ROSACEA

Dr. Christian Diehl

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. [6], 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 peri-orificially (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 interconnecting.
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	INTRINSIC 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]	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 red ox balance [38, 48, 49, 50, 51, 52, 53, 54] • Increased generation of reactive species [55, 56]

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. [28]
Usually, clinicians recommend that patients use sunscreens or sunblocks.
However, an increase in UV sensitivity has not been demonstrated in rosacea patients [29, 60] and individuals with rosacea experience improvement more often than impairment from exposure to sunlight [30]

IV-1-b/ Chemicals and ingested agents

Skin-care products may be triggering agents for rosacea [13], depending mainly on their nature and quality.
As the skin barrier appears to be damaged in rosacea [40], 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. [32]
In that way, alcohol consumption is obviously an important triggering factor for rosacea. [33, 34]

Hot drinks are also susceptible of causing flushing in an oral thermal-induced manner in patients with erythematotelangiectatic rosacea. [35] 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 [12, 14, 15, 35]
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. [34]
Structural alterations of cutaneous vasculature are present in most patients, if not all, with rosacea. [14, 15] In one study, in the capillaroscopic examinations, atypical capillaries were found in all patients with rosacea. [61]
The most common features were Raynaud loops (62,5%), meandering capillaries and their elongation (62,5%) and increasing number of the capillaries. (81, 25%)

Increased angiogenesis [15], with subsequent changes in cutaneous blood flow [14, 35, 36] are also broadly reported. Blood flow in rosacea patients was found to be three to four times that of controls. [71]
In a recent study, [36] 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 [15] are also frequently reported.
Histological examination [62] 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 afore mentioned study [36] 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. [63]

Expression of VEGF receptors (VEGF-R1 and VEGF-R2) both by vascular endothelium and infiltrating mononuclear cells, was also observed in rosacea. [47]
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. [64] and increased plasma levels of VEGF were observed in patients with hereditary hemorrhagic telangiectasia. [65]

IV-2-b / Cutaneous disorders

Abnormalities of the pilosebaceous units [15] 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. [59]
However, follicular inflammation is characteristic of the granular type of phymatous rosacea. [67]
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, [15] 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 to-day 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.

YEAR	AUTHOR	N° of Patients	CHARACTERISTICS	INCIDENCE of DF	REMARKS
1981	Rufli et al 69	18	Rosacea	88,9%	
1988	Ramelet (70)	75	Rosacea	62 %	
1992	Sibenge (71)	25	Rosacea	80%	
1992	Basta-Juzbasic (40)	50	Rosacea	86%	92% in patients treated with topical CTC
1993	Forton (72)	49	13 Erithemato-telangiectatic rosacea 3 Squamous rosacea 33 Papulopustular rosacea	Higher Demodex density only in papulopustular rosacea patients	
1993	Bonnar (73)	42	Rosacea	Higher density in patients with rosacea than in controls.	Highest density found on the cheeks
1997	Abd-El-Al (74)	16	Papulopustular rosacea	100% (vs 76% in controls)	Cheeks >forehead >chin
1998	Erbagci (75)	38	Rosacea	Higher density in rosacea patients than in control group.	Highest density on the cheeks.
1998	Roihu (76)	80	Rosacea	51%	Forehead > cheeks Males>females
2000	Aydingöz (77)	40	Pregnant women (indemn of rosacea)	No statistically significant difference with control group.	
2001	Georgala (78)	92	Papulopustular rosacea	90% (vs 12% in controls) Higher density in patients with rosacea.	
2001	El-Shazly (79)	46	Females with rosacea	44% vs 23% in normal controls 66% in squamous rosacea 67% in erythematotelangiectatic rosacea 83% in papulopustular rosacea	Cheek > orbital area >nose > chin >month
2004	Hu (80)	260	Rosacea	74,2%	80,4% of patients with rosacea were infected with bacteria
2004	Rasjeza-Kotelba (81)	74	Rosacea	45%	
2007	Moravejj (82)	75	Rosacea	38,6%	21,3% in LE 10,6% in lichen planus
2007	Aycan (83)	117	Rosacea	61,5%	27,6% in acne vulgaris 33,3% in digestive allergies
2007	Aroni (36)	69	Rosacea	67%	-

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 tits 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 erythemato-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 37ºC compared with 30ºC.

