In the name of God

Acnea

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INTRODUCTION

- Acne vulgaris is a multifactorial disorder of the pilosebaceous unit.
- The clinical picture can vary significantly, from mild comedonal acne to fulminant systemic disease.
- Although all age groups may be affected by its many variants, the peak incidence is during adolescence.
- Acne has an undeniable psychosocial impact, and affected individuals have an increased likelihood of self-consciousness, social isolation, anxiety disorders, depression, and even suicidal ideation
- Insights into the pathogenesis of acne have aided significantly in further defining the subtypes of acne and establishing effective treatment regimens

EPIDEMIOLOGY, INCLUDING GENETIC AND DIETARY FACTORS

- Acne vulgaris affects approximately 40–50 million individuals each year in the US alone, leading to an estimated annual cost in the US of at least $2.5 billion.
- Globally, acne accounts for ~0.3% of the total and ~16% of the dermatologic disease burden.
- With a peak incidence during adolescence, acne affects approximately 85% of young people between 12 and 24 years of age and is therefore a physiologic occurrence in this group.
- With the general trend over the past few decades for earlier puberty, preadolescent acne affecting children 7 to 11 years of age has also become more common.
- While typically thought of as a disease of youth, acne often continues to be problematic well into adulthood.

- In a survey-based study in the US, 35% of women and 20% of men reported having acne in their 30s, while 26% of women and 12% of men were still affected in their 40s
- Caucasian boys and men have a tendency to have more severe nodulocystic disease than other groups
- Individuals at increased risk for the development of acne include those with an XYY karyotype or endocrine disorders such as polycystic ovarian syndrome, hyperandrogenism, hypercortisolism, and precocious puberty.
- Patients with these conditions tend to have more severe acne that is less responsive to standard therapy

Genetic Factors

- The precise role of genetic predisposition in the multifactorial pathogenesis of acne remains to be determined.
- The number, size, and activity of sebaceous glands is inherited.
- In addition, the concordance rate for the prevalence and severity of acne among identical twins is extremely high.
- It is a widely held belief that the tendency to have substantial acne (including the nodulocystic variant) runs in families, and an association between moderate to severe acne and a family history of acne has been observed in several studies .
- Genes found to have a possible link to acne via genome-wide association studies (GWAS) and other methods include those encoding components of the tumor growth factor-β pathway, other inflammatory mediators, and regulators of androgen metabolism

Dietary Factors

- The relationship between diet and acne remains a subject of controversy.
- Several observational studies in different ethnic groups have found that intake of milk, especially skim milk, is positively associated with acne prevalence and severity.
- Exacerbation of acne with the use of whey protein supplements for body building has also been reported.
- In addition, prospective studies have documented a link between a high glycemic-load diet and acne risk.
- A recent investigation found that vitamin B12 supplementation can potentially trigger the development of acne by altering the transcriptome of skin microbiota, leading to increased production of proinflammatory porphyrins by. Propionibacterium acnes

PATHOGENESIS

The development of acne involves the interplay of a variety of factors, including:
(1) follicular hyperkeratinization;
(2) hormonal influences on sebum production and composition;
and (3) inflammation, in part mediated by P. acnes

Follicular Hyperkeratinization

- The microcomedo is thought to be the precursor of all clinically apparent acne lesions.
- It forms in the upper portion of the follicle within the lower portion of the infundibulum, the infrainfundibulum.
- Coenocytes, which are normally shed into the lumen of the follicle and extruded, accumulate due to increases in both follicular keratinocyte proliferation and corneocyte cohesiveness, leading to the development of a hyperkeratotic plug and a bottleneck phenomenon.
- The inciting event for microcomedo formation is unknown, but data support a putative role for interleukin-1α (IL-1α)

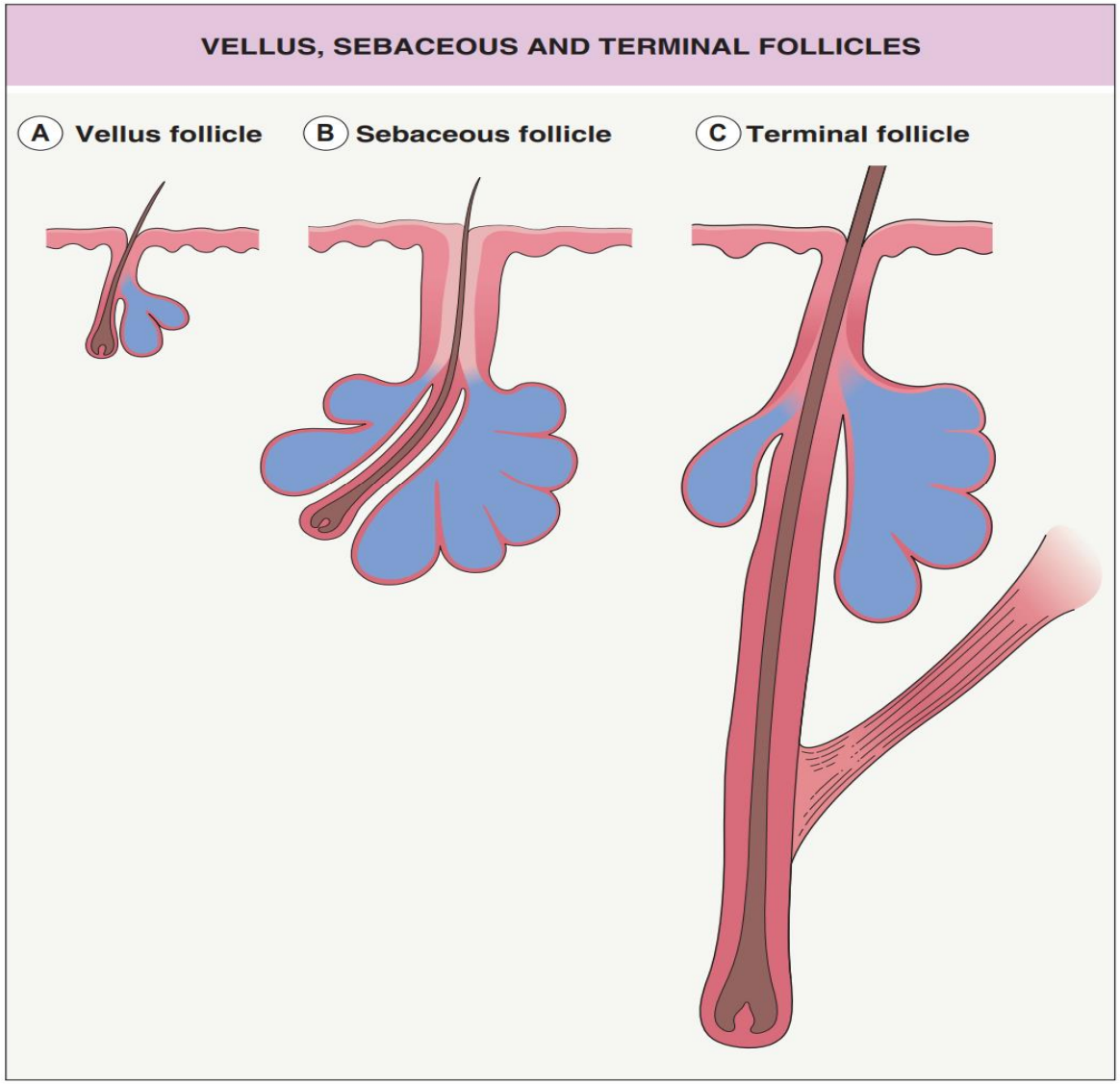

Fig. 35.3 Vellus, sebaceous and terminal follicles. Three different types of pilosebaceous units. **A** Vellus follicle with a small sebaceous gland and short thin hair. **B** Sebaceous follicle with a large multilobular sebaceous gland and mid-sized hair. **C** Terminal follicle with a fairly large sebaceous gland and thicker hair. *Adapted from Plewig G, Kligman AM. Acne and Rosacea, 3rd edn. Berlin: Springer, 2000.*

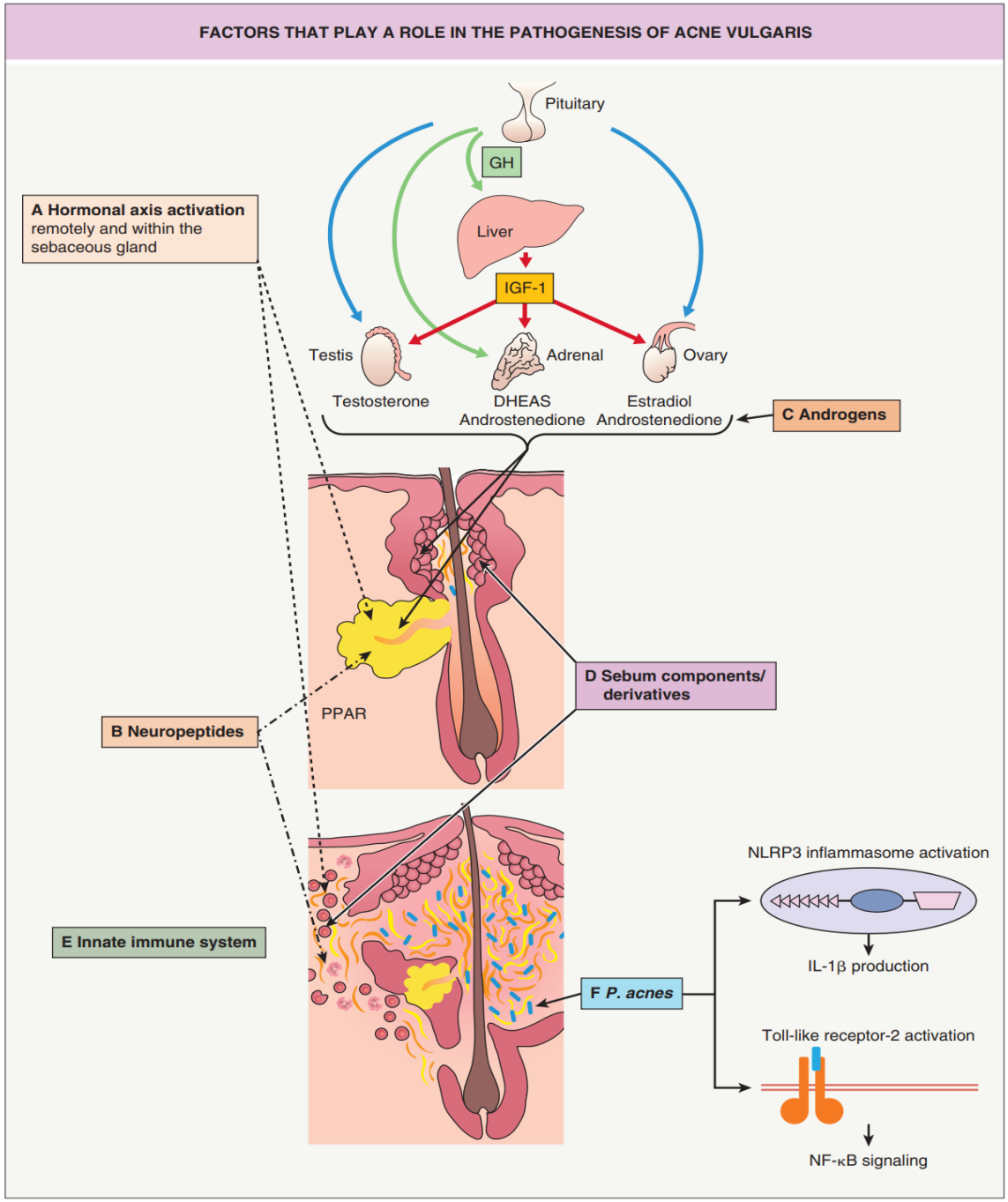

Fig. 35.4 Factors that play a role in the pathogenesis of acne vulgaris. A–F correspond to the sections of Table 35.4. DHEAS, dehydroepiandrosterone sulfate; GH, growth hormone; IGF-1, insulin-like growth factor-1; IL, interleukin; NLRP3, NOD-like receptor pyrin domain-containing protein 3; PPAR, peroxisome proliferator-activated receptor.

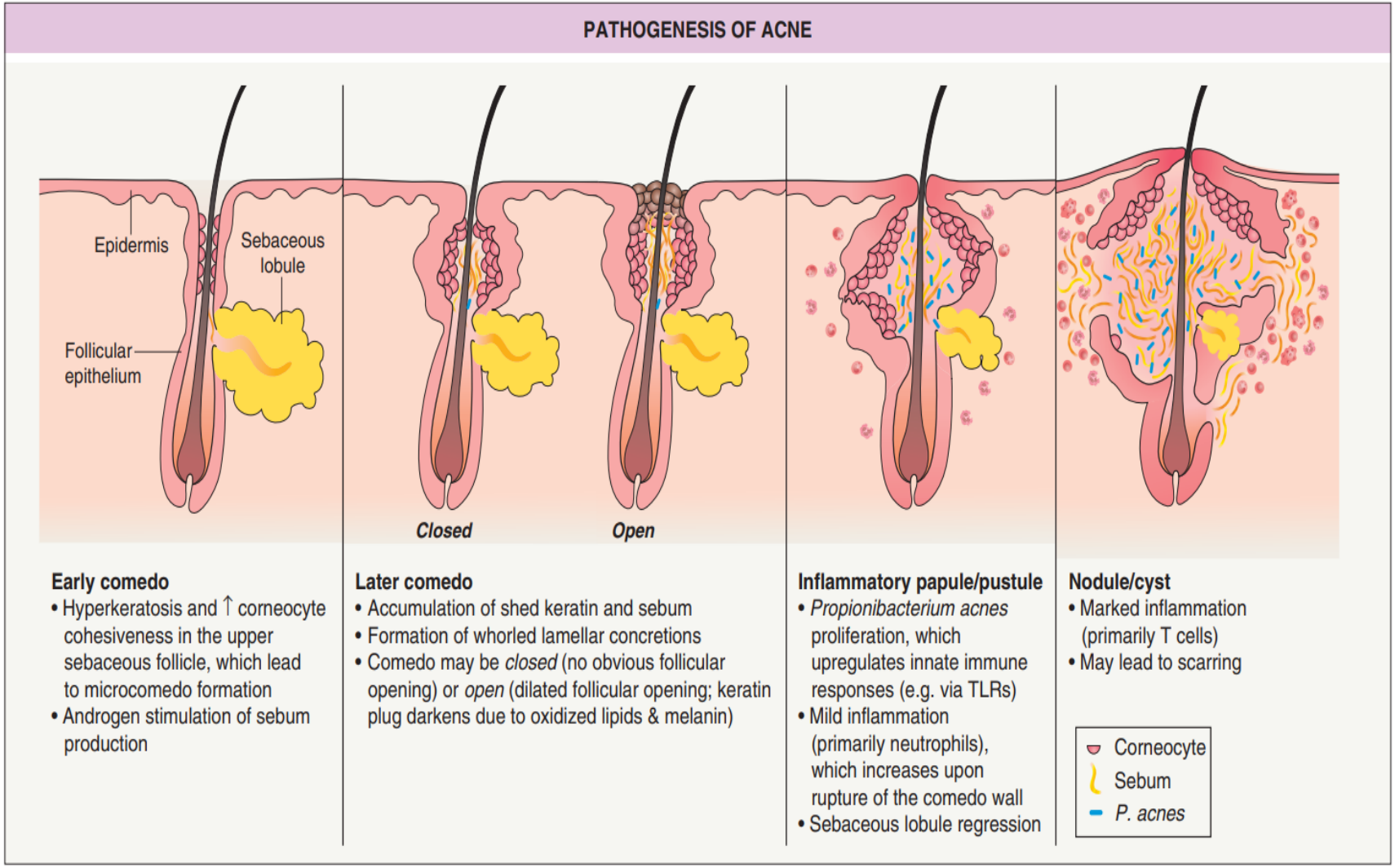

Fig. 36.1 Pathogenesis of acne.

Hormonal Influences on Sebum

- Production and Composition The sebaceous gland is controlled primarily by androgens, with additional influences from other hormones and neuropeptides
- Androgens are produced both outside the pilosebaceous unit, mainly by the gonads and adrenal glands, and locally within the sebaceous gland via the action of androgen-metabolizing enzymes such as 3β- hydroxy steroid dehydrogenase (HSD), 17β-HSD and 5α-reductase
- Androgen receptors, found in the cells of the basal layer of the sebaceous gland and the outer root sheath of the hair follicle, are responsive to testosterone and 5α-dihydrotestosterone (DHT), the most potent androgens.
- DHT has a 5–10-fold greater affinity than testosterone for the androgen receptor and is thought to be the principal androgen mediating sebum production.

ROLES OF THE SEBACEOUS GLAND IN PATHOGENESIS OF ACNE VULGARIS AND ROSACEA		
Sebaceous gland component	**Actions in sebaceous glands**	**Observations in sebaceous glands of patients with AV and R**
A – Hypothalamic–pituitary–adrenal(-like) and other hormonal axes		
Corticotropin-releasing hormone (CRH)* and CRH receptors (CRH-Rs)	↑ lipid and androgen synthesis ↑ production of IL-6, IL-8 (CRH-R2)	↑ levels of CRH and (in sebaceous ducts) CRH-R1 in **AV**
α-Melanocyte stimulating hormone (MSH)* and melanocortin-1 & -5 receptors (MC1-R, MC5-R†)	↑ sebocyte differentiation and lipid synthesis (MC5-R)	↑ levels of MC1-R in **AV**
Growth hormone and insulin-like growth factor-1 (IGF-1) receptors	↑ sebocyte proliferation ↑ lipid and androgen synthesis	Association of high glycemic-load diets and intake of insulinotropic dairy products with **AV**
B – Other neuropeptides		
Substance P	↑ sebocyte proliferation/differentiation ↑ production of inflammatory cytokines	↑ substance P-containing nerves in **AV**
C – Androgens		
Testosterone* and dihydrotestosterone (DHT)*	↑ sebocyte proliferation/differentiation and lipid synthesis (especially DHT) May ↑ infundibular keratinization	↑ conversion of testosterone to DHT in **AV** Association of hyperandrogenic disorders with **AV**‡
D – Sebum components and derivatives		
Monounsaturated fatty acids (MUFAs), lipoperoxides (LPs), other proinflammatory lipids (e.g. generated via 5-lipoxygenase), linoleic acid (LA)	↑ infundibular keratinization (MUFAs, LPs, *deficient* LA) ↑ cytokine production, chemotaxis, and PPAR activation (MUFAs, LPs)	↑ overall sebum production, MUFAs, and LPs in **AV** ↑ 5-lipoxygenase in **AV** ↓ linoleic acid in **AV**
E – Innate immune system		
Toll-like receptors (TLRs, especially TLR2)	Upon stimulation (e.g. by *P. acnes*), ↑ production of IL-1, IL-8, IL-12, TNF-α (TLR2)	↑ expression of TLR2 and TLR4 in **AV** Possible ↑ expression of TLR2 in **R**
Defensins, cathelicidins, MUFAs (e.g. sapienic acid)	Antimicrobial properties ↑ cytokine production and chemotaxis	↑ levels of cathelicidin (especially a proteolytically processed form with ↑ proinflammatory and vasoactive effects) in **R**
F – Organisms		
Propionibacterium acnes§	↑ production of antimicrobial peptides & inflammatory cytokines/chemokines, especially IL-1β and IL-17, via stimulation of TLR2 and the NLRP3 inflammasome ↑ free fatty acids (e.g. via lipase activity) May ↑ infundibular keratinization	↑ *P. acnes* in **AV**
Demodex folliculorum	May stimulate or carry bacteria (e.g. *Bacillus oleronius*) that stimulate innate and adaptive immune reactions	↑ density of *D. folliculorum* and reactivity to *B. oleronius* in **R**

*Can be produced locally by the sebaceous gland as well as remotely.
†Marker of sebocyte differentiation.
‡Most AV patients have normal levels of circulating androgens.
§Different phylogenetic clusters of *P. acnes* vary in their ability to induce immune responses.

Table 35.4 Roles of the sebaceous gland in pathogenesis of acne vulgaris (AV) and rosacea (R). IL, interleukin; PPAR, peroxisome proliferator-activated receptor; TNF, tumor necrosis factor.

