Rosacea is one of the most common skin disorders in adults. Because it affects mainly the face, it is disfiguring for many patients and has serious psychosocial sequelae. Rosacea progresses over many years, in intermittent episodes that result in different manifestations of the disease, and clinically discrete stages are differentiated. This article provides the classification and stages of rosacea as agreed in recent consensus conferences.

The course of the disease is different in every individual, but rosacea may occur at any stage. Acne and rosacea may have similarities but are fundamentally different disorders. Exact morphological knowledge is necessary for a definite diagnosis and treatment that is appropriate for the stage. No causative treatment leading to permanent cure exists. However, rosacea can be controlled adequately with therapy that is appropriate for the respective stage and phase (1, 3). Treatment concepts are explained below.

Epidemiology

An estimated 2–5% of adults in Germany develop rosacea. Rosacea affects middle aged people; it usually starts in the third or fourth decade of life and peaks between age 40 and 50. Children are rarely affected. In the countries of northern Europe, where people are predominantly light skinned, red haired, and of the Celtic skin type, rosacea is notably more common than in the south. In the north, the reported prevalence is up to 10% and in the south, 2% (4). Women develop rosacea more often than men, but as a rule it takes a milder course.

Pathogenesis

No scientifically based, comprehensive, pathogenetic principle for rosacea has thus far been developed. Well defined and known stimuli result in initial manifestations or exacerbate the disease. A variety of physical and chemical agents can induce rosacea in predisposed individuals and trigger exacerbations of preexisting disease. Treatment of the various forms of rosacea should be adapted to the stage and phase of the disease. Rosacea is not curable but the symptoms can for the most part be effectively controlled, thus preventing permanent damage to the skin, such as scarring and permanent edema.

Key words: rosacea, dermatosis, chronic disease, topical therapy
existing rosacea. These include sun radiation, irritants (cosmetics, soaps, synthetic soaps, peelings, and others), changes in temperature, heat, and psychovegetative influences. Since flushing (strong persistent blushing) initially determines the disorder in all rosacea patients, and since the angular venous system of the face is connected to the cooling circulation mechanism for the brain, a dysregulation of the thermoreactive mechanism has been postulated. Brinnel et al. (5), however, demonstrated in an experimental study that this thermoreactive mechanism is disrupted in rosacea patients. Further studies (e1, 6) showed that rosacea patients react to certain stimuli with a stronger and prolonged erythematous facial reaction than control patients.

On the basis of these data, the following hypothesis is formulated: patients with rosacea have a genetic predisposition for the disorder. Many well documented factors result in vascular dilatation and damage and subsequently to alterations to the connective tissues in a context of increased activity of reactive oxygen radicals. A chronic inflammatory reaction with flooding of inflammatory cells and inflammatory mediators then leads to the rosacea phenotype, with erythema, papules, and pustules. Involvement of the lymphatic system results in edema. Chronic inflammation and lymphedema induce a tissue hyperplasia that phenotypically manifests as a hyperplastic-glandular form of rosacea. In the sense of an amplification cycle, the chronic inflammation may damage the dermal vessels and surrounding connective tissues (1, 7, 8).
Clinical presentation and subtypes
Rosacea presents with different symptoms and in different phenotypes, which may occur together but also independently. The following centrofacial manifestations indicate rosacea:
- Transient, intense erythema (“flushing and blushing”)
- Persistent facial erythema
- Papules and pustules
- Telangiectasia
- Burning and stabbing sensations
- Erythematous plaques
- Dry skin, occasionally in association with seborrheic dermatitis
- Extrafacial manifestations.

Clinical stages
Building on detailed clinical descriptions and investigations, consensus conferences confirmed the valid classification of rosacea, which considers the different manifestations of the disorder and defines them clinically. Distinction is made between one preliminary stage, three main stages, and special manifestations (8, 9).

Preliminary stage – the rosacea diathesis
Most patients notice transient erythema as their first symptom of rosacea. This recurs increasingly often and has a flush-like character. Intermittently occurring erythematous blushing occurs in rosacea patients at all stages and is felt to be particularly disagreeable. The skin is easily irritable and reacts to minor stimuli. The initially transient erythema then develops into persistent erythema.

Stage I – Rosacea erythematosa teleangiectatica
Enduring erythema characterizes the first stage of rosacea (rosacea I), with telangiectasia of different severity (figure 1). The irritability of the skin increases notably throughout this stage. Stabbing, burning, and itching are among the subjective symptoms of this stage that particularly impair patients.

Stage II – Rosacea papulopustulosa
Inflamed erythematous papules and pustules occur centrofacially on erythematous skin at this stage (rosacea II). These persist usually for longer periods of time (weeks) (figure 2). This presentation is sometimes confused with Acne vulgaris, although in rosacea, the primary acne efflorescences – comedones – are absent. As a rule, the efflorescences occur symmetrically; after a lengthier amount of time, the chin and cheeks are affected and then the entire face. The rash does not usually spread beyond the facial area but it has been known to occur on occasion. In extrafacial rosacea, the entire integumentary system (skin) of the patient should be investigated.