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 cathelicidin (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 cathelicidin 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 cathelicidin-derived peptide LL37, also found in rosacea, was shown to induce IL-1 ß processing and release. [89]
All these data strongly suggest that high expression and abnormal processing of cathelicidin 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-ß2 and TGF-ß2 receptors was demonstrated in rhinophyma tissues [102], as well as TGF-ß1 and TGF-ß1 mRNA expression, which was reported as being five-fold higher in rhinophyma tissues than in normal skin. [103] Meanwhile, TGF-ß3 levels and TGF-ß-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-ß1 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]
[48] 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 metrodinazole 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

Product	Author	Study Design	Frequency and duration	Number of patients	Percent reduction in lesion count vs. placebo	Significant reduction in erythema	Adverse effects	Onset of efficacy (weeks)
0,75 %gel	Aronson [113]	R, SF, DB	Twice daily 9 weeks	47	51% vs 4%	Yes	None	3 w
0,75% gel	Bleicher [114]	R, SF, DB	Twice daily 9 weeks	40	65% vs 15%	Yes	None	3 weeks
1% gel	Beutner [115]	R, PG, SB	Once daily 10 weeks	>1200	67% (1% gel) Vs 58% (1% cream) Vs 46% (vehicle)		3% (1%gel) 4% (1%cream) 4% (vehicle)	
0,75% cream	Drake [116]	R, PG, DB	Twice daily 12 weeks	143	62,5% vs 43%			
1% cream	Breneman [117]	R, PG, DB	Once daily 10 weeks	89	53% vs 17%	Yes	2%	2-4
1% cream	Jorizzo [118]	R, PG, DB	Twice daily 12 weeks	61	65% vs 25%	Yes	Mild reactions	4
1% cream + sunscreen	Tan [119]	R, PG, DB	Twice daily 12 weeks	61	65% vs 25%	Yes		4
0,75% lotion	Breneman [120]	R, PG, DB	Twice daily 12 weeks	65	57% vs 27%			
0,75% gel	Wolf [121]	Open MC	Twice daily 12 weeks	582	53%	Yes		4

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

Year	Authors	Products compared	Design of study	Results
1999	Maddin (124)	20% Azelaic acid Cream Vs 0,75% Metrodinazole cream	Single-center Double-blind Randomized Controlateral Split-face	Similar reductions in lesions but better global improvement with azelaic acid.
2003	Elewski (125)	15% Azelaic acid Gel Vs 0,75 metrodinazole gel	Multicentrical Randomized Double-blind Parallel-group	Azelaic acid gel demonstrated significant superiority over metronidazole gel in improving principal signs of rosacea. (inflammatory lesions and erythema)

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. [128]

Authors year	Type of study	N° of patients	Product used	Control	Posology	Duration of treatment	Results
Bjerke [131] 1999	R, DB,	114	20% AZA cream	Vehicle	2x daily	3 months	N° of inflammatory lesions Before/after AZA 30.8/8.3 Before/after vehicle 31.7/15.3 Reduction in erythema score 47.9 % vs 37.9 % Reduction in telangiectasia score 22.3% vs 23.5%
Carmichael [132] 1993	R,DB	33	20% AZA cream	Vehicle	2x daily	9 weeks	N° 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%
Thiboutot study I [129] 2003	R,DB	329	15% AZA Gel	Vehicle	2x daily	12 weeks	N° 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%
Thiboutot study II [129] 2003	R,DB	335	15% AZA Gel	Vehicle	2x daily	12 weeks	N° 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%
Bamford [130] 1999	R,DB	53	20% AZA Cream	Vehicle		9 weeks	N° 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%

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. [128] 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-garrnet 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.