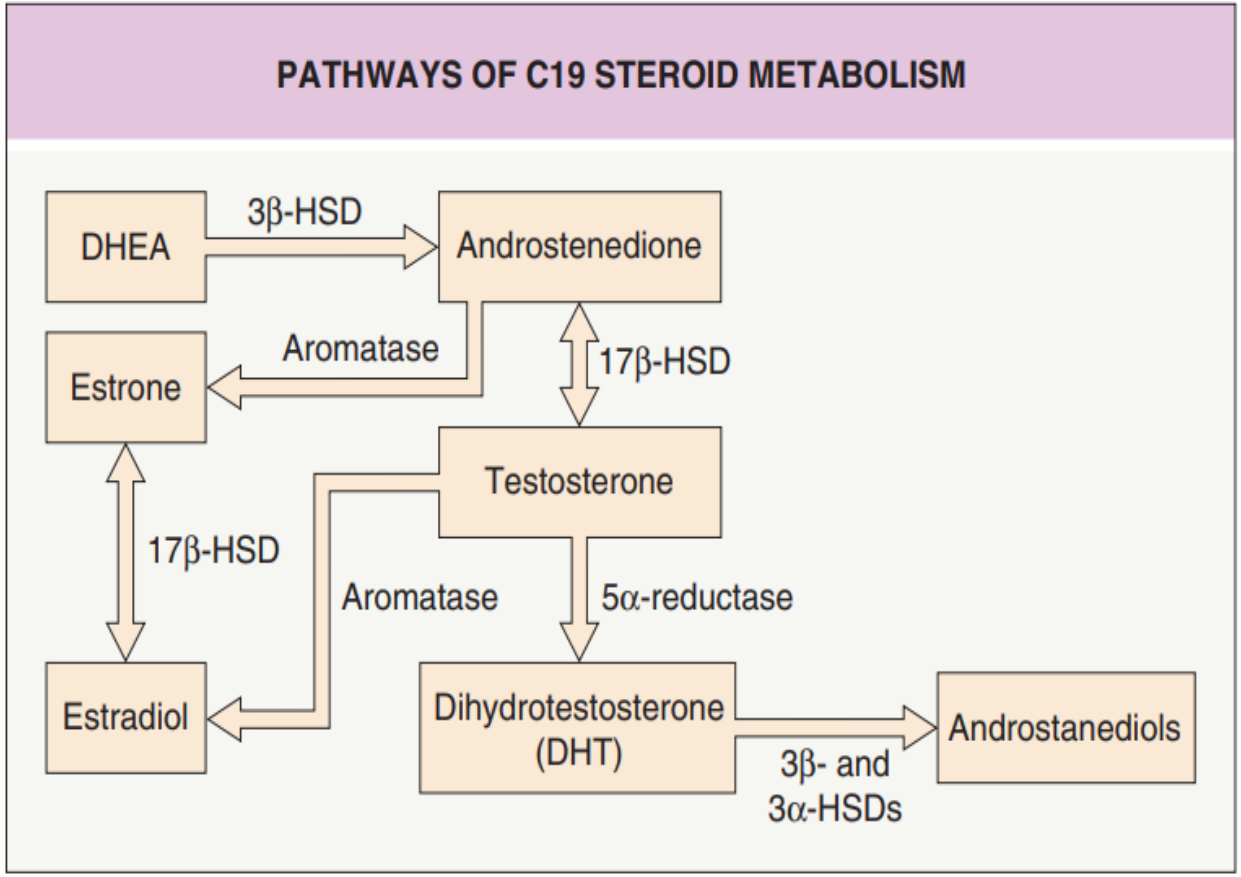

Fig. 36.2 Pathways of C19 steroid metabolism. Dehydroepiandrosterone (DHEA) is a weak androgen that is converted to the more potent testosterone by 3β-hydroxysteroid dehydrogenase (HSD) and 17β-HSD. 5α-reductase then converts testosterone to dihydrotestosterone (DHT), the predominant hormonal effector on the sebaceous gland. Both DHEA and testosterone can be metabolized to estrogens by the enzyme aromatase. The sebaceous gland expresses each of these enzymes.

- The impact of androgens on sebaceous gland activity begins during the neonatal period.
- From birth until approximately 6–12 months of age, infant boys have elevated levels of luteinizing hormone (LH), which stimulates testicular production of testosterone.
- In addition, both male and female infants exhibit increased levels of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) secondary to a large, androgenproducing “fetal zone” in the adrenal gland that involutes during the first year of life.
- Of note, sebaceous gland activity in infants is not due to persistent maternal hormonal stimulation, as was previously hypothesized.
- Both testicular and adrenal androgen production decrease substantially by 1 year of age and remain at a stable nadir until adrenarche.
- With the onset of adrenarche, typically at 7–8 years of age, circulating levels of DHEAS begin to rise due to its production by the adrenal gland.
- This hormone can serve as a precursor for the synthesis of more potent androgens within the sebaceous gland

- The rise in serum levels of DHEAS in prepubescent children is associated with an increase in sebum production and often the initial development of comedonal acne

- Although the overall composition of sebum is similar in persons with or without acne, those with acne have variable degrees of seborrhea and their sebum tends to have higher levels of squalene monounsaturated fatty acids but less linoleic acid.

- Little is known about the physiologic role of estrogens in modulating sebum production.

- Estrogen administered systemically in sufficient amounts decreases sebum production, although the dose of estrogen needed is greater than the dose required to suppress ovulation and increases the risk of thromboembolic events.

- However, acne often responds to treatment with lower-dose oral contraceptives containing 20–50 mcg of ethinyl estradiol or its esters, because suppression of ovulation itself inhibits ovarian androgen production.

- Postulated mechanisms for estrogen-mediated downregulation of sebogenesis include direct opposition of androgens within the sebaceous gland, a negative feedback loop that decreases androgen production via inhibition of pituitary gonadotropin release, and regulation of genes that affect sebaceous gland activity

Inflammation in Acne

- Although tremendous progress has been made in our understanding of acne as an inflammatory process, several questions remain regarding inflammation during acne lesion development.
- It is clear that when a follicle involved with acne ruptures, it exudes keratin, sebum, P. acnes, and cellular debris into the surrounding dermis, thereby significantly intensifying inflammation.
- However, inflammation is also seen early in acne lesion formation. For example, in acne-prone sites, the number of CD4+ T cells and levels of IL-1 have been shown to be increased perifollicularly prior to hyperkeratinization.
- In addition, insulin-like growth factor-1 has been found to increase the expression of inflammatory markers and sebum production in cultured sebocytes.
- The type of inflammatory response determines the clinical lesion seen.
- If neutrophils predominate (typical of early lesions), suppuration occurs and a pustule is formed.

- Neutrophils also promote the inflammatory response by releasing lysosomal enzymes and generating reactive oxygen species;
- levels of the latter in the skin and plasma may correlate with acne severity.

- An influx of lymphocytes (predominately T helper cells), foreign body-type giant cells, and neutrophils results in inflamed papules, nodules, and cysts.

- The type of inflammatory response also plays a role in the development of scarring.

- Early, nonspecific inflammation results in less scarring than does a delayed, specific inflammatory response

Propionibacterium acnes and the Innate Immune System

- P. acnes is a Gram-positive, anaerobic/microaerophilic rod that is found deep within the sebaceous follicle, often together with smaller numbers of P. granulosum.

- In adults, P. acnes is the predominant organism in the microbiome of the face and other sebaceous skin.

- P. acnes produces porphyrins (primarily coproporphyrin III) that fluoresce with Wood's lamp illumination.

- For the most part, P. acnes is considered to be a commensal organism of the skin rather than a pathogen per se

- Although studies have documented increased levels of P. acnes on the facial skin of acne patients, the P. acnes density does not correlate with clinical severity
- Because P. acnes is nearly ubiquitous yet not everyone has acne, differences in the pathogenicity of particular P. acnes strains and variable host responses to P. acnes have been postulated.

- In a comparison of the microbiome of facial skin in individuals with and without acne, certain ribotypes of P. acnes (types 4 and 5) were more frequently found in acne patients, suggesting that these strains are either more capable of inducing acne or better suited to survive in an acne environment

- However, another study showed that monocytes from the peripheral blood of patients with acne exhibited more robust cytokine release in response to P. acnes stimulation than did monocytes from individuals without acne, but no differences were observed when P. acnes strains isolated from acne lesions were compared to strains from the normal skin of unaffected adults

- The pathogenicity of P. acnes includes the direct release of lipases, chemotactic factors, and enzymes that contribute to comedo rupture, as well as stimulation of inflammatory cells and keratinocytes to produce proinflammatory mediators and reactive oxygen species.

- Interactions between the skin's innate immune system and P. acnes play an important role in acne pathogenesis.

- One mechanism is via Toll-like receptors (TLRs), a class of transmembrane receptors that mediates the recognition of microbial pathogens by immune cells (monocytes, macrophages, and neutrophils) as well as by keratinocytes

- TLR2, which recognizes lipoproteins and peptidoglycans as well as CAMP factor 1 produced by inflammatory strains of P. acnes, is found on the surface of macrophages surrounding acne follicles

- P. acnes has also been shown to increase expression of TLR2 and TLR4 by keratinocytes. Through activation of the TLR2 pathway, P. acnes stimulates the release of proinflammatory mediators such as IL-1α, IL-8, IL-12, tumor necrosis factor-α [TNF-α], and matrix metalloproteinases

- IL-8 leads to neutrophil recruitment, the release of lysosomal enzymes, and subsequent disruption of the follicuar epithelium, while IL-12 promotes Th1 responses

- P. acnes has also been shown to activate the NOD-like receptor protein 3 (NLRP3) of inflammasomes in the cytoplasm of both neutrophils and monocytes, resulting in the release of proinflammatory IL-1β

- In addition, recent studies have shown that P. acnes stimulates Th17 responses in acne lesions

- Lastly, P. acnes can induce monocytes to differentiate into two distinct innate immune cell subsets:
- CD209+ macrophages, which more effectively phagocytose and kill P. acnes and whose development is promoted by tretinoin;
- and CD1b+ dendritic cells that activate T cells and release proinflammatory cytokines31

CLINICAL FEATURES

- Acne is typically found in sites with well-developed sebaceous glands, most often the face and upper trunk.
- Despite evidence that inflammation is present in even the earliest comedones, acne lesions are divided into non-inflammatory and inflammatory groups based upon their clinical appearance.
- Non-inflammatory acne is characterized by open and closed comedones
- Closed comedones (whiteheads) are generally small (~1 mm), skin-colored papules with no apparent follicular opening or associated erythema.
- These lesions may be subtle and better appreciated upon palpation, stretching, or side-lighting of the skin.
- In contrast, open comedones (blackheads) have a conspicuous dilated follicular opening that is filled with an inspissated core of shed keratin
- Melanin deposition and lipid oxidation within the debris may be responsible for the black color.

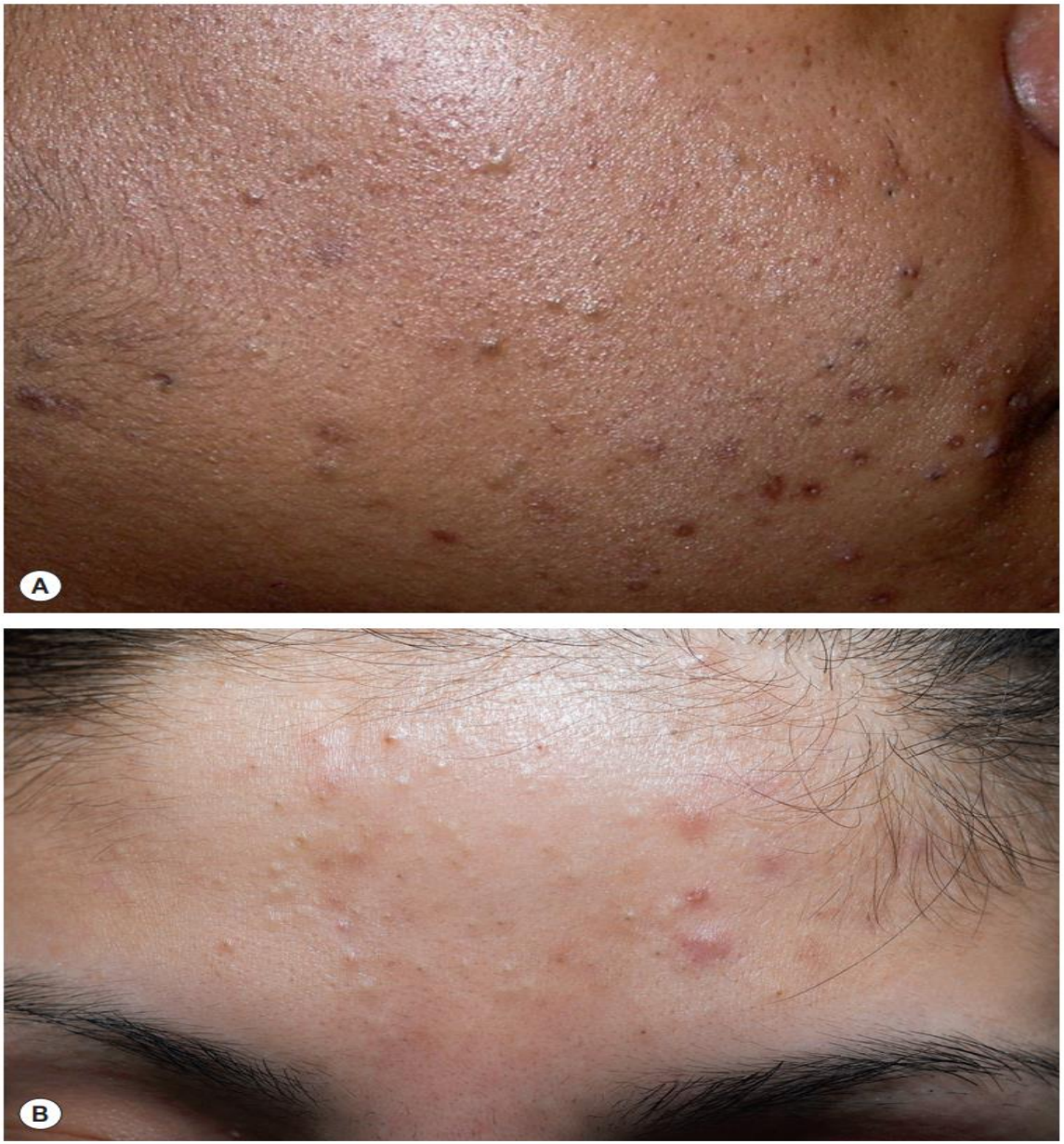

Fig. 36.3 Comedonal acne vulgaris. On the cheek (**A**) and forehead (**B**), there are open and closed comedones as well as postinflammatory hyperpigmentation (**A**) and inflammatory papules (**B**). *B, Courtesy, Kalman Watsky, MD.*

- Inflammatory acne is characterized by papules, pustules, and nodules of varying severity

- Erythematous papules typically range from 1 to 5 mm in diameter.

- Pustules tend to be approximately equal in size and are filled with white purulent material and normal flora, including P. acnes.

- As the severity of lesions progresses, nodules form and become markedly inflamed, indurated and tender.

- The pseudocysts of acne are deeper and filled with a combination of puserosanguineous fluid.
- In patients with severe nodulocystic acne, these lesions frequently coalesce to form large, complex, inflamed plaques that can include sinus tracts.

- Early treatment of acne is essential for the prevention of lasting cosmetic disfigurement due to scarring.

- Erythema and postinflammatory hyperpigmentation often persist after resolution of inflammatory acne lesions.

- Although the pigmentary changes usually fade over many months if the acne is brought under control, occasionally they can be permanent. Unfortunately, pitted scars or hypertrophic scars are often sequelae of nodulocystic acne

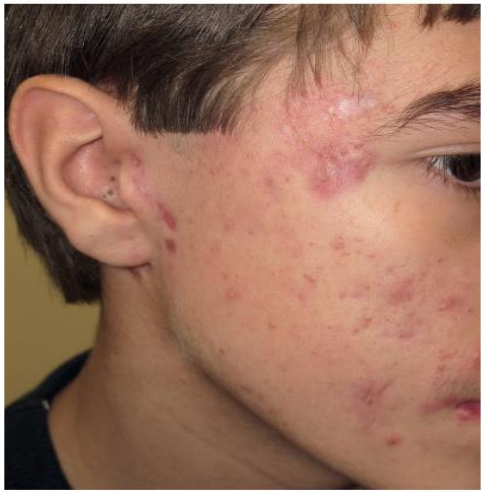

Fig. 36.5 Moderate to severe acne vulgaris. Inflammatory papules and pustules as well as both open and closed comedones are evident on the cheek, forehead and chin. Note the nodular lesion on the temple and open comedones in the concha of the ear. Scarring is present in the preauricular area.

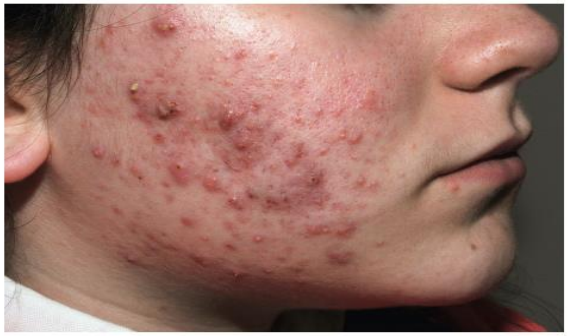

Fig. 36.6 Moderate to severe acne vulgaris. Multiple coalescing papules, pustules, and small nodules are present on the cheek. *Courtesy, Kalman Watsky, MD.*

serosanguineous fluid. In patients with severe nodulocystic acne, these lesions frequently coalesce to form large, complex, inflamed plaques that can include sinus tracts.

Early treatment of acne is essential for the prevention of lasting cosmetic disfigurement due to scarring. Erythema and postinflammatory hyperpigmentation (Fig. 36.8) often persist after resolution of inflammatory acne lesions. Although the pigmentary changes usually fade over many months if the acne is brought under control, occasionally they can be permanent. Unfortunately, pitted scars (Fig. 36.9) or hypertrophic scars (most commonly on the trunk; see eFig. 98.1) are often sequelae of nodulocystic acne.

Acne Variants

Post-adolescent acne in women

Inflammatory acne beyond 25 years of age is most common in women and may be associated with a high level of psychological stress[31a]. The

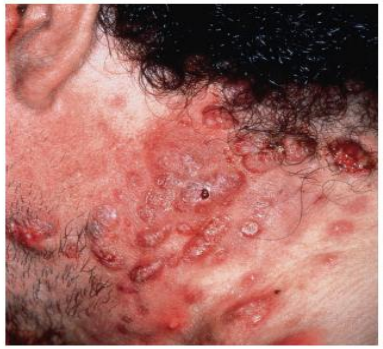

Fig. 36.7 Severe nodular acne. This form is best treated with low doses of isotretinoin initially, to avoid precipitating a flare.

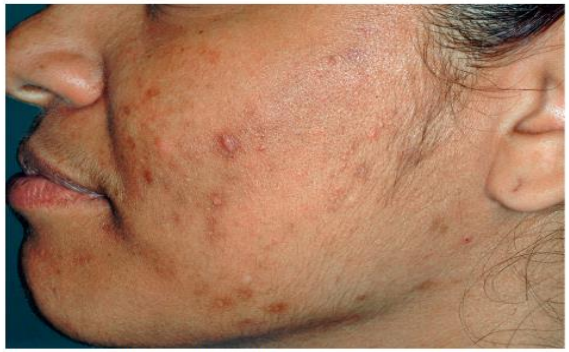

Fig. 36.8 Postinflammatory hyperpigmentation secondary to acne. Such pigmentary changes are most common in patients with darker skin colors.

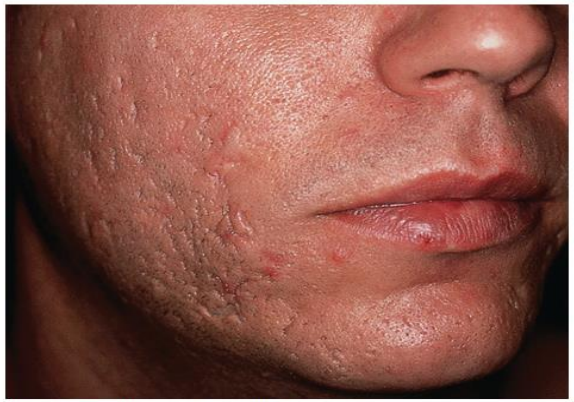

Fig. 36.9 "Ice-pick" scarring secondary to acne.