Stage III – glandular hyperplastic rosacea
Large inflammatory nodules and plaques with infiltrations as well as tissue hyperplasia characterize this stage of rosacea (rosacea III). The nose and cheeks are the most commonly affected sites (figure 3).

Extensive inflammatory infiltrates occur, as does an increase in connective tissue and massive hyperplasia of the sebaceous glands. The result of the tissue hyperplasias is the development of the different phymas (figure 4). Phymas (phyma, Greek: swelling, mass, tuberosity) develop in different facial sites; rhinophyma is most common, whereas gnatophyma, otophyma, blepharophyma, and metophyma are rarer.

Special forms
Rosacea conglobata
Similar to acne conglobata, patients with rosacea may develop confluent hemorrhagic nodular abscesses. Painfully indurated strands are further signs of rosacea conglobata. Women are more often affected than men; the course is chronic-progressive. This condition differs from acne conglobata only in that it is limited to the face, comedones do not occur, and chest, back, shoulders, and extremities are spared. Only in exceptional cases do conglobating nodules occur on the chest.
**Rosacea fulminans**

Large conglobating nodules develop acutely on the face, and abscessing fistulas may affect the entire facial area (10). Seborrhea, abscesses, numerous pustules, and carbuncular nodules characterize this condition (*figure 5a*). This, the most severe form of rosacea, always affects younger women.

Most women report during their medical history for rosacea that the sudden start of the condition on the face was preceded by strong seborrhea. In 1940, O'Leary and Kierland described this dramatic pathology for the first time, using the term pyoderma faciale (11), a misleading term as microbiological investigations never found germs that were responsible for the condition. The patient's general condition is normally barely affected; the patients are primarily affected psychologically, owing to the disfiguring skin condition. Although this most severe form of rosacea is very disfiguring, early and intensive therapy usually yields good results (*figure 5b*). Equally positive and encouraging is the finding that recurrences have not been observed after successful treatment (12).

**Granulomatous rosacea**

This special form of rosacea is particularly difficult to treat. Reddish-brown nodules or papules develop on the basis of a diffusely reddened skin. Such lupoid epitheloid granulomas are disseminated over the face. Histology shows lymphohistiocytic infiltrates with giant cells and epitheloid cellular tuberculoid granulomas. This manifestation was previously referred to as lupus miliaris disseminatus faciei, but this term is not used anymore. Germs (mycobacteria) were excluded as causative agents.

**Persistent edema in rosacea (Morbihan's disease)**

Rough facial edema in rosacea develops owing to more involvement of the lymphatic system in addition to the blood vessels. Forehead, glabella, nose, and cheeks are most commonly affected. Histologically notable are increased mastocytes in all levels of the connective tissue (13).

This led to the concept that the particular induration through chronic inflammation is caused concomitantly with fibrosis induced by mastocytes. The condition ("curse of the Celts") is said to be common in the Morbihan region (Brittany), where a large part of the population is of Celtic origin.

A recent study (14) found immunological dysregulations in patients, in the form of contact urticaria with disrupted lymphatic flow, by using laser Doppler investigation. This mechanism is also under discussion as a pathogenetic contributing cause in rosacea.

**Steroid rosacea**

Steroid rosacea presents clinically as a mixture of rosacea papulopustulosa and the steroid side effects atrophy and telangiectasia (15, 16). Topical treatment with potent corticosteroids,
as well as occasional systemic application of such preparations, will result in steroid rosacea over a longer period of time. If corticosteroid treatment is stopped, severe exacerbations will occur; strict abstinence from steroids is the only way to control this condition, which is difficult to treat (16). As a new therapeutic option, calcineurin inhibitors (pimecrolimus, tacrolimus) have been applied successfully (e2).

**Skin changes owing to inhibitors of epidermal growth factor receptor**

Different side effects on the skin have been described after use of inhibitors of epidermal growth factor receptor (EGFR), among others, these included "acneiform skin reactions" or "rosacea-like dermatitis."

According to the author's observations (figures 6a, 6b) and studies of some case descriptions (17, 18), the skin changes in some of these cases were very similar to rosacea manifestations of different grades. These side effects may, however, affect the entire integumentary system (skin) and induce further, eczema-like changes in addition to the rosacea-like changes. EGFR inhibitor treatment should not be stopped because the skin side effects obviously correlate with the therapeutic response to the underlying condition. Two of the author's patients responded well to phase adapted rosacea therapy. Further studies should further evaluate this undesirable effect because the patients suffer severely from these disfiguring side effects, in addition to their serious underlying condition.

