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REVIEW ARTICLE

Rosacea

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Abstract. Rosacea is a chronic inflammatory skin disease appearing in the central area of the face of middle-aged patients. It is characterized by flushing, permanent erythema, telangiectasia, papules, pustules, and the absence of comedones. Its underlying pathophysiologic mechanisms are not completely understood, although a number of hypotheses point to vascular abnormalities and infection by microorganisms such as *Demodex folliculorum*. Rosacea is classified into 4 subtypes, which determine the therapeutic approach based on skin care, topical anti-inflammatory agents, topical and oral antibiotics and retinoids, and, in some instances, light-based therapy and surgery.

Key words: rosacea, flushing, *Demodex folliculorum*, metronidazole, azelaic acid, tetracyclines, retinoids.

ROSACEA

Resumen. La rosácea es una dermatosis inflamatoria crónica que asienta en el área centrofacial de pacientes de mediana edad. Se caracteriza por episodios transitorios de rubor, eritema permanente, telangiectasias, pápulas y pústulas, con ausencia de comedones. Se desconocen los mecanismos fisiopatológicos subyacentes, aunque se dispone de varias hipótesis que implican principalmente las alteraciones vasculares y la infestación por microorganismos como *Demodex folliculorum*. La rosácea se clasifica en 4 variantes, que tienen un manejo terapéutico distinto, basado en el cuidado de la piel, los antiinflamatorios tópicos, los antibióticos y los retinoides tópicos o sistémicos y, en determinados casos, la terapia basada en la luz y la cirugía.

Palabras clave: rosácea, rubefacción, *Demodex folliculorum*, metronidazol, ácido azelaico, tetraciclinas, retinoides.

Introduction

Rosacea is a chronic inflammatory skin disease characterized by the appearance of erythema, telangiectasia, papules, and pustules affecting the central area of the face. Its etiology is unknown, although various factors such as abnormal vascular reactivity and immune responses to microorganisms such as *Demodex folliculorum* and *Helicobacter pylori* have been suggested to play a role. As a result of the limited understanding of the pathophysiology of the disease, treatment options do not target the pathogenic mechanisms and are not curative. Treatment is based on the use of topical or systemic antibiotics, anti-inflammatory drugs, and retinoids. Certain signs can be treated with lasers, and in severe cases surgery may be considered.

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Epidemiology

Rosacea is a disease mainly affecting individuals aged between 30 and 50 years.[1-4] According to the National Rosacea Society, it is calculated that there are 14 million people with the disease in the United States.[5-7] In Europe, the percentage of the population with rosacea is estimated at between 1.5% and 10%.[1] Between 1990 and 1997, the disease accounted for 1.1 million outpatient hospital visits and physician's appointments in the United States.[4] Some authors have reported that it is responsible for 1% of visits to dermatologists.[7] It is more common in women (3:1 ratio)[2] and in individuals with Fitzpatrick skin phototypes I and II,[1,4,5,8] although it affects all races.[3] The disease tends to be more severe in men,[5,7,9,10] with a higher incidence of complications[9] and a higher prevalence of the phymatous variant.[3,7] It is thought that there is a genetic predisposition to rosacea, since a third of patients report a family history of the disease.[1] Risk factors are chronic actinic damage, use of topical corticosteroids, a spontaneous tendency for flushing, genetic factors, and northern or eastern European origin.[5,10] Since the disease usually affects the face, there is a considerable psychological, social, and occupational impact[11]: up to 70% of patients report loss of self-esteem

and self-confidence,[6] and another 70% report that their professional relationships are negatively affected by the esthetic appearance of the disease; a third of patients have lost their job for this reason.[6]

Signs and Symptoms

Rosacea is a disease affecting the central region of the face: nose, cheeks, chin, forehead, and glabella.[7,8] Occasionally, lesions may be found outside the face in areas with a tendency towards sun damage, such as the ears, neckline, neck, back, and scalp.[7,8] The characteristic signs are erythema (transient or fixed), episodes of flushing, telangiectasia, edema, papules, and pustules.[5,8] The lesions are distributed symmetrically,[12] avoiding the periocular region.[11] Unlike in acne, rosacea does not present with comedones.[13] Some authors consider erythema of the central facial region for more than 3 months to be the most important finding and propose that it be the only obligatory criterion for diagnosis.[11] Spontaneous blushing, telangiectases, papules, and pustules are common but not a requirement for diagnosis.[11] Other secondary findings (Table 1) may coincide with the primary features or occur independently.[7] The coexistence of scaling associated with seborrheic or perioral dermatitis is not uncommon. On the basis of the predominant type of lesion, the National Rosacea Society Expert Committee proposed in 2002 a clinical classification of rosacea that included 4 subtypes[14]:

1. *Erythematotelangiectatic rosacea*. The most important factor is a history of flushing. Episodes usually last more than 10 minutes[8] and may be triggered by certain factors that will be mentioned later. Persistent erythema, telangiectasia, and edema of the central facial region may also be reported (Figure 1).[4,8] The ears, neck, and neckline may also be involved.[7] Patients occasionally report pruritus, a burning sensation, or scaling,[13] and their skin has a greater tendency to suffer local adverse effects of topical preparations.[8]
2. *Papulopustular (classic) rosacea*. Papulopustular rosacea is characterized by papules and pustules in the central facial region,[8] or in the perioral, perinasal, or periocular areas[7] (Figures 2 and 3). Central erythema is also present[4,7] and comedones are not observed.[4,13] Episodes of flushing and persistent erythema may lead to soft edema that hardens on some days or solid edema without dimpling on the forehead, glabella, upper eyelids, nose, and cheeks. This presentation is known as Morbihan disease and can be confused with cellulitis.[7] Periorbital edema may be the initial presentation. Telangiectases are less common than in erythematotelangiectatic rosacea, and episodes of flushing are less frequent and less severe.
3. *Phymatous rosacea*. Most patients with phymatous rosacea are men. It involves papules or nodules and thickening of the skin,[8] with accentuation of the follicular orifices, which may contain sebum or keratin plugs[7] (Figure 4). Nasal telangiectases tend to be frequent.[13] It is possible to encounter signs of