Acne Variants

- Post-adolescent acne in women Inflammatory acne beyond 25 years of age is most common in women and may be associated with a high level of psychological stress
- The majority of affected women present with findings similar to those of adolescent acne, with a mixture of inflammatory and comedonal lesions involving various facial sites and sometimes the trunk
- Although the mandibular area is involved in ~80% of women with acne, a distinct smaller subset has inflammatory papules, pustules, and nodules exclusively in this location.
- Half of women report persistence of their acne since its onset, often during adolescence, while one-quarter describe periods of remission followed by recurrences.
- Premenstrual flares are common, but only ~20% of women with acne have irregular menses.
- Up to 30% of those in the latter group have other signs of hyperandrogenism, such as hirsutism and androgenetic alopecia .
- A predominantly comedonal, adult-onset form of acne that is associated with smoking has also been described

Acne fulminans

- Acne fulminans is the most severe form of acne and is characterized by the abrupt development of nodular and suppurative acne lesions in association with systemic manifestations.
- This uncommon variant primarily affects boys 13–16 years of age.
- Patients typically have mild to moderate acne prior to the onset of acne fulminans, when numerous microcomedones suddenly erupt and become markedly inflamed.
- There is rapid coalescence into painful, oozing, friable plaques with hemorrhagic crusts
- The face, neck, trunk, and arms are all affected.
- Lesions tend to ulcerate and can lead to significant scarring.
- Osteolytic bone lesions may accompany the cutaneous findings; the clavicle and sternum are most commonly affected, followed by the ankles, humerus and iliosacral joints.

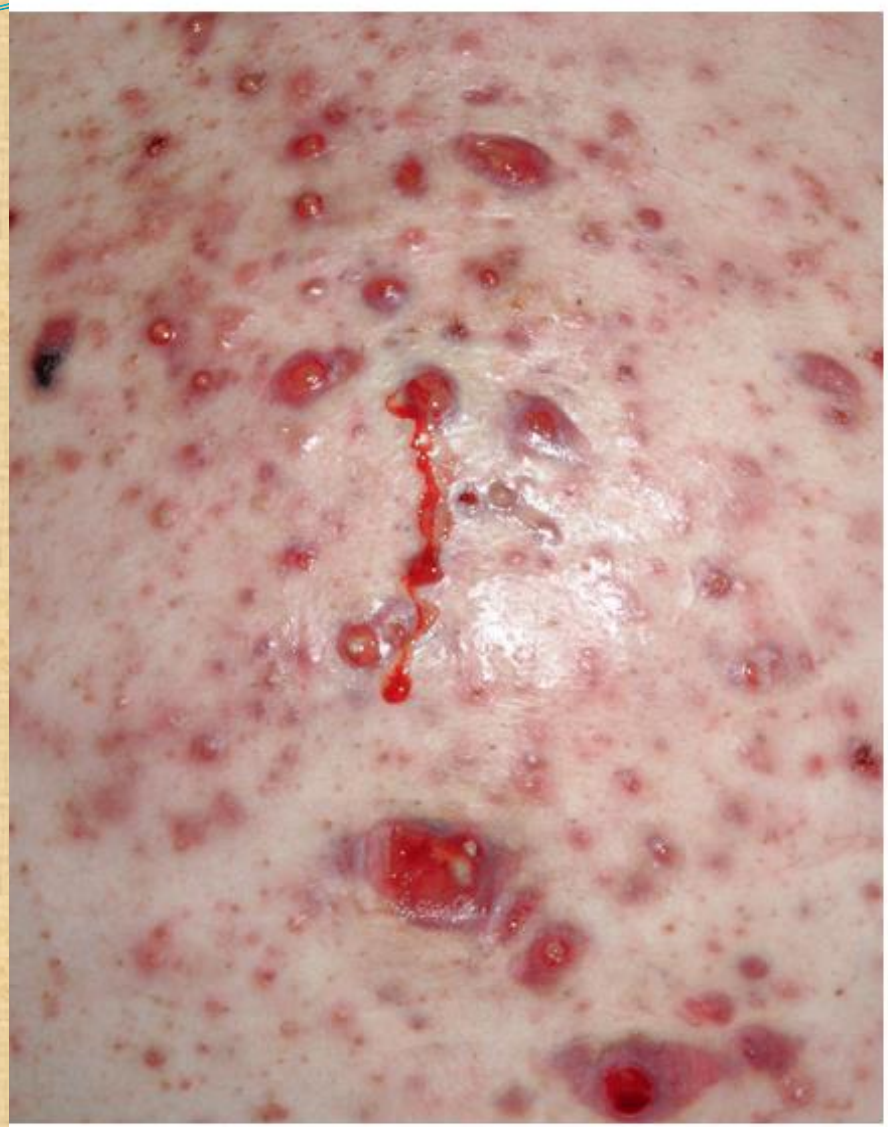

Fig. 36.10 Acne fulminans. Eruptive, friable papulopustules with erosions, oozing and formation of granulation tissue.

- Systemic manifestations include fever, arthralgias, myalgias, hepatosplenomegaly, and severe malaise.
- Erythema nodosum may also arise in association with acne fulminans.
- Laboratory abnormalities vary and include an elevated ESR, proteinuria, leukocytosis, and anemia.
- Laboratory studies are not required to establish the diagnosis, but their evolution may parallel the clinical course and response to therapy.
- The related synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome, which can accompany acne fulminans
- Acne fulminans has also been associated with late-onset congenital adrenal hyperplasia and anabolic steroid use, including therapeutic testosterone

- Recommended treatment of acne fulminans includes prednisone 0.5–1 mg/kg/day as monotherapy for at least 2–4 weeks, followed by initiation of low-dose isotretinoin (e.g. 0.1 mg/kg/day) after the acute inflammation subsides;
- after at least 4 weeks of this combination, the isotretinoin dose can be slowly increased and the prednisone tapered over a period of 1–2 months
- Paradoxically, an acne fulminans-like flare occasionally develops during the first few weeks of isotretinoin therapy for acne;
- this may be avoided by starting with a low dose of isotretinoin and concomitant administration of oral corticosteroids at the first sign of a flare or possibly preemptively in high-risk patients
- Additional treatment options for acne fulminans include topical or intralesional corticosteroids, oral antibiotics (generally of limited efficacy), TNF-α inhibitors, interleukin-1 antagonists, and immunosuppressive agents (e.g. azathioprine, cyclosporine).
- Dapsone may be particularly beneficial in the treatment of acne fulminans associated with erythema nodosum

Acne conglobata and associated conditions

- Acne conglobata is a severe form of nodulocystic acne that may have an eruptive onset but without systemic manifestations.
- This recalcitrant acne variant is part of the follicular occlusion tetrad, along with dissecting cellulitis of the scalp, hidradenitis suppurativa, and pilonidal sinus
- The association of sterile pyogenic arthritis, pyoderma gangrenosum, and acne conglobata can occur in the context of an autosomal dominant autoinflammatory disorder referred to as PAPA syndrome,
- which is caused by mutations in PSTPIP1 which encodes proline–serine–threonine phosphatase interacting protein .
- Of note, a possible association between nodulocystic acne and inflammatory bowel disease may potentially confound links that have been observed between the latter disorder and acne therapies such as tetracyclines and isotretinoin

Solid facial edema

- An unusual and disfiguring complication of acne vulgaris is solid facial edema (Morbihan disease).
- Clinically, there is a distortion of the midline face and cheeks due to soft tissue swelling
- The woody induration may be accompanied by erythema.
- Impaired lymphatic drainage and fibrosis (potentially induced by mast cells) in the setting of chronic inflammation are thought to be involved in the pathogenesis of solid facial edema, and a report of its occurrence in identical twins with acne suggests that genetic factors may also have a role.
- Similar changes have been described in patients with rosacea
- Although fluctuations in severity are common, solid facial edema does not usually resolve spontaneously.
- Treatment with isotretinoin (0.2–1 mg/kg/day) for 4–6 months has been reported to lead to improvement, although a more extended course of 9–24 months is often required
- Combination of isotretinoin with ketotifen 1–2 mg/ day or prednisone 10–30 mg/day may have additional benefit

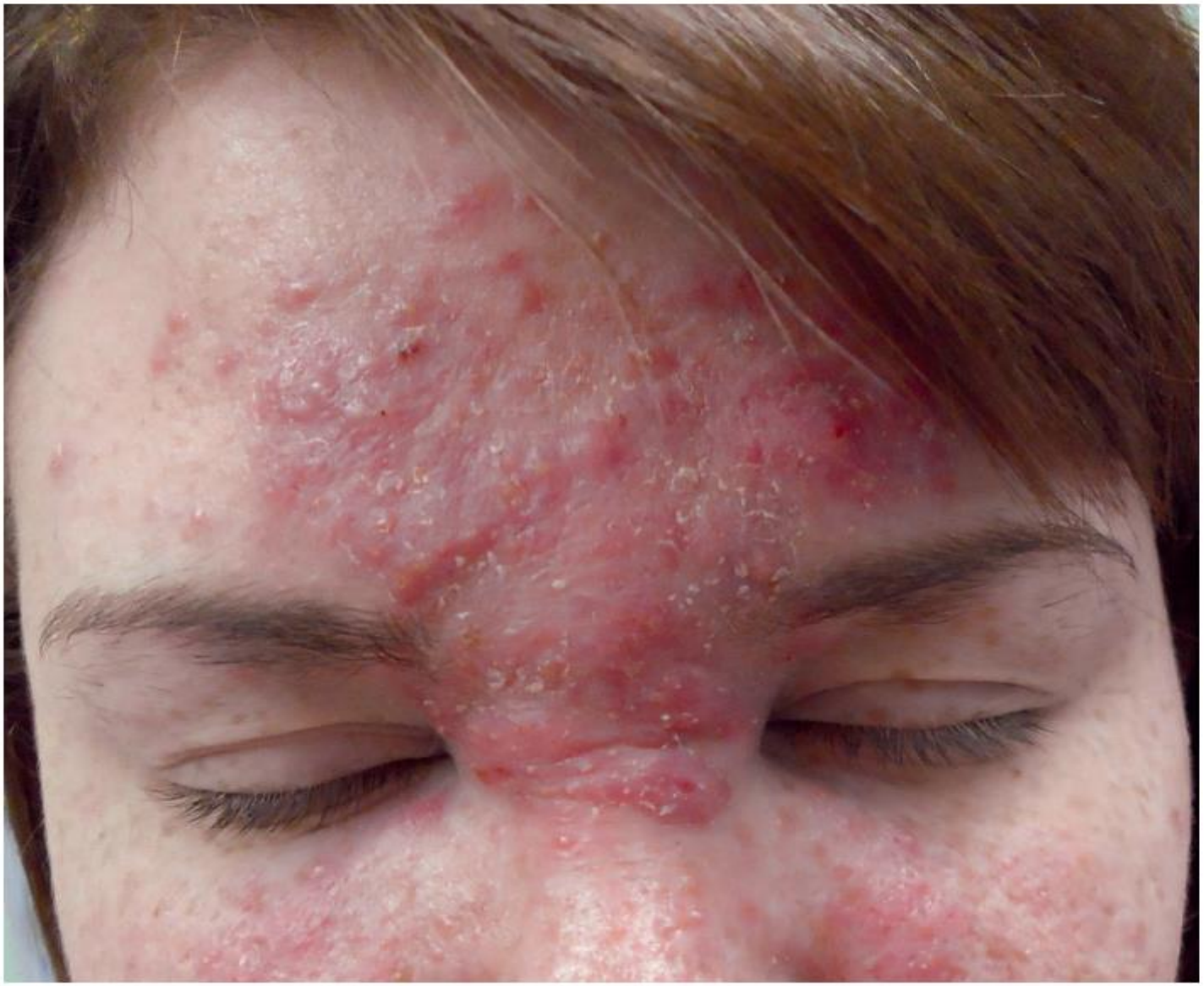

Fig. 36.11 Solid facial edema due to acne vulgaris. There is soft tissue swelling in the central portion of the face. *Courtesy, Boni Elewski, MD.*

Neonatal acne (neonatal cephalic pustulosis)

- Neonatal acne occurs in more than 20% of healthy newborns
- Lesions usually appear at about 2 weeks of age and generally resolve within the first 3 months of life.
- Small papulopustules (not comedones) arise primarily on the cheeks, forehead, eyelids and chin, although the neck and upper trunk can also be involved
- The pathogenesis of neonatal acne has been the subject of debate.
- An inflammatory response to Malassezia spp. (e.g. sympodialis, furfur) has been proposed as the etiology by some investigators, leading to a renaming of the disorder as “neonatal cephalic pustulosis”.
- Additional support for this view comes from the clinical response to treatment with topical imidazoles (e.g. ketoconazole 2% cream).
- The active sebaceous glands and high sebum excretion rate in neonates (see Pathogenesis) are also thought to play a role.
- The substantial decline in sebum production after the first few months of life helps to explain the limited period of susceptibility to neonatal acne.
- Given the transient and benign nature of this eruption, parental reassurance alone is usually adequate.
- However, as noted previously, therapy with topical imidazoles can be effective.

Infantile acne

- Typically, infantile acne initially presents at 2–12 months of age.
- In contrast to neonatal acne, comedo formation is prominent and pitted scarring may develop in up to half of patients
- Deep, suppurative nodules are occasionally seen.
- Its pathogenesis reflects the androgen production intrinsic to this stage of development (see above), including elevated levels of LH stimulating testicular production of testosterone in boys during the first 6–12 months of life and elevated levels of DHEA produced by the infantile adrenal gland in both boys and girls.
- These androgen levels normally decrease substantially by 12 months of age and remain at nadir levels until adrenarche.
- Patients with infantile acne should be assessed for signs of hyperandrogenism (see below), precocious puberty, or abnormal growth; if these findings are present, endocrinologic evaluation including a hand/wrist X-ray to determine bone age and laboratory testing of hormone levels should be performed.
- Infantile acne usually resolves within 6–18 months and remains quiescent until around puberty, with an increased risk of severe acne during adolescence having been observed
- Topical retinoids (e.g. tretinoin, adapalene) and benzoyl peroxide are first-line treatments for infantile acne.
- Oral antibiotics (e.g. erythromycin, azithromycin) can be helpful for patients with a more severe inflammatory component, and isotretinoin is occasionally required for recalcitrant or nodulocystic presentations

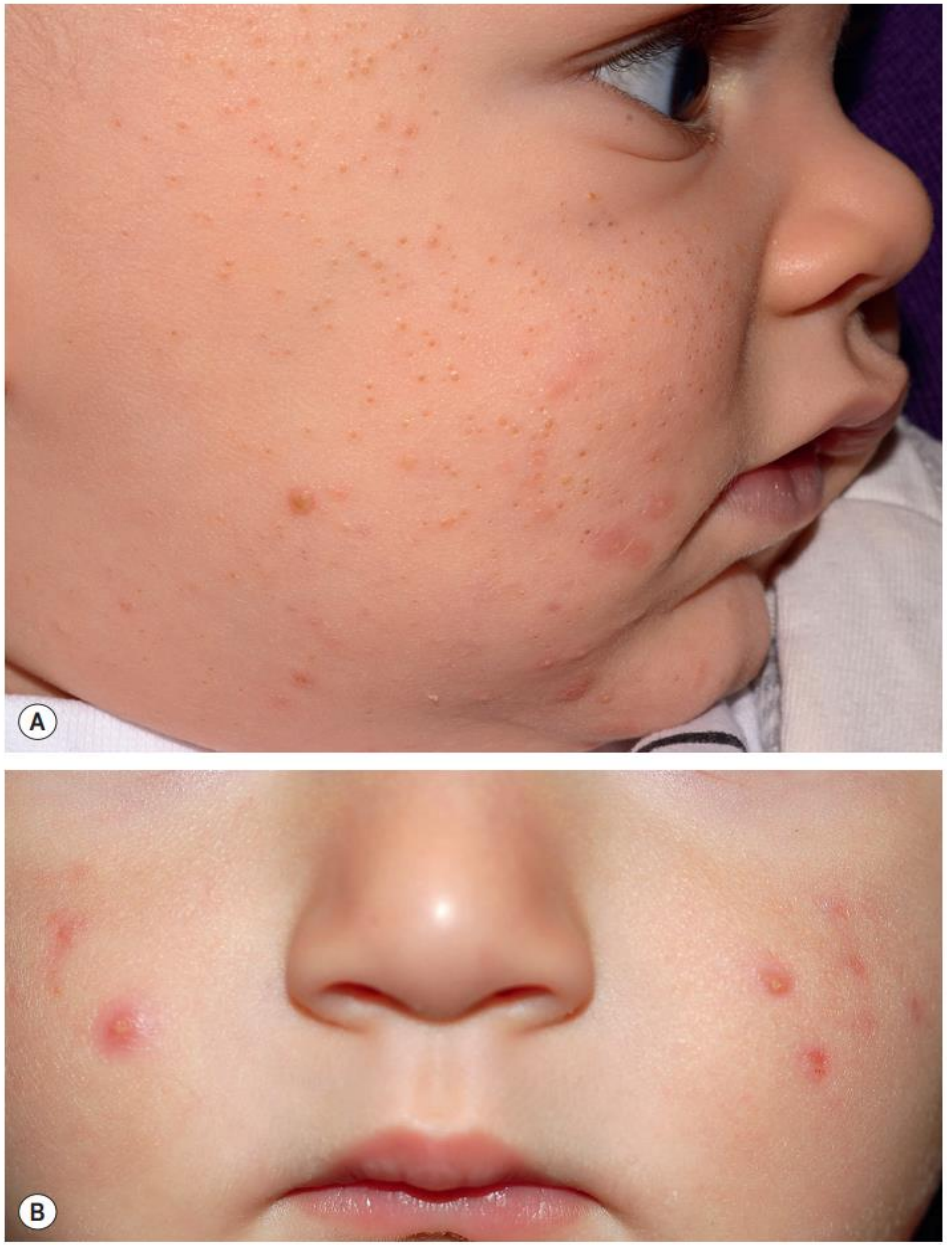

Fig. 36.12 Infantile acne. Presentations can range from numerous open comedones (**A**) to primarily papulopustules (**B**). *A, Courtesy, Julie V Schaffer, MD; B, Courtesy, Kalman Watsky, MD.*

Mid-childhood acne

- Acne presenting between 1 and 6 or 7 years of age is categorized as “mid-childhood acne”
- Because this is an uncommon time for acne development due to quiescent androgen production, the possibility of an underlying hyperandrogenic condition such as premature adrenarche, congenital adrenal hyperplasia, or an androgen-secreting tumor should be considered.
- In addition to a thorough history and physical examination to assess for signs of hyperandrogenism and precocious puberty, the child’s growth curve should be carefully reviewed and a hand/wrist bone age X-ray performed if there are signs of accelerated growth.
- A complete endocrine evaluation is required if any abnormalities are present
- Treatment strategies are the same as for infantile acne.

Preadolescent acne

- It is common for acne to begin to develop in children 7 or 8 to 11 years of age, often prior to other signs of pubertal maturation
- Preadolescent acne tends to be primarily comedonal and favors the forehead and central face (“T-zone”).
- Polycystic ovary syndrome (PCOS) and other endocrinologic abnormalities should be considered
- when the acne is unusually severe or accompanied by signs of hyperandrogenism.
- Treatment is similar to that for adolescent acne, although tetracyclines should be avoided in children

Acne excoriée

- Acne excoriée occurs more often in young women, in whom it may be referred to as acne excoriée des jeunes filles.
- Typical comedones and inflammatory papules are systematically excoriated in a ritualistic manner, leaving crusted erosions that may scar
- Linear erosions suggest self-manipulation, and an underlying psychiatric component should be considered.
- Individuals with an anxiety, obsessive compulsive, or body dysmorphic disorder are particularly at risk, and antidepressants or psychotherapy may be helpful in these patients.

Acne associated with endocrinologic abnormalities

- Although most patients with acne do not have overt endocrinologic abnormalities, hyperandrogenism should be suspected in women and late adolescent girls with irregular menstrual periods.
- Acne in such patients is often severe or more difficult to treat, and the onset can be fairly abrupt.
- Other signs and symptoms of hyperandrogenism in women and children include hirsutism , coarsening of the voice, a muscular habitus, androgenetic alopecia, clitoromegaly with variable posterior labial fusion, and increased libido.
- Insulin resistance and acanthosis nigricans can occur in association with hyperandrogenism in the HAIR-AN syndrome.
- These patients are at increased risk for accelerated cardiovascular disease and diabetes mellitus, and they should be followed by appropriate medical specialists.
- The evaluation of patients suspected of having hyperandrogenism includes a thorough history and physical examination; the age of the patient and pubertal status are also important parameters.
- Prepubertal children, adolescent girls, and women with signs of hyperandrogenism should undergo appropriate evaluation, and laboratory studies should not be performed while the patient is taking oral contraceptives

- Initial tests typically include serum levels of total and free testosterone, DHEAS, and 17-hydroxyprogesterone.

