ROSACEA
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I/ Introduction
Rosacea is a common condition, in particular among skin types I-II patients. Although not being a life-threatening condition, it can have a deep impact on the patient’s self-esteem and quality of life, and hence justifies a high number of consultations by the dermatologists.
The clinical pattern is well-known, consisting of facial flushing, appearance of telangiectases and persistent redness of the face, eruption of inflammatory papules and pustules, hypertrophy of the sebaceous glands of the nose with fibrosis. Recent classification schemes resulted to be helpful in the management of patients with rosacea. The etiology of rosacea remains unknown, and multiple intrinsic and extrinsic factors have been related with the etiopathogenesis of rosacea, suggesting a multifactorial condition. Besides obvious extrinsic factors as climatic exposure, chemicals or ingested foods, intrinsic factors are focusing on a series of vascular disorders with structural alterations of cutaneous vasculature, less of vascular integrity and increased angiogenesis and expression of angiogenesis factors (in particular VEGF). Demodex folliculorum has certainly a key role, not certainly as a causative factor of rosacea, but more probably in the worsening of the conditions of the patients and maintenance of the disease, and its mechanism of action in much better understood than it was in the past. Recently, focus was given on the great importance on the mechanisms of matrix degradation, especially the high levels of matrix metalloproteinases (MMPs) constantly observed in the tissues of patients with rosacea. The current trend is to consider that the main causative factor of rosacea could be an antioxidant system defect in these patients, leading to the abnormal generation of reactive oxygen species (ROS) provoking inflammation and vascular abnormalities. The treatment of rosacea is mainly based upon topical therapies: Metronidazole and azelaic acid are the major players, acting more as anti-inflammatory agents than as antibiotics or antiparasitic, but also more and more topical antioxidants are used in rosacea. Second-line therapies are oral antibiotics (tetracyclines and metronidazole) at anti-inflammatory and antioxidant doses. Laser therapies and surgical procedures are also sometimes required.

2- EPIDEMOLOGY:
Rosacea is a common condition accounting for approximately 1% of all visits to the dermatologist (1), although it often occurs that the patients are asking for recommendations to their pharmacist or beautician. The extract incidence of rosacea is difficult to determine, and varies greatly from one country to another one, and even from one region to another one. It is estimated to affect 1.5% to 10% of people in Europe, based on population studies (2,3).
Not fitting exactly with these results, recent papers claimed a frequency of 0.47% over 76,697 patients in Germany (4) and 2.63% in Belgium (5). Rosacea was told to be the diagnosis for approximately 13 millions Americans, i.e. a prevalence of 4.29%. Anyway, most individuals diagnosed with Rosacea are white adults, usually of Celtic Northern and eastern European origin, with Fitzpatrick skin types I & II, on the face (7,8,9), and rosacea is commonly named the “curse of the Celts”(10) for this reason. However, rosacea can occur in all racial and ethnic groups, but it is uncommon in persons with dark skin. (7)

The onset of rosacea usually occurs between the ages of 30 and 50 years. (7,11,12)

Women are affected more commonly than men, (3) but men with rosacea are more prone to the development of thickening and distorting phymatous skin changes (7) and phymatous rosacea is seen almost exclusively in men aged > 40 years of age. (13)

Epidemiologic data suggest a genetic predisposition for the development of rosacea, with several intrinsic and extrinsic factors potentially correlating with the phenotypic expression of the disorder; (14,15) up to 30 percent of patients report a family history of rosacea. (11)

Although not a life-threatening condition, rosacea produces conspicuous facial redness and blemishes that can have a deep impact on the patient’s self esteem and quality of life. (17)

Rhinophyma, the most prominent feature of advanced rosacea, is often mistakenly associated with alcoholism, further stigmatizing rosacea patients.

A survey by the National Rosacea Society reported that 75% of rosacea patients felt low self-esteem, 70% felt embarrassment, 69% report frustration, 56% felt that they had been “robbed of pleasure or happiness, 60% felt the disorder negatively affected their professional interactions and 57% believed that it adversely affected their social lives. (18)

III / Diagnosis

A constellation of clinical symptoms and signs are included under the broad rubric of rosacea. These consist of facial flushing, the appearance of telangiectasic vessels and persistent redness of the face, eruption of inflammatory papules and pustules on the central facial convexities, and hypertrophy of the sebaceous glands of the nose, with fibrosis (rhinophyma). (19)

There is often an overlapping of clinical features, but in the majority of patients, a particular manifestation of rosacea dominates the clinical picture. (7)

The clinical features of rosacea primarily affect sites of facial convexity and include transient erythema (flushing), non-transient erythema, papules, pustules and telangiectases. (20)

Clinical signs and symptoms of rosacea include stinging, burning, pruritus, edema, and dry skin. (21)

The varied clinical presentations of rosacea appear to reflect a spectrum of heterogeneous responses to multiple pathogenic factors. (15)

Patients may report increased sensitivity of the facial skin (22) and may have dry, flaking facial dermatitis, edema of the upper face (15) or persistent granulomatous papulonodules. The disorder in characterized by intermittent episodes of exacerbation and variable periods of remission. (20)
Some patients identify exacerbating factors, particularly in regard to flushing, such as heat, alcohol, sunlight, hot beverages, stress, menstruation, certain medications and certain foods. (23)

Ocular changes are present in more than 50% of patients and range from mild dryness and irritation with blepharitis and conjunctivitis (common symptoms) to sight-threatening keratitis. (24)

As a useful approach to the guidance of therapy, the disease has been classified by the US National Rosacea Expert Committee (21) into four subtypes, with the severity of each subtype graded as (1-mild, 2-moderate, 3-severe as follows:

- **Subtype 1: Erythematotelangiectatic rosacea**
  Mainly characterized by flushing and persistent central facial erythema. The appearance of telangiectases is common but not essential for a diagnosis of this subtype. Central facial edema, stinging and burning sensations, and roughness and scaling may also be reported. A history of flushing alone is common among patients presenting with erythematotelangiectatic rosacea.