Table 1. Clinical Presentation of Rosacea

Primary Findings	*Secondary Findings*
Transient erythema (flushing)	Burning, pruritus
Persistent erythema	Plaques (thickened erythematous areas)
Telangiectases	Dryness
Papules	Edema
Pustules	Ocular involvement Phymatous lesions Extrafacial lesions

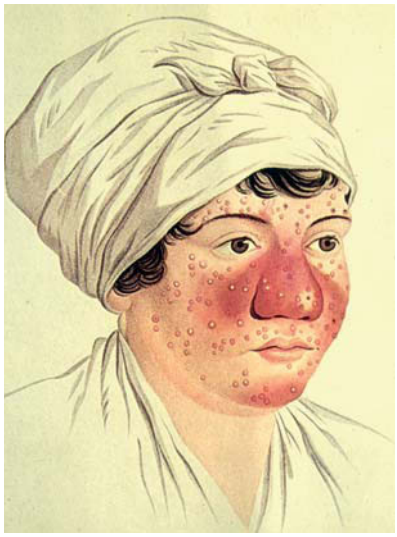

Figure 1. Classical illustration showing the most characteristic elements of rosacea: malar erythema and pustules.

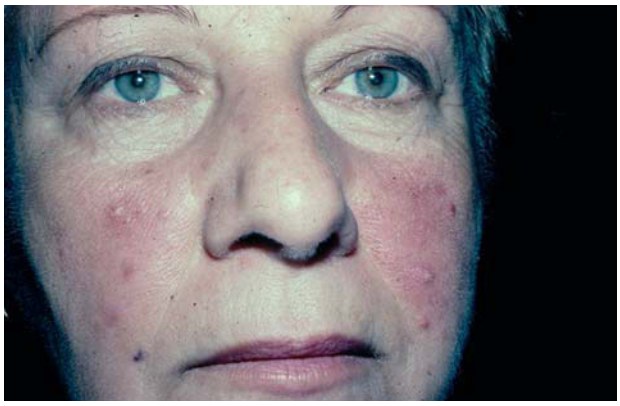

Figure 2. Erythematotelangiectatic rosacea with a minimal papular component.

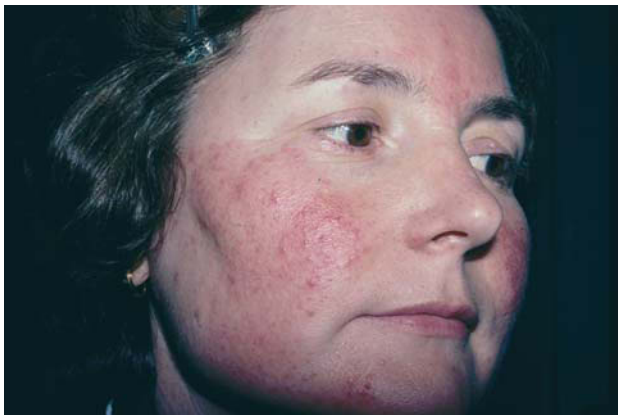

Figure 3. Mild papulopustular rosacea.

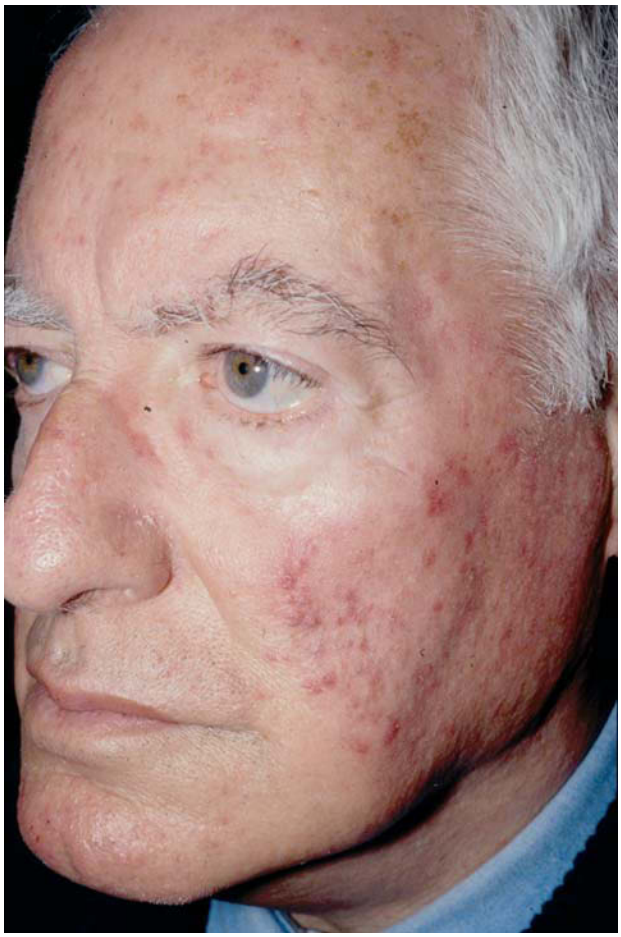

Figure 4. Severe papulopustular rosacea prior to treatment.

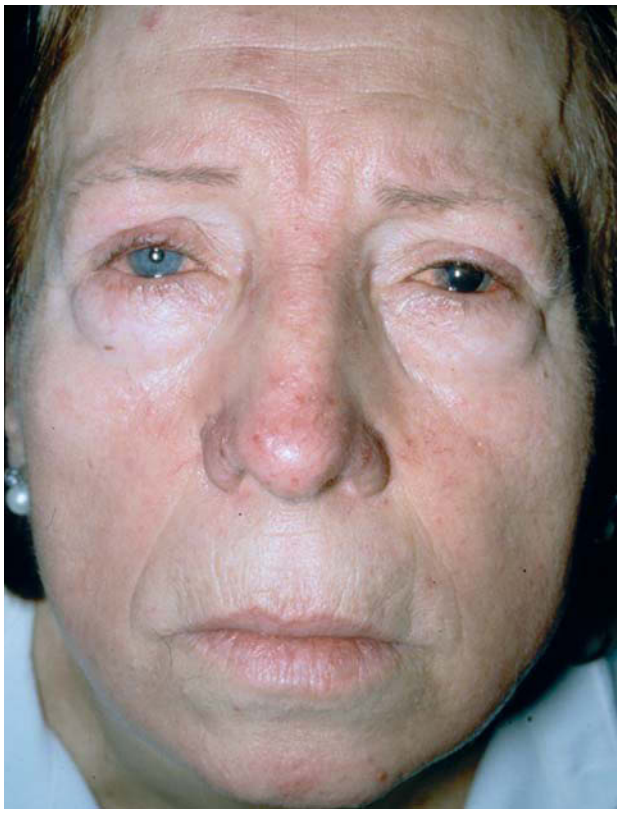

Figure 5. Ocular rosacea. Note the conjunctival lesion (blepharitis).