- Patients with clinical findings suggestive of hypercortisolism should also be initially assessed with either a late-night salivary cortisol level, 24-hour urine cortisol level, or low-dose dexamethasone suppression test.

- X-rays of the hand and wrist to evaluate bone age should be obtained in prepubertal children

- Understanding pathways of hormone production is essential in the valuation of hyperandrogenic states

- For example, an elevated serum DHEAS or 17-hydroxyprogesterone level indicates an adrenal source of excess androgen production. The degree to which levels of these hormones are increased is then useful in discerning an etiology.

- DHEAS values in the range of 4000–8000 ng/ml or 17-hydroxyprogesterone levels >3 ng/ml may be indicative of congenital adrenal hyperplasia.

- Defects in adrenal enzymes, most commonly 21-hydroxylase or (less often) 11-hydroxylase, lead to this condition.
- Patients with severe deficiencies of these enzymes become symptomatic during infancy, whereas those with partial deficiencies present in adolescence.
- If the serum DHEAS is >8000 ng/ml, with or without an elevated testosterone level, an adrenal tumor should be suspected.
- If the testosterone levels (total and free) are elevated and the DHEAS level is relatively normal, an ovarian source is likely.
- Polycystic ovary syndrome (PCOS) is the most common condition associated with an elevated serum testosterone, with levels typically ranging from 100 to 200 ng/dl.
- An increased LH/FSH ratio (>2–3) is also commonly observed. Symptoms of PCOS include irregular menstrual periods, hirsutism, obesity, insulin resistance, and reduced fertility
- When levels of serum testosterone exceed 200 ng/dl, an ovarian tumor should be considered.

- **Acneiform Eruptions Drug-induced acne**

- Acne or acneiform eruptions (e.g. folliculitis) can be seen as a side effect of a number of medications

- An abrupt, monomorphous eruption of inflammatory papules and pustules is often observed in drug-induced acne , in contrast to the heterogeneous morphology of lesions seen in acne vulgaris.

- When a history of prescription medication use is not elicited, a comprehensive review of all over-the-counter medications and supplements, as well as recent medical procedures, may reveal the responsible agent
- Bodybuilders and athletes should be questioned about anabolic steroid use.

- High-dose intravenous or oral corticosteroids commonly induce characteristic acneiform eruptions with a concentration of lesions on the chest and back

- Steroid-induced acne (and rosacea) can also result from the inappropriate use of topical corticosteroids on the face. Inflamed papules and pustules develop on a background of erythema that favors the distribution of corticosteroid application.

- Lesions eventually resolve following discontinuation of the corticosteroid, although “steroid dependency” can lead to prolonged and severe flares post-withdrawal

- Acne Vulgaris Epidermal growth factor receptor (EGFR) inhibitors used for the treatment of solid tumors also have a high incidence of acneiform papulopustular eruptions

CAUSES OF DRUG-INDUCED ACNE	
Common	**Uncommon**
Anabolic steroids (e.g. danazol, testosterone)	Azathioprine
Bromides*	Cyclosporine
Corticosteroids (see Fig. 36.13)	Disulfiram
Corticotropin	Ethosuximide
EGFR inhibitors (see Fig. 36.15 and Ch. 21)	Phenobarbital
Iodides†	Propylthiouracil
Isoniazid (see Fig. 36.14)	Psoralen + ultraviolet A
Lithium	Quinidine
MEK inhibitors (e.g. trametinib)	Quetiapine
Phenytoin	TNF inhibitors
Progestins (see text)	Vitamins B_6 and B_{12}

*Found in sedatives, analgesics and cold remedies.
†Found in contrast dyes, cold/asthma remedies, kelp, and combined vitamin–mineral supplements.

Table 36.1 Causes of drug-induced acne. EGFR, epidermal growth factor receptor.

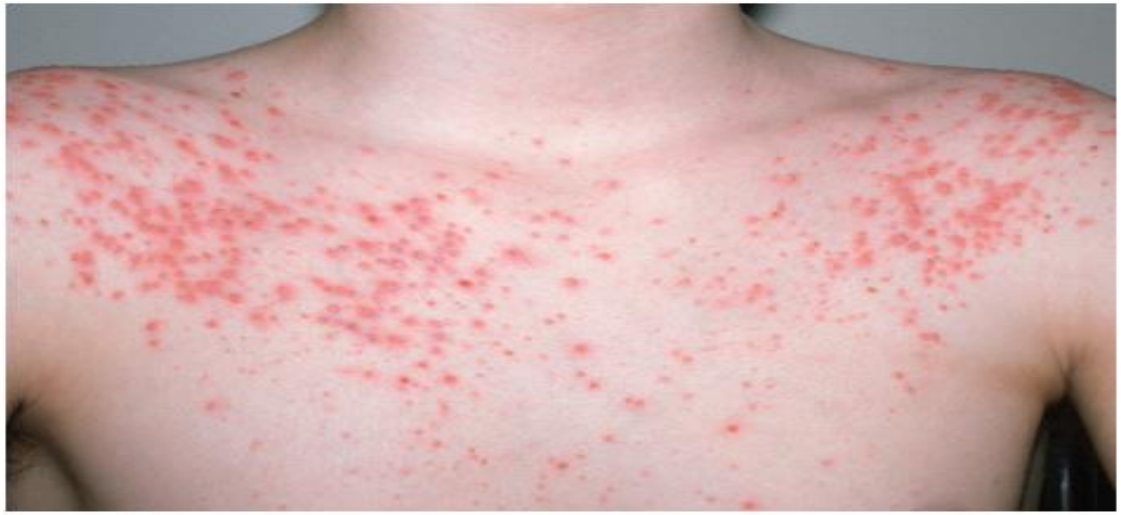

Fig. 36.13 Acneiform eruption secondary to high-dose dexamethasone. Abrupt eruption of monomorphous follicular papules and pustules on the chest.

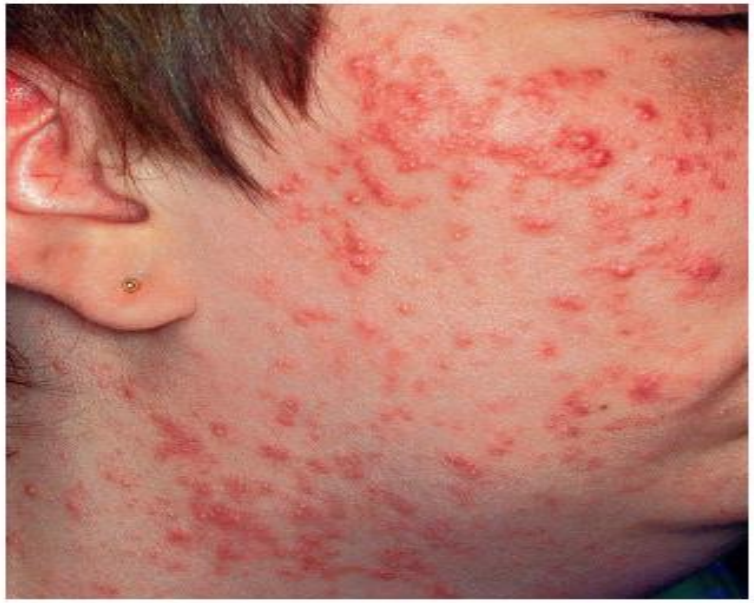

Fig. 36.14 Drug-induced acne due to isoniazid. *Courtesy, Kalman Watsky, MD.*

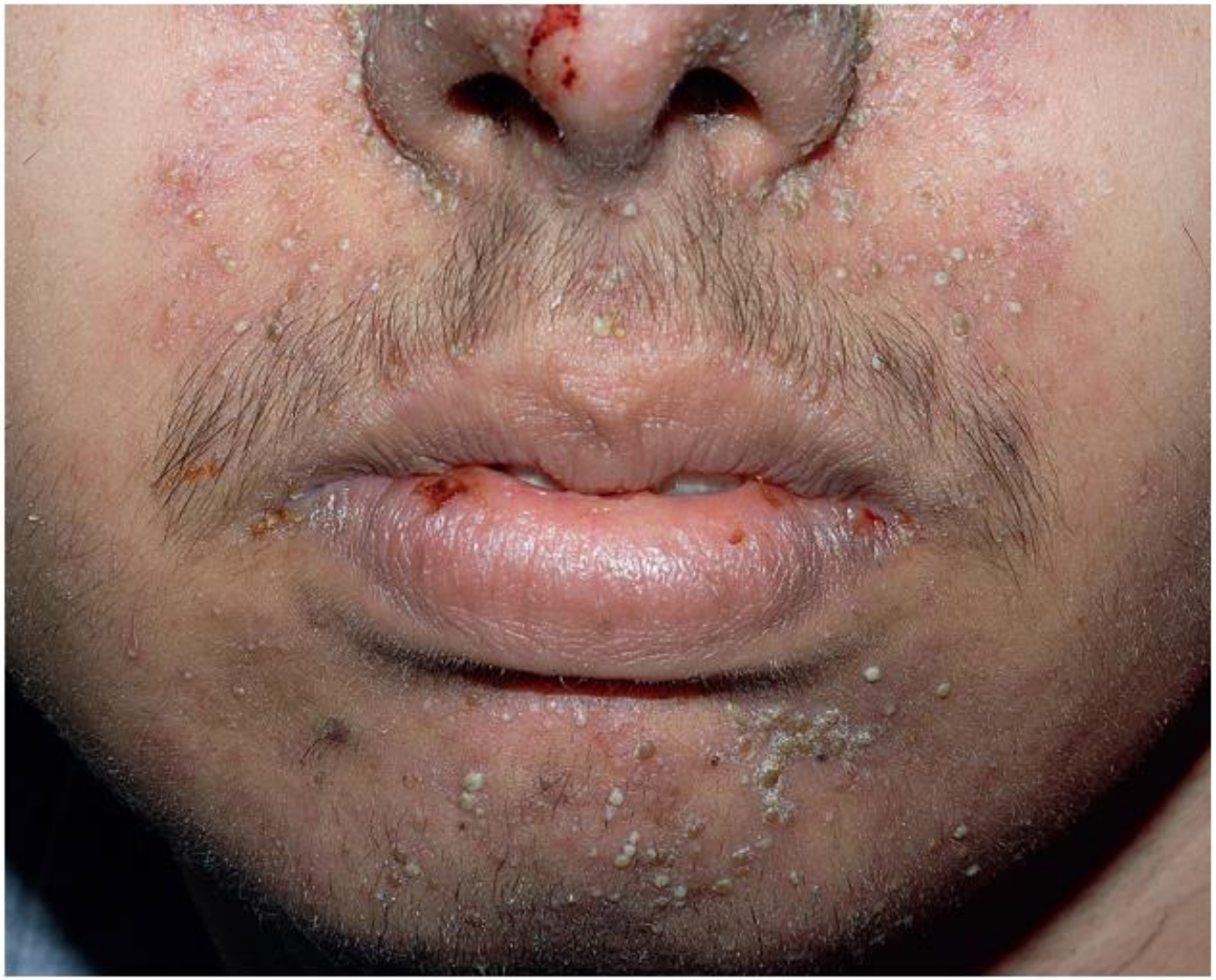

Fig. 36.15 Acneiform eruptions due to epidermal growth factor receptor inhibitors. Numerous monomorphous follicular pustules on the face of an adolescent boy treated with erlotinib.

Occupational acne, acne cosmetica, and pomade acne

- Exposure to insoluble, follicle-occluding substances in the workplace is responsible for occupational acne
- Offending agents include cutting oils, petroleum-based products, chlorinated aromatic hydrocarbons, and coal tar derivatives.
- Comedones dominate the clinical picture, with varying numbers of papules, pustules and cystic lesions distributed in exposed as well as typically covered areas.
- Primarily comedonal facial acne, with a predominance of closed comedones, can also develop in sites chronically exposed to follicle-occluding cosmetics (acne cosmetica) or hair products.
- The latter, referred to as pomade acne, favors the forehead and temples.

- **Chloracne**

- Chloracne is due to exposure to halogenated aromatic hydrocarbons.

- It typically develops several weeks after systemic exposure, which can occur via percutaneous absorption, inhalation, or ingestion.

- The following agents, found in electrical conductors and insulators, insecticides, fungicides, herbicides and wood preservatives, have all been implicated:

- polychlorinated naphthalenes, biphenyls, dibenzofurans and dibenzodioxins; polybrominated naphthalenes and biphenyls; tetrachloroazobenzene; and tetrachloroazoxybenzene.

- Comedo-like lesions and yellowish cysts with relatively little associated inflammation most commonly affect the malar and retroauricular areas of the head and neck , as well as the axillae and scrotum.

- The extremities, buttocks, and trunk are variably involved.

- Cystic lesions can heal with significant scarring, and the condition may persist for several years following cessation of exposure. Additional findings may include hypertrichosis and grayish discoloration of the skin.

- Initial management is aimed at removal of the source of exposure. Topical or oral retinoids may be beneficial, but chloracne is often recalcitrant to therapy

Acne mechanica

- Acne mechanica is due to repeated mechanical and frictional obstruction of the pilosebaceous outlet.
- Comedo formation is the result.
-
- Welldescribed mechanical factors include rubbing by helmets, chin straps, suspenders, and collars.
- Orthopedic causes include acne mechanica in the axillae due to the use of crutches and on amputee stumps due to friction from prostheses.
- A classic example of acne mechanica is fiddler's neck, where repetitive trauma from violin placement on the lateral neck results in a well-defined, lichenified, hyperpigmented Plaque interspersed with comedones.
- Linear and geometrically distributed areas of involvement suggest acne mechanica.
- Treatment is aimed at eliminating the inciting for

- **Tropical acne**

- Tropical acne is a follicular acneiform eruption that results from exposure to extreme heat.

- This can occur in tropical climates or secondary to scorching occupational environments, as in furnace workers.

- Historically, tropical acne caused significant morbidity among military troops.

- Markedly inflamed nodulocystic acne involving the trunk and buttocks is typically seen, and secondary staphylococcal infection is a frequent complication.

- Treatment is often of limited efficacy until the patient returns to a more moderate climate.

- Radiation acne Radiation acne is characterized by comedo-like papules occurring at sites of previous exposure to therapeutic ionizing radiation.

- The lesions begin to appear as the acute phase of radiation dermatitis starts to resolve.

- The ionizing rays induce epithelial metaplasia within the follicle, creating adherent hyperkeratotic plugs that are resistant to expression.

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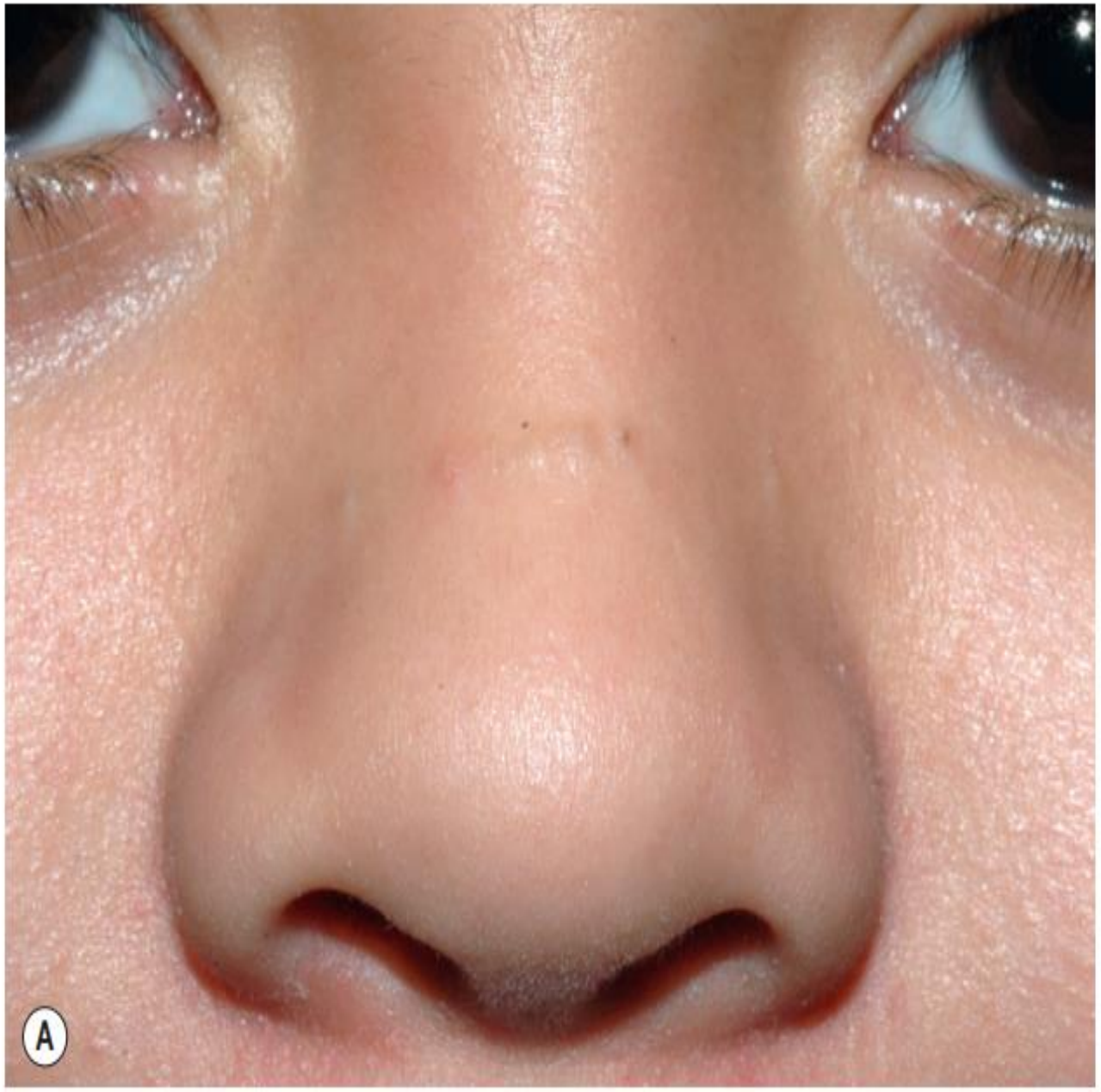
“Pseudoacne” of the nasal crease

- The transverse nasal crease is a horizontal anatomical demarcation line found in the lower third of the nose, which corresponds to the separation point between the alar cartilage and the triangular cartilage.
- Milia, cysts, and comedones can line up along this fold
- These acne-like lesions are not hormonally responsive and arise during early childhood prior to the onset of puberty.
- Treatment consists of mechanical expression or topical therapy with a retinoid or benzoyl peroxide as needed.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Idiopathic facial aseptic granuloma

- This painless nodule with an acneiform appearance typically develops on the cheeks of young children (mean age, ~3.5 years)

- Multiple lesions are uncommon.
- Histopathologic evaluation reveals a dermal lymphohistiocytic infiltrate with foreign body-type giant cells.

- In general, cultures are negative and the lesions do not respond to antibiotic therapy.

- Eventually, after an average of one year, the lesions resolve spontaneously

- It has been suggested that idiopathic facial aseptic granuloma represents a form of childhood rosacea as >40% of patients have at least two other clinical signs of rosacea including recurrent chalazions, facial flushing, telangiectasias, or papulopustules.

Childhood flexural comedones

- This entity is characterized by discrete, double-orifice comedones localized to the axillae and, less commonly, the groin
- The majority of patients have a single lesion and the average age at diagnosis is 6 years, with boys and girls equally affected.
- Occasionally it is familial.
- There is no association with hidradenitis suppurativa, acne vulgaris, or precocious puberty

DIFFERENTIAL DIAGNOSIS

- Although classic acne vulgaris is usually easily recognized clinically, the differential diagnosis of acneiform eruptions is broad and depends upon the age of onset, lesional morphology, and location

- During the neonatal period, acne must be differentiated from other common dermatoses.

