The Proposed Inflammatory Pathophysiology of Rosacea: Implications for Treatment

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Abstract and Introduction

Abstract

The pathophysiology of the vascular and inflammatory stages of facial rosacea and proposes an underlying cause is reviewed. It can be argued that all the stigmata of rosacea are manifestations of an inflammatory process: neutrophilic dermatosis. For this reason, treatments that block neutrophil involvement in the development of rosacea, such as topical metronidazole and systemic antibodies, should be considered first-line therapy for all stages of the disease.

Introduction

Rosacea is a dermatologic condition commonly seen in clinical practice. A number of theories regarding its pathogenesis have been proposed. Rosacea has been viewed as a disorder provoked by various environmental stimuli, a disorder based on lability of the vasculature, or a disorder predicated on derangements of the immune system. Treatment regimens that have been shown to be effective are those that interfere with inflammatory processes. Thus, the recommended treatment for rosacea involves an initial regimen of an oral antibiotic with anti-inflammatory properties, such as tetracycline or doxycycline, in combination with topical metronidazole, an antimicrobial also exhibiting anti-inflammatory actions. Once remission is achieved, the oral antibiotic is tapered off and treatment with topical metronidazole is continued in order to maintain remission.[1-4]

Rosacea as a Clinically-Defined Condition

Rosacea is not actually a disease, but rather a chronic dermatologic condition that predominantly affects the convexities of the central aspect of the face.[5-7] Facial rosacea is usually delineated into four distinct clinical stages, but there are two consistent characteristics present in all stages of rosacea -- frequent facial flushing (Figure 1) and facial actinic damage, especially solar elastosis (Figure 2).[2,5,8-10]

