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Dr. Michael Sidiropoulos is a board-certified dermatologist, pathologist and dermatopathologist, in both Canada and the United States. He completed his undergraduate training in the immunology specialist program and graduate studies in pathology both at the University of Toronto, where he studied kallikrein serine proteases in the skin which have been shown to be involved in both rosacea and eczema. Dr. Sidiropoulos completed his medical degree, and pathology and dermatology residency training, all at the University of Toronto and a dermatopathology fellowship at Northwestern University, Chicago. He works both in academic and community settings in both dermatology and dermatopathology.

AN OVERVIEW OF ROSACEA

Rosacea is a well-described chronic cutaneous syndrome with a constellation of different clinical signs and symptoms, with key components including persistent facial erythema and inflammatory papules and pustules primarily affecting the central face, and often with repeated remissions and exacerbations.[1] Characteristic additional features are facial telangiectasias, frequent facial flushing, facial erythema and edema that is non-pitting and ocular and phymatous changes (**Figure 1**).

Epidemiology

Rosacea is commonly diagnosed in Caucasian females, being less common in men, with a typical age of onset after age 30, but can occur at any age.[2,3] In women it occurs at a younger age and in children, rosacea-like conditions such as periorificial dermatitis and steroid-induced rosacea are quite common. Surveys on the racial/ethnic distribution of rosacea range from approximately 2 to 4% in patients of black, Asian, Latino or Hispanic descent. However, the disease is underrecognized as epidemiologic reports often point to rosacea as a disease of fair-skinned people with Fitzpatrick skin phototypes I and II, leading to the erroneous perception that rosacea does not occur in people with skin of color.[4] Recent studies have found that adults greater than 60 years of age and with rosacea, may be at increased risk for Alzheimer's disease.[5]

Pathogenesis

Key factors in the pathogenesis of rosacea include neurovascular dysregulation, an abnormal innate as well as adaptive immune response and mast cells, which can lead to abnormal inflammation of the skin.[6] *Demodex* mites, both *demodex folliculorum* and *demodex brevis*, are present on the face normally as commensal microbes; however, in rosacea, a significantly greater number of these mites are detected.[7,8] The mites are associated with a bacterium (*Bacillus oleronius*) and colonize pilosebaceous follicles, stimulating inflammation. They are often seen as a dense perifollicular infiltrate on histopathology, and upregulate local proteases and cause dysregulation of the innate immune response in the skin.[9,10]

Current Classification System

In 2017, the global ROSacea COnsensus (ROSCO) panel recommended transitioning to a phenotype-based approach to rosacea diagnosis and classification. The output of the panel's recommendations included establishing two features as independent diagnostic markers for rosacea: (i) persistent, centrofacial erythema associated with periodic intensification; and (ii) phymatous changes. The ROSCO panel concluded that flushing, telangiectasia, inflammatory lesions and ocular manifestations were not considered to be individually diagnostic and reached agreement on dimensions for phenotype severity measures and established the importance of assessing the patient burden of rosacea. This current classification system bases rosacea on phenotype-observable characteristics that can result from genetic and/or environmental influences, in order to provide a means of assessing and treating rosacea (**Table 1**).[13]

Previous Classification System

The diagnosis of rosacea is based on clinical observation and patient history, which is essential as features may often not be visually present at the time of presentation.[11] Rosacea was previously categorized into four subtypes: erythematotelangiectatic rosacea (subtype 1; ETTR), which consists of flushing, persistent facial erythema and telangiectasias; papulopustular rosacea (subtype 2; PPR), characterized by an eruption consisting of papules and pustules in varying stages of evolution; phymatous rosacea (subtype 3), which manifests through sebaceous gland hypertrophy and fibrosis, occurring commonly in men, and ocular rosacea (subtype 4), which commonly presents as a spectrum of disease with nonspecific symptoms of dryness, crusting, styes and pruritus, and signs of concretions and scaling of the eyelids and blepharitis, eyelid swelling and conjunctival