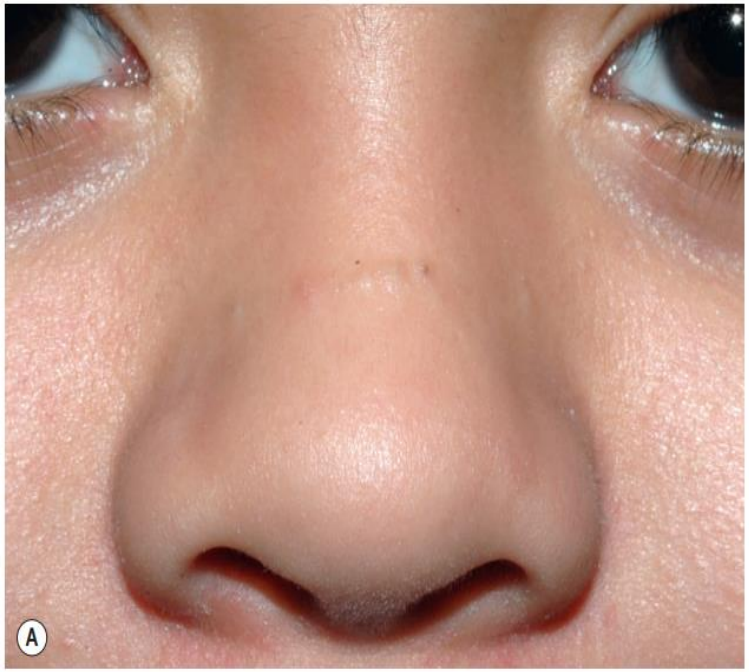
- Sebaceous hyperplasia occurs in the majority of healthy neonates, presenting as transient yellowish papules on the cheeks, nose and forehead.

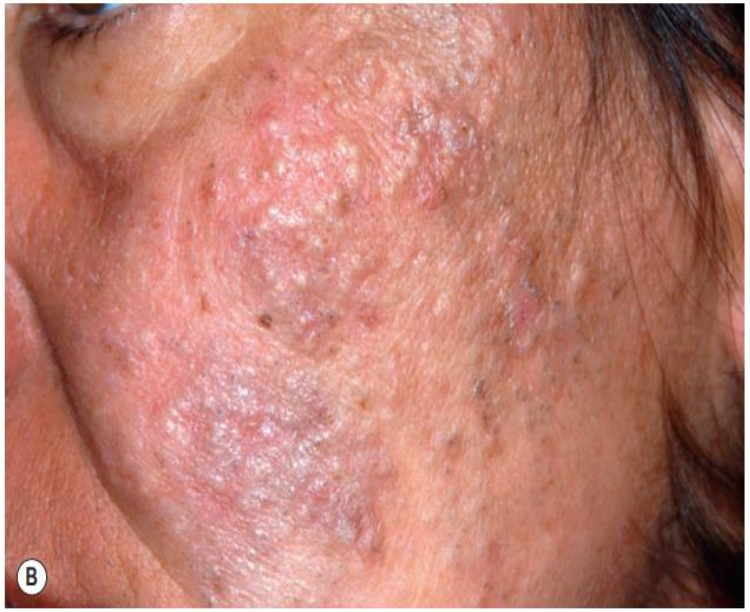
- Miliaria rubra is also very common during the neonatal period, when overheating and bundling can cause temporary eccrine duct obstruction that leads to the formation of small inflammatory papulopustules.

- Small, white milia are often apparent on the cheeks and nose of neonates, but they generally resolve within a few months.

- Predominantly comedonal acne vulgaris needs to be differentiated from comedonal eruptions caused by follicular occlusion or friction, including acne mechanica, acne cosmetica, pomade acne, and occupational acne ;

- history as well as location can help to make the diagnosis of these forms of “contact acne”.
- Sebaceous hyperplasia, a very common finding in adults, is relatively uncommon in adolescents.





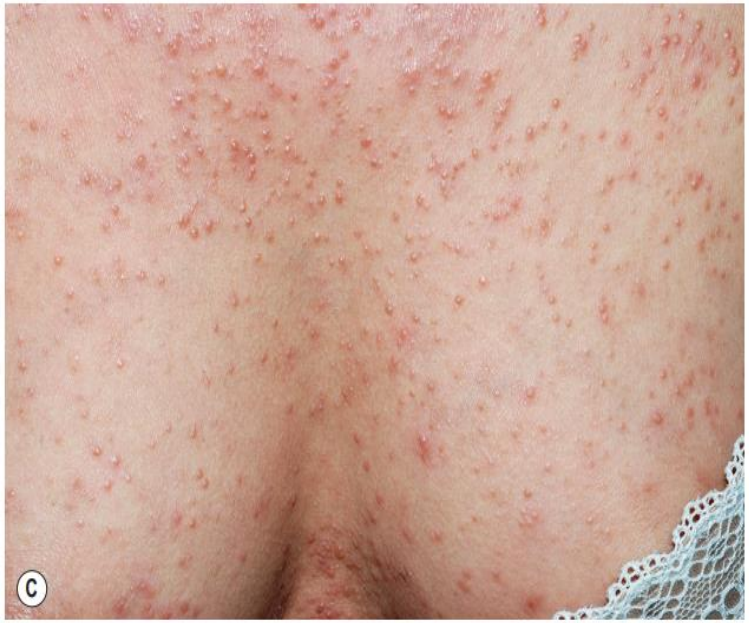


Fig. 36.16 Disorders in the differential diagnosis of acne vulgaris. A Pseudoacne of the transverse nasal crease in a young child. Note the milia and comedones located along this anatomical demarcation line. **B** Acneiform follicular mucinosis on the cheek of a woman. **C** Follicular mycosis fungoides that presented as numerous lesions with a comedonal appearance on the chest, abdomen, and back. *A, C, Courtesy, Julie V Schaffer, MD; B, Courtesy, Lorenzo Cerroni, MD.*

- A solitary enlarged comedo is better classified as a dilated pore of Winer; such lesions rarely represent a large-pore basal cell carcinoma.
- Multiple open comedones are clustered in the lateral malar region in Favre–Racouchot syndrome or appear in a linear array in nevus comedonicus
- If multiple vellus hairs arise from a dilated follicular orifice in association with keratinous debris, trichostasis spinulosa is the likely diagnosis.
- The most common location is the nose.
- Angiofibromas and appendageal tumors of follicular origin, e.g. trichoepitheliomas, trichodiscomas and fibrofolliculomas, often present as multiple facial papules
- They are typically noninflammatory, and trichoepitheliomas are concentrated in the nasolabial folds.
- Non-inflammatory, closed cystic papules and nodules on the central chest and back characterize steatocystoma multiplex

- This autosomal dominant disorder must be differentiated from a related clinical condition, eruptive vellus hair cysts.
- These smaller cysts may become inflamed and, as the name implies, contain multiple vellus hairs that can be easily visualized histologically.
- The follicle-based inflammatory papules and pustules of acne vulgaris must be distinguished from the many forms of folliculitis, including staphylococcal, Gram-negative, and eosinophilic variants
- In folliculitis, the lesions are relatively monomorphous and comedones are not present.
- Gram-negative folliculitis can complicate acne vulgaris treated with oral antibiotics for a prolonged period; the inflammatory lesions typically appear on the central face, including the upper lip, and cheeks.
- In contrast, Pseudomonas (“hot tub”) folliculitis favors the lower trunk and other sites covered by a bathing suit.
- Eosinophilic folliculitis usually occurs in the setting of HIV infection and is markedly pruritic

- Pseudofolliculitis barbae and acne keloidalis nuchae most often affect men of African descent

- The papular component of rosacea favors the malar region, chin, and forehead; the presence of telangiectasias, an absence of comedones, and a history of easy flushing can aid in diagnosis

- Rosacea typically occurs at a later age than acne, but both can develop in a single individual.

- Prolonged use of topical corticosteroids on the face may lead to rosacea-like lesions or perioral/periorificial dermatitis, and patients treated with oral corticosteroids can develop an eruption of monomorphous papulopustules that favors the trunk (“steroid folliculitis”;

- This can occur at any age and resolves upon discontinuation of the corticosteroid.

- Lastly, psychogenic (neurotic) excoriations and factitial dermatitis concentrated on the face, chest, and back can mimic acne, particularly acne excoriée.

- Linearity and the lack of clinically detectable primary lesions are clues

TREATMENT

- A thorough history and physical examination are key to developing an appropriate and maximally effective treatment plan
- The physician should review with the patient all prescription and over-the-counter medications used for acne or other conditions, and note the clinical responsiveness to them.
- A review of cosmetics, sunscreens, cleansers, and moisturizers is also helpful.
- In female patients, a menstrual and oral contraceptive history is important in determining hormonal influences on acne.
- Some patients may report an improvement following sun exposure while others experience an exacerbation.
- On physical examination, lesional morphology should be assessed, including the presence of comedones, inflammatory lesions, nodules, and cysts.

HISTORY AND PHYSICAL EXAMINATION OF THE ACNE PATIENT	
History	**Physical examination**
Sex Age Motivation Lifestyle/hobbies Occupation Current and previous treatments Use of cosmetics, sunscreens, cleansers, moisturizers Menstrual history Medications • Corticosteroids • Oral contraceptives • Anabolic steroids • Other (e.g. lithium, EGFR inhibitors; see Table 36.1) Concomitant illnesses Family history (including severity of acne, polycystic ovary syndrome, inflammatory disease)	Skin type (e.g. oily versus dry) Skin color/phototype Distribution of acne • Face (e.g. "T-zone", cheeks, jawline) • Neck, chest, back, upper arms Overall degree of involvement (mild, moderate or severe) Lesion morphology • Comedones • Papules, pustules • Nodules, cysts • Sinus tracts Scarring • Pitted • Hypertrophic • Atrophic Postinflammatory pigmentary changes

Table 36.3 History and physical examination of the acne patient. EGFR, epidermal growth factor receptor.

TREATMENT OF ACNE VULGARIS					
	Mild		Moderate		Severe
	Comedonal	Papular/pustular	Papular/pustular	Nodular	Conglobata/fulminans
First line	Topical retinoid	BPO ± topical antibiotic Topical retinoid + topical antimicrobial(s)*	Oral antibiotic† + topical retinoid ± BPO Topical retinoid + BPO ± topical antibiotic	Oral antibiotic† + topical retinoid ± BPO	Oral isotretinoin (may require concurrent oral corticosteroid, esp. for acne fulminans)
Second line	Alternative topical retinoid Azelaic acid Salicylic acid	Alternative topical retinoid and/or topical antimicrobial Azelaic acid Salicylic acid Topical dapsone	Alternative oral antibiotic‡ + alt. topical retinoid ± BPO/ azelaic acid	Oral isotretinoin Alternative oral antibiotic‡ + alt. topical retinoid ± BPO/azelaic acid	Oral antibiotic (± high dose)+ topical retinoid + BPO Oral dapsone
Options for female patients			Oral contraceptive/ antiandrogen	Oral contraceptive/ antiandrogen	Oral contraceptive/ antiandrogen
Procedural options	Comedo extraction		Comedo extraction	Comedo extraction Intralesional corticosteroid	Intralesional corticosteroid
Refractory to treatment		Exclude Gram-negative folliculitis	Exclude Gram-negative folliculitis		
			Female patient: exclude adrenal or ovarian dysfunction Exclude use of anabolic steroid or other acne-exacerbating medications		
Maintenance			Topical retinoid ± BPO	Topical retinoid ± BPO	Topical retinoid ± BPO

*Antibiotic (e.g. clindamycin (preferred), erythromycin, or sodium sulfacetamide [level 1 evidence for all 3]) and/or BPO (level 1 evidence).
†Tetracycline derivatives: tetracycline, doxycycline, minocycline (level 1 evidence for all 3).
‡e.g. azithromycin (level 1 evidence) or trimethoprim–sulfamethoxazole.

Table 36.4 Treatment of acne vulgaris. Lack of response should also lead the clinician to consider non-adherence with treatment or another diagnosis. In general, monotherapy with a topical or oral antibiotic should be avoided these agents are best used in combination with BPO, which can prevent the development of

TIPS FOR TOPICAL ACNE THERAPY	
Improve adherence – often compromised due to patients having busy schedules or quitting when the response is not rapid	• Simplify the regimen: once daily when possible; consider combination products (e.g. benzoyl peroxide + adapalene or clindamycin; tretinoin + clindamycin), especially in less motivated adolescents • Inform patients that it will take 6–8 weeks of treatment for substantial improvement • Ask specifically about adherence: "Out of 7 nights, how many times do you apply the medication?"
Educate on proper use	• In general, topical medications (especially retinoids) should be used to the entire acne-prone region rather than as "spot treatment" of individual lesions • Provide instructions on where to apply the medication and how much to use
Minimize irritation – most common in adolescents with atopic dermatitis and adults	• Note that using too much medication or applying it too frequently can increase irritation • Devise a gradual initial approach to improve tolerance in patients with sensitive skin; for example, a single agent may be used for the first 2–3 weeks (starting every other day for retinoids), followed by slow introduction of a second medication (e.g. transitioning from alternate days to daily) • Advise to avoid harsh scrubs and other irritating agents (e.g. toners, acne products that are not part of the regimen) • Suggest use of a non-comedogenic sensitive skin moisturizer if dryness occurs
Avoid exacerbation	• Review all skin care products and cosmetics; having patients bring everything that they apply to their face to a visit may help to determine the source of problems • Advise non-comedogenic products (e.g. moisturizers, sunscreens, make-up) and to avoid having oily hair or using pomades that may contribute to acne. • Instruct patients not to pick or manipulate lesions
Reinforce the plan – patients often forget what is recommended and are bombarded by advertising and false information about acne	• Provide a written handout with your specific instructions • Recommend additional reliable educational resources about acne and its treatment, e.g.: www.aad.org/dermatology-a-to-z/diseases-and-treatments/a---d/acne www.webmd.com/skin-problems-and-treatments/acne/default.htm

Table 36.5 Tips for topical acne therapy.

- Secondary changes such as scarring and postinflammatory pigmentary changes are also important clinical findings.
- The patient's skin color and type can influence the chosen formulation of a topical medication
- For example, patients with oily skin tend to prefer the more drying gels and lotions, whereas those with drier skin types may prefer creams.
- provides an overview of the approach to acne therapy.
- Lack of adherence to the recommended acne treatment plan is a frequent reason for therapeutic failure.

Topical Treatments

Topical retinoids

- The anti-acne activity of topical retinoids involves normalization of follicular keratinization and corneocyte cohesion, which aids in the expulsion of existing comedones and prevents the formation of new ones.
- Topical retinoids also have significant anti-inflammatory properties and therefore may be used as monotherapy for acne with both comedonal and mild inflammatory components.
- In addition, concurrent use of a topical retinoid can enhance the efficacy of benzoyl peroxide and topical antibiotics by increasing the penetration of the latter medications into the sebaceous follicle.
- Topical retinoids used for acne include tretinoin, adapalene, tazarotene, and isotretinoin ; topical products that combine tretinoin with clindamycin or adapalene with benzoyl peroxide are also available

- The most common side effect of topical retinoids is local irritation resulting in erythema, dryness, peeling, and scaling.
- This tends to peak after 2–4 weeks of treatment and improve with continued usage; transient application of a low-potency topical corticosteroid may be of benefit for patients with significant irritation
- Delivery systems have been developed to permit a greater concentration of retinoid while decreasing irritancy, primarily through controlled slow release, e.g. tretinoin impregnated into inert microspheres or incorporated within a polyolprepolymer.
- An acne flare may occur during the initial month of treatment with a topical retinoid, but resolves spontaneously with continued usage.
- Although not true photosensitizers, if a retinoid causes skin peeling or irritation, this may increase the user's susceptibility to sunburn.
- Appropriate use of sunscreens should therefore be advised.

- Tretinoin (all-trans-retinoic acid), a naturally occurring metabolite of retinol, was the first topical comedolytic agent used for the treatment of acne.
- To decrease the potential for irritation, treatment is often started with a lower-concentration cream formulation of tretinoin and the strength later increased.
- Alternate-night to every-third-night application may be necessary initially, with increased frequency as tolerated.
- Because the standard generic tretinoin formulation is photolabile, night-time application is recommended to prevent early degradation; it is also inactivated by concomitant application of benzoyl peroxide, so the two medications should not be used at the same time.
- However, specialized microsphere formulations of tretinoin are not photolabile and can be applied together with benzoyl peroxide without degradation.
- Although epidemiologic studies have not shown an increased risk of birth defects in infants of mothers using topical tretinoin during the first trimester, sporadic case reports of birth defects have been published,
- Because of this and the fact that systemic retinoids are known teratogens, the use of topical tretinoin in pregnancy is discouraged.
- That said, dietary intake of vitamin A has been shown to have a greater influence on serum retinoid levels than facial application of tretinoin.

- The synthetic retinoid adapalene is an aromatic naphthoic acid derivative
- In the skin, it primarily binds the retinoic acid receptor γ (RARγ), whereas tretinoin binds to both RARα and RARγ.
- Although animal studies have shown adapalene to have milder comedolytic properties than tretinoin, it is also less irritating
- Unlike tretinoin, adapalene is light-stable and resistant to oxidation by benzoyl peroxide.
- Tazarotene is a synthetic acetylenic retinoid that, once applied, is converted into its active metabolite, tazarotenic acid.
- Like adapalene, this metabolite selectively binds RARγ but not RARα or RXR
- Both daily overnight application of tazarotene and short contact therapy regimens have been shown to be effective in the treatment of comedonal and inflammatory acne.
- Topical tazarotene has been designated pregnancy category X, so contraceptive counseling should be provided to all women of childbearing age who are prescribed this medication.
- Like adapalene, it is light-stable and can be applied together with benzoyl peroxide

- Benzoyl peroxide and other topical antibacterial agents
- Benzoyl peroxide is a potent bactericidal agent that reduces P. acnes within the follicle.
- It also has mild comedolytic properties and is particularly effective when used in combination with other therapies.
- In contrast to topical antibiotics, microbial resistance to benzoyl peroxide has not been reported.
- Many preparations for all skin types are available in both over-the-counter and prescription formulations.
- These include bar soaps, washes, gels, lotions, creams, foams, and pads in concentrations ranging from 2.5% to 10% as well as products that combine benzoyl peroxide with clindamycin, erythromycin, or adapalene.
- As benzoyl peroxide is a bleaching agent, whitening of clothing and bedding can occur.
- Development of contact dermatitis (irritant > allergic) to benzoyl peroxide is also possible, and this should be suspected in patients who develop marked erythema with its use.

- Topical antibiotics are widely used for the treatment of acne and are available alone as well as in combination with benzoyl peroxide or a retinoid.
- Clindamycin and erythromycin represent the two most commonly utilized antibiotics and the formulations vary from creams and gels to solutions and pledgets however, resistance of >50% of P. acnes strains to these macrolides has been reported in some countries
- Azelaic acid is a naturally occurring dicarboxylic acid found in cereal grains.
- It is available as a topical 20% cream, which has been shown to be effective in inflammatory and comedonal acne, as well as a 15% gel marketed for rosacea.
- By inhibiting the growth of P. acnes, azelaic acid reduces inflammatory acne.
- It also reverses the altered keratinization of follicles affected by acne and thus demonstrates comedolytic properties.
- The activity of azelaic acid against inflammatory lesions may be greater than its activity against comedones..

- Azelaic acid is applied twice daily and its use is reported to have fewer local side effects than topical retinoids.
- In addition, it may help to lighten postinflammatory hyperpigmentation.
- Sodium sulfacetamide is a well-tolerated topical antibiotic that is thought to restrict the growth of P. acnes through competitive inhibition of the condensation of para-aminobenzoic acid with pteridine precursors
- It is formulated in a 10% lotion, suspension, foam and cleanser, either alone or in combination with 5% sulfur.
- Tinted formulations are also available.
- Topical dapsone 5% and 7.5% gels are approved for the treatment of acne vulgaris.
- Of note, a temporary yellow–orange staining of the skin and hair occasionally occurs with concomitant application of topical dapsone and benzoyl peroxide

Oral Treatments

Antibiotics

- Moderate to severe inflammatory acne is often treated with oral tetracycline derivatives, especially doxycycline and minocycline, and less often macrolides such as erythromycin and azithromycin.
- In this setting, a primary mechanism of action of these medications is suppression of the growth of P. acnes, thereby reducing bacteria-mediated inflammation.
- However, several of these antibiotics also possess intrinsic anti-inflammatory properties.
- Recent guidelines suggest that the duration of oral antibiotic courses for acne should be limited to 3 to 6 months
- Resistance of P. acnes to erythromycin and less commonly the three major tetracyclines (tetracycline and doxycycline more so than minocycline) can occur56a.
- Minocycline, a lipophilic derivative of tetracycline, has greater penetration into the sebaceous follicle; although this has been postulated.
- While doxycycline-related phototoxicity can be problematic, minocycline is associated with a higher incidence of serious adverse events, including a minocycline-induced hypersensitivity syndrome and autoimmune reactions
- The latter typically develop after many months to years of therapy and can include hepatitis, a lupus erythematosus-like syndrome, and cutaneous polyarteritis nodosa that is often associated with antineutrophil cytoplasmic antibodies

Hormonal therapy

- Hormonal therapy is an established second-line treatment for female patients with acne and can be very effective, irrespective of whether or not the serum androgen levels are abnormal.
- Although women and adolescent girls with acne may have higher serum levels of androgens than those without acne, the levels in acne patients are often within the normal range.
- Combined oral contraceptive pills, which block both ovarian and adrenal production of androgens, are particularly effective for inflammatory acne.
- A recent meta-analysis found that oral contraceptive pills are equivalent to oral antibiotics in reducing the number of acne lesions after 6 months of therapy
- Combined oral contraceptive formulations contain an estrogen plus a progestin in order to minimize the risk of endometrial cancer, which is known to occur with unopposed estrogen administration.
- Although progestins have intrinsic androgenic activity, second-generation progestins (e.g. ethynodiol diacetate, norethindrone, levonorgestrel) have lower androgenic potential.
- Newer, third-generation progestins (e.g. desogestrel, norgestimate, gestodene [Europe]) have even less androgenic activity than their predecessors, and other progestins (e.g. drospirenone, cyproterone acetate, dienogest) have antiandrogenic properties.