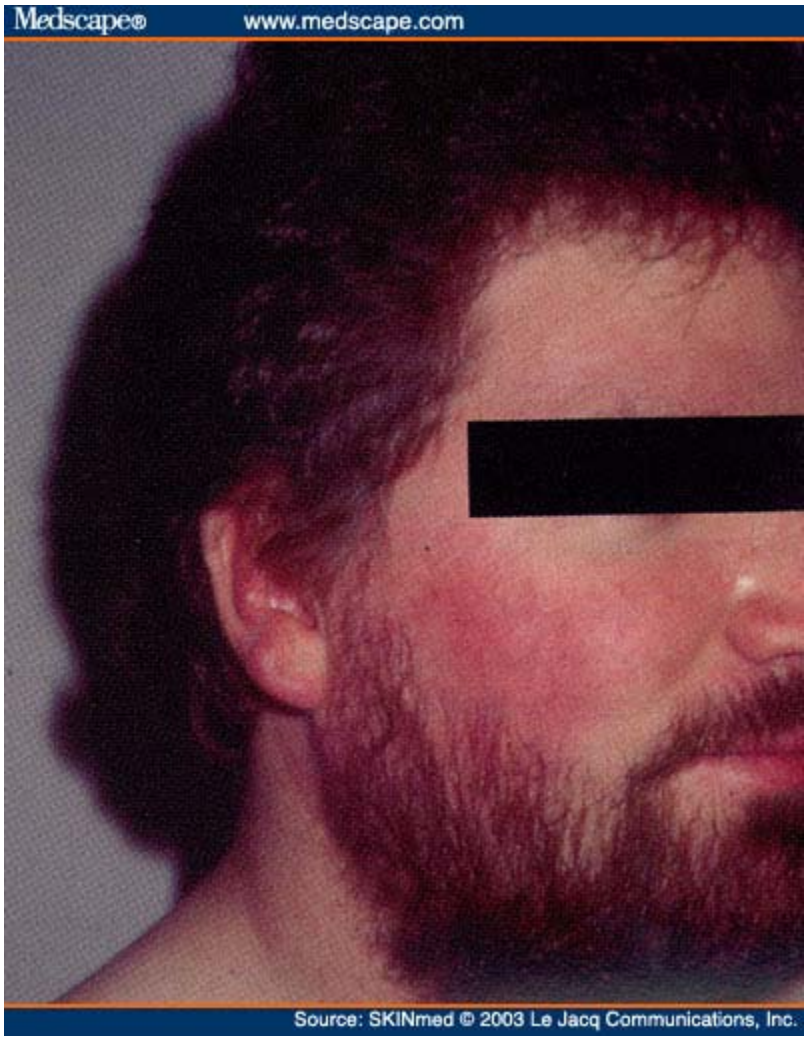

Figure 1. Chronic erythema, flushing, blushing with cyclical crops of pustules, papules. After medication (minocycline and metronidazole), flares are minimized.

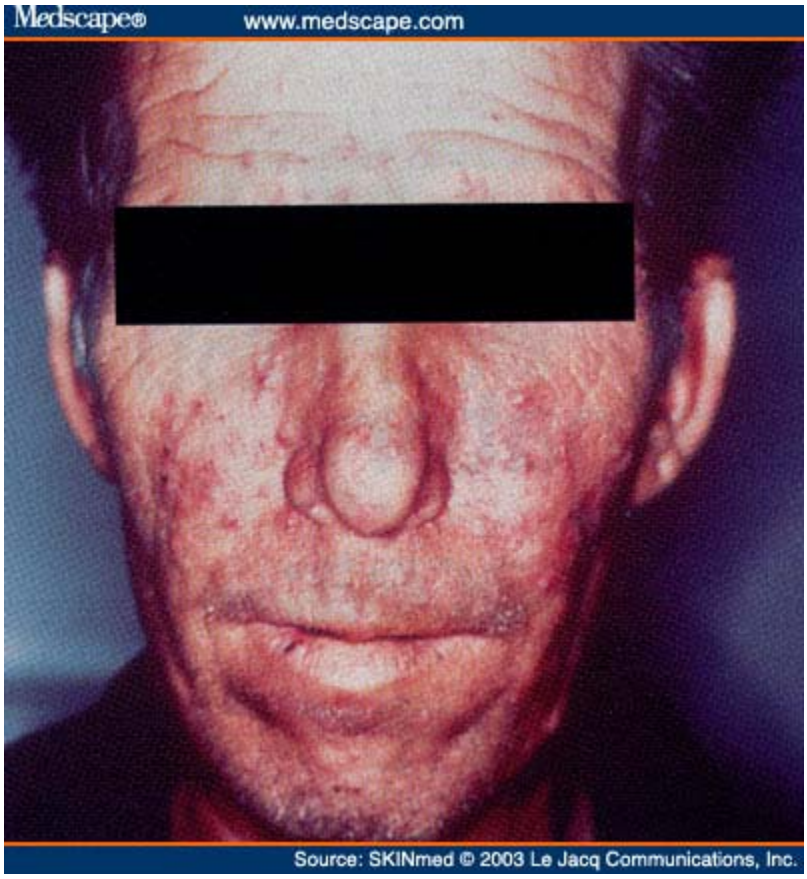

Figure 2. Chronic recurring inflammatory lesions of several years' duration, now responding to metronidazole.

The first clinical presentation of facial rosacea involves frequent and intense vasodilatation of superficial facial vasculature. These signs constitute the pre-rosacea stage.[5,6,8,11] In susceptible individuals, this brisk flushing can be easily induced by a number of nonspecific triggers[5,12] (Table I).