- **Subtype 2: Papulopustular rosacea**
  Characterized by persistent central facial erythema, with transient papules or pustules or both in a central facial distribution. However, papules and pustules may also occur periorificially (that is, they may occur in the perioral, perinasal or periocular area). The papulopustular subtype resembles acne vulgaris, except that comedones are absent. Rosacea and acne may occur concomitantly, and such patients may have comedones as well as the papules and pustules of rosacea. Burning and stinging sensations may be reported by patients with papulopustular rosacea.
  This subtype has often been seen after or in combination with subtype I, including the presence of telangiectases. The latter may be obscured by persistent erythema, papules or pustules, and lend to become more visible after successful treatment of these masking components.

- **Subtype 3: Phymatous rosacea**
  It includes thickening skin, irregular surface nodularities, and enlargement. Rhinophyma is the most common presentation, but phymatous rosacea may occur in other locations, including the chin, forehead, cheeks and ears. Patients with this subtype also may have patulous, expressive follicles in the phymatous area, and telangiectases may be present. This subtype is frequently observed after or in combination with subtype 1 or 2, including persistent erythema, telangiectases, papules and pustules. In the case of rhinophyma, these additional stigmata may be especially pronounced in the nasal area.

- **Subtype 4: Ocular rosacea**
  The diagnosis of ocular rosacea should be considered when a patient’s eyes have one or more of the following signs and symptoms: watery or bloodshot appearance (interpalpebral conjunctival hyperemia), foreign body sensation, burning or stinging,
dryness, itching, light sensitivity, blurred vision, telangiectases of the conjunctiva and lid margin, or lid and periocular erythema. Blepharitis, conjunctivitis, and irregularity of the eyelid margins may also occur. (25)

Meibomian gland dysfunction presenting as chalazion or chronic staphylococcal infection as manifested by hordeolum (stye) are common signs of rosacea-related ocular disease. Some patients may have decreased visual acuity caused by corneal complications (punctate keratitis, corneal infiltrates/ulcers, or marginal keratitis). (26)

Treatment of cutaneous rosacea alone may be inadequate in terms of lessening the risk of vision loss resulting from ocular rosacea, and an ophthalmologic approach may be needed.

Ocular rosacea is most frequently diagnosed when cutaneous signs and symptoms of rosacea are also present. However, skin signs and symptoms are not prerequisite to the diagnosis, and limited studies suggest that ocular signs and symptoms may occur before cutaneous manifestations in up to 20% of patients with ocular rosacea. There is one variant of rosacea: granulomatous rosacea. It is characterized by hard, yellow, brown or red cutaneous papules or modules that may be severe and lead to scarring. These lesions tend to be less inflammatory than papules and pustules and sit upon relatively normal-appearing skin. They can vary in size among patients but are monomorphic in each individual patient, and typically appear on the cheeks and periorificial areas. Granulomatous rosacea may occur in locations other than those in which the phymas are observed. The presence of other rosacea signs is not needed for a diagnosis of this variant of rosacea.

**Differential diagnosis**

Rosacea must not be mistaken for rosacea fulminans, popularly known as pyoderma faciale, characterized by the sudden appearance of papules, pustules and nodules, along with fluctuating and draining sinuses that may be interconnected. Steroid-induced acneiform eruption is not a variant of rosacea and can occur as an inflammatory response in any patient during or after chronic corticosteroid use. Perioral dermatitis: without rosacea symptoms, it cannot be classified as variant of rosacea. It is characterized by such stigmata as microvesicles, scaling and peeling.

Rosacea is likely associated with seborrhoeic dermatitis (7) and with migraine in women. (27)

**IV / ETIOLOGY and PATHOGENESIS**

The etiology of rosacea remains unknown, although its pathogenesis is broadly described. Multiple intrinsic and extrinsic factors have been related with the etiopathogenesis of rosacea, suggesting a multifactorial condition.

The following table is an update of the excellent work performed by Del Rosso (20), with an intent to classify the mechanisms associated with the pathogenesis of rosacea according to the categories mentioned by Crawford. (15)
### EXTRINSIC FACTORS

#### CLIMATIC EXPOSURE
- UV-exposure \(^{(13, 28)}\)
- Hot weather \(^{(13, 34)}\)
- Exercise \(^{(13, 31)}\)
- Cold weather \(^{(13, 34)}\)
- Wind \(^{(13)}\)
- Hot baths \(^{(13)}\)

#### CHEMICALS & INGESTED AGENTS
- Skin-care products \(^{(13)}\)
- Spicy foods \(^{(13)}\)
- Hot drinks \(^{(13, 34, 35)}\)
- Alcohol \(^{(13, 32, 33, 34)}\)

#### EMOTIONAL STRESS \(^{(13, 34)}\)

### INTRINSIC FACTORS

#### Vascular disorders
- Altered vascular response to ambient or oral heat temperature \(^{(12, 14, 15, 34)}\)
- Changes in cutaneous blood flow \(^{(14, 15, 35, 36)}\)
- Increased angiogenesis \(^{(15)}\)
- Loss of vascular integrity \(^{(15)}\)
- Structural alterations of cutaneous vasculature \(^{(14, 15, 35, 36)}\)
- Telangiectasia formation \(^{(15)}\)
- Imp Exaggerated expression of VEGF receptors \(^{(47)}\)

#### Cutaneous disorders
- Abnormalities of the pilosebaceous units \(^{(15)}\)
- Degeneration of dermal matrix \(^{(15, 36, 37)}\)
- Features also associated with photo-ageing \(^{(3, 8, 14, 15, 36, 38)}\)
- Impaired epithelial barrier function \(^{(39, 40)}\)

#### Skin cell biology-related events
- Immune response to microbial organism
  - Demodex mites \(^{(41)}\)
  - Other microbial organisms \(^{(42, 43)}\)
- Altered cutaneous redox balance \(^{(38, 48, 49, 50, 51, 52, 53, 54)}\)
- Increased generation of reactive species \(^{(55, 56)}\)

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**IV-1/ Extrinsic factors**

**IV-1-a/ Climatic exposure**

Patients with rosacea may be more susceptible to environmental factors than the normal population, although the casual role of these factors remains to be elucidated. \(^{(57)}\)

Common triggers of flushing include hot and cold weather, sudden changes in temperatures, wind \(^{(34, 13)}\).

