ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 12, Issue, 05, pp.11529-11534, May, 2020

DOI: https://doi.org/10.24941/ijcr.38700.05.2020

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

GENERAL APPROACH TO ROSACEA

[1,*]Emily Sanderson Chacón and [2]Daniel Vasquez Valverde

[1]Bachelorship in Health Sciences, San José, Costa Rica
[2]General Physician in Private Practice, San José, Costa Rica

ARTICLE INFO

Article History:
Received 18th February, 2020
Received in revised form
24th March, 2020
Accepted 28th April, 2020
Published online 30th May, 2020

Key Words:

Rosacea, Blepharitis,
Erythema, Demodex, Flushing, Therapy.

ABSTRACT

Rosacea is a common chronic recurrent inflammatory dermatosis of the face that affects more women than men. It is characterized by paroxysmal flushing, persistent erythema and cheek, perioral or nasal telangiectasia, papules or pustules. Ocular involvement is found in more than 50% of rosacea patients, with symptoms including dryness, irritation, blepharitis, conjunctivitis and, more rarely, keratitis that may ultimately compromise eyesight. The specific pathogenesis of this disease is still unknown. It may be a chronic inflammatory disease with natural immunity and abnormal vasomotor function induced by multiple factors on the basis of a certain genetic background. Despite its severe, potentially devastating impact, and its epidemiologic richness, rosacea is incurable. The diagnosis is made clinically, and management consists of education, the avoidance of triggers that can exacerbate the condition, skin care measurements, and various topical and oral treatment options.

Citation: ***Emily Sanderson Chacón and Daniel Vasquez Valverde.*** **2020.** "General Approach to Rosacea", *International Journal of Current Research*, 12, (05), 11529-11534.

INTRODUCTION

Rosacea is a common chronic inflammatory skin disease of the central facial skin and is of unknown origin. Currently, two classifications of rosacea exist that are based on either "preformed" clinical subtypes such as erythematotelangiectatic, papulopustular, phymatous, and ocular or patient-tailored analysis of the presented rosacea phenotype. Rosacea etiology and pathophysiology are poorly understood (Buddenkotte, 1885). The red, pimply facial rash can cause embarrassment, low self-esteem, and anxiety and may lead to feelings of depression and stigmatization, with a marked negative effect on quality of life, this should prompt clinicians to diagnose it early and start treatment (Van Zuuren, 2017). In the ultimate years they have been a minor improvement in understanding Rosacea's pathogenesis, therefore, only a few new available treatments have occurred during the last years making unclear which options are the most effective. This review aims to assess the correct approach to diagnosis and adequate management of treatment options for rosacea.

Epidemiology: In the United States alone, more than 16 million patients are affected by rosacea, and worldwide incidences peak as high as 18%, particularly in populations with a predominant "Celtic" heritage, such as is observed in Ireland. Worldwide, the prevalence of rosacea across populations has been reported to range from less than 1% to 22%. The condition usually starts in affected persons when they are between 30 and 50 years of age, overall around 57% of cases are diagnosed in the under-50's and is characterized by episodes of exacerbation and remission (Van Zuuren, 2017; Buddenkotte, 2018). Women are more commonly affected than men, however, men with the condition are more likely to develop phymatous change (Elewski, 2011). It's important to note that 58-72% of rosacea patients ultimately develop ophthalmic findings related to their illness (Wladis, 2018).

Pathogenesis: The pathophysiology of rosacea remains uncertain. Genetic factors, dysregulation of the innate and adaptive immune system, vascular and neuronal dysfunction, and microorganisms such as *Demodex folliculorum* appear to be involved. Triggers such as heat, stress, ultraviolet light, spicy food, hot beverages, smoking, and alcohol may exacerbate symptoms. Rosacea is associated with impairment of the skin barrier, which results in excess transepidermal water loss, making the skin dry, prone to scaling and peeling, and sensitive to burning and stinging (Van Zuuren, 2017).