After years of transient, prolonged blushing or flushing, most patients eventually progress to the vascular stage of rosacea, developing erythema that persists for hours or days.[8] The persistent erythema often masks concurrent development of telangiectases, dilated superficial veins.[2,6,7] Many patients remain stable at the vascular stage of rosacea, never developing the more severe manifestations associated with advanced rosacea.[13]

A subset of patients, however, progress within a few years to the inflammatory stage, which is characterized by a bilateral, symmetrical array of papules and pustules on a background of permanent erythema and telangiectasia.[1,5,7,9,13] The bouts of inflammatory lesions are often sudden and intense, without apparent triggers.[13] If left untreated, the inflammatory state can become constant.[13]

A few patients, mostly men, progress to the ultimate stage of rosacea (Table II), easily recognized by distinctive tissue hyperplasia and disfiguring phyma.[2,5] The most common is rhinophyma, a bulbous hypertrophy of the nose.[2,7]

The Genetic Contribution to Rosacea

There is a genetic predisposition to flushing, the earliest manifestation of facial rosacea.[2,5] Rosacea, sometimes referred to as the curse of the Celts, usually occurs in adults with fair skin, especially those of Northern and Eastern European heritage.[2,8,12] Facial rosacea is less prevalent in dark-pigmented individuals, who are less prone to flushing or actinic damage.[5,8] Like many diseases and disorders, the pathogenesis of rosacea appears to involve both genetic and environmental factors.

Rosacea as Provoked by Environmental Factors

Various environmental factors can also provoke flushing in susceptible individuals (Table I). Extreme temperatures, and exposure to sunlight or harsh wind can initiate a flushing episode. Consuming spicy foods, hot foods or drinks, or alcoholic beverages can also induce a flushing reaction. Finally, extreme emotions also have been reported to induce this response.[5,12] Although not pathogenic, chronic exposure to any of these triggers may play a role in the development of permanent vasodilatation typical of erythrotic rosacea or the lesions associated with inflammatory rosacea.[2,5,10,11]

Microorganisms may also trigger rosacea stigmata. Several studies have explored the possibility that *Helicobacter pylori* infection has a causative role in the development of rosacea.[1,10,14-16] Most studies do not support *H. pylori* as a causative factor. A recent study[15] using gastroscopic biopsy found the prevalence of *H. pylori* infection to be the same in 50 patients with rosacea and 39 controls.

Evidence supports the theory that patients with rosacea experience a hypersensitivity reaction to *Demodex* mites or their products.[1] Immunohistochemical findings suggest *Demodex* mites may trigger a delayed hypersensitivity reaction in rosacea patients with mite infestation.[17] An infiltration of lymphocytes has been documented in rosacea patients with *Demodex* infestation.[1,17] These immunologic reactions probably contribute to the formation of papules and pustules (Figure 3).[1,2,5,9,12,17,18]

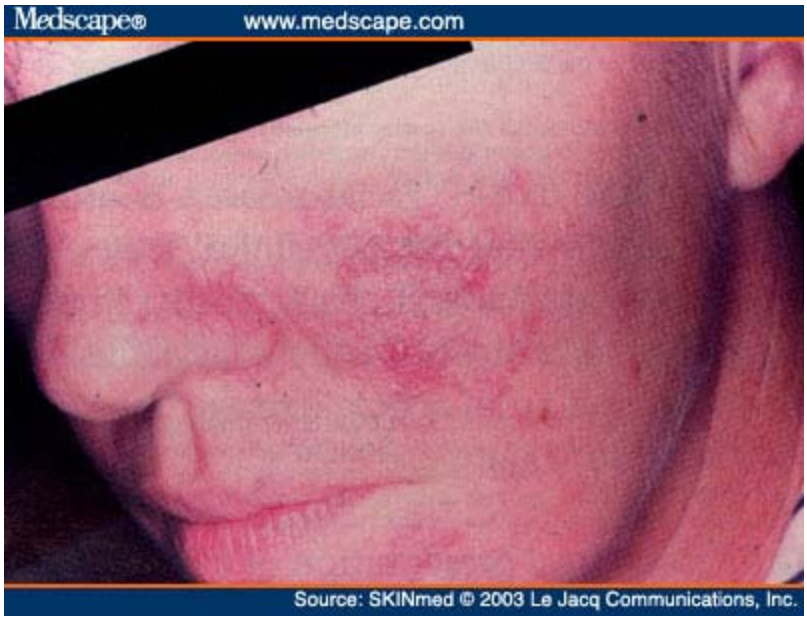

Figure 3. Chronic scaling and erythema, with flares of 4-6 weeks of papules and pustules; responded to sulfacetamide.