erythematotelangiectatic and papulopustular rosacea,[8] and the condition is usually preceded by these subtypes of rosacea.[7] It is normally located on the nose (rhinophyma) but can also occur on the chin (gnathophyma), forehead (metophyma), ears (otophyma), and eyelids (blepharophyma).[7]

4. *Ocular rosacea*. Ocular rosacea is centered on the eyelids, conjunctiva, and cornea. It tends to be accompanied by skin lesions, although these are not essential for diagnosis. The ocular disease may precede cutaneous involvement in 20% of cases.[7] The incidence of the disease is underestimated and it has been calculated that up to 58% of patients with rosacea have ocular symptoms ranging from mild blepharitis to corneal lesions with a risk of opacities, scarring, and loss of vision.[7,8] Blepharitis and conjunctivitis are the most common findings[7] (Figure 5), although there may be a number of other symptoms (Table 2).

This classification includes 2 other variants: (1) *Granulomatous rosacea*. Granulomatous rosacea is characterized by yellow, brown, or erythematous papules or nodules in the perioral or periocular regions, or on the cheeks (Figure 6). They tend to be less inflammatory than in papulopustular rosacea.[13] In up to 15% of patients the disease also affects regions other than the face.[7] Some authors prefer to consider this entity as a granulomatous dermatitis that is distinct from rosacea, since it does not include erythema or localization to the central facial region.[8] The

presence of other rosacea lesions is common but not obligatory for diagnosis of the disease.[7] (2) *Rosacea fulminans*, initially known as *pyoderma faciale*, is currently considered an extreme variant of rosacea. It usually appears suddenly in young women in the form of coalesced papules, pustules, and nodules on the chin, cheeks, and forehead.[7] It can present initially as mild rosacea.

Classification of rosacea into subtypes is essential, as it facilitates better therapeutic management.[11]

Histology

The histologic appearance of rosacea lesions varies according to the stage that is biopsied. In initial stages, there is a superficial perivascular lymphocytic infiltrate, telangiectases, and infiltrates of neutrophils and lymphocytes around the follicular infundibula.[7] In more advanced stages, the neutrophils accumulate within the follicles and infiltrates containing histiocytes, epithelioid cells, and lymphocytes form around the follicles. Noncaseating epithelioid granulomas may be encountered surrounded by lymphocytes and plasma cells in the inflammatory infiltrates, which are usually a consequence of rupture of the affected follicles. Marked telangiectasia is commonly found in the upper dermis, and in some patients there is a notable actinic elastosis.[7] The histologic changes occurring in rhinophyma involve hyperplasia of the sebaceous glands, dilation of the follicular infundibula, telangiectasia, and perifollicular infiltrates containing lymphocytes and histiocytes or plasma cells. Suppuration, granulomas, and fibroplasia are often observed.[7]

Table 2. Clinical Presentation of Ocular Rosacea

Blepharitis
Conjunctivitis
Sensation of dryness, burning, pruritus, or sensitivity to light
Blurred vision
Telangiectases of the conjunctiva and sclerocorneal limbus
Punctate epithelial erosions
Corneal infiltrates
Corneal ulcers
Corneal vascularization

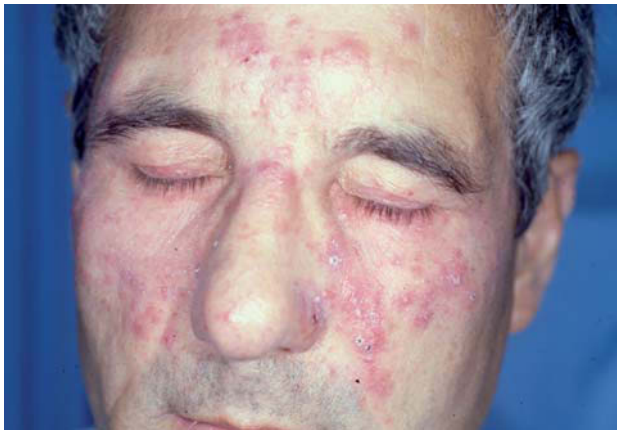

Figure 6. Severe papulopustular rosacea prior to treatment with oral isotretinoin.

Diagnosis and Differential Diagnosis

For diagnosis of rosacea at least 1 primary sign must be present on the convex areas of the face[11,15] (Table 1). The presence of secondary findings is not obligatory for diagnosis, although they usually occur in association with the primary signs or even in isolation. The combination of 2 or more secondary signs does not necessarily imply a diagnosis of rosacea.[13] No specific tests or clinical markers are available to confirm the clinical diagnosis of the disease, and as a result, observation and patient histories are fundamental.[5] The patient history should include those factors that precipitate or alleviate episodes of flushing, the frequency and duration of the episodes, the morphology and time-course of the lesions, and the factors that lead to improvement or worsening of the symptoms. The National Rosacea Society has described the triggers of flushing that are most often reported by patients, the most common being exposure to the sun.[15] Table 3 shows the trigger factors associated with flushing and lesions. The differential diagnosis of rosacea should be established with acne, seborrheic dermatitis, perioral dermatitis, carcinoid syndrome,[5] connective tissue diseases (lupus erythematosus, dermatomyositis, and mixed connective tissue disease), polycythemia vera, and mastocytosis.[11] On occasions, differential diagnosis can be considered with allergic or photoallergic contact dermatitis.[11] Tests are available to facilitate diagnosis in all of these diseases.