Immunity: During recent years, evidence has accumulated suggesting that rosacea might be associated with an exacerbated response of the innate immune system. This

Corresponding author: **Emily Sanderson Chacón,**

includes the release of cathelicidin antimicrobial peptides. Cathelicidins are a family of multifunctional peptides that normally act as effect or molecules in innate immunity and provide a first line of host defence in skin infection, modify the local inflammatory response, exert angiogenic activity by a direct action on endothelial cells and activate adaptive immunity (Elewski, 2011). Indeed, cathelicidin messenger RNA transcription and protein expression are strongly increased in lesional skin in rosacea compared with the skin of non-affected individuals despite the absence of an obvious infectious trigger in rosacea (5). The adaptive immune system along with the innate immune system might take a central part in rosacea's pathophysiology. Both the early stage perivascular and later-stage pilosebaceous infiltrates are strongly composed of T helper type 1 (T_{H1}) and TH17 cells and show marked expression of innate immune cells such as additional macrophages and mast cells in papules and erythema and additional neutrophils in pustules and plasma cells in phymata (Buddenkotte, 2018).

Microbes: Rosacea's association with facial *Demodex* spp. colonization was described quite some time ago, but its consequence for rosacea pathophysiology is still not understood and is even disputed by some. For example, Lacey et al. isolated a bacterium, Bacillus oleronius, from Demodex folliculorum mites, which had been extracted from the face of a patient with papulopustular rosacea. Investigation showed that antigenic proteins related to this bacterium have the potential to stimulate an inflammatory response in patients with papulopustular rosacea. These concerns were substantiated by multiple clinical trials that achieved a reduction or eradication of *Demodex* colonization but often did not observe a marked amelioration of the clinical presentation in patients (Buddenkotte, 2018; Elewski, 2011)

UV Radiation: Although acute UV exposure is an undisputed trigger factor for rosacea, it remains unclear how much chronic photodamage contributes to the pathophysiology of the disease, especially because photodamage is not a characteristic sign in patients presenting with the early transient flushing type of rosacea. Thus, although UV exposure is definitely a trigger factor for the exacerbation of rosacea flushing, and many patients during rosacea development present with signs of chronic photodamage, it still needs to be explored whether this characteristic is a primary cause or secondary symptom in many patients with rosacea (Steinhoff, 2013).

Alcohol: Alcohol intake is associated with increased risk of rosacea in a dose-dependent manner. Of individual types of alcoholic beverage, increased consumption of white wine or liquor was significantly associated with an elevated risk for rosacea. A variety of mechanisms might be involved, subsequent temperature elevation. Specifically, alcohol intake might induce catecholamine release, ultimately leading to bradykinin-induced facial vasodilatation. Alcohol intake has been shown to increase production of inflammatory cytokines (Li, 2017).

Vascular Hyperreactivity: Here, we have to differentiate between different critical roles of the blood and lymphatic vessel system. The increased vasculature response and persistent facial erythema in rosacea is of particular interest because of the increasing evidence that blood vessels and possibly lymphatic vessels have significant roles in the control of acute and chronic inflammatory disorders. In rosacea, activation of precapillary arterioles results in vasodilation, expressing flushing and erythema, whereas activation of postcapillary venules leads to protein leakage, expressing edema and recruitment of leukocytes through up-regulation of selectins and cell adhesion molecules. In contrast, upon stimulation by growth factors or external stimuli, blood vessels can grow in numbers (angiogenesis). Increased VEGF-A levels as well as enhanced angiogenesis and/or lymphangiogenesis have been reported in lesional skin of rosacea. Accordingly, lymphatic vessel expansion was observed in rosacea subtypes, but no lymphangiogenesis. Until today, no convincing pathophysiology seems to be capable of explaining these lymphatic vessel changes in rosacea. Further research in this area is highly warranted, because many patients with rosacea significantly experience the disfigurement induced by the lymphedema (Steinhoff et al., 2013).

Genetics: Epidemiologic data comparing disease prevalence and skin phenotype in different geographic regions suggest that rosacea has a genetic component, but 1 or more ''rosacea gene(s)'' have yet to be identified (Steinhoff et al., 2013).

