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Review

Rosacea: a wholistic review and update from pathogenesis to diagnosis and therapy

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Abstract

Rosacea is a chronic inflammatory disorder of the central face with multiple overlapping presentations. Recent advancements are reshaping our understanding of rosacea from both a pathophysiologic perspective and clinical approach to therapy, introducing novel agents that have improved patient outcomes and reduced morbidity. In this article, we aim to outline the advancements in understanding, diagnosing, and managing rosacea and to familiarize physicians with the literature, thereby allowing us to better practice safe and effective medicine.

Introduction

Diagnostic continuum of transient or persistent erythema and telangiectasias, papules and/or pustules, phymata and/or ocular manifestations is often associated with neurogenic symptomatology.[1] It is estimated that upwards of 10% of individuals are afflicted by rosacea with over 13 million diagnosed in the United States alone.[2,3] Prevalence is higher in women, perhaps due to a reporting bias. Although it can be seen at any age, presentation is most common around the fourth decade of life.[2,3] Historically said to be more common in persons of Northern European descent, it is frequently seen in patients of color in whom it is often grossly underdiagnosed as a result of a low index of suspicion and difficulty recognizing erythema in darker skin colors. It is estimated that its prevalence is upwards of 5% worldwide.[2]

While not life-threatening, rosacea is associated with significant psychosocial morbidity. Individuals with rosacea report increased depression and anxiety that may negatively impact routine daily activities.[4,5] Furthermore, ocular rosacea has the potential to cause ocular discomfort (i.e., burning, stinging), direct transient vision changes, and even permanent vision damage resulting from continual inflammation to the cornea.[1,6] Many recent studies have reported possible associations with systemic conditions including inflammatory bowel disease, Alzheimer's dementia, cardiovascular disease, and autoimmune conditions including celiac disease and type 1 diabetes.[7–12] Whether these associations are due to shared biochemical, neurogenic, or vascular abnormalities, common inflammatory dysfunction, or merely the co-occurrence of disorders common to older individuals is unknown.

Our aim is to outline the advancements in the understanding, diagnosis, and management of rosacea to help physicians keep apace with the rapid influx of new information to ensure patients recieve safe and effective care.

Pathophysiology

The current pathophysiologic model of rosacea implicates an upregulated, dysregulated innate immune system prone to excessive inflammation and vasodilation coupled with neurogenic dysregulation and extrinsic triggers and exacerbating factors.

Hyperreactive neurovasculature

Studies have implicated vasodilation and lymphatic dilatation, not (lymph) angiogenesis, in the "flushing" (physiologic acute neurogenic inflammation) and "blushing" (sympathetic driven transient pinkness of central face, cheeks from emotion and stress) patients report and the erythema and telangiectasias that patients observe.[13,14] The current framework suggests that individuals with rosacea have a higher expression and density of nonspecific cation channels found on sensory neurons and keratinocytes. These transient receptor potential channels (vanilloid 1 [TRPV-1] and ankyrin 1 [TRPA-1]) may conduct various triggers of rosacea into cellular pathways and are stimulated by spices, hot and cold temperatures, exercising, and potentially alcohol.[14] Once stimulated, cells release vasoactive peptides such as substance P, pituitary adenylate cyclase-activating polypeptide (PACAP), vasoactive intestinal peptide (VIP), or calcitonin gene-related peptide (CGRP).[14]