Pathophysiology

The mechanism underlying the development of rosacea is not known. Due to the clinical variability of the disease, it is likely that there is no single cause and that there are multiple pathophysiologic mechanisms involved. Analysis of the theories proposed to explain the pathophysiology of rosacea has produced inconsistent data in all cases.

Table 3. Triggers of Flushing or Lesions and Common Irritants in Rosaceaa

Foodstuffs	Liver, yoghurt, sour cream, eggplant, tomatoes, spinach, limes, white beans, peas, avocado, bananas, red plums, raisins, figs, citrus fruits, chocolate, vanilla, soy sauce, vinegar, hot and spicy foods, yeast products, alcohol, hot drinks
Emotional factors	Stress, anxiety
Climatic factors	Sun, strong wind, cold, damp
Temperature	Hot environments, saunas, hot baths
Cosmetics and drugs	Cosmetics and sprays, especially those containing alcohol, witch hazel, or fragrances. Hydroalcoholic substances or substances containing acetone Vasodilators, topical corticosteroids
Health-related factors	Menopause, caffeine withdrawal syndrome, chronic cough
Physical exercise	Intensive exercise or weight lifting
Common irritants in rosacea	Acetone, alcohol, propylene glycol, α-hydroxy acids, sodium lauryl sulfate, formaldehyde-releasing compounds, ascorbic acid, para-amino benzoic acid, cinnamates, benzophenones, menthol, benzyl alcohol, camphor

[a]Adapted from Gupta and Chaudhry[10] and Pelle et al[51]

Vascular Disease

Vascular disease is one of the most commonly mentioned factors due to the importance of flushing among the symptoms of rosacea. It involves an increase in blood flow in the upper dermis. The physiologic vasodilator response to hormonal and neural stimuli appears to remain intact in erythematotelangiectatic and papulopustular rosacea, while baseline facial blood flow is increased.[16] Erythema is more visible in the central facial region because the blood vessels are more superficial, larger, and more numerous there than in other areas.[8,11] Repeated episodes of flushing can lead to loss of vascular tone, with dilation of small dermal vessels and lymphatics.[7] The normal response to hyperthermia is an increase in flow from the cutaneous vessels towards the brain in order to cool it. This phenomenon appears to be defective in rosacea, leading to flushing more easily in response to thermal stimuli.[7,8,11] The hypothetical predisposition to vasodilation is further supported by the clinical deterioration observed with use of vasodilators and the increased incidence of migraine in patients with rosacea.[7]

Reliable data have not been obtained regarding possible alterations in the concentration of vasodilators such as substance P, vasoactive intestinal polypeptide, serotonin, gastrin, histamine, or prostaglandins.[8,11]

UV Radiation

Various observations support a role for UV radiation in rosacea, such as the preferential involvement of sunlight-exposed areas and the sparing of photoprotected skin, the higher frequency in patients with light phototypes, the increase in outbreaks in the spring, the low frequency of the disease in young people, and the presence of actinic elastosis in histologic samples.[7,11,17] Chronic sun damage would lead to an accumulation of proteoglycans and elastotic material in the dermis, resulting in damaged structural support of the blood vessels and favoring extravasation of fluid, proteins, and inflammatory mediators.[1,7,17] UV radiation induces expression of activator protein 1 and production of reactive oxygen species, which increase the activity of metalloproteinases, enzymes that degrade collagen.[1,17] UV-B induces the expression of nitric oxide synthase by endothelial cells and keratinocytes, resulting in production of nitric oxide by those cells.[18] Nitric oxide is a modulator of inflammation and vascular response, and it also increases synthesis of metalloproteinases.[18] Nevertheless, conflicting data have been obtained regarding the role of UV radiation[11]: some studies have shown that the percentage deterioration of rosacea with sunlight exposure is low[19-21]; others report that it is very high[15] or even that it leads to improvement.[21] The improvement in lesions may be explained by an immunosuppressant effect of UV radiation.[17] Various studies have failed to demonstrate an increase in sensitivity to UV radiation with photoprovocation,[8,20-22] or a greater history of sunlight exposure or sun-damaged skin among patients.[21] Thus, it is difficult to reach clear conclusions regarding the true role of sunlight exposure in the generation of rosacea.

Degradation of the Dermal Matrix

According to one hypothesis, vascular lesions precede the development of matrix abnormalities occurring as a consequence of extravasation of serum proteins, inflammatory mediators, and metabolic waste products from the affected vessels.[1,11] Other authors claim that UV radiation causes deterioration of the elastic and collagen fibers in the dermal matrix, resulting in damage to the blood vessels and lymphatics, which under these conditions would lose some of their contents.[7,23-35] Conservation of the vasoconstrictive response to vasoactive agents supports the theory of primary damage to the matrix.[10]

Demodex Mites

The role of *D folliculorum* and *Demodex brevis* has been widely debated.[7] It is common commensal organism of the central facial follicular infundibula[8] of the nose and cheeks.[8,26] Some authors have reported an increased prevalence of infestation in patients with rosacea,[27,28] supporting a causal relationship between this microorganism and the disease. The density of *Demodex* mites increases with age, in parallel with the incidence of rosacea. Patients appear to generate immune responses to antigens from the mites,[22,29] and this could lead to inflammatory lesions as a result of delayed hypersensitivity[30] and granulomas when the organism penetrates the dermis.[31,32] Nevertheless, the prevalence of *Demodex* mites is 100% in healthy adults, suggesting that lesions would not be related so much to the presence of the mites as to their density and localization around the follicles.[11] However, contradictory findings have been reported. Increased density of the microorganism has been found in biopsies from papulopustular rosacea but not in the erythematotelangiectatic variant.[33,34] Some studies have linked *Demodex* mites with perifollicular lymphohistiocytic inflammation, while others have failed to observe an association.[24,25] It is not known whether the therapeutic success of metronidazole is due to an immune response or to the generation of a metabolite that acts on the mites, since these survive at high concentrations of the antibiotic.[35-37] Likewise, no reduction in the numbers of *Demodex* mites have been observed in patients following courses of oral tetracycline.[27]