BIBLIOGRAPHY

1. Buechner SA. Rosacea: an update. *Dermatology* 2005;210:100-108.
2. Del Rosso JQ. A status report on medical management of rosacea: focus on topical therapies. Cutis. 2002;70:271-275.
3. Berg M, Liden S. An epidemiological study of Rosacea. Acta Derm Venereol. 1989;69:419-42.
4. Jappe U, Schnuch A, Uter W. Rosacea and contact allergy to cosmetics and topical medicaments--retrospective analysis of multicentre surveillance data 1995-2002. Contact Dermatitis. 2005 Feb;52(2):96-101
5. Forton F, Germaux MA, Brasseur T, De Liever A, Laporte M, Mathys C, Sass U, Stene JJ, Thibaut S, Tytgat M, Seys B. Demodicosis and rosacea: epidemiology and significance in daily dermatologic practice. J Am Acad Dermatol. 2005 Jan;52(1):74-87.
6. Zuber TJ. Rosacea: beyond first blush. Hosp Pract (Off Ed) 1997;32:188 –9.
7. Frank C. Powell, Rosacea. n engl j med 352;824, 2005
8. Bamford JT. Rosacea: current thoughts on origin. Semin Cutan Med Surg. 2001;20:199-206.
9. Jansen T, Plewig G. Rosacea: classification and treatment. *J R Soc Med* 1997; 90:144-150.
10. Charles L Bevins & Fu-Tong Liu Rosacea: skin innate immunity gone awry? Nature Med. 2007;13,8: 904-905.
11. Rebora A. The red face: Rosacea. Clin Dermatol. 1993;11:225-234.
12. Bamford JT. Rosacea: current thoughts on origin. Semin Cutan Med Surg. 2001;20:199-206
13. WAYNE BLOUNT B. PELLETIER M.P.H. & A.L.Rosacea: A Common,Yet Commonly Overlooked, Condition. Am Fam Physic. 2002; 66(3):435-440.
14. Dahl M.V. Pathogenesis of Rosacea. Adv. Dermatol. 2001;17:29-45.
15. Crawford GH, Pelle MT, James WD. Rosacea: 1.etiology, pathogenesis and subtype classification. J Am Acad Dermatol. 2004;51:327-341.
16. Bryld LE, Jemec GB. Photodynamic therapy in a series of rosacea patients.J Eur Acad Dermatol Venereol. 2007 Oct;21(9):1199-202
17. Cohen AF, Tiemstra JD Diagnosis and Treatment of Rosacea. JABFP May–June 2002. 15(3): 214-217.
18. Coping with rosacea: tips on lifestyle management for rosacea sufferers. Barrington, Ill: National Rosacea Society, 1996.
19. Wilkin JK. Rosacea. Int J Dermatol 1983;22:393-400.
20. Del Rosso JQ. Update on rosacea patogénesis and correlation with medical therapeutis agents. Cutis. 2006; 78:97-100.
21. Wilkin JK, Dahl M, Detmar M, Drake L, Feinstein A, Odom R, Powell K. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. J Am. Acad. Dermatol. 2002; 46:584-587.
22. Lonne-Rahm SB, Fischer T, Berg M. Stinging and rosacea. Acta Derm Venereol 1999;79:460-1.
23. Kligman AM. A personal critique on the state of knowledge of rosacea. Dermatology 2004;208:191-7.
24. Starr PA. Oculocutaneous aspects of rosacea. Proc R Soc Med 1969;62:9-11.
25. Macsai MS, Mannis MJ, Huntley AC. Acne rosacea in : eye and skin disease. Philadelphia:Lippincott-Raven;1996.p.335-341.
26. Chen DM, Crosby DL. Periorbital edema as an initial presentation of rosacea. J Am. Acad. Dermatol. 1997;37:346-348.
27. Ramelet AA. Rosacea: a reaction pattern associated with ocular lesions and migraine? Arch Dermatol 1994;130:1448.
28. Murphy G.Ultraviolet light and rosacea. Cutis. 2004 Sep;74(3 Suppl):13-6, 32-4.
29. Lee M, Koo J. Rosacea, light, and phototherapy.J Drugs Dermatol. 2005 May-Jun;4(3):326-9
30. Berg M. Epidemiological studies of the influence of sunlight on the skin. Photodermatol. 1989;6(2):80-84.
31. Karamfilov T, Elsner P. [Sports as a risk factor and therapeutic principle in dermatology]. Hautarzt. 2002 Feb;53(2):98-103
32. Kostovic K. Lipozencic J. Skin diseases in alcoholics. Acta Dermatovenereol Croat. 2004;12(3):181-190.
33. Wegrzynek I, Budzanowska E. [Alcohol and the skin]Przegl Lek. 2001;58(4):198-203
34. Grosshans E. [Rosacea]Presse Med. 1988 Dec 17;17(45):2393-8.
35. Wilkin JK. Oral thermal-induced flushing in erythematotelangiectatic rosacea.
36. Aroni K. Tsagroni E. Kavantzas N. Patsouris E. Ioannidis E. A study of the pathogenesis of Rosacea: how angiogenesis and mast cells may participate in a complex multifactorial process. Arch Dermatol Res 2007.
37. Helm KF, Menz J, Gibson LE, Dicken CH. A clinical and histopathologic study of granulomatous rosacea. J Am Acad Dermatol. 1991 Dec;25(6 Pt 1):1038-43.
38. Oztas MO, Balk M, Ogus E, Bozkurt M, Ogus IH, Ozer N. The role of free oxygen radicals in the aetiopathogenesis of rosacea. Clin Exp Dermatol. 2003 Mar;28(2):188-92.