Classification: The first classification of rosacea was published in 2002, recognizing rosacea as a syndrome that is comprehensively depicted by four distinct clinical subtypes, with subtypes I-III defining different presentations of the disease with different degrees of inflammatory involvement, namely erythematotelangiectatic rosacea, papulopustular rosacea and phymatous rosacea. Subtype IV was defined as ocular rosacea. But in 2017 the Global Rosacea Consensus Panel (ROSCO), an international group of 17 dermatologists and 3 ophthalmologists representing 13 countries from South and North America, Africa, Europe and Asia, re-evaluated rosacea features to propose a diagnostic and classification system based on observed phenotypes. This group proposed a series of diagnostic, major, and minor features (Wladis, 2018). We will see this in the diagnostic section.

Clinical features: The presence of at least one of the following primary features indicates rosacea: flushing (transient redness), non-transient redness, papules, pustules and telangiectases. In addition, at least one of the secondary features of burning or stinging, a dry appearance, plaque formation, edema, central facial location, ocular manifestations and phymatous changes are considered enough to make the diagnosis accurately in most cases. Rosacea usually follows a pre-rosacea stage that involves flushing only.

Exacerbating factors: Various environmental stimuli and endogenous factors have been shown to stimulate an augmented innate immune response and aberrant neurovascular signaling (Rainer, 2017). UV radiation is a well-known rosacea trigger. Exposure to UV radiation may cause flushing and worsening of rosacea symptoms. UV-A promotes expression of MMP and causes collagen denaturation whereas UV-B increases production of fibroblast growth factor 2 and vascular endothelial growth factor (Ahn, 2018). Flushing is better prevented rather than treated, in addition to patient education and skin care. Patients who find that they flush frequently, or have a family history of rosacea, are advised to avoid the physiological and environmental stimuli that can cause increased facial redness, such as the following: (Abokwidir, 2016).

- **Environmental stimuli:** exposure to temperature extremes, hot or cold, moving to a warm or hot environment from a cold one, cold wind, and heat from sunlight and severe sunburn.
- **Emotional stimuli:** stress and anxiety.
- **Physiological stimuli:** some foods and drinks, including alcohol, caffeine, spicy foods, and strenuous exercise.
- **Exogenous stimuli:** microdermabrasion, chemical peels, and products containing alcohol, menthol, peppermint, eucalyptus, clove oils, and other irritants.

Standard measures, including avoidance of triggers, gentle cleansers, and moisturizers in combination with sun protection, may mitigate flares, control signs and symptoms in some patients, others will require more specific therapy (Rainer, 2017).

Associated diseases: Rosacea is considered a disease that is limited to the skin; however, there is accumulating evidence of significant associations between rosacea and systemic comorbidities. Recent case-control study showed that patients with rosacea had significantly higher odds of having allergies (airborne and food), respiratory diseases, gastrointestinal (GI) diseases, hypertension, metabolic diseases, urogenital diseases, and female hormone imbalance compared with age, sex, and race-matched control subjects without rosacea.

Moderate to severe rosacea has been associated with hyperlipidemia, hypertension, metabolic, cardiovascular, and GI diseases. Population-based cohort studies confirmed these findings and reported further associations of rosacea and type 1 diabetes mellitus, celiac disease, multiple sclerosis, rheumatoid arthritis, Parkinson disease, migraine. In addition to physical comorbidities, rosacea was associated with a disease severity-dependent, increased risk of depression and anxiety disorders. Thus, assessing cardiovascular risk factors, GI and psychiatric morbidity in patients with rosacea seems prudent, especially in those presenting with more severe disease (Rainer, 2017) Among rosacea patients with severe symptoms, 88% cited the disorder as adversely affecting their professional interactions, and 51% had missed work because of their condition. In addition,41% experienced anxiety over their condition and 25% suffered depression, stemming from cosmetic disfigurement, painful burning sensations, and decreases in quality of life (Schaller, 2017).