Helicobacter pylori

The proposed role of *H pylori* is based on the historical association between rosacea and some gastrointestinal diseases (eg, gastritis and achlorhydria), seasonal fluctuations shared by gastroduodenal ulcers and rosacea, and the effectiveness of metronidazole for the treatment of both rosacea and *H pylori*.[8,11] Some studies have observed a high prevalence of antibodies against *H pylori* among individuals with rosacea,[38-40] and others have reported improvement of the disease following treatment to eradicate the bacterium.[38,41,42] In contrast, other studies have found no quantitative differences in antibodies against *H pylori* when comparing rosacea patients and control subjects, nor improvement of the skin lesions following eradication of the bacterium.[43-45] Strains of *H pylori* that synthesize the cytotoxins CagA or VacA can release vasoactive substances such as histamine, prostaglandins, leukotrienes, and some cytokines, and these may be implicated in rosacea. Of the subjects with rosacea infected with *H pylori*, 67% have CagA strains while only 32% of control subjects carry these strains. In those patients, tumor necrosis factor α and interleukin 8 are elevated, but the levels are normalized following treatment to eradicate the bacterium.[46]

Abnormalities of the Pilosebaceous Unit

The importance of follicular abnormalities in rosacea is still subject to debate. Histologic studies of rosacea lesions observed a higher frequency of perivascular than periadnexal infiltrates.[24,25] Nevertheless, the distribution of the lesions in areas with a higher density of pilosebaceous follicles and the occasional association of ocular inflammation suggest a role for the pilosebaceous unit in the pathophysiology of the disease.[47] The theory of follicular involvement is also supported by the fact that various treatments attack follicular microorganisms (*Propionibacterium acnes* or *Demodex* mites)[8,11] and that in rhinophyma there is sebaceous gland hyperplasia and a perifollicular infiltrate with loss of pilosebaceous structures in the most severe cases.[8,47]

Ingested Agents

There is no evidence available supporting a role for diet or other gastrointestinal factors in the genesis of rosacea.[11] No studies have found an association between alcohol consumption and the appearance of rhinophyma.[11] In contrast, external agents such as amiodarone, topical corticosteroids, and vitamins B6 and B12 can induce rosaceiform or acneiform lesions.[8,48-50]

Genetic Factors

There is evidence supporting a genetic predisposition toward rosacea, since there is an increased prevalence of the disease within affected families (up to 40% of patients also have a relative with the disease)[51] and various factors that trigger flushing are common among patients.[52]

Defective Epidermal Barrier

The increase in transepidermal water loss that has been observed in areas affected by rosacea supports the hypothesis of epidermal barrier defects, although further studies will be required before a conclusion can be reached.[53]

Treatment

Due to our limited understanding of the pathophysiology of the disease, treatment is essentially symptomatic. The range of treatments used includes skin-care preparations,

Table 4. Subtypes, Variants, Characteristics, and Management of Rosacea[a,b]

Subtype or Variant	*Clinical Features*	*Primary Management*	*Alternatives*
Erythematotelangiectatic	Flushing, erythema, telangiectasia, edema	Topical metronidazole Topical azelaic acid Sodium sulfacetamide with sulfur Oral tetracyclines Topical tretinoin	Nonablative lasers β-Blockers Clonidine Rilmenidine NSAIDs Acetylsalicylic acid Topical antibiotics Topical calcineurin inhibitors
Papulopustular	Papules, pustules, erythema, edema	If mild, monotherapy with a topical antibiotic If not mild, topical treatment plus oral: Topical metronidazole Topical azelaic acid Sodium sulfacetamide with sulfur Oral tetracyclines Following a good response to oral antibiotics, topical maintenance treatment can be used alone	Topical tretinoin Benzoyl peroxide Permethrin, 5% Topical calcineurin inhibitors Oral ampicillin Oral metronidazole Oral macrolides Oral co-trimoxazole Oral isotretinoin Nonablative laser therapy
Phymatous	Papules, nodules, thickened skin, enlarged follicular orifices	Oral retinoids Oral tetracyclines Ablative lasers Electrosurgery	
Ocular	Telangiectases, blepharitis, conjunctivitis, keratitis	Eye care Artificial tears Oral tetracyclines	Topical metronidazole Topical fusidic acid Oral metronidazole Oral erythromycin
Granulomatous	Brown perioral, periocular, and malar papules	Oral retinoids Oral tetracyclines Potassium iodide	
Rosacea fulminans	Pustules, nodules, abscesses, sinuses	Oral isotretinoin	

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.
[a]Skin care, sun protection, use of makeup, and avoidance of triggers for flushing are applicable for all subtypes of rosacea.
[b]Adapted from Buechner,[7] van Zuuren et al,[12] Sherertz,[50] Draelos,[55] and Del Rosso and Bikowski[57]

sun protection, anti-inflammatory drugs, antibiotics, retinoids, laser therapy, and surgical techniques. To achieve a more targeted therapy it is useful to take advantage of the current classification of rosacea and follow the treatment regimen recommended for each of its subtypes (Table 4). It should be remembered that both topical and oral treatments are ineffective for the resolution of the telangiectases[5] and that, in all of the variants, these may be improved with laser therapy. The treatments approved for use with rosacea by the US Food and Drug Administration are shown in Table 5.

Generic Treatment

Avoid Triggers

Patients with rosacea or a tendency toward the disease suffer episodes of flushing or lesions when exposed to certain factors (Table 3). Up to 78% of subjects with rosacea report clinical improvement if triggers are avoided.[54]

Skin Care

The skin of patients with rosacea tends to be highly sensitive and reactive. Repair of the stratum corneum is an important factor in subjects with epidermal barrier defects.[51] In addition to avoiding aggressive skin care products, patients should use an emollient once or twice a day prior to applying other products. Soap-free cleansers are less irritant, have a more appropriate pH, contain fewer surfactants, and are less dehydrating than soaps.[52] In addition, they relieve irritation and reduce itching, dryness, and erythema; their use is therefore recommended whether in the form of bars or liquids.[52] Table 6 shows the most relevant aspects of the use of sunblocks, makeup, and skin care products.