39. Dirschka T, Tronnier H, Fölster-Holst R. Epithelial barrier function and atopic diathesis in rosacea and perioral dermatitis. Br J Dermatol. 2004 Jun;150(6):1136-41.
40. Basta-Juzbasić A, Marinović T, Dobrić I, Bolanca-Bumber S, Sencar J. The possible role of skin surface lipid in rosacea with epitheloid granulomas. Acta Med Croatica. 1992;46(2):119-23.
41. N. Lacey, S. Delaney, K. Kavanagh and F.C. Powell. Mite-related bacterial antigens stimulate inflammatory cells in rosacea. Journal Compilation 2007 British Association of Dermatologists British Journal of Dermatology.
42. Charles L Bevins & Fu-Tong Liu Rosacea: skin innate immunity gone awry? Nature Med. 2007;13,8: 904-905.
43. Dahl MV, Ross AJ, Schlievert PM. Temperature regulates bacterial protein production: possible role in rosacea. J Am Acad Dermatol. 2004 Feb;50(2):266-72.
44. Nybaek H, Jemec GB. Photodynamic therapy in the treatment of rosacea. Dermatology. 2005;211(2):135-8.
45. Määttä M, Kari O, Tervahartiala T, Peltonen S, Kari M, Saari M, Sorsa T. Tear fluid levels of MMP-8 are elevated in ocular rosacea--treatment effect of oral doxycycline. Graefes Arch Clin Exp Ophthalmol. 2006 Aug;244(8):957-62. Epub 2006 Jan .
46. Katz B, Patel V. Photodynamic therapy for the treatment of erythema, papules, pustules, and severe flushing consistent with rosacea. J Drugs Dermatol. 2006 Feb;5(2 Suppl):6-8.
47. Smith JR, Lanier VB, Braziel RM, Falkenhagen KM, White C, Rosenbaum JT. Expression of vascular endothelial growth factor and its receptors in rosacea. Br J Ophthalmol. 2007 Feb;91(2):226-9.
48. Akamatsu H, Oguchi M, Nishijima S, Asada Y, Takahashi M, Ushijima T, Niwa Y. The inhibition of free radical generation by human neutrophils through the synergistic effects of metronidazole with palmitoleic acid: a possible mechanism of action of metronidazole in rosacea and acne. Arch Dermatol Res. 1990;282(7):449-54.
49. Baz K, Cimen MY, Kokturk A, Aslan G, Ikizoglu G, Demirseren DD, Kanik A, Atik U. Plasma reactive oxygen species activity and antioxidant potential levels in rosacea patients: correlation with seropositivity to Helicobacter pylori. Int J Dermatol. 2004 Jul;43(7):494-7
50. Jones D. Reactive oxygen species and rosacea. Cutis. 2004 Sep;74(3 Suppl):17-20, 32-4.
51. Bakar O, Demirçay Z, Yuksel M, Haklar G, Sanisoglu Y. The effect of azithromycin on reactive oxygen species in rosacea. Clin Exp Dermatol. 2007 Mar;32(2):197-200. Epub 2007 Jan 18
52. Miyachi Y. Potential antioxidant mechanism of action for metronidazole: implications for rosacea management. Adv Ther. 2001 Nov-Dec;18(6):237-43