Diagnosis: The phenotypes and diagnostic criteria are largely in agreement with those recommended by the global rosacea consensus panel in 2017, and at least 1 diagnostic or 2 major phenotypes are required for the diagnosis of rosacea (Gallo, 2018). A patient with rosacea often has a history of acne diagnosis and failed acne treatments and might report having had unrelieved symptoms for many years. A patient with rosacea will also describe an onset of symptoms that corresponds to typical rosacea triggers, such as heat, spicy foods, and stress. (Alexis, 2019). A diagnosis of rosacea may be considered in the presence of 1 of the following diagnostic cutaneous sign. (Gallo, 2017)

Fixed centrofacial erythema in a characteristic pattern that may periodically intensify. Persistent redness of the facial skin is the most common sign of rosacea in Fitzpatrick photo types I to IV; however, erythema may be difficult to detect in the darker photo types V and VI.

Phymatous changes these can include patulous follicles, skin thickening or fibrosis, glandular hyperplasia, and a bulbous appearance of the nose. Rhinophyma is the most common form.

Major phenotypes: Major cutaneous signs often appear with 1 or more of the diagnostic features although some can occur independently. Without a diagnostic phenotype, the presence of 2 or more major features may be considered diagnostic (11). Major phenotypes include:

- **Papules and pustules:** Dome-shaped red papules with or without accompanying pustules, often in crops and dominant in the centrofacial area, are typical.
- **Flushing:** Frequent and typically prolonged flushing (sometimes blushing) is common except in darker skin tones, in which case flushing may be subjectively experienced without obvious erythema.
- **Telangiectasia:** Which are common signs of rosacea and are predominantly centrofacial in photo types I to IV, are rarely seen in the darker phototypes V and VI.
- **Ocular manifestations:** Ocular manifestations occur in many patients. Common symptoms that may suggest ocular rosacea but are not specific to the disorder include burning, stinging, light sensitivity and foreign object sensation.

Secondary phenotypes: Secondary signs and symptoms may appear with1 or more diagnostic or major phenotypes and may include the following (Gallo et al., 2018).

Table 1. Phenotypes of rosacea (11)

Diagnostic	Major	Secondary
Fixed centrofacial erythema in a characteristic pattern that may periodically intensify Phymatous changes	Flushing Papules and pustules Telangiectasia Ocular manifestations • Lid margin telangiectasia • Interpalpebral conjunctival injection • Spade-shaped infiltrates in the cornea • Scleritis and sclerokeratitis	Burning sensation Stinging sensation Edema Dryness Ocular manifestations • ‘‘Honey crust’’ and collarette accumulation at the base of the lashes • Irregularity of the lid margin • Evaporative tear dysfunction (rapid tear breakup time)

- **Burning or stinging:** Burning or stinging sensations may occur typically on erythematous skin without scales, although scaling may also occur, especially on malar skin.
- **Edema:** Facial edema may accompany or follow prolonged erythema or flushing as a result of postcapillary extravasation during inflammation. Sometimes soft edema may last for days or be aggravated by inflammatory changes.
- **Dry appearance:** Central facial skin may be rough and scaly so as to resemble dry skin and suggest an eczematous dermatitis, and rosacea may often include the coexistence of seborrheic dermatitis

Additional tests for Diagnosis: In some cases the diagnosis cannot be made clinically orsome discords occurred between subtypes and phenotypes, so other test can be necessary. Skin swabs and scraping for microbiology studies are used primarily

to exclude staphylococcal infections. Antinuclear antibody test can be useful in cases when photosensibility is prominent.

Additional tests for Diagnosis: In some cases the diagnosis cannot be made clinically or some discords occurred between subtypes and phenotypes, so other test can be necessary. Skin swabs and scraping for microbiology studies are used primarily to exclude staphylococcal infections. Antinuclear antibody test can be useful in cases when photosensibility is prominent. At last, skin biopsy is very useful when other diagnoses such as lupus or chronic folliculitis can be considered (Rivero, 2018)

Differential diagnosis

Acne vulgaris: Pustules and erythematous papules on face and upper trunk, usually accompanied by open and closed comedones and no telangiectasia, with initial onset typically occurring in adolescence and young adulthood

Steroid acne: Acne vulgaris induced by steroid-containing topical agents; patient will have history of using such products.