Rosacea as a Vascular Disorder

It has been argued that facial rosacea is a cutaneous vascular disorder[2,6,8]; however, researchers have not found any evidence that a vascular dysfunction causes rosacea.

The association of rosacea with migraine headaches suggests an inherent vascular lability in individuals with rosacea.[5,9,12] Migraine headaches, which are caused by vascular instability, are 2- to 3-times more common in individuals with rosacea than in an age- and sex-matched cohort.[8] A hormonal imbalance can lead to vasomotor instability and subsequent intense flushing episodes comparable to that seen in patients with early rosacea. Not surprisingly, many perimenopausal women develop rosacea.[8,11]

Rosacea as an Inflammatory Disorder

As rosacea progresses, inflammatory lesions (papules and pustules) become evident. These lesions are almost always follicular in origin, affecting both sebaceous and hair follicles.[5] Unlike acne vulgaris, however, inflammatory rosacea is not a bacterial disease of the pilosebaceous unit.[2,8] Comedones are usually not present, and only normal bacterial flora have been demonstrated in skin samples taken from patients with rosacea.[2,5,8] The inflammatory stage of rosacea could be considered a form of chronic sterile cellulitis (Figure 4).[6]

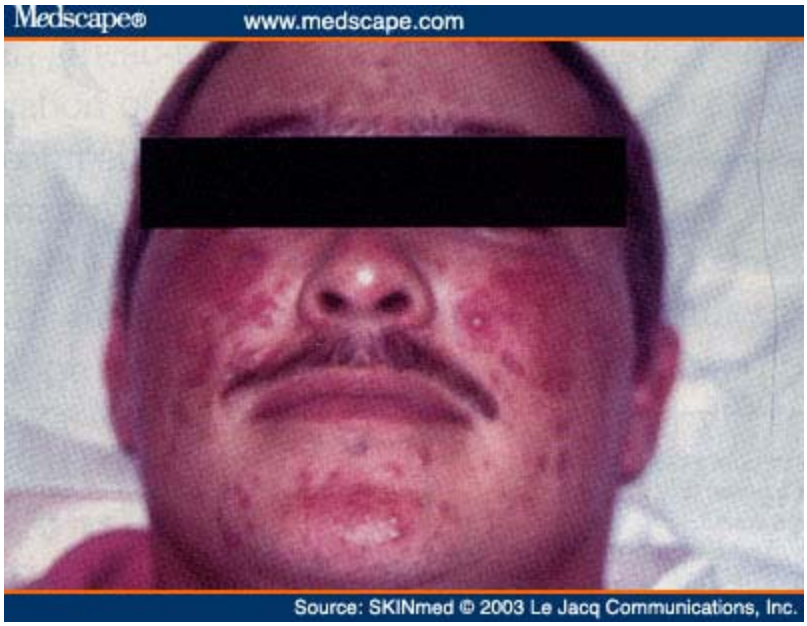

Figure 4. Recent flare of erythema "juicy" nodules and pustules, only responding to systemic steroids.

The Relationship Between Vascular Events and Inflammatory Events

As noted, inflammatory mediators may be operative in the vasodilation seen in rosacea patients. Inflammatory mediators such as substance P, histamine, serotonin, bradykinin, or prostaglandins have been implicated.[5,11,19]

The Role of Photoaging in Rosacea Pathogenesis

Tissue damage caused by photoaging also contributes to the development of both vascular and inflammatory rosacea. Actinic degradation of vascular and perivascular collagen and elastic tissues directly weakens the mechanical integrity of blood vessels and increases the hyper-responsiveness of facial microvasculature (Figure 5).[6,8]