53. Narayanan S, Hünerbein A, Getie M, Jäckel A, Neubert RH. Scavenging properties of metronidazole on free oxygen radicals in a skin lipid model system. J Pharm Pharmacol. 2007 Aug;59(8):1125-30
54. Briganti S., Picardo M. Antioxidant activity, lipid peroxidation and skin diseases. What's new. *JEADV* (2003), 663–669
55. Amin AR, Attur MG, Thakker GD. A novel mechanism of action of tetracyclines: effects on nitric oxide synthases. Proc Natl Acad Sci USA. 1996;93:14014-14019.
56. Golub LM, Lee HM, Ryan ME. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. Adv Dent Res. 1998;12:12-26.
57. Turchin I., Sasseville D. Rosacea. Dermatology Rounds 2006.5(4)
58. Guzman-Sanchez DA, Ishiuji Y, Patel T, Fountain J, Chan YH, Yosipovitch G. Enhanced skin blood flow and sensitivity to noxious heat stimuli in papulopustular rosacea. J Am Acad Dermatol. 2007 Nov;57(5):800-5. Epub 2007 Jul 20 .
59. Marks R, Harcourt-Webster JN. Histopathology of rosacea. *Arch Dermatol* 1969;100:683-91.
60. Marks R. Concepts in the pathogenesis of rosacea. *Br J Dermatol* 1968; 80:170-7.
61. Kamińska-Winciorek GM, Brzezińska-Wcisło LA. [Assessment of microcirculatory system with conventional capillaroscopy in patients with rosacea--preliminary study] Wiad Lek. 2006;59(9-10):618-22.
62. Helm KF, Menz J, Gibson LE, Dicken CH. A clinical and histopathologic study of granulomatous rosacea. J Am Acad Dermatol. 1991 Dec;25(6 Pt 1):1038-43.
63. Gomaa AH, Yaar M, Eyada MM, Bhawan J. Lymphangiogenesis and angiogenesis in non-phymatous rosacea. J Cutan Pathol. 2007 Oct;34(10):748-53
64. Xu B, Wu YQ, Huey M, Arthur HM, Marchuk DA, Hashimoto T, Young WL, Yang GY. Vascular endothelial growth factor induces abnormal microvasculature in the endoglin heterozygous mouse brain. J Cereb Blood Flow Metab. 2004 Feb;24(2):237-44.
65. Sadick H, Riedel F, Naim R, Goessler U, Hormann K, Hafner M, Lux A. Patients with hereditary hemorrhagic telangiectasia have increased plasma levels of vascular endothelial growth factor and transforming growth factor-beta1 as well as high ALK1 tissue expression. Haematologica. 2005 Jun;90(6):818-28.
66. Goldberg DJ. Lasers and light sources for rosacea. *Cutis* 2005;75 (suppl 3):22-6.
67. Aloi F, Tomasini C, Soro E, Pippione M. The clinicopathologic spectrum of rhinophyma. *J Am Acad Dermatol* 2000;42:468-72.
68. Brodie RC. Rosacea: the role of demodex folliculorum. Aust J Dermatol. 1952 Apr;1(3):149-52
69. Rufli T, Mumcuoglu Y, Cajacob A, Büchner S. [Demodex folliculorum: aetiopathogenesis and therapy of rosacea and perioral dermatitis (author's transl)] Dermatologica. 1981;162(1):12-26.