Diagnostic Features (≥ 75% consensus)	Major Features (≥ 50% agreement)	MInor Features (≥ 75% consensus)
Persistent centrofacial erythema associated with periodic intensification by potential trigger factors Phytamous changes	Flushing/transient centrofacial erythema Inflammatory papules and pustules Telangiectasia Ocular manifestations • Lid margin telangiectasia • Blepharitis • Keratitis/conjunctivitis/ sclerokeratitis	Burning sensation of the skin Stinging sensation of the skin Oedema Dry sensation of the skin

Table 1. Diagnostic, major and minor features of rosacea; adapted from Tan et al, 2017

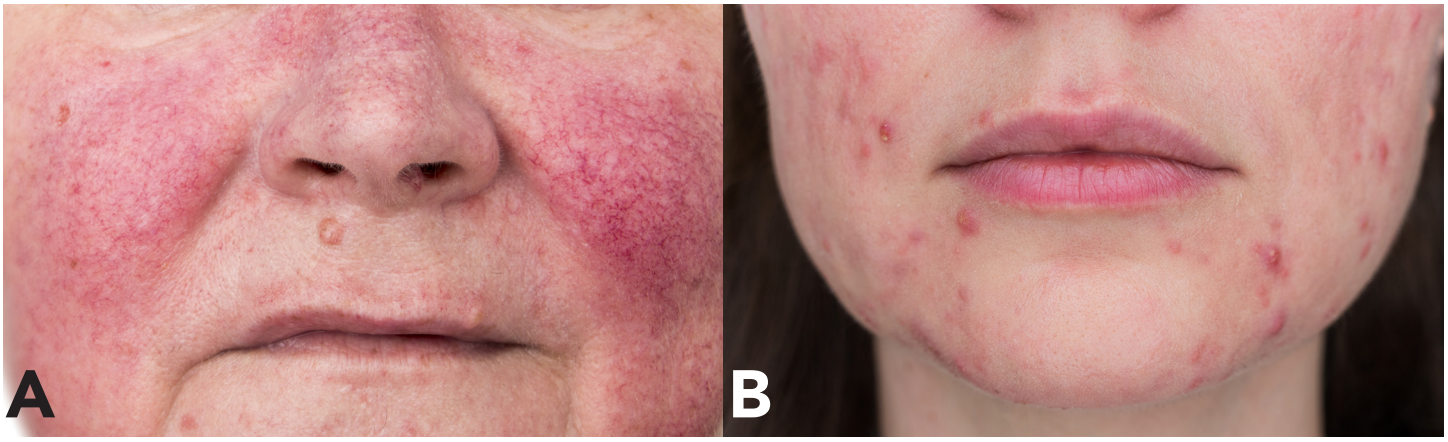

Fig 1. A, Erythema of rosacea on white skin. B, Papules and pustules of rosacea on white skin.

injection.[1] Approximately 20% of patients with rosacea have ocular findings before evidence of skin involvement.[12] In addition to the above subtypes, in granulomatous rosacea, there are small (1 to 3 mm) monomorphous and persistent skin papules colored reddish-brown involving the central face, occurring in both adults and children and often with spontaneous resolution after a few years.

Pathology

Histologic changes in rosacea vary with subtypes, such as subtle vascular ectasia and mid edema seen with ETTR and prominent perivascular and perifollicular lymphohistiocytic infiltrate present in PPR.[1] In phymatous rosacea, sebaceous hyperplasia is prominent with dermal fibrosis. In all forms of rosacea, comedone formation is not identified. In granulomatous rosacea, non-caseating epithelioid granulomas are identified within the perifollicular inflammation. Lupus miliaris disseminatus faciei is thought to be a severe form of granulomatous rosacea showing central caseation necrosis in granulomas[14], which commonly affects the periocular region and lesser central face and can subsequently involve facial scarring.