It was demonstrated \(^{(58)}\) that there was an enhanced sensitivity to noxious heat stimuli in rosacea-affected skin than in control patients, and that this phenomenon was more prominent in patients affected by papulopustular rosacea.

Sparing of sun-protected areas, an association with fair skin, and the presence of solar elastosis are among the clues that implicate ultraviolet (UV) exposure in the pathogenesis of rosacea. \(^{(59)}\)

Thus, the general consensus among clinicians is that rosacea is a photo-aggravated disorder. Pathophysiological processes induced by UV radiation, which are similar to
those seen in photo-ageing, contribute to the signs and symptoms of rosacea. Usually, clinicians recommend that patients use sunscreens or sunblocks. However, an increase in UV sensitivity has not been demonstrated in rosacea patients and individuals with rosacea experience improvement more often than impairment from exposure to sunlight

IV-1-b/ Chemicals and ingested agents
Skin-care products may be triggering agents for rosacea, depending mainly on their nature and quality. As the skin barrier appears to be damaged in rosacea, this makes obvious that skin-care products, cosmetics or toiletries not designed specially for the purpose of this particular skin-type will be at high risk of triggering the symptoms of rosacea. A special mention must be made for alcoholic lotions or products: as alcohol is a potent vasodilator, and vasodilatation is one of the most commonly identified histological finding in the biopsies of patients with rosacea, a strict ban of any alcoholic topical product must be respected by these patients.

Of course, the same restrictions apply to alcoholic drinks. As a small, water- and lipid-soluble molecule, alcohol reaches all tissues of the body, including dermis and epidermis. In that way, alcohol consumption is obviously an important triggering factor for rosacea. Hot drinks are also susceptible of causing flushing in an oral thermal-induced manner in patients with erythematotelangiectatic rosacea. On the contrary, there is no scientific evidence that coffee, tea or any caffeine-containing drink could cause or trigger rosacea.

IV-2 / Intrinsic factors
IV-2-a / Vascular disorders
As it was afore mentioned, patients with rosacea usually display an altered vascular response to ambient oral heat temperature. The basic abnormality seems to be a microcirculatory disturbance of the function of the facial angular veins directly involved in the brain-cooling vascular mechanism. Structural alterations of cutaneous vasculature are present in most patients, if not all, with rosacea. In one study, in the capillaroscopic examinations, atypical capillaries were found in all patients with rosacea. The most common features were Raynaud loops (62.5%), meandering capillaries and their elongation (62.5%) and increasing number of the capillaries. Increased angiogenesis, with subsequent changes in cutaneous blood flow are also broadly reported. Blood flow in rosacea patients was found to be three to four times that of controls. In a recent study, the microvessels density (MVD) and total vascular area (TVA) were found to have significantly higher values in the lesional skin than in the clinically uninvolved skin of patients with rosacea.
Furthermore, high MVD and TVA values were found to correlate with the papulopustular rosacea clinical type and the presence of ocular manifestations. High MVD values were also found to correlate with granuloma formation in the dermis.

**Loss of vascular integrity and telangiectasia formation** are also frequently reported. Histological examination shows mixed lymphohistocytic inflammation (primarily lymphocytic inflammation in 40% of patients and primarily histiocytic with a few giant cells in 34%), epithelioid granulomas in 11% of patients and epithelioid granulomas with caseation necrosis in 11%. In an aforementioned study, the mast cells (MC) number was found significantly higher in the lesional vs. clinically uninvolved skin. Statistically important results have been showed in the relation of MCs density with the duration of the disease. These data suggest a potential involvement for MCs in disease pathogenesis. MCs are known to potentiate a number of inflammatory processes upon degranulation and to occur in increased numbers in conditions associated with angiogenesis. Angiogenic factors such as VEGF induce a direct chemotactic effect on MCs through enhanced adhesion to E and P selectin of post capillary venules and also indirect through releasing from endothelial cells, MC’s recruiting factors, such as stem cell factor and nerve growth factor (NGF). All these data suggest that MCs may not play an essential early role in angiogenesis of rosacea but rather may be related to the maintenance and maturation of blood vessels in rosacea lesions. Recent papers are pointing out a significantly increased dermal expression of Vascular Endothelial Growth Factor (VEGF) in lesional vs. non lesional skin of rosacea patients.

**Expression of VEGF receptors** (VEGF-R1 and VEGF-R2) both by vascular endothelium and infiltrating mononuclear cells, was also observed in rosacea. Although not expressed by endothelium, VEGF in present in epidermis and epithelium, and may contribute to the vascular changes and cellular infiltration occurring in rosacea. On the other hand, excessive VEGF stimulation was considered as susceptible of playing a pivotal role in the irritation and development of brain vessel malformations in mice and increased plasma levels of VEGF were observed in patients with hereditary hemorrhagic telangiectasia.

**IV-2-b / Cutaneous disorders**

**Abnormalities of the pilosebaceous units** are a matter of controversy. Marks and Harcourt-Webster found pilosebaceous units abnormalities in 20% of rosacea papules and perifollicular inflammatory infiltrates in 51% of specimens. However, follicular inflammation is characteristic of the granular type of phymatous rosacea. Along with vasodilatation, actinic elastosis with dermal matrix degradation are the most prominent and commonly identified histological findings in biopsy specimens of patients with rosacea, features also associated with photo-ageing. Based on these
common clinical characteristics and dermatopathologic findings, it has been broadly suggested that chronic photodamage significantly contributes to the pathogenesis of rosacea. (12, 15, 28)

It has been suggested that chronic dermal matrix degradation and degenerative changes to superficial cutaneous vasculature lead to leakage into perivascular tissue with accumulation of serum and proinflammatory mediators, fluid outflow in excess of dermal lymphatic capacity, and loss of perivascular structural support, all producing greater persistence of erythema, edema and telangiectases over time. (12, 14, 15)

Impaired epithelial barrier function was also involved (39, 40) as a causative factor for rosacea. In one study, (40) the normal value of the skin surface lipids was found in only 30% of rosacea patients, and lower amounts were present in 63%. Contrarily to perioral dermatitis, TEWL levels remain normal in rosacea patients. (39)

IV-2-c/ Skin cell biology-related events

Here, the role of Demodex folliculorum must be discussed. We made an in-depth review of the literature available, and according to our knowledge, the first paper even published about the role of Demodex folliculorum in Rosacea was that of Brodie, in 1952, in the Australasian Journal of Dermatology (68). Hence, the way was a long one, and today authors still continue to debate about, probably, the most famous mite in dermatology.