Dysregulated innate and adaptive immunity

Within the keratinocytes of individuals with rosacea, there is an increased expression in the toll-like receptor 2 (TLR-2), which acts as a sentry for inflammatory stimuli. TLR-2 then triggers a cascade of inflammatory and vasoactive peptides including cathelicidins, which are processed into LL-37, an antimicrobial peptide, by the enzyme kallikrein 5. Both cathelicidins and kallikrein 5 are present in the epidermis of rosacea patients in abnormally high levels.[15–17] Mast cells (MCs) are one of the primary sources of cathelicidin in the skin, and they are also the main source of enzymes that trigger cathelicidin to its active form. MC activity has been shown to be increased in the skin of rosacea patients. After LL-37 has been released from the epidermis, it in turn activates MCs to induce inflammation and neutrophil recruitment, which results in a feedback loop to produce more LL-37. Neutrophil recruitment has the potential to create a feedback loop as they produce (or cause to be produced) nitric oxide, reactive oxygen species (ROS), and matrix metalloproteinases (MMPs). MMPs, in turn, increase the production of kallikrein 5 and 7 which causes the production of more LL-37. Activation of the inflammasome leads to additional neutrophil recruitment (and its downstream effects) as well as increased inflammation via tumor necrosis factor. Together, this can be seen clinically as papules and pustules.[15–18]

Adaptive immunity is also dysregulated in rosacea. In all types of rosacea manifestations (papules, pustules, and phymata), there is a dominant of Th1/Th17 gene expression (especially in the papulopustular subtype) and increased prevalence of MCs and macrophages.[19] Upregulation of Th17 gene expression may even exacerbate keratinocyte LL-37 expression.[20] Furthermore, papulopustular and, more so, phymata subtypes had significantly increased neutrophils and plasma cells.[19] Ultraviolet (UV) light may stimulate matrix metalloproteases, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and also create free radicals which further aggravate the innate immune system.[21,22]

The stimulation of MMPs by UV light triggers the feedback loop discussed previously, increasing LL-37 and causing further inflammation. VEGF-A also upregulates MMPs. Interestingly, there are biochemical similarities between the background erythema seen in erythematotelangiectatic rosacea and chronically photoaged skin, which sometimes present a confusing differential diagnosis. In both conditions, chronic sun exposure results in changes in keratinocytes, melanocytes, fibroblasts, and endothelial cells. UV radiation results in the generation of ROS, which contribute to the dermal degradation seen in both conditions.[23,24]

Phymatous rosacea is also accompanied by sebaceous gland hypertrophy and follicular plugging. While the etiology of this finding and its implications in the disease process are unknown, studies have found that even the fibrotic cellular changes typically associated with phymatous rosacea are present at a subclinical level in erythematous and papulopustular subtypes of rosacea.[14] Together, these findings suggest that the "subtypes" of rosacea may actually represent a spectrum of inflammation and immune system dysregulation.

Role of the microbiome

Literature has also investigated the role of the microbiome in instigating or propagating a dysfunctional immune system. Several cutaneous microbes have been implicated in the inflammatory response of rosacea, most notably *Demodex folliculorum* (and its native microbe *Bacillus oleronius*). Although it is not known if this is the cause or effect, *Demodex* density has been shown to be higher in areas of rosacea than in healthy skin in the same patient and 5.7 times higher in subjects with rosacea versus healthy volunteers.[25,26]

Data regarding the role, if any, of *B. oleronius* in the inflammatory response of patients with rosacea are unclear. *Demodex*-associated bacterial proteins have been associated with corneal tissue inflammation in patients with ocular rosacea.[27] Not only has sera taken from patients with *Demodex* been shown to have reactivity to *B. oleronius* proteins, but also antigenic proteins related to *B. leronius* isolated from *Demodex* mites may stimulate an inflammatory response in patients with papulopustular rosacea (PPR).[28,29] Fortunately, B. *oleronius* is sensitive to the tetracycline class of antibiotics utilized in the treatment of PPR.[30] Although further studies have also found additional *Bacillus* species, including B. cereus, within rosacea and rosacea-like lesions, their significance and contribution to disease pathogenesis and severity have yet to be determined.[31–34]