Treament options	Persistent erythema	Phymas	
		Active (inflamed)	Fixed (not inflamed)
Topical therapies			
Brimonidine	●●		
Oxymetazoline	●●		
Retinoids		❍/**C**	
Devices and surgical interventions			
Intense pulsed light	❍❍		
Pulsed dye laser	❍❍		
Potassium titanyl phosphate	❍❍		
Carbon dioxide		**C**	❍❍❍❍
Erbium†		**C**	❍❍❍❍
Cold steel†		**C**	❍❍❍❍
Electrosurgery†		**C**	❍❍❍❍
Radiofrequency†		**C**	❍❍❍❍
Oral therapies			
Carvedilol	❍		
Doxycycline (subantimicrobial)	❍	❍/**C**	
Doxycycline	❍	❍/**C**	
Minocycline	❍	❍/**C**	
Tetracycline	❍	❍/**C**	
Izotretinoin		❍❍/**C**	
Azithromycin		❍/**C**	
Trimethoprim/sulfamethoxazole		❍/**C**	

C Used in combination therapy only
* The number of circles indicates the committee's expert opinion on relative efficacy up to 4, with 4 indicating the most effective. Filled vs open circles indicate strength of trial evidence, with solid circles as strong as open circles are weak.
† Skill dependent; postinflammatory hyperpigmentation risk.

Table 2. *Treatment options for diagnostic features; adapted from Thiboutot et al, 2020*

Management

Rosacea can be managed through a combination of appropriate skin care, lifestyle management changes, a range of topical and oral therapies and light devices[11], and effective therapies that are used to target specific features of each patient (e.g. erythema).

Skin care and lifestyle management

Gentle skin care is important as rosacea patients have sensitive skin that is easily irritated. Patients need to use cleansers and moisturizers that are non-occlusive and that do not irritate the skin. A gentle cleansing regimen using a non-irritating cleanser, or a synthetic detergent is recommended. In addition, washing the face gently and waiting for the face to dry completely before applying topical therapies is advised, as stinging tends to occur when the skin is wet.[11] The appearance of redness may be reduced with cosmetics containing a tint of green or yellow. Education on the importance of sun avoidance and regular sunscreen use is advised to prevent further progression and improve flushing and erythema. Mineral inorganic products containing zinc oxide or titanium dioxide are recommended, as they primarily (physically) reflect light and do not produce heat as a by-product. Cosmetics with protective silicones may help as well. Moisturizers containing humectants such as glycerin and occlusives such as petrolatum can help to repair the epidermal barrier. There are many over-the-counter topical skin care products containing forms of sulfur and botanical ingredients that may potentially provide a degree of anti-inflammatory effect; however, published clinical studies of their effectiveness is lacking.[11] Avoidance of astringents, toners and abrasive exfoliators and cosmetics that contain alcohol, menthols, camphor, fragrance, peppermint and eucalyptus oil is recommended.[1,15,16,17]

Patient education is critical in the management of rosacea and directing patients to easily accessible information on websites such as the National Rosacea Society (www.rosacea.org) may be beneficial in augmenting adherence and compliance with therapy and making lifestyle changes.[1] Rosacea patients need reassurance about the benign nature of the condition and a constant reminder that it is a chronic disease requiring ongoing vigilance in order to optimize outcomes. It is important for patients with rosacea to identify and avoid personal triggers, as these may provoke a worsening of the condition and become a source of stress which can further trigger exacerbations.[18,19] The use of a daily diary of lifestyle and environmental factors that patients notice affects their rosacea may be an important tool in identifying triggers. Common factors that are typically identified include: sun exposure, emotional stress, hot and cold weather, humidity, wind, heavy exercise, consumption of alcohol, hot baths, spicy foods, certain fruits and vegetables, dairy products, marinated meats, specific medications and underlying medical conditions.[20]

Topical and oral therapies

Patient education on the importance of compliance with topical and oral regimens is of paramount importance, as clinical response to therapy will take time. A combination of topical and oral therapies are often initially prescribed, followed by long-term use of a single therapy alone to maintain remission (**Tables 2, 3**).[11] For persistent erythema (a diagnostic feature of the current classification system), topical agents brimonidine tartrate (0.33% gel) or topical oxymetazoline HCL (1% cream), both selective alpha adrenergic agonists, can improve erythema.[1] For inflammatory papules and pustules (a major feature of the current classification system), metronidazole (0.75% gel or cream or 1% cream), ivermectin 1% cream, azelaic acid (15% gel), or sodium sulfacetamide (10%) and sulphur (5%) in a cream or lotion (often with 10% urea) can be used. Topical erythromycin (2% solution), clindamycin (1% lotion) or benzoyl peroxide 5% plus clindamycin 1% can also help clear inflammatory lesions. In addition, tretinoin (0.025% cream, 0.05% cream or 0.01% gel) and pimecrolimus (1% cream) or tacrolimus (0.03% or 0.1% ointment), have been shown to improve inflammation and also erythema, but both may be poorly tolerated by patients (irritation, exacerbations).[1]