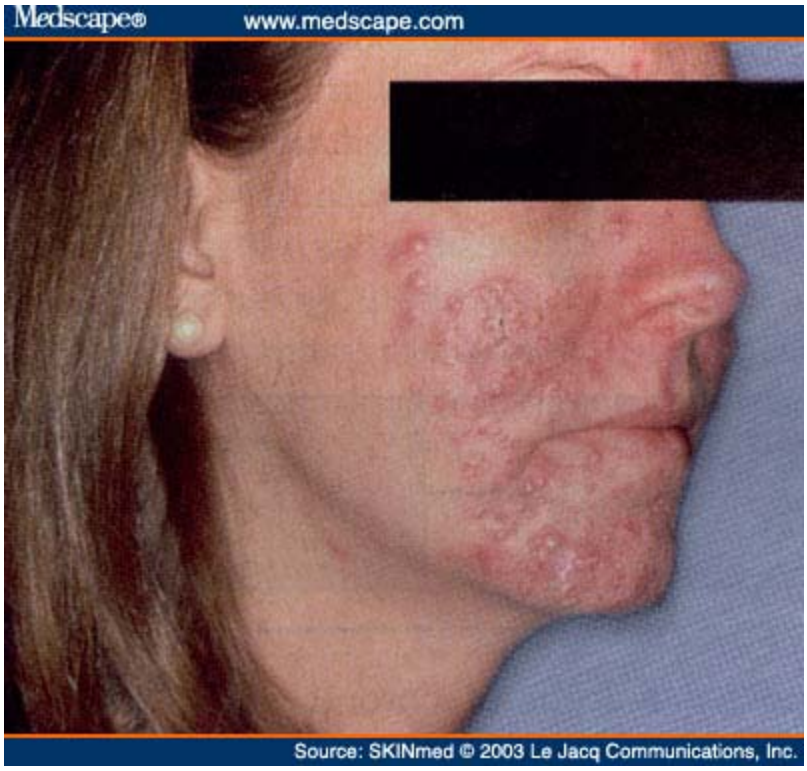

Figure 5. Severe flare of papules and pustules in early pregnancy.

The ensuing inflammatory processes play a pathogenic role in the development of erythema and telangiectasia, as well as inflammatory stigmata.[6] Degradative enzymes, including proteases, such as elastase, are released from activated neutrophils attracted to the area, further degrading the connective tissue surrounding blood vessels.[6]

Angiogenesis triggered by the inflammation may also be involved in the development of telangiectases. Angiogenic factors stored in extracellular matrix may be released by neutrophilic proteases, or released and activated by macrophages.[6]

Solar elastosis can also lead to lymphatic failure.[6] When the volume of protein exudate exceeds lymphatic drainage, extracellular fluids accumulate in the superficial dermis.[17] The result is self-sustaining cutaneous edema and inflammation, which frequently precede the development of connective tissue hypertrophy.[6] Attracted neutrophils release proteins that degrade matrix proteins, leading to fibroplasia, a precursor to rhinophyma.

A Unifying Theory of Rosacea Pathophysiology

The Role of Neutrophils. The intimate relationship between the vasculature and the immune system, as well as the success of anti-inflammatory agents in the treatment of rosacea, suggests that inflammatory cells such as neutrophils, and other inflammatory mediators, are key pathophysiologic factors in the development of rosacea[21] (Figure 6). The stigmata of rosacea may be manifestations of an inflammatory process: neutrophilic dermatosis.[21] Therefore, pharmacologic modulation of neutrophilic function is critical to the resolution of rosacea.[22]