Several studies have initially highlighted specific pathogens thought to be associated with the pathogenesis of rosacea, including virulent strains of *Staphylococcus epidermidis*, cytotoxin-associated gene A-positive ($CagA^+$) *Helicobacter pylori*, and *Chlamydophila pneumoniae*.[1,35,36] A recent study suggested that microbiome-wide disruption at the genus level may play a role.[37] Studies have also shown altered gastrointestinal

microbiome of patients with rosacea. Although minimal change was observed in gastrointestinal bacterial loads, individuals with rosacea had altered biome compositions with decreased prevalence of *Peptococcaceae* and *Methanobrevibacter*, and increased abundance of *Acidaminococcus* and *Megasphaera*. In a recent study evaluating the entire Danish national healthcare population, 49,475 rosacea patients were compared to more than 4.3 million general population controls. Hazard ratios of new onset disease showed significant associations between rosacea and celiac disease, Crohn's disease, ulcerative colitis, and inflammatory bowel syndrome but not small intestinal bacterial overgrowth (SIBO) or *H. pylori* infection.[9] These findings suggest a possible framework for both rosacea's association with gastrointestinal disorders and other systemic inflammatory conditions.

While therapeutic eradication of these microbes correlates with symptomatic improvement, it is still unclear if they create the maladapted immune response or simply fuel an already primed system.[22]

Management

Diagnosis

The diagnosis of rosacea currently relies on open communication with the patient to elicit the necessary history and close observation for physical exam findings. Per the recommendations of the 2017 National Rosacea Society, the diagnostic criteria now reflect the evolving understanding of rosacea as a continuum of inflammation with nonmutually exclusive symptoms and can guide physicians in recognizing and further managing rosacea (Table 1).[1] With or without secondary phenotypes, the diagnosis of rosacea is made if one diagnostic criteria or two or more major phenotypes are present. The differential diagnosis of rosacea should also include systemic lupus erythematosus, *Demodex folliculitis*, and steroid-induced acne and rosacea. Interestingly, topical calcineurin inhibitors have both been recommended as therapeutic options and reported as causative for rosacea flares.[38–41] Interestingly, there has been debate about the role of *Demodex* and the phenomena of "demodicosis," otherwise defined as papulopustular lesions without persistent central facial erythema (a major criteria necessary for rosacea diagnosis).[42] Given the similarities in presentation and increased *Demodex* load within patients with PPR even compared to individuals with demodicosis, demodicosis may represent a milder form of PPR along a spectrum of rosacea. Just as we are redefining rosacea to be a spectrum of severity with phymatous changes at one extreme, perhaps "demodicosis" represents the other milder side.

Table 1 2017 National Rosacea Society Diagnostic Criteria

Diagnostic criteria
- Fixed erythema affecting central third of the face +/− transient, intermittent intensification
- Phymatous changes (e.g., nose, ears, chin)

Major criteria
- Flushing
- Papules, pustules
- Telangiectasias
- Ocular symptoms
  - Scleritis, sclerokeratitis
  - Lid margin telangiectasia
  - Conjunctival injection
  - Spade-shaped corneal infiltrates

Secondary criteria
- Burning, stinging
- Edema
- Dryness
- Ocular symptoms
  - Lid margin irregularities
  - Evaporative tear dysfunction
  - Honey crusting
  - Collarette accumulation

Therapeutics

While studies indicate that rosacea is a spectrum of inflammation, physicians may find it beneficial to consider rosacea therapy as targeting the individual "subtypes." Furthermore, in designing a therapeutic approach, it is also important for physicians to not only determine severity but also ask the patient (i) their perception of disease severity and (ii) what about the disease process concerns them the most. These two principles in turn can help guide development of the therapeutic regimen. That said, recent studies have determined that clear and "near clear" are not equivalent and that aiming for complete resolution of even mild disease prolongs remission and improves the quality of life.[43]

Skin hygiene and lifestyle modifications

Individuals with rosacea report exacerbating factors including (but not limited to): spicy foods, hot or cold temperatures, exercise, sun exposure, cosmetic products, medications, alcohol, specific fruits and vegetables, dairy, and marinated meat products.[44] Patients should be counseled to keep a log of symptoms to identify triggers and then modify their routines to avoid them to mitigate disease severity.