Contact dermatitis: Skin inflammation or rash that is usually itchy; condition associated with exposure to chemical or physical allergens or irritants; condition might involve erythema, scaling, blistering, thickening, or cracking of skin in a localized or diffuse presentation, sometimes with pain, burning, or stinging.

Seborrheic dermatitis: Skin inflammation occurring near eyebrows, ears, nose, and glabellar region.

Periorificial dermatitis: Self-limiting eruption of erythematous papules and pustules near mouth, nose, and eyes, primarily in young women.

Facial Afro-Caribbean childhood eruption: Self-limiting, monomorphic flesh-colored or hypopigmented papules, especially around mouth, ears, and eyelids, primarily in black children, usually male.

Keratosis pilaris rubra: Marked erythema and keratotic follicular papules covering cheeks and proximal arms.

Lupus erythematous: Erythematous rash spanning cheeks and nasal bridge in butterfly pattern.

Sarcoidosis: Granulomatous disorder usually involving multiple organs and affecting middle-aged and older patients with comorbid hypertension, thyroid disease, type 2 diabetes mellitus, hearing loss, or eye disease; facial manifestations characterized by persistent plaques with papules and nodules, often asymptomatic.

Dermatomyositis: Red or purplish rash along with edema commonly manifesting on eyelids; on knuckles or fingers along with scaly, re papules in V pattern on neck, in shawl pattern on shoulders, or on trunk, extremities, scalp, or face; often accompanied by muscle weakness; more commonly found in female patients.

In considering differential diagnoses, be aware that inflammatory lesions of acne are often located beyond the central face like for example in the chest, back, or arms. (Alexis, 2019)

Treatment: The Key in management of Rosacea is based on individualizing the management. First starting by confirming diagnosis and severity of disease, evaluate treatment history and exacerbating factors. Then routinely screen for risk of factors and comorbidities associated with Rosacea and raise quality of life concerns: self-esteem, social impairment, work activities. General recommendations: chronic disease needing life-long treatment intervention, avoidance of trigger factors, gentle skin care regimen, photoprotection and range of treatment modalities.

General Measures and Skin Care: Management of rosacea usually starts with educating patients about the skin condition and potential exacerbating factors to help patients identify triggers and improve their coping mechanisms. Sun avoidance and photoprotection are an important part of management. Reducing skin irritability is also key, that's why skin care should include a gentle facial cleanser and a moisturiser or barrier repair product, as this can adjunctively improve therapeutic outcomes and reduce skin irritation in patients undergoing medical therapy. Avoiding triggers such as extreme temperatures (hot or cold), ultraviolet radiation exposure, spicy foods, hot or alcoholic beverages, wind, exercise and stress, should be recommended to all patients. (Van Zuuren, 2017; Rivero , 2018).

Table II: Rosacea Skin Care (11)

Recommended types of products	Product types to avoid
•Gentle, non-alkaline, fragrance-free, emollient cleanser once per day in the evening •Silicone-based moisturizer daily •Light, water-based cosmetics (but powders are preferable to creams) •Physical sunblock (eg, zinc oxide)	•Alcohol-based cleansers, astringents, or abrasive exfoliating cleansers •Nonsilicone-based moisturizers •Cosmetics with iridescent effects •Chemical sunscreens (if sensitivity reported)

Episodic erythema (flushing): Treatment for flushing and erythema may involve oral drugs with vasoconstriction properties including adrenergic antagonists including mirtazapine (alpha blocker), propranolol (beta blocker) or carvedilol (both alpha and beta blocker). These are used at low doses to avoid adverse effects such as hypotension, somnolence, fatigue and bronchospasm (Rivero, 2018). Ivermectin 1% cream is approved as a treatment to rosacea related inflammation its efficacy is based on anti-inflammatory and anti-parasitic action by reducing the Demodex mite's density. Also, Ivermectin can also be combined with brimonidine; analpha2 receptor agonist that was the first topical treatment approved for treatment of rosacea-related facial redness and erythema. Ivermectin has been proved to have a superior efficacy compared to topical metronidazole 0.75% (Feaster, 2019).