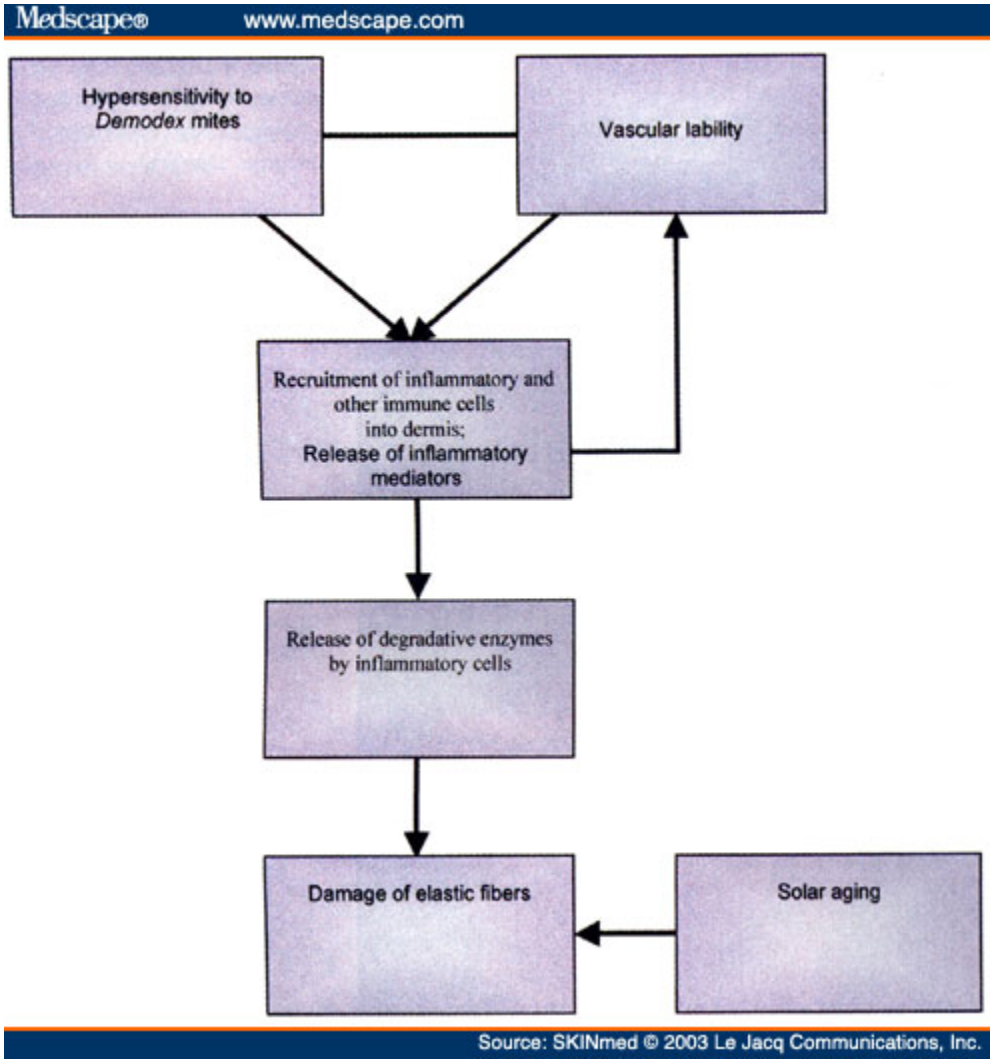

Figure 6. Proposed inflammatory pathophysiology leading to symptoms of rosacea.

How Treatment Targets Inflammatory Events.As noted, topical metronidazole and certain systemic antibiotics constitute first-line therapy for rosacea. Oral tetracycline, doxycycline, and minocycline have been used for the treatment of rosacea. The efficacy of oral antibiotics is thought to be due more to anti-inflammatory rather than antibiotic effects.[1] Other traditional topicals that have been used "off label" include clindamycin, sulfacetamide, and sulfur, and their mechanism is less obvious.

