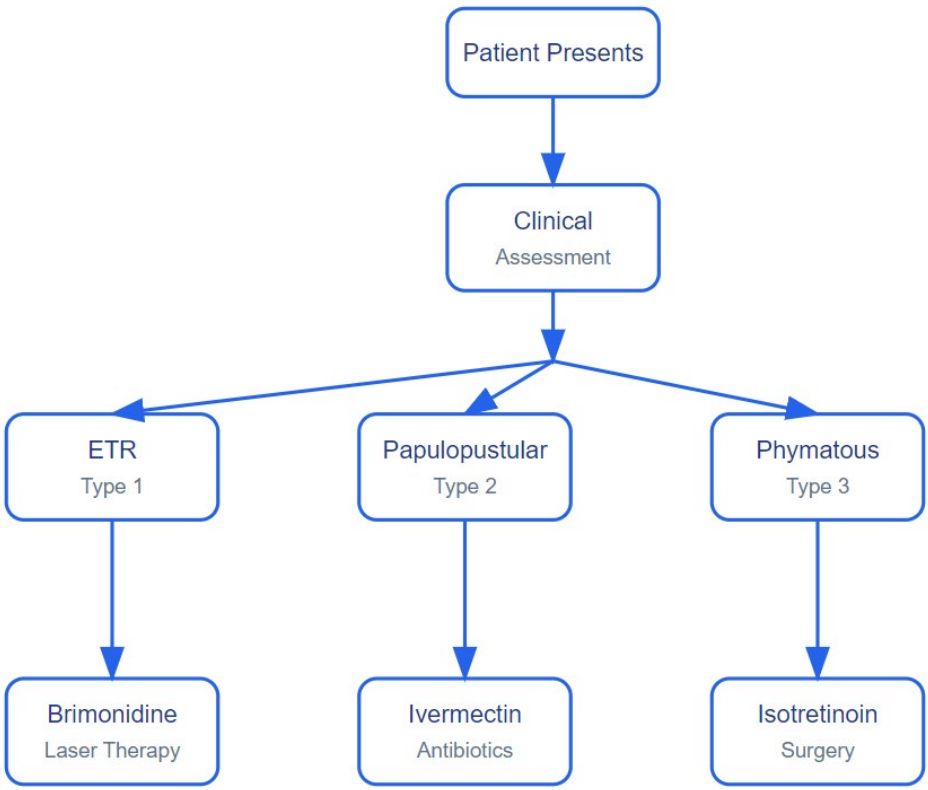

Figure 2. Treatment algorithm for Rosacea

4.2. Systemic Treatment

4.2.1. Tetracycline Derivatives

Oral tetracyclines, particularly doxycycline at sub-antimicrobial doses, demonstrate significant anti-inflammatory properties. These agents inhibit matrix metalloproteinases, reduce pro-inflammatory cytokine production, and decrease neutrophil activity. Modified-release formulations provide enhanced tolerability and reduced risk of antimicrobial resistance [40, 41].

4.2.2. Isotretinoin

In severe or refractory cases, oral isotretinoin provides effective control through multiple mechanisms including sebum production reduction, anti-inflammatory effects, and matrix metalloproteinase inhibition. Careful patient selection and monitoring remain essential due to potential adverse effects and teratogenicity concerns [42].

4.3. Physical Interventions

4.3.1. Laser Therapy

Vascular lasers, particularly pulsed-dye laser systems, effectively target telangiectasia and persistent erythema through selective photothermolysis. Treatment protocols require optimization based on individual patient characteristics and vessel depth. Multiple sessions typically yield optimal results with sustained improvement [43, 44].