Table 5. Treatments Approved for Use in Rosacea by the US Food and Drug Administration[a]

Topical Treatments	*Light-Based Treatments*
Metronidazole emulsion, 0.75%	Intense pulsed-light
Azelaic acid, 15% gel	Other devices emitting at wavelengths of 560-900 nm, with a spot diameter between 4-8 mm and 10-50 mm and a maximum fluence of 10-90 J/m
Sodium sulfacetamide, 10%, with sulfur, 5% Gel containing green pigment Gel and cleanser without pigment Aqueous gel and cleanser in vehicle with 10% urea Alcohol-free emollient cream and foam soap Cleanser with neutral pH Combined with a sun-protection cream	

[a]Adapted from Draelos[55]

Sun Protection

Daily use of high-protection-factor sunblocks such as titanium dioxide or zinc oxide is recommended. They are well tolerated and available in combination with metronidazole or sodium sulfacetamide and sulfur. To reduce the potential irritation, sunblock should contain silicons such as dimethicone and cyclomethicone, which reduce transepidermal water loss and improve the cosmetic appearance and application of the product.[51]

Makeup

The appearance of rosacea can be camouflaged with makeup, and this also has psychological benefits for the patient.[10] Creams are used to cover the defects with a finish that is adjusted to the type of skin and has a long-lasting effect. Ideally, they should contain high-protection-factor sunscreens and silicons, and they should be in a noncomedogenic liquid preparation that is easily applied.[55] Green pigment is used to camouflage red defects.[51] The depressions and irregularities that occur on the skin surface make it difficult to achieve a good cosmetic result.[10]

Table 6. Recommendations for Sun Protection and Use of Cosmetics in Rosacea[a]

Cleansing products should be soap free
Mild water-based, oil-free formulations are recommended and thick preparations that are difficult to apply and remove should be avoided
Sun protection and cosmetics should contain silicones such as dimethicone and cyclomethicone in order to increase tolerance and improve cosmetic result
Astringent preparations, menthol, camphor, eucalyptus or clove oil, pepper, witch hazel, strong fragrances, and sodium lauryl sulfate should be avoided
The preparation should be applied with the fingers to avoid damaging the epithelial barrier
Protection against UV-A and UV-B such as titanium dioxide or zinc oxide should be used
The base cream should be of a similar color to the patient's skin. Makeup and sun protection with a green pigment can help to mask erythematous defects.
Reddish or orange tones should be avoided.

[a]Adapted from Buechner[10] and van Zuuren et al[50]

Topical Treatment

The topical treatments approved by the US Food and Drug Administration are shown in Table 5.

Metronidazole

Metronidazole is a nitroimidazole with antibacterial and antiprotozoan activity, and it is the drug that has been most widely used for rosacea with the largest number of studies on its effect.[5] It belongs to category B for use during pregnancy.[51] Its mechanism of action is not known, although it appears to be anti-inflammatory or immunosuppressant.[7] It is used for the treatment of papulopustular rosacea[7] and its efficacy has been demonstrated as a cream, gel, or lotion at concentrations of 0.75% or 1% applied once or twice daily.[51,56] It reduces erythema by more than 50%, papules by 77%, and pustules by 80% after 12 weeks of use.[57] Various studies have demonstrated an efficacy clearly greater than placebo[12] and with excellent tolerance.[56] No significant differences have been observed between treatment with topical metronidazole and oral oxytetracycline at 8 weeks.[12] The local adverse effects are mild and include pruritus, irritation, and dryness.[12] No differences in patient-reported response have been found between azelaic acid and metronidazole, although when assessed by the investigator azelaic acid is more effective.[12] Adverse effects are more frequent with azelaic acid, although they are mild with both drugs and the tolerance is good.[12] Topical metronidazole allows the period of remission to be maintained following

a course of oral tetracyclines[10,56] and is the only drug validated by studies lasting up to 6 months.[56] It is the recommended drug for use as maintenance treatment.[5,58]

Azelaic Acid

Azelaic acid is a saturated dicarboxylic acid with antibacterial and anti-inflammatory activity, and acts to normalize keratinization[7] and inhibit production of reactive oxygen species by neutrophils.[51] It belongs to category B for use during pregnancy.[51] At a concentration of 20% in a cream and 15% in a gel it is effective for the treatment of papulopustular rosacea, reducing erythema and inflammatory lesions, and representing a comparable or even better option than metronidazole.[6] At a concentration of 20% it is more effective than metronidazole, 0.75%, in reducing inflammatory lesions at 15 weeks (78.5% and 69.4%, respectively).[59] The therapeutic response to azelaic acid increases over 15 weeks, while that of metronidazole reaches a maximum at 8 weeks and progressive improvement is not observed.[60] Two randomized controlled studies, each lasting 12 weeks, showed it to be effective at a concentration of 15% twice daily in comparison with placebo for the reduction of inflammatory lesions (58% and 51% reductions) and erythema (44% and 46% compared with 28% and 29% with placebo).[61] Local adverse effects are more common (38%) than with placebo, although they are mild (burning, pruritus, and irritation[12]). Another double-blind study reported that the frequency of local adverse effects was 26%, and 90% of patients stated that tolerance was good or acceptable.[62]

Sodium Sulfacetamide, 10%, With Sulfur, 5%

Sodium sulfacetamide is a competitive inhibitor of paraaminobenzoic acid, an essential compound for bacterial growth, and it also has a comedolytic and keratolytic effect.[5] It belongs to group C for use during pregnancy. It is usually used as an adjuvant (lotion or cleanser) in severe cases, and it is well tolerated.[7] It is effective as monotherapy, although the combination of a cleanser containing sodium sulfacetamide/sulfur with metronidazole gel produces the best results.[51] Sulfacetamide/sulfur lotion produces good results in terms of reduction of both erythema and inflammatory lesions.[63] In a blinded study, mild local adverse reactions were observed in 19% of cases.[64]

Benzoyl Peroxide

Patients without a defective epidermal barrier obtain a rapid improvement in pustules and papules with benzoyl peroxide. In contrast, secondary pruritus and erythema may be severe.[51] The combination of benzoyl peroxide and clindamycin has yielded promising results, although further studies are required to determine its efficacy.[12,51]

Other Antibiotics

Topical clindamycin and erythromycin have both yielded favorable results in the reduction of papules and pustules.[65,66]