- Three oral contraceptives are currently FDA-approved for the treatment of acne, although others also have evidence of efficacy
- The first is a triphasic oral contraceptive composed of a norgestimate–ethinyl estradiol (35 mcg) combination.
- The second contains a graduated dose of ethinyl estradiol (20–35 mcg) in combination with norethindrone acetate, while the third contains a stable dose of ethinyl estradiol (20 mcg) plus drospirenone (3 mg) with a 24-day dosing regimen.
- Side effects from oral contraceptives include nausea, vomiting, abnormal menses, weight gain, and breast tenderness.
- Agents containing drospirenone can lead to elevations in serum potassium levels, but this is generally not clinically significant in otherwise healthy individuals.
- Rare but more serious complications include hypertension and thromboembolism (e.g. deep venous thrombosis, pulmonary embolism).
- The increase in risk of venous thromboembolism ranges from 2–4-fold with levonorgestrel or norethindrone to 3.5–7-fold with desogestrel, drospirenone and cyproterone acetate, and risk of thrombosis is greatest early on during treatment
- Overall the risk is highest for women over the age of 35 years, smokers, and those with other prothrombotic risk factors such as hereditary thrombophilia

COMMONLY USED COMBINED ORAL CONTRACEPTIVES	
Oral contraceptive®	**Estrogen mcg/Progestin mcg**
FDA-approved for acne vulgaris	
Ortho Tri-Cyclen	Ethinyl estradiol 35/norgestimate 180, 215, 250
Estrostep	Ethinyl estradiol 20, 30, 35/norethindrone 1000
Yaz, Loryna, Nikki, Beyaz*	Ethinyl estradiol 20/drospirenone 3000
Clinical data to support use	
Alesse	Ethinyl estradiol 20/levonorgestrel 100
Diane-35†	Ethinyl estradiol 35/cyproterone acetate 2000
Yasmin, Syeda, Yaela, Safyral*	Ethinyl estradiol 30/drospirenone 3000
Natazia	Estradiol valerate 1000, 2000, 3000/ dienogest 2000, 3000
No/insufficient clinical data	
Various combinations of ethinyl estradiol 10, 20, 25, 30, or 35 **plus** norethindrone 400, 500, 750, 800, or 1500 *OR* levonorgestrel 50, 75, 125, or 150 *OR* desogestrel 100, 125, or 150 *OR* norgestrel 300 *OR* ethynodiol diacetate 1000	
*Also contains levomefolate calcium for protection against neural tube defects. †Not available in the US.	

Table 36.6 Commonly used combined oral contraceptives.

- Its anti-acne effects re mediated primarily through androgen receptor blockade.
- The standard contraceptive formulation combines cyproterone acetate (2 mg) with ethinyl estradiol (35 or 50 mcg).
- This preparation is widely used in Europe as the treatment of choice for sexually active women with hormonally responsive acne.
- Formulations of cyproterone acetate alone are also available.
- Approximately 75–90% of patients treated with either the standard contraceptive formulation or higher doses of 50–100 mg daily (with or without ethinyl estradiol 50 mcg) show substantial improvement
- The most frequent side effects are breast tenderness, headache, nausea, and irregular menses; hepatotoxicity and thromboembolism represent uncommon complications.

- Spironolactone functions as both an androgen receptor blocker and an inhibitor of 5α-reductase.
- In doses of 50–100 mg twice daily, it has been shown to reduce sebum production and improve acne
- Up to two-thirds of women treated with spironolactone note marked improvement or clearance of their acne66.
- Side effects are dose-related and include irregular menstrual periods, breast tenderness, headache, and fatigue.
- Hyperkalemia is rare and monitoring of potassium levels is not required in young healthy patients
- Although breast tumors have been reported in rodents given spironolactone, this drug has not been directly linked to the development of cancer in humans
- Because it is an antiandrogen, there is a risk of feminization of a male fetus if a pregnant woman takes this medication.
- Side effects can be minimized if therapy is initiated at a low dose (25–50 mg/day).

- Effective maintenance doses range from 25 to 200 mg/day.
- As with other hormonal therapies, a clinical response may take up to 3 months.
- Flutamide, a nonsteroidal androgen receptor blocker approved by the FDA for the treatment of prostate cancer, may be of benefit for acne in women at doses of 62.5–500 mg/day.
- In addition to side effects similar to those of other antiandrogens (e.g. menstrual irregularities, breast tenderness, risk of feminization of a male fetus), severe dose-related hepatotoxicity limits its use.

Isotretinoin

- Since 1971, oral isotretinoin (13-cis-retinoic acid) has been available in Europe for the treatment of acne.
- In the US, it was FDA-approved in 1982 for patients with severe, nodulocystic acne refractory to treatment, including oral antibiotics.
- Over time, have also been shown to benefit greatly from the use of isotretinoin
- These include significant acne that is unresponsive to therapy (including oral antibiotics) and/or results in scarring, as well as Gram-negative folliculitis, pyoderma faciale, and acne fulminans.
- Patients with acne are typically treated with an isotretinoin dose of 0.5–1 mg/kg/day taken with a fatty meal to increase gastrointestinal absorption, often with a lower dose during the first month of treatment to prevent an initial acne flare and allow the patient to adjust to dose dependent side effects.
- Reaching a cumulative dose of 120–150 mg/kg (e.g. 4–5 months of treatment with 1 mg/kg/day) has been shown to reduce the risk of relapse.

However, a 6-month course of low-dose isotretinoin (e.g. 0.25–0.4 mg/kg/day, 40–70 mg/kg cumulative) can be effective in the treatment of moderate acne, with fewer side effects and improved patient satisfaction70.

- Subsets of patients who are less likely to respond to isotretinoin and/or more likely to require multiple or longer courses of treatment include adolescents under 16 years of age who have nodulocystic acne, individuals with endocrine abnormalities, and women with less severe acne.

- Scarred nodules and sinus tracts which represent sequelae from previously active cystic acne do not respond to isotretinoin but may improve with surgical modalities;

- the latter are generally delayed for at least 6–12 months after completing isotretinoin therapy to avoid the possible risk of atypical healing or scarring responses

- The most common adverse effects of isotretinoin involve the skin and mucous membranes and are dose-dependent.

- These include cheilitis, dryness of the oral and nasal mucosa, generalized xerosis, and skin fragility.

- With the institution of isotretinoin therapy, induction of an acne fulminans-like flare, formation of excessive granulation tissue, paronychia, and cutaneous infections (in particular with Staphylococcus aureus) can also occur

- Teratogenicity is a serious potential complication and female patients of childbearing potential must have at least one (in the US, two) negative pregnancy test(s) before starting treatment and must practice effective contraception for 1 month prior to, during, and for 1 month after completing therapy

- Isotretinoin therapy leads to elevated serum triglyceride and/or cholesterol levels in ~20–50% of patients; however, severe elevations are uncommon and typically develop within the first two months of therapy

- Other potential side effects involve the musculoskeletal system (e.g. myalgias, elevation of serum creatine kinase levels), eyes, liver (occasionally elevated transaminases), intestines (controversial; no link with inflammatory bowel disease found in a recent meta-analysis) and central nervous system

- To date, no firmly established causal association with depression or suicide attempts has been demonstrated.

- A recent metaanalysis did not show an association between isotretinoin treatment and increased risk of depression; instead, acne therapy led to a decreased prevalence of depression

Rosacea and Related Disorders

INTRODUCTION

- The term “rosacea” encompasses a constellation of clinical findings, with the key components being persistent facial erythema and inflammatory papulopustules.
- Additional features are facial telangiectasias, a tendency for frequent facial flushing (sometimes referred to as “prerosacea”), non-pitting facial edema with erythema, ocular inflammation, and phymatous changes.
- The latter predominantly affect the nose and rarely the ears, forehead, chin, or eyelids.
- In 2002, rosacea was classified into four clinical subtypes1 : (1) erythematotelangiectatic; (2) papulopustular; (3) phymatous; and (4) ocular.
- There is also a granulomatous variant in which more monomorphous and persistent skin-colored to dull red–brown facial papules are seen.
- Some authors consider rosacea conglobata, characterized by an eruption of inflammatory cystic lesions that heal with scarring and rosacea fulminans (pyoderma faciale) to be within the rosacea spectrum.
- In rosacea fulminans, an explosive onset of inflammatory papules and pustules is superimposed on a background of facial erythema, usually occurring in young women and sometimes during pregnancy

EPIDEMIOLOGY

- In a 1989 study of over 800 office workers in Sweden, the prevalence of rosacea was found to be 10%

- The majority of affected individuals had facial erythema and telangiectasias without inflammatory skin lesions, presumably representing erythematotelangiectatic rosacea (ETTR); changes consistent with papulopustular rosacea (PPR) were observed in 1.8%.

- Utilizing a consensus definition of PPR , a population study of 1000 individuals in Ireland detected a point prevalence of 2.7% .

- A similar rosacea point prevalence rate of 2.3% was noted in a review of 90880 German workers, although in this study clinical subtypes were not defined .

- Epidemiologic studies from countries where darkly pigmented individuals predominate population-wise suggest that the prevalence is far lower than in countries where the population is predominantly fair-skinned.

- Recently, a national study of all adults in Denmark found that the risk of dementia, particularly Alzheimer disease, was increased for adults with rosacea who were >60 years of age.

PATHOGENESIS

- In rosacea, several different but interrelated pathomechanisms have been proposed with predominant pathways reflecting clinical features.
- Both environmental triggers and genetic predisposition play a role, with up to 20% of patients in some studies reporting a family history of rosacea.
- Two of the major abnormalities are neurovascular dysregulation and an aberrant innate immune response, both of which can lead to cutaneous inflammation.
- Several clinical features of rosacea, including transient erythema, persistent centrofacial erythema, telangiectasias and flushing, point to the important role the vascular system plays in its pathogenesis.
- An increase in blood flow within skin lesions of rosacea has been demonstrated, and patients with rosacea flush more readily in response to heat.
- Histopathologic studies of lesional skin found an elevated expression of vascular endothelial growth factor (VEGF), CD31, and the lymphatic endothelial marker D2-40 (podoplanin), implying increased stimulation of vascular and lymphatic endothelial cells

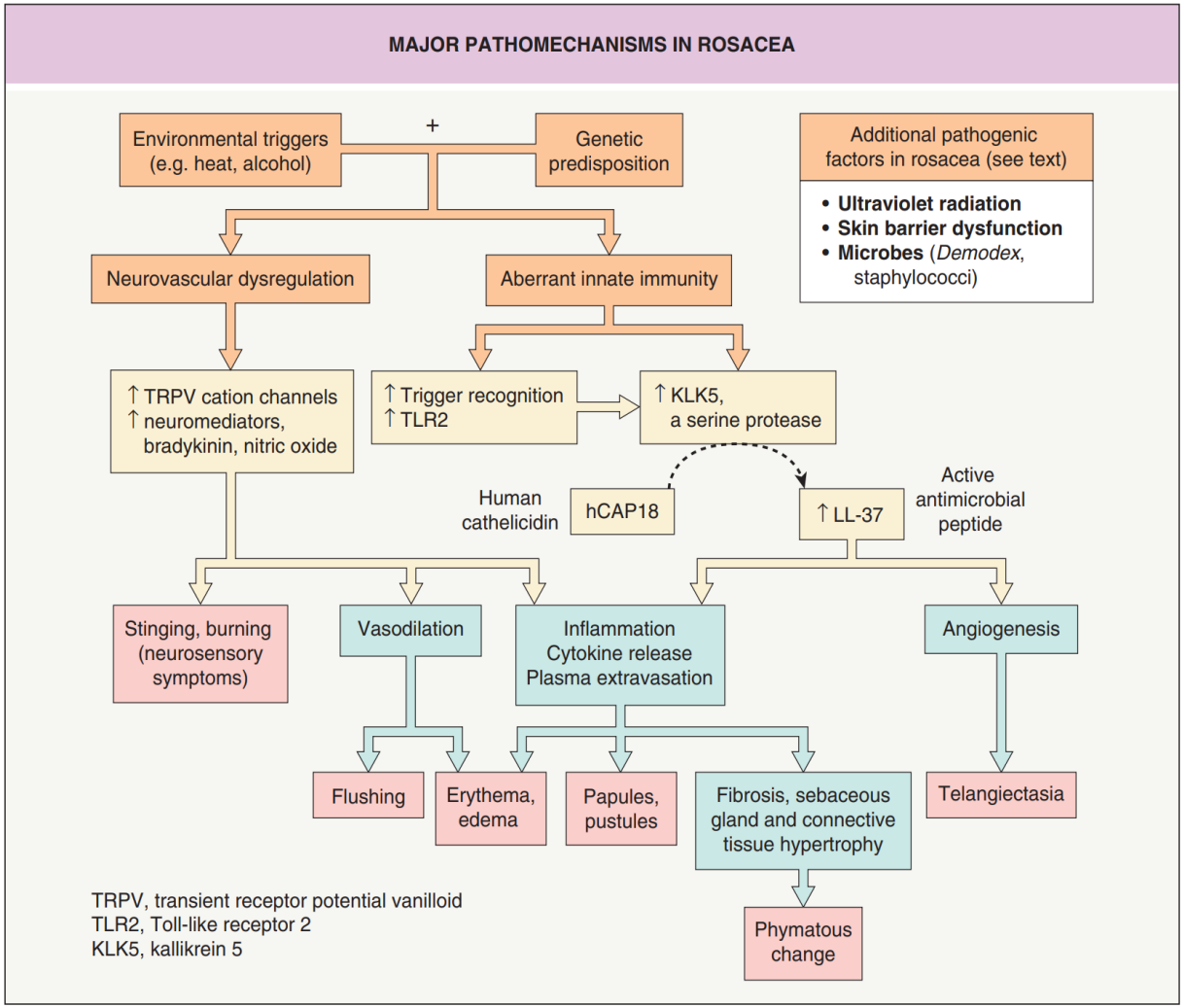


Fig. 37.1 Major pathomechanisms in rosacea. In genetically predisposed individuals (e.g. HLA-DRB1*03:01, HLA-DQA1*05:01, HLA-DQB1*02:01, SNP rs763035), environmental factors can trigger neurovascular dysregulation and an aberrant innate immune response, both of which can lead to cutaneous inflammation, including the clinical manifestations of rosacea. *Adapted from Steinhoff M, Buddenkotte J, Aubert J, et al. Clinical, cellular, and molecular aspects in the pathophysiology of rosacea. J Invest Dermatol Symp Proc. 2011;15:2–11.*

- In patients with rosacea, including ETTR, sensations of stinging or burning of the skin are commonly reported and affected individuals also exhibit lower heat pain thresholds, as compared to controls.

- Stimulation of cutaneous nerve endings expressing transient receptor potential vanilloid (TRPV) cation channels by trigger factors (e.g. spicy food, heat, alcohol) can lead to dysesthesia, flushing, and erythema

- Heightened TRPV activity within the skin of patients with rosacea is associated with neurogenic inflammation, an inflammatory response induced by sensory nerves in which neuromediators are released at the site of inflammation.

- The latter can result in vasodilation, plasma extravasation of proteins, and recruitment of inflammatory cells

- Evidence that an aberrant innate immune response also plays a role in the pathogenesis of rosacea includes upregulation of LL-37 via enhanced processing of cathelicidin by the trypsin-like serine protease kallikrein

- When injected into mouse skin, cathelicidin peptides induced proinflammatory and angiogenic activity, leading to the proposal that dysfunction of the innate immune system could unify many of the clinical features of rosacea, especially the inflammatory lesions

- In histopathologic studies of PPR, inflammatory changes were noted to be most pronounced near the bulge region of the pilosebaceous follicle, the site of stem cells whose expression profile overlaps with that of the innate immune system.

- Based upon a higher prevalence in those with skin phototypes I and II , ultraviolet light has been proposed as an additional contributing factor to the pathogenesis of rosacea.
- Exposure to UVB can induce angiogenesis and it increases the secretion of angiogenic factors (e.g. VEGF) from keratinocytes.
- UVR also induces production of reactive oxygen species, which upregulate matrix metalloproteinases that lead to vascular and dermal matrix damage.
- Although clinically ETTR can resemble telangiectatic photoaging,
- In contrast, PPR does not appear to be significantly related to cutaneous photodamage or UV exposure .
- Several clinical features of rosacea imply skin barrier dysfunction.
- Rosacea patients often report facial dryness, and studies have confirmed a lowered threshold for skin irritancy.
- Both ETTR and PPR patients have increased transepidermal water loss, a marker of epidermal barrier dysfunction, and it has been suggested that disruption or abnormality of the stratum corneum allows penetration of sensory irritants

- In addition, patients with PPR have an abnormal skin surface fatty acid profile as well as reduced epidermal hydration levels; the latter were noted to improve following treatment with minocycline and resolution of inflammatory lesions.
- Demodex mites (folliculorum and brevis) are normally present on the face as commensal microbes, but in rosacea, greater numbers of these mites are detected by skin surface biopsy techniques.
- In routine histologic sections, the mites often appear prominently within pilosebaceous follicles and follicular infestation with multiple mites can be associated with an intense perifollicular infiltrate of predominantly CD4 T helper cells.
- Antigenic proteins from a bacterium (Bacillus oleronius) isolated from Demodex mites can stimulate inflammation in patients with PPR
- It has been suggested that Demodex mites and their associated bacteria upregulate local proteases, thereby potentiating dysregulation of the cutaneous innate immune response.
- Lastly, it seems unlikely, based upon current evidence, that Helicobacter pylori infection plays an etiologic role in the pathogenesis of rosacea

CLINICAL FEATURES

- Rosacea usually has its onset during middle age, with women often affected at a younger age than men.
- While rosacea is not commonly observed in children, the rosacea-like conditions periorificial dermatitis and steroid-induced rosacea are fairly common.
- From a clinical perspective it is useful to classify rosacea into the following four subtypes.
- However, this classification is intended as a guide given that there is some overlap amongst the subtypes and a patient can have more than one subtype

- **Erythematotelangiectatic rosacea** (subtype 1; ETTR):

✓ Individuals have a tendency to flush combined with a background of persistent facial erythema and sometimes telangiectasias.