Persistent erythema: May last for hours or days, in contrast to flushing. Treatment with 0.5% brimonidine tartrate gel, a highly selective α_2-adrenergic agonist with vasoconstrictive activity, was shown to reduce persistent erythema in two randomized controlled trials involving a total of 553 patients (Van Zuuren, 2017). Also, treatment with Oxymetazoline cream 1.0% is a vasoconstrictive alphaadrenergic agonist, it has been previously utilized in nasal endophthalmic formulations, oxymetazoline is FDA approved as a topical treatment principally for "persistent facial erythema" in rosacea. This persistent facial erythema can have a

presentation indifferent episode during and/or between rosacea flares due to cutaneous vascular changes (Feaster, 2019).

Telangiectasia: Laser therapy, including vascular lasers or intense pulse light, may help to reduce refractory background erythema and clinically significant telangiectases, but will not reduce the frequency of flushing episodes (Rivero, 2018). However, there is evidence that although laser therapy is widely used in the treatment of erythema and telangiectasia, these methods of treatment have been investigated primarily in observational studies. The few randomized trials from which data are available are hampered by small sample sizes (Van Zuuren, 2017).

Papules and pustules: In case of low to moderate degrees of inflammation with only few to several papules and pustules the effectiveness of topical mono therapy with azelaic acid (four times daily or twice daily), metronidazole, ivermectin and sodium sulfacetamide sulphur may be satisfactory (Elewski, 2011).

Nodules and plaques: When rosacea is more severe at presentation, combining topical treatments with oral antibiotics may be needed for more severe papulopustular rosacea. Topical treatments include metronidazole, azelaic acid, ivermectin and dapsone. The only oral treatment approved by both the FDA and the European Medicines Agency for inflammatory lesions associated with rosacea is modified-release doxycycline at a dose of 40 mg once daily. This dose is considered to have antiinflammatory effects but not an antimicrobial effect (Rivero, 2018).

Phymas: Oral isotretinoin is recommended. The main mechanism of isotretinoin in the treatment of rosacea is its anti-sebaceous gland hyperplasia and sebum secretion, direct or indirect anti-inflammatory effect and can strongly and effectively downregulate TLR2 expression, which is an important component of connective nerve stimulation and natural immunity (Juliandri, 2019). Phymas may require ablation by surgical interventionwith YAG lasers, scalpel surgery, electrosurgery, cryosurgery, dermabrasion to remove excess tissue and ⁄or resculpturing. Treatment is aimed at debulking the excess tissue and then sculpting the disfigured area (Elewski, 2011).

Ocular signs and symptoms: Ocular involvement occurs in up to three quarters of patients with rosacea but is often under-diagnosed and remains understudied. Most guidelines advise eyelid hygiene twice daily with warm water and the use of artificial tears. One small, randomized trial suggested that cyclosporine eye drops improved quality of life, as measured on the Ocular Surface Disease Index, and also increased tear production (both of which were primary outcomes in the trial) (Van Zuuren, 2017).

Treatment duration: The duration of therapy needs to be tailored to the individual needs of a patient. Frequently, long-term treatment is required to prevent worsening of the condition. Topical therapies can be combined safely with oral medications. Initial treatment duration is usually for at least 12 weeks, improvement is usually gradual and may take several weeks to become apparent. Following discontinuation of oral component, treatment may be continued with topical maintenance therapy for another 6 months provided the condition is controlled satisfactorily (Elewski, 2011).