Table 2 in reporting most (not all) of the papers related with Demodex and its putative role in rosacea.
<table>
<thead>
<tr>
<th>YEAR</th>
<th>AUTHOR</th>
<th>Nº of Patients</th>
<th>CHARACTERISTICS</th>
<th>INCIDENCE of DF</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>Rufli et al 69</td>
<td>18</td>
<td>Rosacea</td>
<td>88.9%</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>Ramelet (70)</td>
<td>75</td>
<td>Rosacea</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>Sibenge (71)</td>
<td>25</td>
<td>Rosacea</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>Basta-Juzbasic (40)</td>
<td>50</td>
<td>Rosacea</td>
<td>86%</td>
<td>92% in patients treated with topical CTC</td>
</tr>
<tr>
<td>1993</td>
<td>Forton (72)</td>
<td>49</td>
<td>13 Erithematotelangiectatic rosacea 3 Squamous rosacea 33 Papulopustular rosacea</td>
<td>Higher Demodex density only in papulopustular rosacea patients</td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>Bonnar (73)</td>
<td>42</td>
<td>Rosacea</td>
<td>Higher density in patients with rosacea than in controls.</td>
<td>Highest density found on the cheeks</td>
</tr>
<tr>
<td>1997</td>
<td>Abd-El-Al (74)</td>
<td>16</td>
<td>Papulopustular rosacea</td>
<td>100% (vs 76% in controls)</td>
<td>Cheeks &gt;forehead &gt;chin</td>
</tr>
<tr>
<td>1998</td>
<td>Erbagci (75)</td>
<td>38</td>
<td>Rosacea</td>
<td>Higher density in rosacea patients than in control group.</td>
<td>Highest density on the cheeks.</td>
</tr>
<tr>
<td>1998</td>
<td>Roihu (76)</td>
<td>80</td>
<td>Rosacea</td>
<td>51%</td>
<td>Forehead &gt; cheeks Males&gt;females</td>
</tr>
<tr>
<td>2000</td>
<td>Aydingöz (77)</td>
<td>40</td>
<td>Pregnant women (indefm of rosacea)</td>
<td>No statistically significant difference with control group.</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Georgala (78)</td>
<td>92</td>
<td>Papulopustular rosacea</td>
<td>90% (vs 12% in controls) Higher density in patients with rosacea.</td>
<td>Cheek &gt; orbital area &gt;nose &gt; chin &gt;month</td>
</tr>
<tr>
<td>2001</td>
<td>El-Shazly (79)</td>
<td>46</td>
<td>Females with rosacea</td>
<td>44% vs 23% in normal controls 66% in squamous rosacea 67% in erythematotelangiectatic rosacea 83% in papulopustular rosacea</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Hu (80)</td>
<td>260</td>
<td>Rosacea</td>
<td>74.2%</td>
<td>80.4% of patients with rosacea were infected with bacteria</td>
</tr>
<tr>
<td>2004</td>
<td>Rasjeza-Kotelba (81)</td>
<td>74</td>
<td>Rosacea</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Moravej (82)</td>
<td>75</td>
<td>Rosacea</td>
<td>38.6%</td>
<td>21.3% in LE 10.6% in lichen planus</td>
</tr>
<tr>
<td>2007</td>
<td>Aycan (83)</td>
<td>117</td>
<td>Rosacea</td>
<td>61.5%</td>
<td>27.6% in acne vulgaris 33.3% in digestive allergies</td>
</tr>
<tr>
<td>2007</td>
<td>Aroni (86)</td>
<td>69</td>
<td>Rosacea</td>
<td>67%</td>
<td>-</td>
</tr>
</tbody>
</table>
All these data taken together are showing that in rosacea, there is a higher incidence of Demodex than in controls. The mean incidence in all the papers collected from literature is 68.32%, based on the examination of 997 patients with rosacea. Anyway, although several studies have attempted to elucidate its pathogenic role, to data there is not enough evidence to implicate Demodex as a primary pathogenic factor in the occurrence of rosacea.\(^{(57, 84)}\)

A definite clue to the pathogenicity of Demodex may not be achieved, by virtue of its prevalence among almost entire populations and the variety of manifestations attributed to it.\(^{(85)}\)

Nevertheless, although lesions attributed to Demodex are extremely rare, at least one case of Demodex attributed rosacea-like lesion was described.\(^{(85)}\) A 38-year old woman presented with erythematous-macular pruriginous lesions in one cheek, clustered in a somewhat semicircular fashion. The histopathological picture was that of a granulomatous dermal inflammation composed of epitheloid granulomas with giant cells and lymphocytes infiltrate, while a well-preserved Demodex mite was seen phagocytized by a multinucleated giant cell, in the vicinity of a hair follicle.

It is commonly thought that an increased mite density may play a role in the pathophysiology of rosacea by mechanically blocking the follicles, triggering inflammatory or specific immune reactions, or acting as a vector for bacteria.\(^{(86, 87)}\)

In the afore mentioned paper\(^{(36)}\) reporting how angiogenesis and mast cells may participate in a complex multifactorial process in rosacea, it was emphasized on the high density of Demodex found in the skin of patients under study.

In a recently published study\(^{(41)}\), a bacterium (Bacillus oleronius) was isolated from a Demodex mite extracted from the face of a patient with papulopustular rosacea; this bacterium was found to produce antigens capable of stimulating peripheral blood mononuclear cells proliferation in 73% of patients with rosacea, but only in 29% control subjects.

It was previously demonstrated\(^{(43)}\) that Staphylococcus epidermidis isolated from patients with rosacea was consistently beta-hemolytic whereas that from control skin was non-hemolytic. Isolates from patients with rosacea secreted more proteins, and generally more of each protein at 37°C compared with 30°C.