✓ These patients typically have skin phototypes I or II and it may be difficult to differentiate ETTR from telangiectatic photoaging, but there are some relative differences

✓ In addition, when patients complain of significant flushing other causes of flushing should be considered as outlined

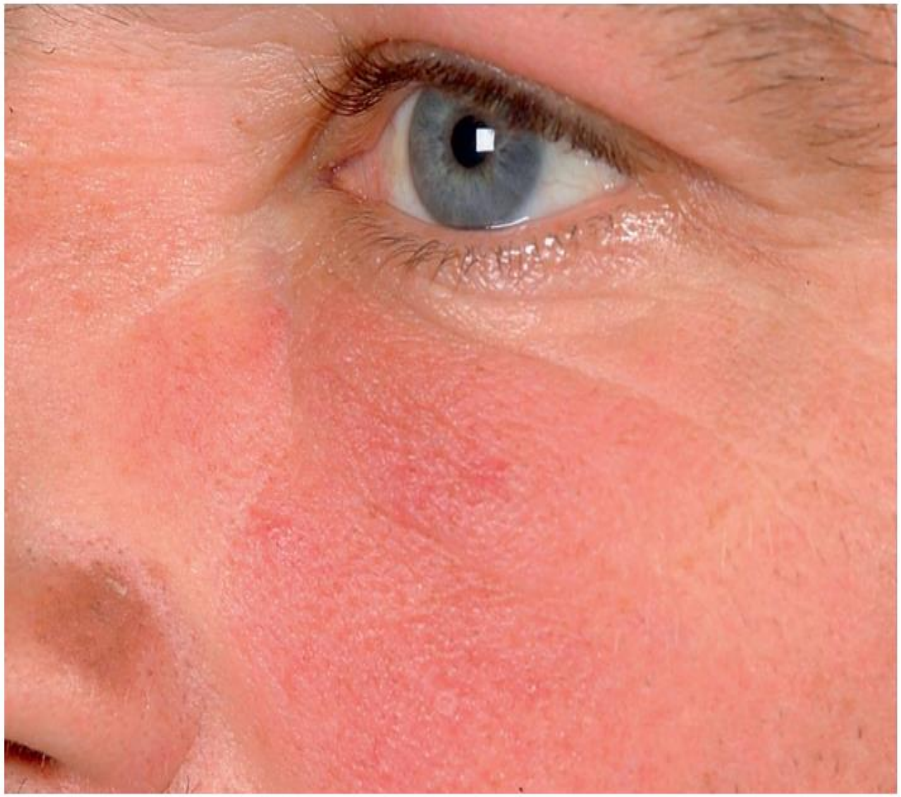


Fig. 37.2 Erythematotelangiectatic rosacea. Persistent erythema of the medial and lateral cheeks is seen. In this patient, there are no telangiectasias, indicating mild (grade 1) disease.

DIFFERENTIAL DIAGNOSIS OF THE FOUR SUBTYPES OF ROSACEA	
Rosacea subtype and differential diagnosis	**Distinguishing feature(s) from rosacea**
Erythematotelangiectatic rosacea	
Actinic damage (telangiectatic photoaging)	• Also characterized by facial telangiectasias and erythema, but the latter favors the lateral more than the central face • There tends to be less transient and nontransient erythema • Some patients have both disorders
Seborrheic dermatitis	• Erythema with greasy scale in the eyebrows, nasolabial folds, auditory meatus, retroauricular sulcus, and scalp • Involvement of eyelid creases • Patients often have both disorders
Keratosis pilaris rubra	• Onset usually during adolescence • Background erythema of the lateral cheeks with superimposed tiny follicular papules
Acute cutaneous lupus erythematosus	• Absence of inflammatory papulopustules and ocular changes • At least 75–80% of patients have systemic signs/symptoms of SLE • Often more well-demarcated edematous plaques with sparing of the nasolabial fold
Flushing (idiopathic or secondary)	• Intermittent erythema and warmth • Flushing in patients with rosacea is usually limited to the face • Consider other common etiologies (e.g. menopause, anxiety disorder) or a tumor-related phenomenon (carcinoid syndrome, occult pheochromocytoma, mastocytosis) when additional anatomic sites are involved or there are associated symptoms such as tachycardia and sweating

- **Papulopustular rosacea** (subtype 2; PPR):

✓ Patients have a centrofacial eruption of multiple, small tages of evolution.

✓ Although the patient may complain of mild discomfort or pruritus and the lesions may be slightly tender, the social distress caused by the appearance of the eruption often far exceeds the physical symptoms.

✓ Individual papules or pustules last about two weeks and are then replaced by blotchy post inflammatory erythema which gradually fades over ~10 days.

✓ Residual scarring is not a feature of PPR.

✓ A halo of erythema may surround larger inflammatory lesions and tiny telangiectatic vessels may be visible within this rim.

✓ Occasionally, when there is more severe disease, scaling or superficial crusting may be seen and this has been referred to as “rosacea dermatitis”

✓ Lastly, some patients will have some degree of persistent erythema of the cheeks that may represent a combination of post inflammatory erythema, telangiectasias, and vasodilation.

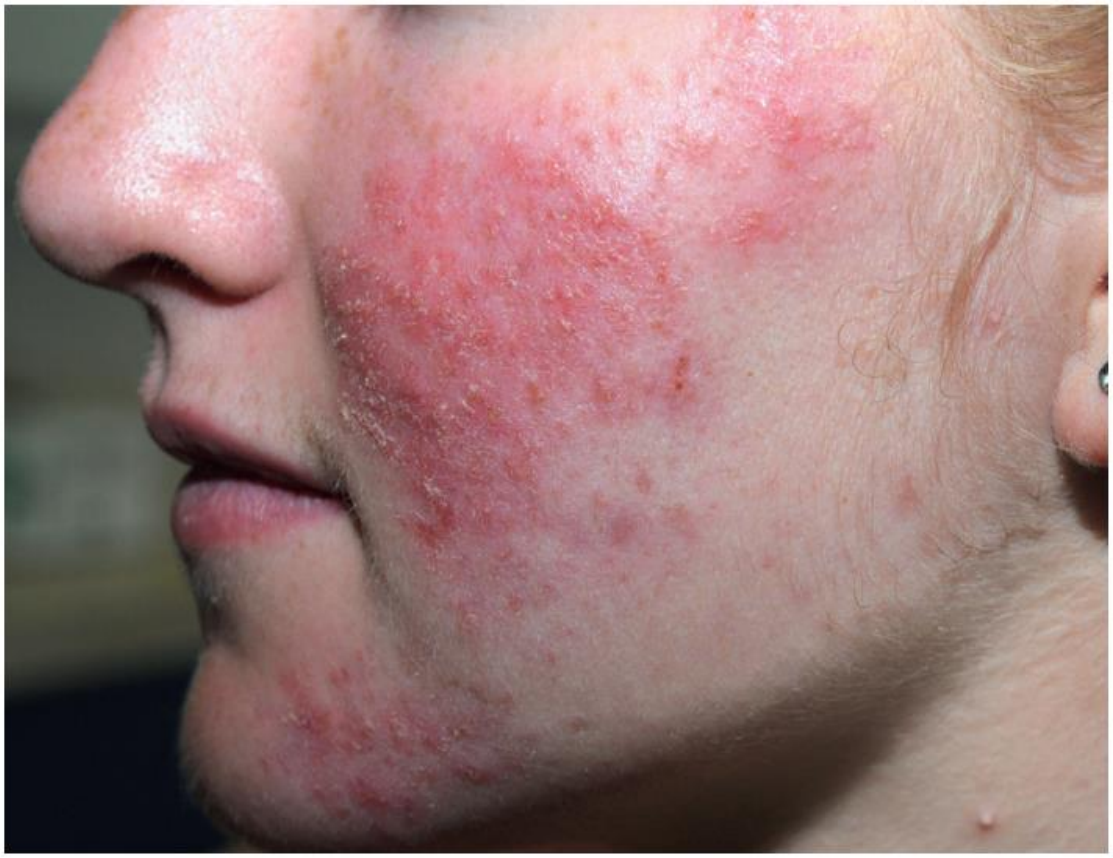


Fig. 37.5 Rosacea dermatitis. When there is more severe disease, scaling and superficial crusting may be seen as on the cheek of this woman. *Courtesy, Kalman Watsky, MD.*

Papulopustular rosacea	
Acne (vulgaris)	• Onset at a younger age • Comedones, both open and closed, and cysts • Greater involvement of the upper trunk
Steroid-induced rosacea	• Clinical overlap with periorificial dermatitis (see text)
Demodicosis (*Demodex* folliculitis)	• Patients often immunosuppressed (HIV infection, leukemia) • Involves face, especially the nose, and upper chest • Responds to topical permethrin ± oral ivermectin
Pityriasis folliculorum	• See text
Tinea incognito, candiasis	• Both can mimic rosacea, especially if topical corticosteroids have been used • KOH examination demonstrates hyphae or budding yeasts
Papulopustular eruptions due to EGFR inhibitors	• Occurs in up to 90% of patients on these drugs (see Fig. 37.15) • Abrupt onset • May also involve scalp, neck, and trunk
Follicular mucinosis	• Multiple papules but not pustules
Ocular rosacea	
Seborrheic dermatitis	• Involvement beyond the eyelid margin; may be accentuated in the eyelid creases
Drug-induced ocular rosacea	• Eyedrops used to treat other ocular disorders, e.g. glaucoma
Phymatous rosacea	
Lupus pernio (sarcoidosis)	• Violaceous indurated plaque of the distal nose
Discoid lupus erythematosus	• Erythema, scaling, follicular plugging, and tendency to scarring
Lupus vulgaris (cutaneous TB)	• See Table 75.6
Neoplasms	• Basal cell carcinoma, lymphoma, angiosarcoma, cutaneous metastases (“clown nose”)

Table 37.3 Differential diagnosis of the four subtypes of rosacea. Occasionally, trichostasis spinulosa has associated erythema, but detection of multiple hairs within the follicular orifice by dermoscopy or microscopic examination of follicular contents establishes the diagnosis. EGFR, epidermal growth factor receptor; SLE, systemic lupus erythematosus.

- **Phymatous rosacea** (subtype 3): In this form of rosacea, sebaceous gland hypertrophy is accompanied by fibrosis.
- Rhinophyma is by far the most common clinical presentation, occurring primarily in men
- Involvement of other anatomic sites has been reported, but it is rare
- Patients with rhinophyma may have other features of rosacea, usually mild to moderately severe PPR.
- However, phymatous rosacea may arise de novo without any preceding skin changes and therefore should not be viewed as “end-stage rosacea”.
- The earliest clinical sign of rhinophyma is the appearance of patulous follicles (“dilated pores”) on the distal portions of the nose.
- It has been suggested that telangiectatic vessels in this same location may predispose to hypertrophic changes
- In severe cases of rhinophyma, the tissue hypertrophy leads to nasal distortion, with soft fleshy nodular growths resulting in significant disfigurement.
- Although basal cell carcinomas have been reported to arise in skin affected by rhinophyma, there is insufficient evidence to suggest that this condition predisposes to malignant change.
- The edematous changes sometimes seen in patients with severe inflammatory rosacea should not be confused with phymatous rosacea.

TYPES OF PHYMATOUS ROSACEA	
Phyma	**Clinical features**
Rhinophyma	• Apparent initially as dilated patulous follicles at the distal end of the nose • When marked, can lead to debilitating nasal deformity
Gnathophyma	• Rare occurrence, with central chin typically involved • May give rise to asymmetrical swelling
Otophyma	• Usually affects the lower half of the helices and lobes of the ears
Metophyma	• Cushion-like, firm swelling of central forehead
Blepharophyma	• Swelling of the eyelids • Usually seen as a component of edematous rosacea but may accompany severe papulopustular or ocular rosacea

Table 37.2 Types of phymatous rosacea.

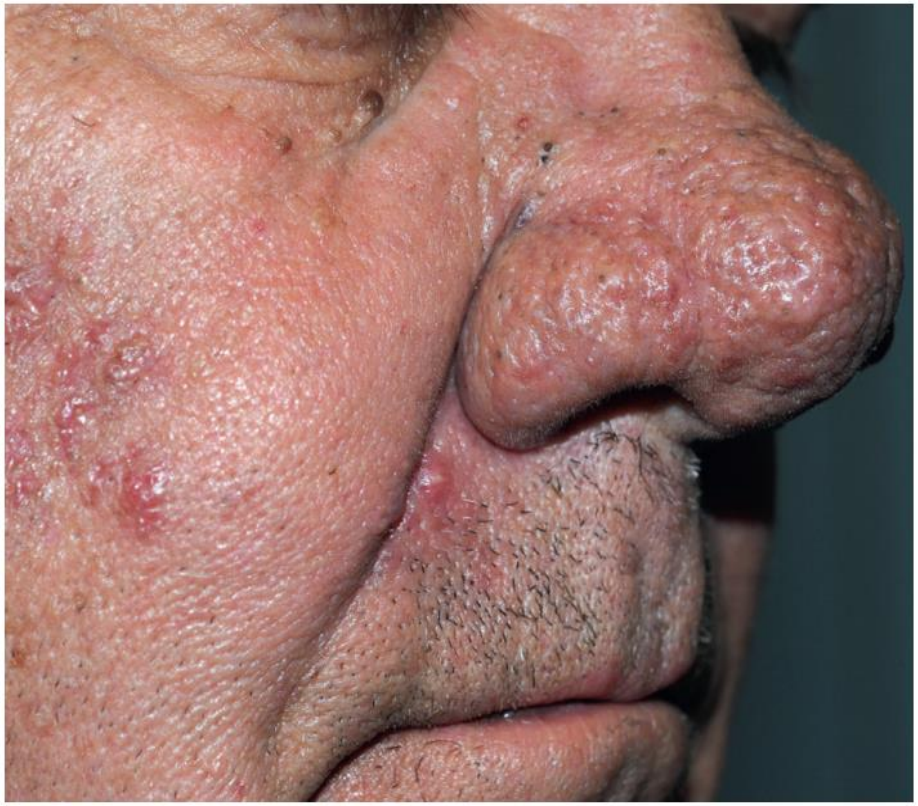
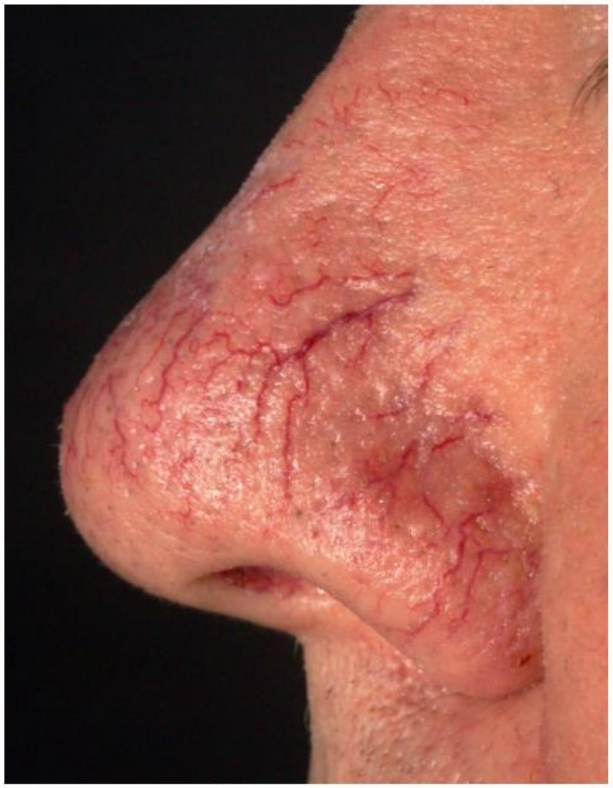


Fig. 37.6 Rhinophyma. Hypertrophy of sebaceous glands and connective tissue as well as patulous follicles are seen. The changes are more prominent in the mid to lower nose. In addition, there is evidence of papulopustular rosacea.
Courtesy, Kalman Watsky, MD.

rosacea but may accompany
papulopustular or ocular ros

Table 37.2 Types of phymatous rosacea.



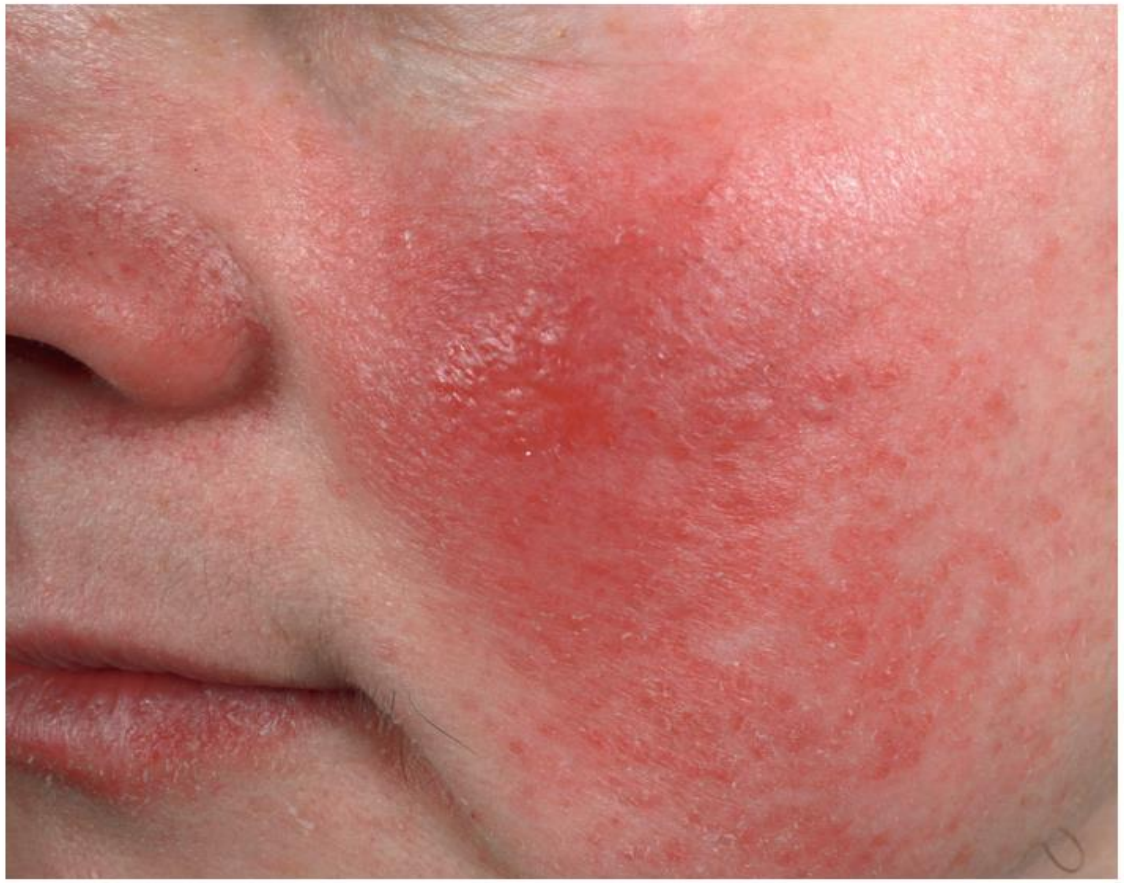


Fig. 37.8 Inflammatory rosacea with edematous changes. An intensely erythematous plaque is present on the medial aspect of the cheek. This may improve once the underlying inflammation is treated appropriately.

- **Ocular rosacea (subtype 4):**

✓ This entity may or may not be accompanied by cutaneous changes of rosacea.

✓ Without cutaneous manifestations, the diagnosis of ocular rosacea can be difficult to establish with certainty.

✓ Patients with ETTR and PPR appear to be particularly vulnerable to the development of ocular inflammation, with up to 50% affected

✓ Symptoms are nonspecific and include dryness, a gritty sensation, an inability to wear contact lenses, tearing, crusting of the eyelid margins, frequent styes (hordeola), and sometimes pruritus.

✓ Patients usually do not associate these ocular symptoms with their rosacea and may not volunteer such information unless specifically asked.

✓ The clinical signs of ocular rosacea are diverse – there may be tiny concretions at the bases of the cilia or mild scaling of the eyelid margins.