Modified-release doxycycline capsules (40 mg) are approved by Health Canada for the treatment of papules and pustules and have been shown to have fewer side effects than higher doses and have not demonstrated an association with bacterial resistance.[21] Many systemic therapies, can be used off-label such as oral antibiotics like tetracycline, doxycycline, minocycline, azithromycin, and erythromycin, often for a 4- to 8-week course, and oral retinoids isotretinoin (0.3 mg/kg/day). Off-label systemic medications used for severe flushing and erythema include beta blockers such as carvedilol or propranolol, antihistamines and nonsteroidal anti-inflammatory drugs.[22]

Ocular rosacea therapy

The treatment of ocular rosacea is based on eyelash hygiene and oral omega 3 supplementation, with topical azithromycin or calcineurin inhibitors.[11] Eyelash hygiene

Treament options	Papules/pustules	Telangiectasia	Flushing
Topical therapies			
Ivermectin	●●●		❍
Azelaic acid	●●		
Metronidazole	●●		
Clyndamycin	❍		
Retinoids	❍	❍	
Sulfacetamide sodium/sulfa	❍		
Brimonidine	C		❍
Oxymetazoline			❍
Oral therapies			
Doxycycline (subantimicrobial)	●●●		
Azithromycin	❍❍❍		
Doxycycline	❍❍❍		
Minocycline	❍❍❍		
Izotretinoin	❍❍❍		
Trimethoprim/sulfamethoxazole	❍❍❍		
Tetracycline	❍❍		
Clyndamycin	❍		
Carvedilol			❍
Clonidine			❍
Propranolol			❍
Light devices			
Intense pulsed light		❍❍❍❍	❍❍
Pulsed dye laser		❍❍❍❍	
Potassium titanyl phosphate		❍❍❍❍	❍

C Used in combination therapy only
* The number of circles indicates the committee's expert opinion on relative efficacy up to 4, with 4 indicating the most effective. Filled vs open circles indicate strength of trial evidence, with solid circles as strong as open circles are weak.

Table 3. *Treatment options for major features; adapted from Thiboutot et al, 2020*

with the regular application of warm compresses with baby shampoo on a wet washcloth rubbed onto the eyelashes of closed eyes, to cleanse the eyelashes twice a day is recommended.[23] Antibiotic ointments or topical cyclosporine drops may be beneficial in decreasing the bacterial burden and decreasing inflammation, respectively, in these patients. An oral tetracycline such as doxycycline may be used, but recent studies have shown that topical azithromycin is equally effective as oral doxycycline, with fewer side effects.[24,25] For severe ocular rosacea, or if there is the presence of corneal ulceration, inflammation or red eye, immediate referral to an ophthalmologist is recommended, in order to prevent reduced visual acuity.[11]

Light treatments

Two types of lasers, pulsed dye and potassium titanyl phosphate, have both been shown to be highly effective in treating telangiectasias and reducing erythema.[26,27] To reduce flushing, intense pulsed light has been found to be effective.[28,29] Intense pulsed light for cutaneous types of rosacea has been found to also improve ocular rosacea (likely a field effect).[30,31] Ablative lasers using carbon dioxide and erbium, and radiofrequency can remove tissue from and resculpt nose rhinophyma. In patients with darker skin, all laser therapies should be used with caution.[11]

Summary

Rosacea is a chronic and relapsing cutaneous disorder with numerous triggers and varying presentations which often overlap and evolve. Patient education is of paramount importance in both understanding the disorder, preventing exacerbations and progression and in treatment compliance. The mainstay of therapies include a combination of topical and oral therapies, often with adjunctive laser treatments.

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