Individuals with rosacea may also have self-reported "sensitive skin" as a result of or exacerbated by epithelial barrier dysfunction.[45] Patients should be encouraged to avoid chemical or physical exfoliants and alcohol-based topical products, use moisturizers, and wash their face with mild, synthetic detergent-based products as traditional soaps may further alkalinize and irritate the skin.[46,47] Patients should also be counseled to use physical sunscreens (i.e., zinc oxide or titanium oxide) SPF 30 or greater, which provide broad-spectrum UV and visible light protection, and may be better tolerated than chemical-based sunscreen.[48]

Erythema, telangiectasias, and flushing

Persistent erythema, telangiectasias, and flushing are thought to be secondary to inflammation-induced vasodilation. While not

curative, brimonidine 0.33% gel, an alpha2-adrenergic agonist, and oxymetazoline 1% cream, an alpha1-adrenergic agonist, functionally constrict facial blood vessels and are US FDA approved for persistent erythema (Table 2).[49,50] In several randomized, placebo-controlled trials, patients reported and clinicians evaluated improved erythema within 3 hours of and for up to 12 hours after application. Overall, therapy is well tolerated with 15% of brimonidine patients and 8% of oxymetazoline patients reporting mild adverse reactions (e.g., dermatitis, burning, pruritus, and erythema).[49,50] Of note, rebound erythema occurred in approximately 20% of individuals using brimonidine and less than 1% of those using oxymetazoline.[50,51]

Laser and light therapy are efficacious in treating persistent erythema and, to a lesser degree, flushing.[52] Pulsed dye (PDL) and potassium-titanyl-phosphate (KTP) lasers target oxyhemoglobin within vasculature, while intense-pulsed light (IPL) emits a broader spectrum of wavelengths.[52,53] Results primarily arise from uncontrolled studies; however, laser and light therapy has been found to be efficacious in diminishing erythema, removing telangiectasias, and improving patient quality of life.[52]

Other pharmacologic interventions are off-label uses of approved mediations and/or have limited data for the efficacy. Inflammation associated with erythema may be trialed with oral tetracyclines used for papules and pustules (see section Papules and pustules). Systemic alpha2-blockers and beta-blockers (e.g., clonidine, carvedilol) and hormone replacement (in menopausal patients) may mitigate flushing in some patients.

Papules and pustules

The therapeutic options for papules and pustules include topical and oral agents (Table 3). Topical ivermectin 1% cream once daily, azelaic acid 15% twice daily, and metronidazole 0.75% gel, cream, or lotion up to twice a day or 1% cream or gel once a day are considered first-line agents for papules and pustules.[52] Although there is limited data regarding its efficacy and some might find its scent off-putting, sodium sulfacetamide 10% with sulfur 5% cream may also be considered.[54] Other topical agents, which may have similar efficacy to their first agents for papules and pustules and potentially erythema, include clindamycin 1% gel with and without 5% benzoyl peroxide, erythromycin, minocycline, permethrin, and topical retinoids.[52,55–58]

Table 2 Recommended erythematotelangiectasia therapeutic options

Topical
Brimonidine
Oxymetazoline
Light/Laser
PDL
KTP
IPL

IPL, intense pulsed light; KTP, potassium titanyl phosphate; PDL, pulsed dye laser.

Table 3 Recommended papulopustular therapeutic options

Topical
Ivermectin
Azelaic Acid
Metronidazole
Sodium Sulfacetamide
Clindamycin
Brimonidine
Oral
Doxycycline MR
Doxycycline
Minocycline
Azithromycin
Bactrim
Isotretinoin

MR, modified release.