Yamasaki et al\(^{(88)}\) showed that high levels of an antimicrobial peptide and its processing serine protease are features of rosacea lesions, suggesting that aberrant innate immunity is central to this disease. It was also found that cathelcidin (a major family of antimicrobial peptides in mammals and in other vertebrates) expression was significantly elevated in rosacea-affected skin compared to healthy skin. Additionally, the rosacea samples contained several additional cathelcidin processing isoforms, creating a rosacea-specific peptide profile.

Two of the rosacea-specific peptides, but not a peptide found in normal skin, induced the release of the pro-inflammatory cytokine Interleukin-8 (IL-8) from human cultured keratinocytes. Previously, the human cathelcidin-derived peptide LL37, also found in rosacea, was shown to induce IL-1β processing and release.\(^{(89)}\)

All these data strongly suggest that high expression and abnormal processing of cathelcidin might underline the inflammation associated with rosacea.
This conception was already suggested in 1982 by Manna et al, who found deposits of IgM and/or IgG and/or complement at the dermo-epidermal junction and/or in the dermal collagen of rosacea patients. (90)

Another controversial issue in the potential role of Helicobacter pylori in rosacea. Helicobacter pylori plays a key role in the etiology of peptic ulcer, gastric cancer and gastric lymphoma. (91)

Crawford et al suggest that interest in its potential role emerged from statistically unsupported associations between rosacea and gastrointestinal diseases. (15, 49, 93, 94)

Eradication of H. pylori has been sometimes associated with an improvement in rosacea (93, 95), but adverse reports (94, 96) did not support this association.

Meanwhile, the cutaneous pathology of H.pylori is far from being clear, but it is speculated (97) that the systemic effects may involve increased muscular permeability to alimentary antigens, immunomodulation, an autoimmune mechanism or the impairment of vascular integrity.

Further, it was shown (98) that H.pylori was up-regulating the production of LL-37 by gastric epithelium.

Back to Demodex folliculorum, it seems that there is a strong link existing between the mite and rosacea through matrix-metalloproteinase-9 (MMP-9) (99).

MMP-9 had already been evaluated as important for the development of the clinical pattern in ocular rosacea. (100, 101)

Later, (99) MMP-9 expression was found to be statistically greater in fibroblasts in the case of rosacea when Demodex was present, as compared to cases of rosacea without Demodex, and a linear correlation was found between the presences of Demodex and the degree of positivity for MMP-9 expression in the fibroblasts of patients with rosacea.

On the other hand, MMP-8 concentration and activation in tear fluid were also reported to be increased in ocular rosacea (45) probably reflecting increased inflammatory activity.

The degradation of extra-cellular dermal matrix with degeneration of collagen and perivascular support, all very important features in the pathogenesis of rosacea, are resulting from increased expression of specific MMPs, a group of enzymes involved in inflammation, collagenolysis and angiogenesis. (20) However, it is not clear whether endothelial damage precedes degeneration of the dermal matrix or dermal matrix degeneration is the primary event. (57) Some authors support a matrix- centered theory, which postulates that telangiectasia, flushing and persistent erythema are all caused by defective dermal matrix support, resulting in a pooling of serum, metabolic waste, and inflammatory mediators.

These changes result in prolonged inflammation and tissue damage.

On the other hand, in rhinophyma, the overexpression of the fibrogenic protein TGF-β2 and TGF-β2 receptors was demonstrated in rhinophyma tissues (102), as well as TGF-β1 and TGF-β1 mRNA expression, which was reported as being five-fold higher in rhinophyma tissues than in normal skin. (103) Meanwhile, TGF-β3 levels and TGF-β-3 mRNA expression were the same in both pathological and normal tissue. These findings support the hypothesis that fibrosis may also play an important role in the pathogenesis of rhinophyma.

Besides, statistically significantly raised plasma concentrations of TGF-β1 were also found in patients with hereditary hemorrhagic telangiectasia. (65)
As regards adhesion molecules, a significant increase of intracellular adhesion-molecule-1 (ICAM-1) expressions by epithelial cells was reported in patients with ocular rosacea, compared to controls. (10h)

Not curiously, it was observed that topically applied dobesilate, an inhibitor of fibroblast Growth factor (FGF) was provoking a clear improvement in erythema and Telangiectasia after two weeks in a patient with erythematotelangiectatic rosacea. (105)

Nitric oxide is a modulator of inflammation and vascular response, has been shown to up-regulate MMP-expression, and inhibits synthesis of dermal matrix components such as collagen. (55) In addition, increased production of eNOS induces vasodilatation. The multitude of described effects related to nitric oxide activity suggests a role in the pathogenesis is of rosacea. (55)

Although the fundamental pathogenesis of rosacea remains unknown, inflammation is a central process in this disorder. Recent evidence suggests that this inflammation is associated with the generation of reactive oxygen species, (ROS) that are released by inflammatory cells such as neutrophils. (50)

Differences were found in superoxide dismutase (SOD) activities between mild rosacea (stage 1 and 2) and severe involvement (stage 3) groups, as well as between disease and control groups. (38) In the mild involvement group, SOD activity was higher than in the control group, while in the severe involvement group, the SOD activity was lower than in the control group.

These finding clearly show that in the first phase of rosacea, SOD activity is stimulated to protect the skin against ROS and in contrast, in more severe disease, due to a decrease in the capacity of the antioxidant defense system, SOD levels were lowered. These data support the antioxidant system defect hypothesis in rosacea patients.

These data were corroborated by another study, where the plasma MDA (malonyldialdehyde) were higher and AOP (antioxidant potential) levels lower in rosacea patients than in controls. (49)

ROS levels were also shown to be higher in rosacea patients than in healthy controls, and were reduced by administration of azithromycin. (51)

Metronidazole was shown to be clinically effective by decreasing neutrophil-generated ROS at the sites of inflammation in rosacea patients with the aid of palmitoleic acid, which is generally present in human skin.

As metronidazole has in vitro antioxidant activity, (52) it may help to prevent and treat rosacea symptoms, and this antioxidant activity might, at least partly, explain its efficacy in this indication.