Tretinoin

The results of treatment with tretinoin are not observed until after 2 months of treatment.[67] Retinaldehyde appears to be better tolerated.[68]

Calcineurin Inhibitors

Calcineurin inhibitors should be used with caution, since both tacrolimus and pimecrolimus can cause rosaceiform dermatitis as an adverse effect in inflammatory skin diseases.[69] Tacrolimus is indicated for the treatment of rosacea occurring as a result of topical corticosteroids.[70]

Oral Treatment

Tetracyclines

Tetracyclines are bacteriostatic drugs with anti-inflammatory activity through reduction of levels of cytokines such as interleukin 1 and tumor necrosis factor α.[3] They also act as inhibitors of metalloproteinases[3,71] and of neutrophil chemotaxis.[7,71] They yield an excellent and rapid response in papulopustular rosacea, although relapses are common when treatment is withdrawn (50%-60% at 6 months).[72] They do not reduce erythema or telangiectasia. The most common dosages are tetracycline, 250-1000 mg/d; doxycycline, 100-200 mg/d; and minocycline 100-200 mg/d.[3] Tetracycline is less effective than doxycycline or minocycline, which obtain similar responses,[7] have greater bioavailability, and can be taken with food.[51] Doxycycline or minocycline at a dose of 100 mg/d are continued for 2 to 4 weeks and then reduced progressively when there is a marked improvement in the condition, until a minimum dose is achieved to control the disease; this dose can be continued for months.[7] Doses of doxycycline below the threshold for antimicrobial or anti-inflammatory activity (20 mg every 12 hours) are effective in reducing lesions, can be continued for long periods, display few adverse effects, and do not favor antibiotic resistance.[51] The use of doxycycline at a dose of 100 mg/d for 12 weeks leads to a substantial improvement in ocular rosacea.[73] Adverse effects of tetracyclines include gastrointestinal complaints, vulvovaginal candidiasis, or intracranial hypertension. Doxycycline can cause photosensitivity and minocycline can cause vertigo, bluish pigmentation, and symptoms reminiscent of lupus.[3]

Macrolides

Macrolides are normally given to pregnant women or patients who do not tolerate tetracyclines.[51] The dose of erythromycin ranges from 250 to 1000 mg/d. Second-generation macrolides such as clarithromycin and azithromycin have a more rapid effect and produce fewer gastrointestinal side effects.[3] Azithromycin at a dose of 250 mg 3 times weekly is safe and effective for the treatment of moderate-to-severe rosacea.[74] A study involving a follow-up period of 3 years found that use of clarithromycin requires fewer treatment cycles than does doxycycline.[75]

Metronidazole

Metronidazole is usually given at a dose of 250 to 1000 mg/d for 10 to 14 days[7] and has an efficacy similar to oxytetracycline.[3] Long-term administration leads to side effects and toxicity[7] including neuropathy, seizures, and headaches through a disulfiram-like effect when combined with alcohol.[3,51]

Isotretinoin

The onset of action of isotretinoin is slower than that of antibiotics,[51] although the response is maintained following withdrawal of treatment.[76] The dose used is between 0.1 and 0.2 mg per kg body weight per day for 6 months.[7] It reduces papules, pustules, erythema, and telangiectasia at a dose of 10 mg/d in papulopustular rosacea,[77] and it is the treatment of choice for granulomatous and phymatous rosacea and rosacea fulminans[7] (Figures 7 and 8).

Light-Based Treatment

Laser therapy produces the best results in erythematotelangiectatic rosacea.[2] Short- and long-pulsed dye lasers (585 and 595 nm, respectively) act on the superficial vessels of the dermis, since they are absorbed most by oxyhemoglobin. Pulsed dye laser at 585 nm reduces inflammatory lesions, although it causes purpura, hypopigmentation, and atrophic scarring.[2,56] Pulsed dye lasers at longer wavelengths cause less epidermal damage but, despite yielding excellent results, can cause purpura, temporary hyperpigmentation, and crusts.[2] Optimal results for erythema and telangiectases appear to be achieved with long pulse duration and 2 or 3 passes in 2 to 6 sessions, reducing the risk of complications.[2] Superficial erythematous vessels can also be treated with potassium-titanyl-phosphate (KTP) lasers and diode-pumped frequency-doubled lasers (532 nm). Deeper blue vessels can be reached with an 810 nm diode laser, long-pulse alexandrite laser (755 nm), and long-pulsed Nd-YAG (neodymium-yttrium aluminium garnet) laser (1064 nm).[2,51]

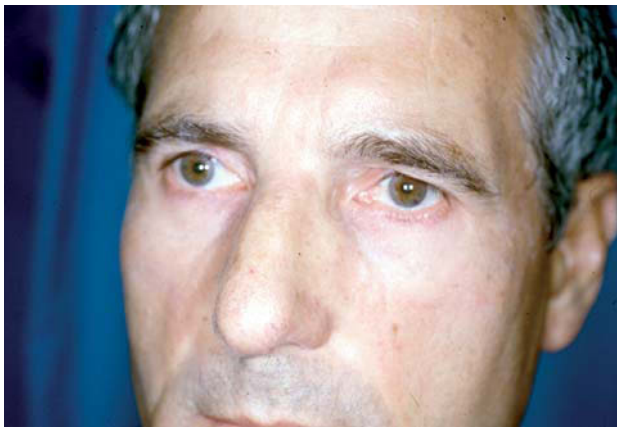

Figure 7. The same patient shown in Figure 6 after treatment.