Topical metronidazole, developed in response to concerns generated by chronic systemic antibiotic therapy, is the mainstay of rosacea therapy.[2,3,23,24] Like systemic antibiotics, the in vitro actions of topical metronidazole include anti-inflammatory as well as antimicrobial actions.[2,8,25] The efficacy of metronidazole in rosacea is believed to be due primarily to its modulation of neutrophilic activity, including inhibition of reactive oxygen species.[21,22] Thus, metronidazole blocks the cascade of inflammatory processes that appear to cause and sustain rosacea symptoms.

The first available formulation of topical metronidazole was an aqueous gel. Metronidazole 0.75% in a gel formulation has demonstrated efficacy in reducing the erythema and inflammatory lesions of rosacea.[23] One recent study[24] demonstrated that continued treatment with topical metronidazole gel maintains remission of moderate to severe rosacea when first achieved by treatment with oral tetracycline and topical metronidazole gel.

Although the aqueous gel is well tolerated, other formulations including metronidazole lotion (0.75%) and cream formulations in 0.75% and 1.0% concentrations were developed for patients with rosacea who have unusually sensitive skin. All formulations of topical metronidazole are well tolerated.[1,23,25-27]

In a head-to-head comparison, once-daily application of either 0.75% or 1.0% creams achieved comparable reduction of erythema and inflammatory lesions. This allows the practitioner flexibility in prescribing. Both formulations reduced the median number of papules and pustules by approximately 60%, and the erythema by 26%-30%.[27]

Conclusion

The pathophysiology of rosacea is still a subject of controversy. Research suggests that various immune cells and inflammatory mediators play a role in the vascular, inflammatory, and hyperplasia stages of this disorder. Neutrophils, in particular, may be implicated in this disorder, with the stigmata of rosacea manifestations of neutrophilic dermatosis. Treatments such as topical metronidazole and certain systemic tetracyclines and macrolides inhibit inflammatory mediator release from these leukocytes. Thus, these agents should be considered first-line therapy for all stages of rosacea.

Tables

Table I.

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Table I. Triggers of Rosacea[1,5,8,12]

Weather
Sunlight exposure
Extreme temperatures, hot or cold
Humidity
Harsh wind
Emotional influences
Anger
Anxiety
Embarrassment
Stress
Temperature-related activities
Saunas, hot baths
Heated work environments (e.g., factories, kitchens)
Physical exertion
Exercise
"Lift and load" jobs
Beverages
Alcohol, especially red wine, beer, bourbon, gin, vodka, champagne
Hot drinks, including hot cider, hot chocolate, coffee, tea
Foods
Hot and spicy foods
Dairy products, including yogurt, sour cream, some cheeses
Chocolate, vanilla
Soy sauce, vinegars
Vegetables, including eggplant, tomatoes, spinach, lima and navy beans, peas
Fruits, including avocados, bananas, red plums, raisins, figs, citrus fruits
Medications
Topical fluorinated corticosteroids
Vasodilators, nicotinic acid
Angiotensin-converting enzyme inhibitors, calcium channel blockers
Cholesterol-lowering statins
Topical skin care products
Cosmetics and hair sprays that contain alcohol, witch hazel, acetone, fragrances
Soaps, astringents

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Table II.

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Table II. Stages of Rosacea[5,8,13,20]

	Clinical Presentation	Proposed Pathogenic Factors
Pre-rosacea	Frequent flushing Erythema or irritation in response to triggers	Non-specific triggers; actinic damage
Stage 1 Vascular rosacea	Persistent facial erythema Scattered telangiectasia Slight edema	Pathologic dilation of veins and lymphatics Solar elastosis
Stage 2 Inflammatory rosacea	Persistent facial erythema Dense telangiectasia Papules, pustules Marked edema Enlarged pores	Gross dilation of vessels Severe solar elastosis Neutrophil infiltration
Stage 3 Hyperplasia rosacea	Persistent facial erythema Tissue hyperplasia Rhinophyma	Prominent dilation of vessels Amorphous masses of degenerated elastic tissue Diffuse expansion of connective tissue Epithelia tunnels filled with inflammatory debris

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