It seems that metronidazole exhibits antioxidative effects via two mechanisms (53): decrease in ROS production through modulation of neutrophil activity and decrease in ROS concentration by exhibiting ROS scavenging properties.
V/ TREATMENTS OF ROSACEA

V-1 Prevention from triggering factors
Prior to initiating any therapy, patients with rosacea should be instructed about triggering factors and avoidance strategies. (57)

Common triggers include hot or cold temperatures, sudden changes of temperature, wind, hot drinks, alcohol, exercise, emotion, topical products, medications that induce flushing, and menopausal flushing. (106) There are several foods known to aggravate rosacea including liver, dairy products (yogurt, sour cream, cheese), vegetables (eggplant, tomatoes, spinach, peas, lima and navy beans), fruits (avocados, bananas, red plums, grapes, figs, and citrus fruits), condiment and flavoring (chocolate and vanilla, soy sauce and vinegar), yeast extraction, hot and spicy foods. (107)

Patient education should emphasize sun protective measures, including broad-spectrum, non-irritating sunscreens, avoidance of midday sun and the use of protecting clothing. (106)

Many rosacea patients have increased sensitivity to certain components of commonly used topical products. Common skin irritants in rosacea include solvents (acetone, alcohol), penetrants (propylene glycol, alpha, hydroxy acids), surfactants (sodium lauryl sulfate), biocides (formaldehyde releasers, sorbic acid), sunscreens (para-aminobenzoic acid, cinnamates, benzophenones) and aromatics (menthol, benzyl alcohol, camphor). (57)

Patients should be advised to use gentle cleansers and silicone-containing moisturizers (dimethicone, cyclomethicone) to prevent irritation. (108)

The number of allergic contact reactions does not appear to be significantly increased in rosacea patients (109); however, a few of the observed allergens are likely related to morbidity-specific exposures and are potentially relevant.

Camouflage cosmetics are important tools in rosacea management and should be discussed initially with the patient.

V-2 Topical therapies
Rosacea should be treated at its earliest manifestations to mitigate progression to the stages of edema and irreversible fibrosis. (17)

The three main agents for the topical management of rosacea are currently metronidazole, azelaic acid and sulfacetamide lotion.

Topical metronidazole is the most broadly-used topical agent in rosacea, and is available in cream, gel and lotion at 0.75% or at 1%.

The mechanism of action of metronidazole in the treatment of rosacea is unclear. (110) The efficacy of this broad spectrum antibiotic has been attributed first to its antimicrobial and anti-inflammatory effects, but later in-vitro studies have shown in vitro antioxidant activity (52) via two mechanism (53): decrease in ROS production through modulation of neutrophil activity and decrease in ROS concentration by exhibiting ROS scavenging properties. This antioxidant activity might be the key for its anti-inflammatory effect in rosacea.

Metronidazole is poorly absorbed after topical application, with either undetectable or trace serum concentrations reported after topical use. (111)

Based on pharmacokinetic data on the original 0.75% gel formulation, it was originally thought that the optimal application frequency should be twice daily, but more recent research has shown that metronidazole was degraded into active metabolites that may prolong the clinical efficacy of the drug. (112)
Metronidazole has been shown to be effective for the treatment of moderate to severe rosacea in a number of placebo-controlled trials.

Table 3: Summary of clinical data regarding topical metronidazole

<table>
<thead>
<tr>
<th>Product</th>
<th>Author</th>
<th>Study Design</th>
<th>Frequency and duration</th>
<th>Number of patients</th>
<th>Percent reduction in lesion count vs. placebo</th>
<th>Significant reduction in erythema</th>
<th>Adverse effects</th>
<th>Onset of efficacy (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75% gel</td>
<td>Aronson</td>
<td>R, SF, DB</td>
<td>Twice daily 9 weeks</td>
<td>47</td>
<td>51% vs 4%</td>
<td>Yes</td>
<td>None</td>
<td>3 w</td>
</tr>
<tr>
<td>0.75% gel</td>
<td>Bleicher</td>
<td>R, SF, DB</td>
<td>Twice daily 9 weeks</td>
<td>40</td>
<td>65% vs 15%</td>
<td>Yes</td>
<td>None</td>
<td>3 weeks</td>
</tr>
<tr>
<td>1% gel</td>
<td>Beutner</td>
<td>R, PG, SB</td>
<td>Once daily 10 weeks</td>
<td>&gt;1200</td>
<td>67% (1% gel) Vs 58% (1% cream) Vs 46% (vehicle)</td>
<td>3% (1%gel) 4% (1%cream) 4% (vehicle)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>0.75% cream</td>
<td>Drake</td>
<td>R, PG, DB</td>
<td>Twice daily 12 weeks</td>
<td>143</td>
<td>62.5% vs 43%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1% cream</td>
<td>Breneman</td>
<td>R, PG, DB</td>
<td>Once daily 10 weeks</td>
<td>89</td>
<td>53% vs 17%</td>
<td>Yes</td>
<td>2%</td>
<td>2-4</td>
</tr>
<tr>
<td>1% cream</td>
<td>Jorizzo</td>
<td>R, PG, DB</td>
<td>Twice daily 12 weeks</td>
<td>61</td>
<td>65% vs 25%</td>
<td>Yes</td>
<td>Mild reactions</td>
<td>4</td>
</tr>
<tr>
<td>1% cream + sunscreen</td>
<td>Tan</td>
<td>R, PG, DB</td>
<td>Twice daily 12 weeks</td>
<td>61</td>
<td>65% vs 25%</td>
<td>Yes</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>0.75% lotion</td>
<td>Breneman</td>
<td>R, PG, DB</td>
<td>Twice daily 12 weeks</td>
<td>65</td>
<td>57% vs 27%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.75% gel</td>
<td>Wolf</td>
<td>Open MC</td>
<td>Twice daily 12 weeks</td>
<td>582</td>
<td>53%</td>
<td>Yes</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

R: Randomized PG: Parallel Group DB: Double Blind MC: Multicentrical

In a recent systematic review of rosacea treatments (122), topical metronidazole was shown to be more effective than placebo (adds ratio 5.96; 95% confidence interval 2.95-12.06). In another review (123), it was reported that twice-daily 1% metronidazole cream is as effective as 250mg tetracycline twice-daily; 1% metronidazole gel used once daily is as effective as 15% azelaic
acid gel used twice daily, and 0.75% metronidazole lotion is more effective when used in combination with doxycycline 20mg dosed twice daily. According to this review, metronidazole in 0.75% strength lotion, cream and gel and 1% metronidazole cream and gel are all efficacious in treating rosacea. Combination treatment with oral antibiotics at both antimicrobial and sub-antimicrobial doses is an efficacious mean of treating rosacea. Further, maintenance treatment with topical metronidazole decrease relapses and allows for longer intervals between flares. Efficacy of topical metronidazole was sometimes compared to that of topical azelaic acid. Table 4 summarizes these comparisons.