Oral tetracycline antibiotics (e.g., doxycycline, minocycline, tetracycline) can be used as monotherapy or coadministered with topical agents.[52] Due to their anti-inflammatory activities, antimicrobial dose minocycline and doxycycline at doses of 50–200 mg QD are highly effective in the treatment of PPR. However, rosacea is a chronic disease requiring long-term care, and the certainty of antibiotic resistance is significant. Doxycycline 40 mg modified release (MR) is FDA approved for the inflammatory lesions of rosacea. This dose has been shown to be as efficacious as 100 mg doxycycline with predominately anti-inflammatory (not antimicrobial) activity, reduced development of bacterial resistance, and fewer side effects (e.g., gastrointestinal distress).[52,59] Adult childbearing age females should be counseled about the teratogenicity of tetracyclines (e.g., tooth discoloration, derangements in bone growth). Alternative oral antibiotics include clarithromycin in conjunction with doxycycline, azithromycin, and metronidazole.[60,61] Off-label use of low-dose isotretinoin (0.25 mg/kg) may be also be considered for refractory cases.[52]

A combination of oral and topical medications may be indicated, particularly in patients with severe disease. In a recent study of 271 severe rosacea patients, concomitant use of doxycycline 40 mg MR with ivermectin 1% cream was compared to ivermectin 1% cream alone.[62] The dual therapy arm showed faster response, statistically significantly better lesion reductions, and higher success rates.

Phymata

In the early active inflammatory stages of phymatous rosacea, there may be benefit in using systemic antimicrobial and anti-inflammatory agents (see section Papules and pustules). Isotretinoin may have similar efficacy as oral antibiotics for early phymatous changes.[52,63]

Advanced disease, marked by gross hypertrophy and nodular growths, is best addressed with procedural techniques to remove excess tissue and reshape the lesional areas and include: ablative CO_2 or erbium laser, radiofrequency, or

surgical debulking.[52] Outcomes from these procedural techniques are dependent on the skill of the user and may also cause dyspigmentation in skin of color (Table 4).

Ocular Rosacea

Ocular rosacea occurs in approximately 50% of individuals with cutaneous rosacea, may precede cutaneous findings in up to 20% of individuals, or can occur entirely independently.[64] Therefore, it is important to screen individuals with rosacea for ocular symptoms, which can range from dryness, burning, and stinging to meibomian gland inflammation to keratitis and scleritis.[1]

As with cutaneous disease, patients should be counseled about lifestyle modifications including increasing dietary intake of omega-3 fatty acids and ocular maintenance including using warm compresses and gentle eyelash/lid cleansing to express entrapped sebum within the meibomian gland.[65,66]

First-line therapeutic management of mild to moderate ocular disease begins with topical azithromycin and topical calcineurin inhibitors independently or in conjunction (Table 5).[52] Azithromycin, oral anti-inflammatory dose doxycycline, and other tetracyclines may also be considered with more severe disease.[52,67] One study also found that IPL may help mitigate symptoms, especially dryness.[68]

When disease progression shows obvious signs of corneal ulceration or severe red eye with inflammation, patients should be referred to ophthalmology for evaluation of visual acuity and additional management.

Combination Rosacea

Most patients with rosacea present with combination disease: papules and telangiectasias, erythema and papules, etc. The medications and physical modalities that we have at our disposal for the treatment of rosacea, while highly effective, rarely cross over to treat more than one phenotypic presentation. This results in the need for combination therapy. Fortunately, there is no contraindication to concomitant therapy and no drug interactions between the medications that are FDA approved for rosacea. In fact, one study demonstrated that the concomitant use of ivermectin and brimonidine accelerated the treatment success of patients with both persistent erythema and inflammatory papules without impairing tolerability.[69] Successful treatment of rosacea patients requires ascertaining what aspects of their disease are most troublesome to them and devising a multi-therapy approach to address all clinical findings.

Table 4 Recommended phymatous therapeutic options

Topical
Retinoids
Oral
Doxycycline MR
Doxycycline
Minocycline
Azithromycin
Bactrim
Isotretinoin
Procedural
CO_2 laser
Erbium laser
Electrosurgery
Radiofrequency

CO_2, carbon dioxide; MR, modified release.