70. Ramelet AA, Perroulaz G. [Rosacea: histopathologic study of 75 cases] Ann Dermatol Venereol. 1988;115(8):801-6.
71. Sibenge S, Gawkrodger DJ. Rosacea: a study of clinical patterns, blood flow, and the role of Demodex folliculorum. J Am Acad Dermatol. 1992 Apr;26(4):590-3
72. Forton F, Seys B. Density of Demodex folliculorum in rosacea: a case-control study using standardized skin-surface biopsy. Br J Dermatol. 1993 Jun;128(6):650-9.
73. Bonnar E, Eustace P, Powell FC. The Demodex mite population in rosacea. J Am Acad Dermatol. 1993 Mar;28(3):443-8.
74. Abd-El-Al AM, Bayoumy AM, Abou Salem EA. A study on Demodex folliculorum in rosacea. J Egypt Soc Parasitol. 1997 Apr;27(1):183-95.
75. Erbağci Z, Ozgöztaşi O. The significance of Demodex folliculorum density in rosacea. Int J Dermatol. 1998 Jun;37(6):421-5.
76. Roihu T, Kariniemi AL. Demodex mites in acne rosacea. J Cutan Pathol. 1998 Nov;25(10):550-2.
77. Aydingöz IE, Dervent B, Güney O. Demodex folliculorum in pregnancy. Int J Dermatol. 2000 Oct;39(10):743-5.
78. Georgala S, Katoulis AC, Kylafis GD, Koumantaki-Mathioudaki E, Georgala C, Aroni K. Increased density of Demodex folliculorum and evidence of delayed hypersensitivity reaction in subjects with papulopustular rosacea. J Eur Acad Dermatol Venereol. 2001 Sep;15(5):441-4.
79. el-Shazly AM, Ghaneum BM, Morsy TA, Aaty HE. The pathogenesis of Demodex folliculorum (hair follicular mites) in females with and without rosacea. J Egypt Soc Parasitol. 2001 Dec;31(3):867-75.
80. Hu Q, Wang Y, Tong L. [Relationship between the Demodex and bacteria infection in human rosacea] Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi. 2004 Feb 28;22(1):50-3.
81. Raszeja-Kotelba B, Jenerowicz D, Izdebska JN, Bowszyc-Dmochowska M, Tomczak M, Dembińska M. [Some aspects of the skin infestation by Demodex folliculorum] Wiad Parazytol. 2004;50(1):41-54.
82. Moravvej H, Dehghan-Mangabadi M, Abbasian MR, Meshkat-Razavi G. Association of rosacea with demodicosis. Arch Iran Med. 2007 Apr;10(2):199-203.
83. Aycan OM, Otlu GH, Karaman U, Daldal N, Atambay M. [Frequency of Demodicosis in various patient and age groups] Turkiye Parazitol Derg. 2007;31(2):115-8
84. Hoekzema R et al. Democidosis or rosacea: what did we treat? Br J Dermatol. 133:294-9, 1995
85. Pena GP, Andrade Filho JDS. Is Demodex really non-pathogenic? Rev Inst Med Trop S Paulo. 2000;42(3)171-173.
86. Powell FC. Rosacea and the pilosebaceous follicle. Cutis. 2004 Sep;74(3 Suppl):9-12, 32-4.
87. Grosshans E, Dungler T, Kien TT, Kremer M. [Demodex folliculorum and rosacea: experimental and immunological studies] Z Hautkr. 1980 Sep 15;55(18):1211-8.
88. Orinska, Z. *et al. Nat. Med.* **13**, 927–934 (2007)**.**
89. Elssner A, Duncan M, Gavrilin M, Wewers MD. A Novel P2X7 Receptor Activator, the Human Cathelicidin-Derived Peptide LL37, Induces IL-1_ Processing and Release. J Immunol. 2004;
90. Manna V, Marks R, Holt P. Involvement of immune mechanisms in the pathogenesis of rosacea. Br J Dermatol. 1982;107(2):203-208.
91. Boni R, Burg G, Wirth HP. Helicobacter pylori and skin diseases-a (still) intact myth? Schweiz Med Wochenschr. 2000;130(37):1305-1308.
92. Goldberg DJ. Lasers and light sources for rosacea. *Cutis* 2005;75 (suppl 3):22-6.
93. Sziachcic A. The link between Helicobacter pilory infection and rosacea. J Eur Acad Dermatol Venereol. 2002;16(4):328-333.
94. Herr H, You CH. Relationship between Helicobacter pylori and rosacea : it may be a myth. J Korean Med Sci 2000;15(5):551-554.
95. Rebora A, Drago F, Picciotto A. *Helicobacter pylori* in patients with rosacea. *Am J Gastroenterol* 1994; 89:1603-4.
96. Bamford J,Tilden R, Blankush J, Gangeness D. Effect of treatment of *Helicobacter pylori* infection on rosacea. *Arch Dermatol* 1999;135-659-663.
97. Wedi B, Kapp A. Helicobacter pylori infection in skin disease: a critical apprisal. Am J Clin Dermatol. 2002;3(4):273-282.
98. Hase K, Murakami M, Iimura M, Cole SP, Horibe Y, Ohtake T, Obonyo M, Gallo RL, Eckmann L, Kagnoff MF. Expression of LL-37 by human gastric epithelial cells as a potential host defense mechanism against Helicobacter pylori. Gastroenterology. 2003 Dec;125(6):1613-25.
99. Bonamigo RR, Bakos L, Edelweiss M, Cartell A. Could matriz-metalloproteinase-9 be a link between Demodex folliculorum and rosacea? J Eur Dermatol Venereol 2005;19(5):646-647.
100. Sobrin L, Liu Z, Monroy DC, Solomon A, Selzer MG, Lokeshwar BL,2 Pflugfelder SC. Regulation of MMP-9 Activity in Human Tear Fluid and Corneal Epithelial Culture Supernatant. IOVS, June 2000, Vol. 41, No. 7.
101. Afonso AA, Sobrin L,Monroy DC,Selzer M, Lokeshwar B, Pflugfelder SC. Tear Fluid Gelatinase B Activity Correlates with IL-1a Concentration and Fluorescein Clearance in