Table 4: Comparative trials between topical metronidazole and topical azelaic acid

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Products compared</th>
<th>Design of study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>Maddin (124)</td>
<td>20% Azelaic acid Cream Vs 0.75% Metrodinazole cream</td>
<td>Single-center Double-blind Randomized Controlateral Split-face</td>
<td>Similar reductions in lesions but better global improvement with azelaic acid.</td>
</tr>
<tr>
<td>2003</td>
<td>Elewski (125)</td>
<td>15% Azelaic acid Gel Vs 0.75 metrodinazole gel</td>
<td>Multicentrical Randomized Double-blind Parallel-group</td>
<td>Azelaic acid gel demonstrated significant superiority over metronidazole gel in improving principal signs of rosacea. (inflammatory lesions and erythema)</td>
</tr>
</tbody>
</table>

In term of tolerance, metronidazole is generally well tolerated, with adverse events reported in less than 5% patients. Local reactions include dryness, redness, pruritus, aggravation of acne or rosacea, burning and stinging. (110) Allergic contact dermatitis was sometimes reported. (126), but no evidence suggested phototoxic or photo-allergic reactions. (127) Topical azelaic acid is the second widely-used treatment for rosacea. Azelaic acid is a naturally occurring dicarboxylic acid. It is currently used as a topical 15% or 20% cream to treat mild to moderate forms of acne vulgaris; its antibacterial and comedolytic activity is responsible mainly for its beneficial effects. A direct anti-inflammatory effect of azelaic acid, by inhibition of neutrophil-generated reactive oxygen radicals may also account for its beneficial effects. (125) A regards the efficacy of topical azelaic acid in rosacea, a recent systematic review of randomized controlled trials published in the literature (128) brought documented responses to this question. In this review, 9 randomized controlled trials involving topical azelaic acid (20% cream or 15% gel formulations) in the treatment of rosacea were identified. Two studies were comparing azelaic acid with metronidazole and were excluded, as well as two other studies, which were duplicate studies. (129, 130)
Table 5: Systematic analysis of clinical assessing the efficacy of topical azelaic acid in rosacea.  

<table>
<thead>
<tr>
<th>Authors year</th>
<th>Type of study</th>
<th>Nº of patients</th>
<th>Product used</th>
<th>Control</th>
<th>Posology</th>
<th>Duration of treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjerke (131) 1999</td>
<td>R, DB</td>
<td>114</td>
<td>20% AZA cream</td>
<td>Vehicle</td>
<td>2x daily</td>
<td>3 months</td>
<td>Nº of inflammatory lesions Before/after AZA 30.8/8.3 Before/after vehicle 31.5/15.3 Reduction in erythema score 47.9 % vs 37.9 % Reduction in telangiectasia score 22.3 % vs 23.5 %</td>
</tr>
<tr>
<td>Carmichael (132) 1993</td>
<td>R,DB</td>
<td>33</td>
<td>20% AZA cream</td>
<td>Vehicle</td>
<td>2x daily</td>
<td>9 weeks</td>
<td>Nº of inflammatory lesions Before/after AZA 14.2/2.5 Before/after vehicle 15.0/6.6 Reduction in erythema score 7.2 % vs 2.8 % Reduction in telangiectasia score -2.3% vs +2.2%</td>
</tr>
<tr>
<td>Thiboutot study I (129) 2003</td>
<td>R,DB</td>
<td>329</td>
<td>15% AZA Gel</td>
<td>Vehicle</td>
<td>2x daily</td>
<td>12 weeks</td>
<td>Nº of inflammatory lesions Before/after AZA 17.5/6.8 Before/after vehicle 17.6/10.5 Reduction in erythema score 44% vs 29% Telangiectasia Unchanged in 77% vs 80%</td>
</tr>
<tr>
<td>Thiboutot study II (129) 2003</td>
<td>R,DB</td>
<td>335</td>
<td>15% AZA Gel</td>
<td>Vehicle</td>
<td>2x daily</td>
<td>12 weeks</td>
<td>Nº of inflammatory lesions Before/after AZA 17.8/8.9 Before/after vehicle 18.5/12.1 Reduction of erythema score 45% vs 28% Telangiectasia Charged in 73% vs 78%</td>
</tr>
<tr>
<td>Bamford (130) 1999</td>
<td>R,DB</td>
<td>53</td>
<td>20% AZA Cream</td>
<td>Vehicle</td>
<td>9 weeks</td>
<td>Nº of inflammatory lesions Before/after AZA 18.1/4.5 Before/after vehicle 19.4/7.6 Reduction of erythema score 56% vs 42% Telangiectasia Unchanged in 73% vs 76%</td>
<td></td>
</tr>
</tbody>
</table>
Taken together the results of these studies permit to conclude that the use of 20% azelaic acid cream or 15% azelaic acid gel appears to be effective in the treatment of papulopustular rosacea, particularly in regard to decreases in mean inflammatory lesion count and severity of erythema.  