Table 5 Recommended ocular rosacea therapeutic options

Topical
Azithromycin
Cyclosporine
Tacrolimus
Light
IPL
Oral
Azithromycin
Doxycycline MR
Doxycycline
Minocycline
Tetracycline
Bactrim

IPL, intense pulsed light; MR, modified release.

Complementary, Alternative, and Adjunct Treatment of Rosacea

Data behind the use of alternative products in rosacea are tenuous at best. Clinical trials are rare; when done, they are almost uniformly underpowered, open-label, and unblinded. However, the absence of conclusive clinical data does not necessarily equate with ineffectiveness. As we have come to recognize that inflammation, neurovascular regulation, barrier dysfunction, and oxidative damage play important roles in the pathophysiology of rosacea as well as the signs and symptoms of the disorder, the use of botanical agents and vitamins that are anti-inflammatory, antioxidant, and hydrating has been evaluated. Barrier repair, resolution of dysbiosis, and maintenance of a healthy microbiome are critical in rosacea patients.[70] To that end, topical products formulated with niacinamide, feverfew, green tea, coffeeberry, aloe vera, soy, oatmeal, and vitamin C have all been shown in small studies to repair and replenish barrier function in rosacea-prone skin.[71]

Conclusion

Rosacea is a spectrum of inflammation that typically affects the central face with or without eye involvement. Current understanding of rosacea as a part of a larger inflammatory picture with ties to other systemic inflammatory processes continues to be investigated with forays into dysbiosis within the cutaneous and gastrointestinal

microbiome. Treatment options for rosacea include lifestyle management, topical and oral anti-inflammatory medications, as well as light and laser therapy and should be targeted at achieving complete clearance (as long as they are in line with patient desire for treatment). Severe forms of ocular rosacea require ophthalmology consult to assess and preserve visual acuity.

Review Questions (answers provided after references)

1 Rosacea is thought to affect up to _____ of the global population.
- a 1%
- b 5%
- c 10%
- d 20%

2 All of the following contribute to the pathophysiology of rosacea except:
- a Upregulated Th1 and Th17 gene expression
- b Decreased concentration of mast cells and neutrophils
- c Overexpression of nonspecific cation channels within keratinocytes and neurons
- d Increased activity of matrix metalloproteases

3 Per the diagnostic guidelines as set forth by the 2017 National Rosacea Society, rosacea can be diagnosed by:
- a Presence of one major criteria and two minor criteria
- b Presence of two major criteria
- c Only when biopsy proven

4 Which of the following microbial species is not thought to contribute to the pathophysiology of rosacea?
- a CagA + *H. pylori*
- b *S. aureus*
- c *Demodex folliculorum*
- d *B. oleronius*

5 The first-line therapy for rosacea includes lifestyle modifications, instituting good skin hygiene, and regular use of SPF 30 or greater inorganic-based sunscreen.
- a True
- b False

6 First-line prescription therapy for erythema include:
- a Topical brimonidine
- b Topical oxymetazoline
- c Carvedilol
- d A & B

7 A 33-year-old female with primarily popular pustular rosacea returns and reports her topical therapies are not working as well as they used to and would like to discuss adding other agents. Which of the following is the next best option to add to her regimen?
- a PO minocycline
- b PO metronidazole and azithromycin
- c PO doxycycline MR
- d Isotretinoin

8 Procedural therapy and surgery are the best therapy for early phymatous changes.
- a True
- b False

9 Of individuals with rosacea, _____ may also have concurrent ocular symptoms.
- a 25%
- b 50%
- c 60%
- d 75%

10 Comparatively, IGA assessments of near-clear and clear produce the same results in terms of patient satisfaction and improvement in quality of life.
- a True
- b False

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Answers to Questions

1) b
2) b
3) b
4) b
5) a
6) d
7) c
8) b
9) b
10) b