Conclusion

Rosacea is an inflammatory skin disease characterized by immune dysfunction and neurovascular dysregulation. It has many potential interventions, physicians can help most patients to alleviate the symptoms of rosacea, although none of these therapies is actually curative. Clinical definition can be challenging due to an overlap with the cutaneous findings of chronic actinic damage in fair-skinned individuals. It has high associations between rosacea and diseases that involve barrier tissues such as the intestinal, respiratory, reproductive, and urinary tracts and the skin that raise the suspicion of dysbiosis, pathology principle, may contribute to the development of rosacea. The spectrum of clinical presentation (phenotypes) has important implications for patient's management. Most importantly the discord between subtypes and phenotypes is really relevant because of their implications for both clinical practice and research. The management of Rosacea is based and focuses principally on three main categories: patient education, skin care, and pharmacological/procedural interventions. Rosacea therapeutic management has expanded and it has become a multifaceted approach, in some cases patients may have multiple subtypes and each phase has its own treatment.

REFERNCES

Abokwidir M, Feldman SR. Rosacea Management. *Skin Appendage Disord*. 2016;2(1-2):26-34. doi:10.1159/000446215

Ahn CS, Huang WW. 2018. Rosacea Pathogenesis. *Dermatol Clin*. 36(2):81-86. doi:10.1016/j.det.2017.11.001

Alexis AF, Callender VD, Baldwin HE, Desai SR, Rendon MI, Taylor SC. 2019. Global epidemiology and clinical spectrum of rosacea, highlighting skin of color: Review and clinical practice experience. *J Am Acad Dermatol*., 80(6):1722-1729.e7. doi:10.1016/j.jaad.2018.08.049

Buddenkotte J, Steinhoff M. 2018. Recent advances in understanding and managing rosacea. *F1000Res*. 7:F1000 Faculty Rev-1885. Published Dec 3. doi:10.12688/f1000research.16537.1

Elewski BE, Draelos Z, Dréno B, Jansen T, Layton A, Picardo M. 2011. Rosacea - global diversity and optimized outcome: proposed international consensus from the Rosacea International Expert Group. *J Eur Acad Dermatol Venereol*. 25(2):188-200. doi:10.1111/j.1468-3083.2010. 03751.x

Feaster B, Cline A, Feldman SR, Taylor S. 2019. Clinical effectiveness of novel rosacea therapies. *Curr Opin Pharmacol*. 46:14-18. doi:10.1016/j.coph.2018.12.001

Gallo RL, Granstein RD, Kang S, et al. Standard classification and pathophysiology of rosacea: The 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol*. 2018;78(1):148-155. doi:10.1016/j.jaad.2017.08.037

Juliandri J, Wang X, Liu Z, Zhang J, Xu Y, Yuan C. 2019. Global rosacea treatment guidelines and expert consensus points: The differences. *J Cosmet Dermatol*. 18(4):960-965. doi:10.1111/jocd.12903

Li S, Cho E, Drucker AM, Qureshi AA, Li WQ. 2017. Alcohol intake and risk of rosacea in US women. *J Am Acad Dermatol*., 76(6):1061-1067.e2. doi:10.1016/j.j aad.2017 .02.040

Rainer BM, Kang S, Chien AL. 2017. Rosacea: Epidemiology, pathogenesis, and treatment. *Dermatoendocrinol*.

2017;9(1):e1361574. Published Oct 4. doi:10.1080/19381980.2017.1361574

Rivero AL, Whitfeld M. An update on the treatment of rosacea. *Aust Prescr*. 2018;41(1):20-24. doi:10.18773/austprescr.2018.004

Schaller M, Almeida LM, Bewley A, et al. 2017. Rosacea treatment update: recommendations from the global ROSacea COnsensus (ROSCO) panel. *Br J Dermatol*. 2017;176(2):465-471. doi:10.1111/bjd.15173

Steinhoff M, Schauber J, Leyden JJ. 2013. New insights into rosacea pathophysiology: a review of recent findings. *J Am Acad Dermatol*., 69(6 Suppl 1):S15-S26. doi:10.1016/j.jaad.2013.04.045

Van Zuuren EJ. 2017. Rosacea. *N Engl J Med*. 377(18):1754-1764. doi:10.1056/NEJMcp1506630

Wladis EJ, Adam AP. 2018. Treatment of ocular rosacea. *Surv Ophthalmol*. 63(3):340-346. doi:10.1016/j.survophthal.2017.07.005

****