The tolerance of azelaic acid seems to be satisfactory, in spite of a few claims of patients regarding a stinging sensation upon its application, and one study (133) reported a significantly greater potential for irritation from azelaic acid compared to Metronidazole. Sodium sulfacetamide 10% and sulfur 5% combination therapy has been successfully used for rosacea management. (57) Unfortunately this combination therapy is limited by poor patient compliance due to the unpleasant odor of sulfur. Permethrin 5% cream: was used in patients diagnosed as having papulopustular rosacea (135), and its effect on Demodex folliculorum was shown to be superior to that of 0,75% metronidazole gel. The effect on erythema and papules was found to be more effective than placebo and as effective as 0,75% metronidazole gel. However, it had no effect on telangiectasia, rhinophyma and pustules. Topical retinoic acid has been shown to have a beneficial effect on the vascular component of rosacea. (134) The drawbacks of retinoic acid therapy include delayed onset of effectiveness, dry skin, erythema, burning and stinging. (134) Retinaldehyde is intermediate in the natural metabolism of retinoids, between retinol and retinoic acid and is generally well tolerated while retaining most of the therapeutic activity of retinoic acid. (134) Daily application of a 0,05% retinaldehyde cream for 6 months was found to yield positive and statistically significant outcomes in 75% of those patients undergoing treatment, with specific improvements in erythema and telangiectases, the vascular components of rosacea. (134) Topical vitamin C preparations have been investigated in the reduction of the erythema in rosacea. (136) Daily use of 5% topical vitamin C permits to observe in 75% patients an objective and subjective improvement in their erythema.

Topical alternatives for rosacea management include also clindamycin phosphate 1% lotion and benzoyl peroxide. (57) The responses to topical calcineurin inhibitors in rosacea and rosacea-like eruptions have been mixed (137) A recent study (138) disclosed that the treatment of rosacea for 4-8 weeks with the topical calcineurin inhibitor pimecrolimus cream 1% was nor more efficacious than treatment with the vehicle cream.

V-3/ Oral therapies
Oral antibiotics, such as tetracycline, doxycycline and metronidazole effectively treat papulopustular rosacea. (139, 140) Tetracycline has been the oral treatment of choice, with initial total daily doses of 1000mg divided BID or QID for up to 4 weeks and then reduced by half for at least a total of 6 months. (57) In 1966, a study by Sneddon (141) was the first to demonstrate the efficacy of tetracycline in rosacea. However, upon discontinuation of tetracyclines, relapses are frequent and can be attenuated or prevented by concomitant use of topical therapies. (57) Other tetracyclines shown to be as effective in rosacea management are minocycline (classically 50 mg to 100 mg QD or BID) and doxycycline, whose standard dose is 100 mg QD or BID, but the sub antimicrobial dose of 20 mg BID has been described as being equally effective (57) all the more when it is combined to topical 1% metronidazole. (142) Anti-inflammatory dose doxycycline, a controlled released 40mg capsule that is devoid of antibiotic activity when administered once daily, was recently approved by US FDA for the treatment of inflammatory lesions and pustules of rosacea, based on large-scale phase 3 pivotal trials and long-term microbiologic and safety data. (143) Minocycline and doxycycline are suitable, but more costly alternatives to tetracyclines. Side effects of tetracyclines include candidal vulvo-vaginitis, gastrointestinal distress, and pseudotumour cerebri. Photosensitivity may be significant with doxycycline. Vertigo, blue dyes pigmentation, lupus-like syndrome, and hypersensitivity reactions have been reported with minocycline. (57)
Macrolide antibiotics are effective alternatives in pregnant rosacea patients, or those intolerant to tetracyclines. \(^{(57)}\) Trials comparing azithromycin and clarithromycin (250mg BID) to doxycycline demonstrated a faster reduction of erythema and inflammatory lesions \(^{(144, 145)}\). Since then, it was demonstrated that azithromycin was working in rosacea mainly through its antioxidant properties. \(^{(146)}\) However, the cost of these drugs limits their widespread use.

Oral metronidazole (200mg BID) is another alternative to oral tetracyclines. It can be used in pregnant women. Isotretinoin (0.5 to 1mg/kg/day) has been effectively used in recalcitrant rosacea, with a quick onset of action and improvement in blepharitis and conjunctivitis. The number, extent and severity of side effects, and its teratogenicity are main factors limiting its use. \(^{(57)}\) Dapsone has been successfully used in severe, recalcitrant rosacea in patients unable to use isotretinoin. \(^{(147)}\)

V-4/ Laser and light therapies \(^{(92)}\)

The main focus of laser therapy for rosacea is a reduction in erythema and telangiectases, and appears to be more beneficial in the erythematelangiectatic subtype of rosacea. \(^{(66)}\) Pulsed-dye laser (PDL 585 to 595 nm) was shown to be efficacious in the reduction of erythema, flushing and telangiectases after 2 to 6 treatments, with maintenance treatments every 4 to 6 months. \(^{(66)}\)

Main side effects include post-treatment purpura, post-inflammatory hyperpigmentation and atrophing scarring. \(^{(46)}\) Potassium titanyl-phosphate (KTP) laser, diode-pumped frequency-doubled laser (532 nm), 810 nm diode laser, the long-pulsed Alexandrite and the long-pulsed 1064 nm neodymium: yttrium: aluminium-garnet laser (Nd-YAG) are also effective in the management of rosacea. \(^{(46)}\) Intense-pulsed light (IPL) therapy was shown to be efficacious in rosacea patients with concurrent photodamage. On average, patients require 2 to 5 sessions, spaced 3 weeks apart. Complications are uncommon, including purpura, persistent edema and transient hyperpigmentation. \(^{(46)}\) A few papers report apparently good results after photodynamic therapy in rosacea with 5-aminolevulinic acid \(^{(44, 46)}\) or methylaminolevulate \(^{(16)}\). However these results are either resulting from case studies, or small series of patients and future randomized controlled trials therefore seems justifiable.

Phymatous rosacea does not respond neither to PDL nor to IPL modalities and is best managed by ablative lasers such as CO2 or Erbium: YAG lasers. \(^{(66)}\)

V-5/ Surgical therapies

Surgical treatment is mainly reserved for patients with phymatous rosacea and is focused on restoration of normal anatomical contours. It can consist in complete or incomplete excision. Complete excision utilizes primary closure for small lesions and skin grafting for large lesions. Incomplete excision techniques are giving better cosmetic results, using cryosurgery, dermabrasion, electrosurgery or sharp blade excision. \(^{(57)}\)

VI/ Conclusion

As being a common condition having a deep impact on the patient’s psychology, rosacea was worth of important efforts in order to elucidate more precisely its pathogenesis aspects, and try to improve the currently available treatments. Major steps were given along the past years in the better knowledge of its etiopathogenesis, and the oxidative hypothesis seems to be a right way for investigation, and for further development of new, innovative and safe treatments for the patients with rosacea.
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