Ocular Rosacea. Opht Vis Sci, October 1999, Vol. 40, No. 11, 2506-2512.

102. Pu LL, Smith PD, Payne WG, Kuhn MA, Wang X, Ko F, Robson MC. Overexpression of transforming growth factor beta-2 and its receptor in rhinophyma: an alternative mechanism of pathobiology. Ann Plast Surg. 2000 Nov;45(5):515-9
103. Payne WG, Wang X, Walusimbi M, Ko F, Wright TE, Robson MC. Further evidence for the role of fibrosis in the pathobiology of rhinophyma. Ann Plast Surg. 2002 Jun;48(6):641-5.
104. Pisella PJ, Brignole F, Debbasch C, Lozato PA, Creuzot-Garcher C, Bara J, Saiag P, Warnet JM, Baudouin CFlow cytometric analysis of conjunctival epithelium in ocular rosacea and keratoconjunctivitis Ophthalmology. 2000 Oct;107(10):1841-9.
105. Cuevas P, Arrazola JM.Therapeutic response of rosacea to dobesilate. Eur J Med Res. 2005 Oct 18;10(10):454-6.
106. Pelle MT, Crawford GH, James WD. Rosacea: therapy. J Am Acad Dermatol 2004; 51:499-512.
107. Gupta AK, Chaudhry MM. Rosacea and its management: anoverview. J Eur Acad Dermatol Venereol 2005;19:273-285.
108. Del Rosso JQ. Adjunctive skin care in the management of rosacea: cleansers, moisturizers, and photoprotectants. Cutis 2005;75(Suppl3):17-21.
109. Jappe U, Schnuch A, Uter W. Rosacea and contact allergy to cosmetics and topical medicaments retrospective analysis of multicenter surveillance data 1995-2002. Contact Dermatitis 2005; 52:96-101.
110. Zip C. An update on the role of topical metronidazole in rosacea. Skin Therapy Letter. 2006;11(2)
111. Nielsen PG. Treatment of rosacea with 1% metronidazole cream. Adouble-blind study. Br J Dermatol 1983;108(3):327-332.
112. Lamp KC, Freeman CD, Klutman NE, Lacy MK. Pharmacokinetics and pharmacodynamics of nitroimidazol antimicrobials. Clin Pharmacokinet. 1999;36(5):353.373.
113. Aronson IK, Rumsfield JA, West DP, Alexander J, Fisher JH, Paloucek FP. Evaluation of topical metronidazole gel in acne rosacea. Drug Intell Clin Pharm. 1987;21(4):346-351.
114. Bleicher PA, Charles JH, Sober AJ. Topical metronidazole therapy for rosacea. Arch Dermatol 1987;123(5):609-614.
115. Beutner K, Calvarese B, Graeber M. A multi-center, investigator-blind clinical trial to assess the safety and efficacy of metronidazole 1% gel as compared to metronidazole gel vehicle and metronidazole cream 1% in the treatment of rosacea. Presented at: American Academy of Dermatology 63rd Annual meeting; 2005 Feb 18-22; New Orleans, P101.
116. Drake L, Leyden J, Lucky A. Evaluation of topical metronidazole cream in rosacea. Presented at: American Academy of Dermatology 55th Annual meeting; 1997 March 21-26; San Francisco, P65.
117. Breneman DL, Stewart D, Hevia O, Hino PD, Drake LA. A double-blind, multicenter clinical trial comparing the efficacy of once-daily metronidazole 1 percent cream to vehicle in patients with rosacea. Cutis 1998;61(1):44-47.
118. Jorizzo JL, Lebwohl M, Tobey RE. The efficacy of metronidazole 1% cream once daily compared with metronidazole 1% cream twice daily and their vehicle in rosacea: a double-blind clinical trial. J Am Acad Dermatol 1998;39(3):502-504.
119. Tan JKL, Girard C, Krol A. Randomized placebo-controlled trial of metronidazole 1% cream with sunscreen SPF 15 in treatment of rosacea. J Cutan Med Surg 2002;6(6):529-534.
120. Breneman D, Bucko A, Friedman D. Evaluation of topical metronidazole lotion in rosacea. Presented at: American Academy of Dermatology 56th Annual meeting; 1998 February 27-March 4; Orlando; P289.
121. Wolf JE Jr, Del Rosso JQ. The CLEAR trial: results of a large community-based study of metronidazole gel in rosacea. Cutis. 2007 Jan;79(1):73-80.
122. Wolf JE Jr, Del Rosso JQ. The CLEAR trial: results of a large community-based study of metronidazole gel in rosacea. Cutis. 2007 Jan;79(1):73-80.
123. Conde JF, Yelverton CB, Balkrishnan R, Fleischer AB Jr, Feldman SR. Managing rosacea: a review of the use of metronidazole alone and in combination with oral antibiotics. J Drugs Dermatol. 2007 May;6(5):495-8.
124. Maddin S. A comparison of topical azelaic acid 20% cream and topical metronidazole 0.75% cream in the treatment of patients with papulopustular rosacea. J Am Acad Dermatol 1999;40(6Pt1):961-965.
125. Elewski BE, Fleischer Jr AB, Pariser DM. A Comparison of 15% Azelaic Acid Gel and 0.75% Metronidazole Gel in the Topical Treatment of Papulopustular Rosacea. Results of a Randomized Trial. ARCH DERMATOL 2003; 139:1444-1450.
126. Madsen JT, Thormann J, Kerre S, Andersen KE, Goossens A. Allergic contact dermatitis to topical metronidazole - 3 cases. Contact Dermatitis. 2007 Jun;56(6):364-6.
127. Beutner KR, Lemke S, Calvarese B. A look at the safety of metronidazole 1% gel: cumulative irritation, contact sensitization, phototoxicity, and photoallergy potential. Cutis. 2006 Apr;77(4 Suppl):12-7.