4.3.2. Intense Pulsed Light

IPL therapy provides broad-spectrum improvement in vascular and inflammatory manifestations. Its versatility in targeting multiple chromophores allows simultaneous treatment of various rosacea features. Treatment parameters require careful adjustment based on skin phototype and specific target lesions [45]

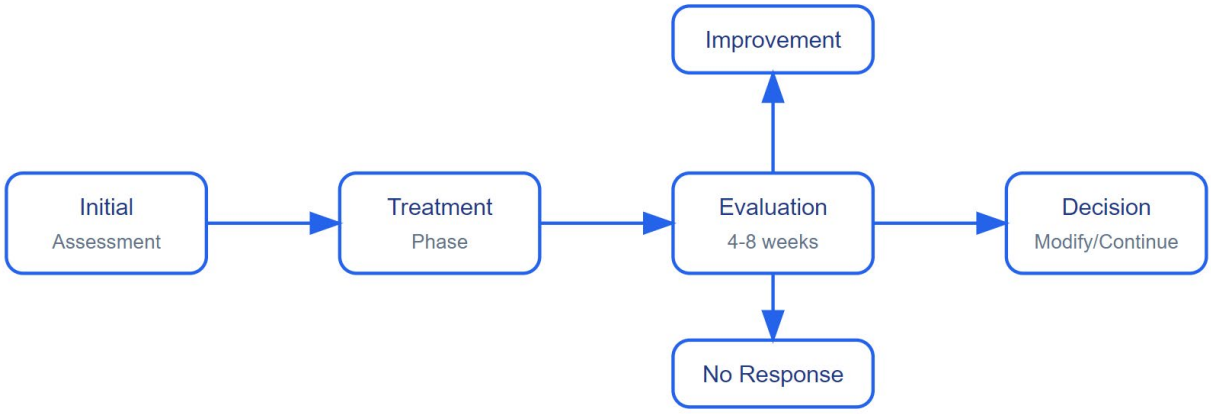

Figure 3. Treatment Response Monitoring

5. Current Research in the Treatment and Management of Rosacea

5.1. Novel Therapeutic Approaches

5.1.1. Microbiome Modulators

Recent advances in understanding the role of microbiome dysbiosis have led to the development of targeted microbiome-based therapies. These include selective antimicrobial peptides, probiotics, and microbiome transplantation approaches. Preliminary studies suggest promising results in restoring cutaneous microbiome homeostasis and reducing inflammation [46, 47].

5.1.2. Targeted Therapy

Emerging biological therapies targeting specific inflammatory pathways show potential in rosacea management. Anti-IL-17 and anti-IL-23 agents, successful in other inflammatory dermatoses, are under investigation for severe or refractory rosacea. Initial data suggests efficacy in reducing inflammatory manifestations [48].

5.1.3. CGRP Antagonists

Given the crucial role of neurogenic inflammation in rosacea pathogenesis, CGRP antagonists represent a novel therapeutic approach. These agents target the neurovascular component of the disease, potentially offering relief from flushing and persistent erythema. Clinical trials are ongoing to evaluate their efficacy and safety profile [49].

5.2. Advanced Drug Delivery Systems

5.2.1. Nanoformulations

Advanced drug delivery systems utilizing nanotechnology show promise in enhancing therapeutic efficacy. Nanocarriers improve drug penetration, stability, and targeted delivery to affected tissues. These formulations may reduce side effects while maximizing therapeutic benefits [50].

5.2.2. Smart Drug Release Systems

Development of environment-responsive drug delivery systems offers potential for improved treatment outcomes. These systems respond to specific triggers such as pH changes or inflammatory mediators, providing controlled release of therapeutic agents [51].

5.3. Personalized Medicine

5.3.1. Genetic Profiling

Advances in genetic analysis enable identification of specific molecular signatures associated with different rosacea subtypes. This information facilitates personalized treatment selection based on individual genetic profiles and disease mechanisms [52].

5.3.2. Biomarker-Based Treatment

Development of reliable biomarkers for disease activity and treatment response may enable more precise therapeutic targeting. Integration of clinical, molecular, and microbiome markers could optimize treatment selection and monitoring [53]

6. Conclusion

The pathophysiology of Rosacea involves neurovascular dysfunction, immune dysregulation, and microbiome alterations. Current treatment includes conventional treatments, including topical agents and systemic medications, alongside emerging targeted therapies. While significant progress has been made in management strategies, challenges persist in treating refractory cases and maintaining long-term remission. Novel treatment trends like personalized medicine, incorporating genetic profiling, novel drug delivery systems, and microbiome modulation, development of targeted biologics and CGRP antagonists shows promise in addressing specific pathogenic pathways for effective and complete mitigation of Rosacea.

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