**Ocular rosacea**

Some 25% of rosacea patients have ocular manifestations, independent of the stage and severity of the underlying illness. The eye is affected by chronic inflammatory processes, sometimes accompanied by ulcerations and nodular infiltrates, which may result in blindness if left untreated (2, 3).

**Therapy**

In contrast to the manifold phenotypes of rosacea, relatively few – compared with acne – controlled studies into the treatment of rosacea exist (19). Independent of stage and phase, it will have to be explained to the patient that skin affected by rosacea reacts unusually sensitively to chemical and physical irritants. All locally irritating agents have to be avoided, such as irritant soaps, alcoholic tinctures, astringents, and peelings. The doctor needs to emphasize especially the harmful effects of sun radiation.

**Topical therapy**

In stages I and II of rosacea, topical therapy is often sufficient. Many different creams, lotions, and gels are recommended for the treatment, but only for few substances is there scientific, evidence
based proof of reliable efficacy. The best and most comprehensive studies exist on the agents metronidazole and azelaic acid (19, 20), so that these substances are officially licensed for use in rosacea as topical drugs.

The effects of azelaic acid versus metronidazole has been investigated in randomized, prospective, multicenter studies in papulopustulous rosacea (22, e3). Both were found to be efficacious; azelaic acid was better at reducing papulopustules than metronidazole. However, the substance with the largest amount of clinically documented experience is metronidazole (19, 20).

For a long time, it could be prescribed in Germany only as a drug confected as a formula magistralis, but since 2001, it has been available as a 0.75% gel preparation and since 2003, as a cream. The efficacy of metronidazole is beyond doubt; numerous double blinded, placebo controlled studies have been conducted for this substance (23, 24).

After some 3 weeks, a reduction in papules and pustules by 50% can be achieved, and the maximum effect will set in after 9 weeks (in more than 75% of patients). In 1%, irritation was noted as a side effect, but this was mostly transient. Antibiotics used in acne treatment are often effective, although the mechanism has not been explained. The assumption is that a generally anti-inflammatory ingredient in several antibiotics is effective in rosacea. Those antibiotics used include erythromycin, clindamycin, and the tetracyclines, in concentrations
between 0.5% and 2%. The strongest effect is assumed for erythromycin, but topical tetracyclines seem relatively ineffective.

Topical retinoids are a possible future therapeutic option, which is currently being investigated for the treatment of rosacea in studies. A recently published randomized controlled prospective study showed the efficacy of adapalene in papulopustular rosacea (21). Topical antibiotics and retinoids are not officially licensed for rosacea, so that these substances are used exclusively off label.

Systemic treatment
Systemic therapy for rosacea is used only for the severe forms. Oral tetracyclines (tetracycline hydrochloride, oxytetracycline) have been the gold standard in oral therapy for severe rosacea for 40 years (3). Three to four week's therapy with 250 mg/day can bring skin and eye symptoms of rosacea under control. Minocycline and doxycycline, second generation tetracyclines, are similarly effective, although well controlled studies are lacking. Attention has to be paid to side effects. Doxycycline is phototoxic, and minocycline may result in discolorations of skin and mucosa and other tissues. Pregnancy is a contraindication for this class of substances. Macrolide antibiotics are an alternative to the tetracyclines.

Isotretinoin: Isotretinoin is effective in medium to severe rosacea, even though it has not been officially licensed for this indication (25, e4). The initially applied doses were 0.5–1 mg/kg body weight, but more recently, an increasingly promoted and well documented low dosage (0.1–0.2 mg/kg body weight) has been proved to be effective.

Glucocorticosteroids: In the most severe forms of rosacea – rosacea conglobata and rosacea fulminans – initially, to reduce the inflammatory component, systemic glucocorticosteroids (0.5–1 mg prednisolone equivalent dose/kg body weight) may be administered, which are normally contraindicated in the treatment of rosacea. After the inflammatory signs have subsided, a combination with isotretinoin and downsstepping of the glucocorticosteroids has yielded the most favorable results (25).

Other pharmacological therapeutic options: Reports exist on the successful use of dapsone, antimarial drugs, antimycotics, cyproteroneacetate, spironolactone, clonidine, and nadolol. For reasons of space, they cannot be dealt with in this article.

Surgical treatment for rosacea
Mainly rhinophyma in rosacea can be treated effectively with surgery. By administering systemic isotretinoin, the rhinophyma can be shrunk, but the most effective therapy is surgical ablation. Different techniques have been described in the literature, and the surgeon's experience seems most important for the success of the respective methods. Excision and cryotherapeutic as well as electrosurgical ablation, vaporization with a CO₂ laser, ablation with an erbium:YAG laser, derma shaving with a scalpel or dermabrasion are effective methods (3).

Conflict of Interest Statement
The author has received lecture honorariums from the companies Galderma and Novartis in the past two years.

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REFERENCES
For e-references please refer to the additional references listed below.


**ADDITIONAL REFERENCES**