128. Liu RH, Smith MK, Basta SA, Farmer ER. Azelaic acid in the treatment of papulopustular rosacea. Arch Dermatol 2006;142:1047-1052.
129. Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: results from two vehicle-controlled, randomized phase-III studies. J Am Acad Dermatol 2003;48:836-845.
130. Thiboutot D, Graupe K, Lavin PT, Thieroff-Ekerdt K. A new static score to assess papulopustular (stage 2) rosacea: experience from two large, vehicle-controlled, phase-III studies comparing a new azelaic acid 15% gel formulation with its vehicle. Presented as a poster at: 61st Annual Meeting of the American Academy of Dermatology; March 21-26, 2003; San Francisco.
131. Bjerke R, Fyrand O, Graupe K. Double-blind comparison of azelaic acid 20% cream and its vehicle in treatment of papulopustular rosacea. Act Derm Venereol 1999;79:456-459.
132. Carmichael A, Marks R, Graupe K. Topical azelaic acid in the treatment of rosacea. J Dermatol Treat 1993;4(sup1)19-22.
133. Colón LE, Johnson LA, Gottschalk RW Cumulative irritation potential among metronidazole gel 1%, metronidazole gel 0.75%, and azelaic acid gel 15%. Cutis. 2007 Apr;79(4):317-21.
134. Vienne MP, Ochando N, Borrel MT, Gall Y, Lauze C, Dupuy P. Retinaldehyde alleviates rosacea. Dermatology 1999;199(Suppl 1):53– 6.
135. Koçak M, Yağli S, Vahapoğlu G, Ekşioğlu M. Permethrin 5% cream versus metronidazole 0.75% gel for the treatment of papulopustular rosacea. A randomized double-blind placebo-controlled study. Dermatology. 2002;205(3):265-70.
136. Carlin RB, Carlin CS. Topical vitamin C preparation reduces erythema of rosacea. Cosmetic Dermatol 2001;Feb:35– 8.
137. Wollina U. The role of topical calcineurin inhibitors for skin diseases other than atopic dermatitis. Am J Clin Dermatol. 2007;8(3):157-73.
138. Weissenbacher S, Merkl J, Hildebrandt B, Wollenberg A, Braeutigam M, Ring J, Hofmann H. Pimecrolimus cream 1% for papulopustular rosacea: a randomized vehicle-controlled double-blind trial. Br J Dermatol 2007;156(4):728-732.
139. Blount BW, Pelletier AL. Rosacea: A Common,Yet CommonlyOverlooked, Condition. Am Fam Phys 2002;66(3):435-440.
140. van Zuuren EJ, Gupta AK, Gover MD, Graber M, Hollis S. Systematic review of rosacea treatments. J Am Acad Dermatol. 2007 Jan;56(1):107-15. Epub 2006 Nov 7.
141. Sneddon I. A clinical trial of tetracycline in rosacea. *Br J Dermatol* 1966; 78:649-652.
142. Fowler JF Jr. Combined effect of anti-inflammatory dose doxycycline (40-mg doxycycline, usp monohydrate controlled-release capsules) and metronidazole topical gel 1% in the treatment of rosacea. J Drugs Dermatol. 2007 Jun;6(6):641-5.
143. Del Rosso JQ. Recently approved systemic therapies for acne vulgaris and rosacea. Cutis. 2007 Aug;80(2):113-20.
144. Torresani C, Pavesi A, Manata G. Clarithromycin versus doxycycline in the treatment of rosacea. *Int J Dermatol* 1998;37:347-349.
145. Bakar O, Demircay Z, Gurbuz O. Therapeutic potential of azithromycin in rosacea. *Int J Dermatol* 2004;43:151.
146. Bakar O, Demirçay Z, Yuksel M, Haklar G, Sanisoglu Y. The effect of azithromycin on reactive oxygen species in rosacea. Clin Exp Dermatol. 2007 Mar;32(2):197-200. Epub 2007 Jan 18
147. Nally JB, Berson DS. Topical therapies for rosacea. *J Drugs Dermatol* 2006;5:23-26.