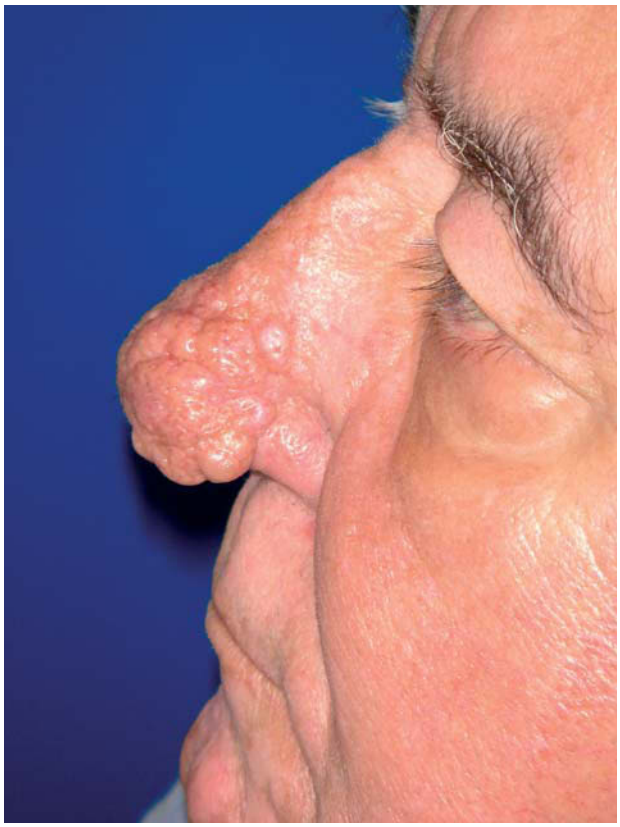

Figure 8. Rhinophyma prior to surgical treatment.

Intense pulsed-light therapy is effective for the treatment of erythema, telangiectasia, and flushing.[56] It has a wide spectrum (515-1200 nm) that can be adjusted to target vessels of differing size and depth,[2] and can also reach the connective tissue.[51] Photodynamic therapy can be used if there is concomitant actinic damage.[56]

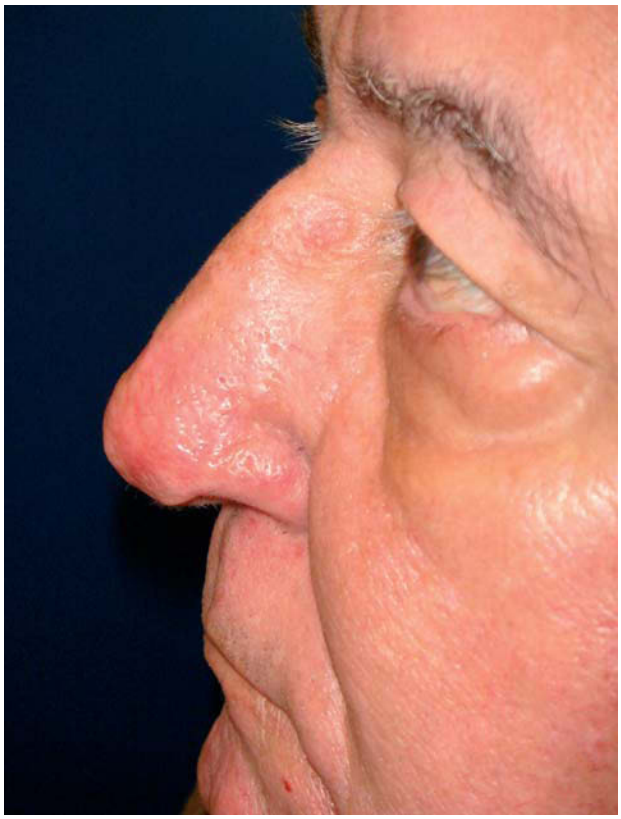

Figure 9. The patient shown in Figure 8 after treatment with radiofrequency electrocautery.

Surgical Treatment

Surgery is used for the treatment of phymatous rosacea to normalize the contours of the structures with a minimum of scarring. Excision may be complete and followed by direct suture or grafting, or it may be incomplete with subsequent reepithelialization. The latter is associated with better cosmetic results and is the treatment of choice.[10] Incomplete excision can be performed by cryosurgery, dermabrasion, electrocautery (especially radiofrequency), scalpel excision, and laser surgery. Cryosurgery employs cycles of freezing for 30 seconds followed by thawing for 4 minutes. Dermabrasion is an adjuvant therapy used to profile the contours of the nose. Electrocautery uses a bipolar device with a metallic ring that removes excess tissue through the use of heat (Figures 4 and 9). Resection with a scalpel achieves excellent results, the main drawback being hemostasis during surgery. Lasers eliminate surplus tissue by vaporization, allowing better visualization and coagulation. Regardless of the method used, the depth of penetration must be carefully controlled and damage to sebaceous glands avoided in order to prevent unsightly scars.

Other Treatments

Inhibitors of Flushing

Inhibitors of flushing such as vasoconstrictors, hypotensives, and modifiers of the vascular response to emotional stimuli are not generally effective.[3] Anecdotally, ondansetron, acetylsalicylic acid, and selective serotonin reuptake inhibitors have achieved good outcomes.[3] Both clonidine and nadolol have limited efficacy, and do not successfully reduce episodes of flushing.[78,79] Subcutaneous naloxone displays better results for the control of alcohol-induced flushing.[80] There are currently no effective drugs available for the long-term control of flushing.[10]

Miscellaneous

Permethrin has shown poorer results compared with topical metronidazole, since it has no effect on the papules. However, it may be a valid therapeutic option in cases with a very high density of *Demodex* mites. Good results have been achieved with spironolactone in isolated cases, although it has notable adverse effects and alters serum concentrations of some sex hormones.[81] Oral contraceptives, as monotherapy or in combination with cyproterone acetate, have yielded positive results in small studies.[51]

Conclusion

Rosacea is a chronic inflammatory skin disease involving erythema, papules, pustules, and telangiectasia in the central facial region, without the presence of comedones. Its etiology is unknown, although the pathophysiologic mechanisms are thought to include principally abnormalities of vascular and connective-tissue structure, microorganisms such as *D folliculorum* and *H pylori*, and chronic actinic damage. Treatment of the disease consists of avoiding triggers of flushing, skin care, use of antibiotics (metronidazole, tetracyclines, and macrolides), anti-inflammatory drugs (sodium sulfacetamide/sulfur or azelaic acid), or topical retinoids (tretinoin and isotretinoin) for mild cases and oral drug therapy for more severe cases (tetracyclines, metronidazole, macrolides, and retinoids). Laser therapy can be used in all stages of rosacea for the treatment of vascular lesions. Surgery is also a treatment option for the phymatous variant of the disease.

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