✓ When the disease is more active, there is evidence of blepharitis, often with eyelid swelling and conjunctival the overall appearance is that of a “red eye”

✓ Such changes, unlike those of phymatous rosacea, often improve following successful management of the inflammatory lesions; however, some degree of lymphedema may persist

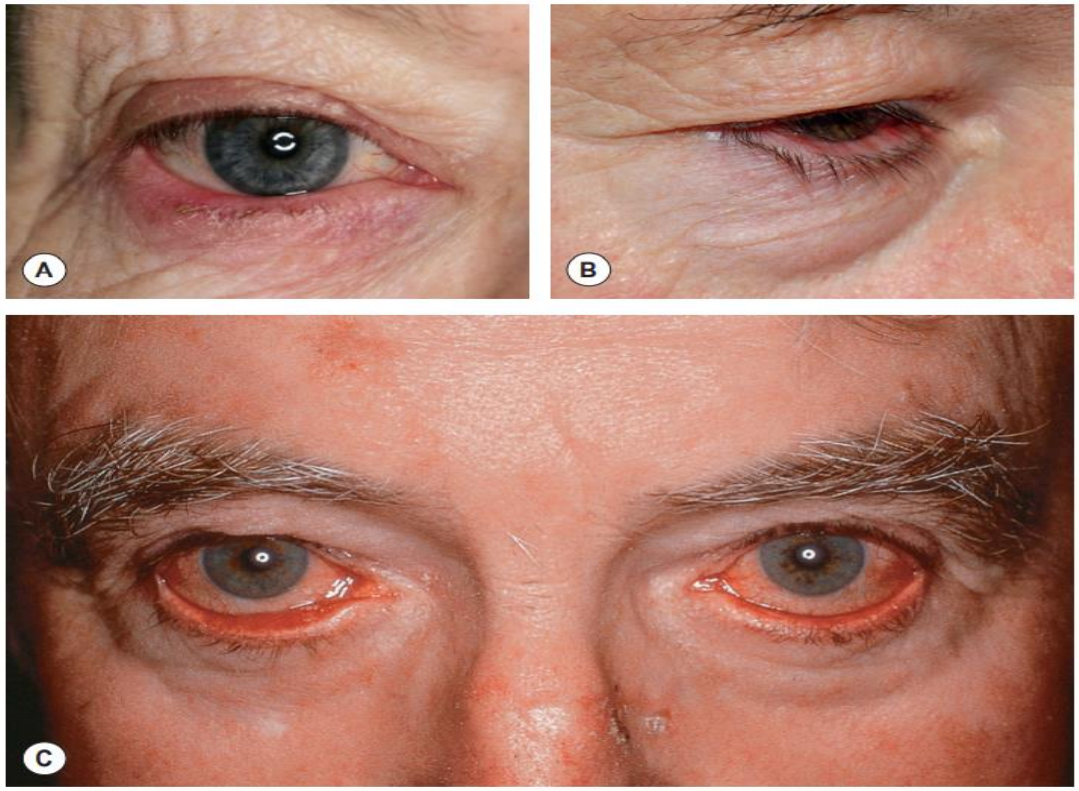


Fig. 37.9 Ocular rosacea. A Tiny concretions of keratin (conical dandruff) are visible at the bases of some of the eyelashes of the lower eyelid. There is also evidence of blepharitis of the lower eyelid and conjunctival injection. **B** Erythema of the mucosal portion of the lower eyelid and ectropion. **C** Marked injection of the conjunctivae, leading to the appearance of red eyes. Ectropion is also present.

- Cysts arising from the meibomian glands (chalazia) present as firm nontender swellings of the cutaneous dome-shaped, favor the central face, and usually measure 1–3 mm in diameter

- his variant occurs in both children and adults and it may resolve spontaneously a few years after lesions first appear and not recur. Histologically, non- caseating epithelioid granulomas are present within the dermis

- Some authors consider lupus miliaris disseminatus faciei (LMDF) to be a severe form of granulomatous rosacea, with a predilection for the periocular region (as well as the central face) and an “apple-jelly” appearance on diascopy.

- However, the dermal granulomas seen in biopsy specimens often have central caseation necrosis, thus explaining why this disorder was initially considered a tuberculid.

- Unfortunately, significant facial scarring can be a permanent sequela.

- Occasionally, there is extrafacial involvement which may be confused with other granulomatous diseases such as sarcoidosis, cutaneous tuberculosis, or the necrobiotic form of granuloma annulare.

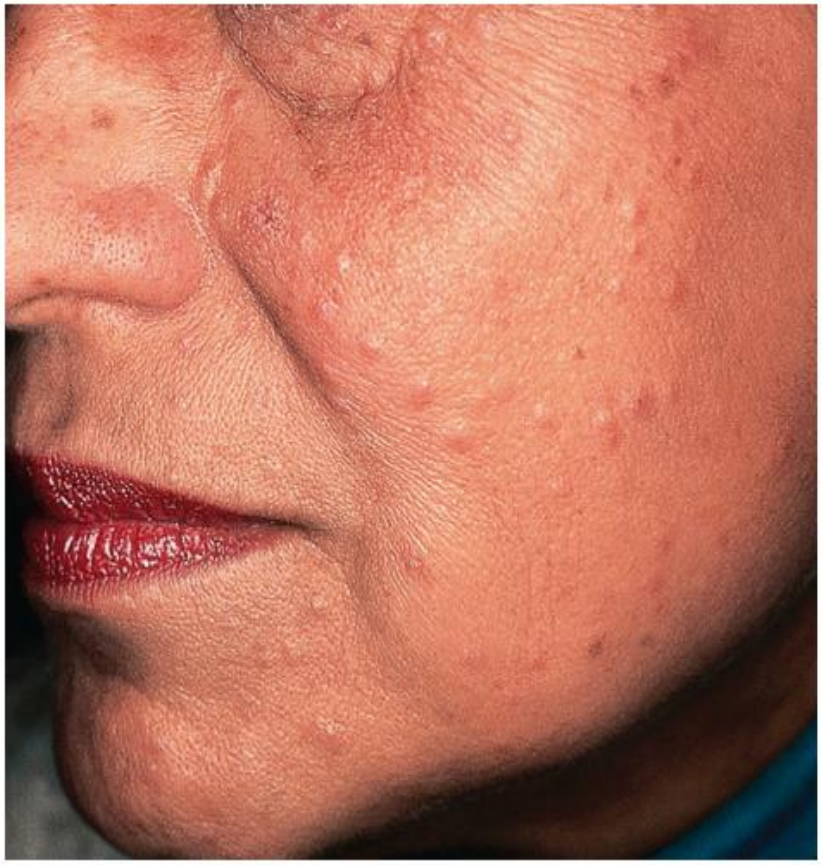


Fig. 37.10 Granulomatous rosacea, lupus miliaris disseminatus faciei variant. Monomorphous, discrete skin-colored to brown papules scattered on the face that are more persistent than the lesions of papulopustular rosacea. Histologically, granulomas with central caseation necrosis were observed, which led to the diagnosis of lupus miliaris disseminatus faciei.

TREATMENT

- Categorizing rosacea into subtypes and grading each subtype into mild, moderate and severe (grades 1–3) assist in guiding initial therapeutic interventions and in monitoring the clinical response.
- At the initial consultation, the patient should be made aware of the chronic relapsing nature of rosacea and the need for maintenance therapy even when in remission.
- Patients with grade 1 ETTR have mild fixed facial erythema and intermittent flushing.
- Frequent flushing with the presence of multiple telangiectasias characterize grades 2 and 3 disease.
- Therapy is directed at diminishing the facial erythema, removing the telangiectasias via vascular laser therapy, and addressing the flushing tendency; the latter includes avoidance of precipitating factors and the use of specific medications
- Topical application of adrenergic agonists, such as brimonidine (selective α2) or oxymetazoline (selective α1A and partial α2), may help to diminish the erythema in individuals with ETTR.

GENERAL RECOMMENDATIONS FOR FACIAL SKIN CARE AND EDUCATION IN PATIENTS WITH ROSACEA

Facial skin care

- Wash with lukewarm water and use soap-free cleansers that are pH balanced
- Cleansers are applied gently with fingertips
- Use sunscreens with both UVA and UVB protection and an SPF ≥30
- Sunscreens containing the inorganic filters titanium dioxide and/or zinc oxide are usually well tolerated
- Use cosmetics and sunscreens that contain protective silicones
- Water-soluble facial powder containing inert green pigment helps to neutralize the perception of erythema
- Moisturizers containing humectants (e.g. glycerin) and occlusives (e.g. petrolatum) help to repair the epidermal barrier
- Avoid astringents, toners, and abrasive exfoliators
- Avoid cosmetics that contain alcohol, menthols, camphor, witch hazel, fragrance, peppermint, and eucalyptus oil
- Avoid waterproof cosmetics and heavy foundations that are difficult to remove without irritating solvents or physical scrubbing
- Avoid procedures such as glycolic peels or dermabrasion

Patient education

- Reassure the patient about the benign nature of the disorder and the rarity of rhinophyma, particularly in women
- Emphasize the chronicity of the disease and the likelihood of exacerbations
- Direct patients to information websites such as those of the National Rosacea Society (www.rosacea.org) or the American Academy of Dermatology (www.aad.org)
- Advise to avoid recognized triggers
- Explain the importance of compliance with topical regimens
- Educate on the importance of sun avoidance

Table 37.4 General recommendations for facial skin care and education in patients with rosacea. *Adapted from refs 36, 39 & 41.*

- Topical and systemic antibiotics used to treat PPR are ineffective in the treatment of ETTR and topical agents may actually irritate the skin.
- Avoidance of sun exposure, diligent use of a high SPF sunscreen, and cosmetic care of the skin are also part of the management strategy for this subtype of rosacea

- In general, patients with PPR are treated with topical and/or systemic antibiotics
- Although many of the antibiotics used to treat PPR are the same as those used for acne vulgaris, the treatment course for rosacea is usually shorter (4 to 8 weeks as opposed to 4 to 6 months).

- Sometimes successful treatment of the inflammatory lesions of PPR may unmask background telangiectasias which then need to be addressed.

- Following successful clearance of inflammatory lesions, maintenance therapy (usually topical) should be instituted to avoid a likely relapse.

- Many patients with moderate and severe (grades 2 and 3) PPR require repeated courses of systemic antibiotic therapy but subsequent courses can often be shorter in duration, i.e. 3 to 4 weeks.

MEDICAL AND SURGICAL THERAPIES FOR ROSACEA	
Treatment	**Comments and/or Doses**
Erythematotelangiectatic	
Facial skin care recommendations (see Table 37.4)	Particularly useful as this subtype is prone to skin irritation and "sensitivity"
Photoprotection	UVR may potentiate dermal matrix damage
Topical agents, e.g. azelaic acid, metronidazole	May reduce erythema, but their use is often limited by their irritant effects
Topical brimonidine tartrate (0.33% gel)*,†	Selective α_2-adrenergic agonist that improves erythema
Topical oxymetazoline HCl (1% cream)*	Selective α_{1A}-adrenergic agonist that improves erythema
Laser therapy†	Use of vascular lasers (e.g. pulsed dye, potassium titanyl phosphate) as well as intense pulsed light may improve grades 2 and 3
Papulopustular	
Topical	
Metronidazole (0.75% gel or cream; 1% cream)*,† once or twice daily	Can be used as initial treatment to clear inflammatory lesions or as indefinite maintenance therapy
Ivermectin (1% cream)*,† once daily	More effective than placebo and slightly more effective than topical metronidazole in randomized controlled trials
Azeleic acid (15% gel)*,† twice daily	Appears to be more effective than topical metronidazole but with more side effects, e.g. irritation Azeleic acid (20% cream twice daily) is a non-FDA-approved alternative dose
Sodium sulfacetamide (10%) and sulphur (5%) in a cream or lotion* once or twice daily	May include 10% urea
Erythromycin (2% solution) twice daily	Alcohol in solution may reduce tolerance
Clindamycin (1% lotion) daily	
Benzoyl peroxide 5% plus clindamycin 1% daily	May cause skin irritation
Tretinoin (0.025% cream; 0.05% cream; 0.01% gel) daily	Alters epidermal keratinization and may improve photodamage Poorly tolerated by some patients
Permethrin (5% cream) daily–weekly	Shown to be as effective as topical metronidazole for the treatment of papules and erythema May have future role in combination with antibiotics, but further studies needed
Pimecrolimus (1% cream) or tacrolimus (0.03%, 0.1% ointment) twice daily	Some studies have shown improvement in erythema, but there have been case reports of exacerbations, so further studies needed

Systemic	
Doxycycline*,†	40 mg daily (30 mg immediate release and 10 mg delayed release) for 4–8 weeks As effective as the 100 mg dose but with fewer adverse effects
Doxycycline	50–100 mg once or twice daily for 4–8 weeks
Minocycline	50–100 mg twice daily or sustained action formula (1 mg/kg) daily for 4–8 weeks**
Tetracycline†	250–500 mg twice daily for 4–8 weeks
Erythromycin	250–500 mg once or twice daily for 4–8 weeks
Azithromycin	250–500 mg (5–10 mg/kg) thrice weekly for 4–8 weeks
Metronidazole	200 mg once or twice daily for 4–8 weeks
Isotretinoin†	0.3 mg/kg/day
Phymatous	
Isotretinoin	May reduce nasal volume and halt the progression of rhinophyma
Surgical excision	Can effectively debulk and resculpt the nose
Electrosurgery	
CO_2 laser	
Ocular	
Eyelid hygiene and artificial tears	Frequently used to treat mild disease Useful for maintaining remission following treatment of grades 2 and 3 disease with systemic antibiotics
Fusidic acid	
Metronidazole gel	
Cyclosporine 0.5% ophthalmic emulsion†	More effective than artificial tears in treatment of ocular rosacea
Systemic antibiotics (see above section)	For grade 2–3 disease

*FDA approved treatments for rosacea (evidence based support – 1)

- Some patients may remain clear of inflammatory lesions even when a single dose of an oral antibiotic is taken every other day and then relapse if the drug is discontinued.
- Topical ivermectin is a recently approved treatment for PPR that has anti-inflammatory and antiparasitic activities
- Low-dose isotretinoin and photodynamic therapy are alternative treatment options in patients whose lesions prove resistant to first-line therapies
- Rhinophyma is the type of phymatous rosacea most amenable to treatment
- Mild disease may be responsive to low-dose isotretinoin, although conclusive evidence of efficacy is lacking.
- More severe (grades 2 and 3) disease responds best to physical modalities such as CO_2 laser therapy, electrosurgery, or surgical excision
- Longitudinal evaluation of patients treated with CO_2 laser therapy suggests that improvement persists long-term.
- Other sites of phymatous rosacea are very rare and there are no established therapeutic interventions.

- Ocular rosacea is a common entity that is commonly underdiagnosed
- Patients with mild ocular rosacea (grade 1 disease) often respond to lavage of eyelid margins with dilute “baby” shampoo using cotton swabs combined with an oily tear replacement.
- Burning or stinging with crusting of the eyelid margins or the formation of a chalazion or hordeolum are manifestations of moderate (grade 2) disease and treatment consists of topical and/or systemic antibiotics
- Pain, photophobia, and visual disturbances are features of severe (grade 3) disease.
- Such symptoms require prompt referral to an ophthalmologist.
- Granulomatous rosacea is difficult to treat and no consensus exists regarding first-line treatments. Anecdotally, therapeutic options include dapsone, minocycline, isotretinoin, hydroxychloroquine, and the 1450-nm diode laser.
- While some authors consider rosacea fulminans and rosacea conglobata to be within the rosacea spectrum , others view them as variants of acne vulgaris.
- Nonetheless, systemic corticosteroids are required to control the aggressive inflammation observed in both of these disorders and this is often followed by the use of oral isotretinoin
- Scarring can be a sequela despite these interventions.

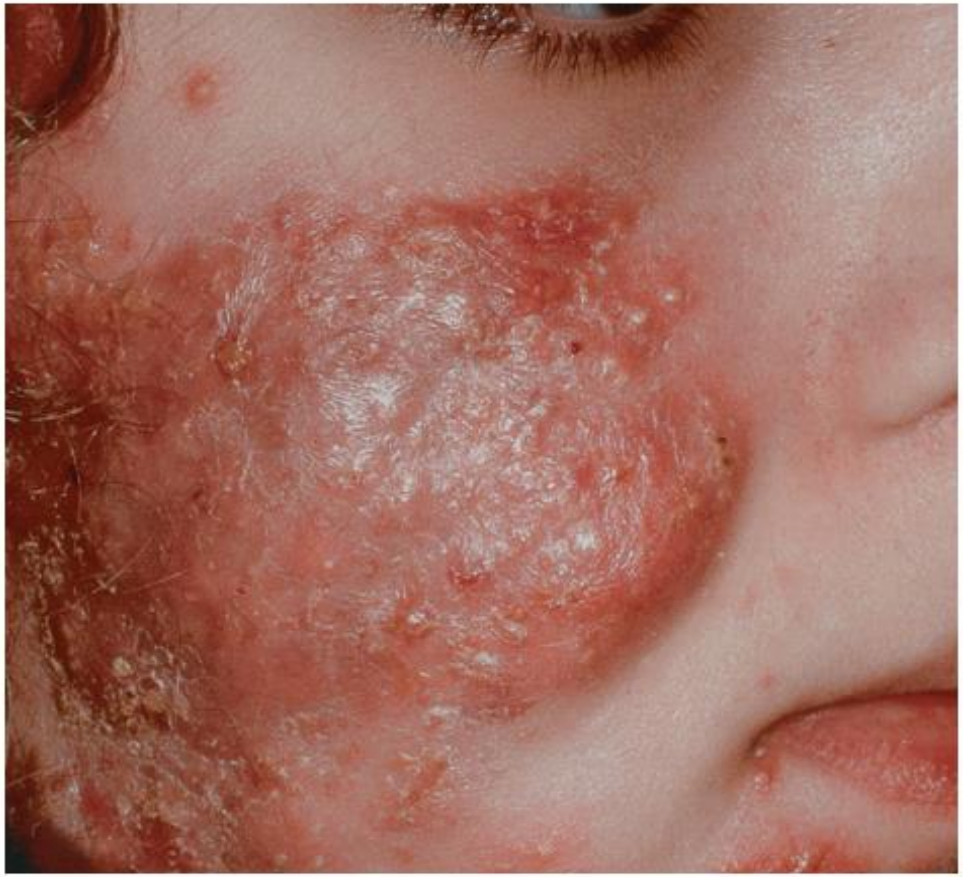


Fig. 37.12 Rosacea fulminans (pyoderma faciale). Striking plaque on the cheek studded with pustules.

ROSACEA-LIKE DISORDERS

• **Periorificial dermatitis**, originally termed perioral dermatitis, bears a superficial resemblance to rosacea, but the distribution pattern – perioral, perinasal, and/or periocular rather than centrofacial – and the lesional morphology differ.

- In periorificial dermatitis, there are monomorphous superficial pinpoint pustules and/or pink papules, patches and thin plaques, some of which have fine scale
- A history of topical or inhaled corticosteroid use may be elicited.
- Overuse of cosmetics and moisturizers has also been implicated in exacerbating periorificial dermatitis, and intolerance of sunlight and hot water are common symptoms.
- A 4- to 8-week course of oral antibiotics (e.g. doxycycline, erythromycin, tetracycline, minocycline) is usually effective in clearing the skin; azithromycin 500 mg three times weekly for 4–8 weeks represents an alternative therapy.
- If topical corticosteroids are implicated in causing perioral dermatitis, they should be discontinued
- However, a reduction in the strength and frequency of application of the topical corticosteroid, as opposed to an abrupt discontinuation, may help to avoid a significant rebound flare of the disease.

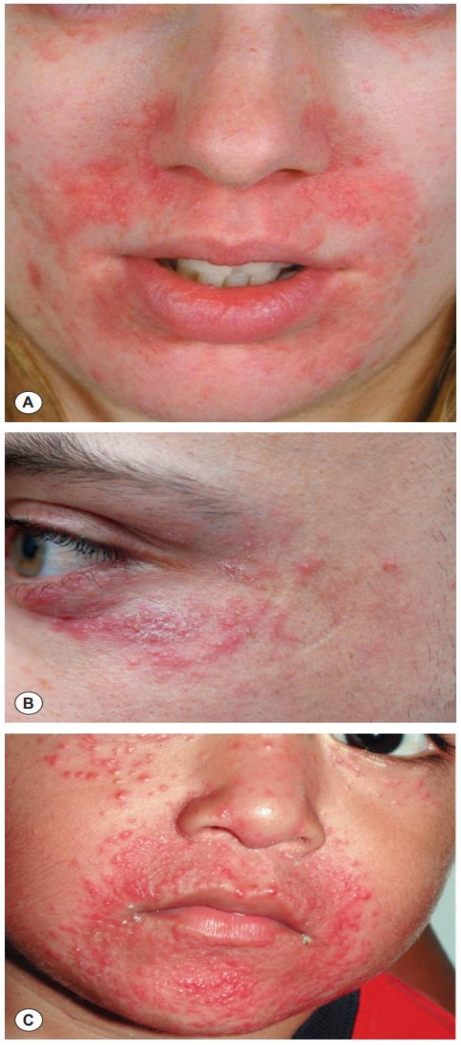


Fig. 37.13 Periorificial dermatitis (often referred to as perioral dermatitis). A,B Pink papules, patches and thin plaques as well as pinpoint superficial pustules around orifices, i.e. in a perioral, perinasal, and/or periorbital distribution pattern. In contrast to papulopustular rosacea, the papules are usually at the same stage of evolution. **C** Granulomatous periorificial dermatitis in a child with monomorphous pink papules that have become confluent around the mouth. The eruption, which had previously worsened upon treatment with topical and oral corticosteroids, resolved with a 6-week course of azithromycin. *B, Courtesy, Kalman Watsky, MD; C, Courtesy, Julie V Schaffer, MD.*

- Clearance is usually not followed by a subsequent relapse unless the patient is re-exposed to the inciting trigger.
- A variant seen in children is referred to as chronic granulomatous periorificial disease of children
- Steroid-induced “rosacea” is a facial eruption in which erythema, papules and pustules, and in some patients atrophic changes such as telangiectasias, develop from the repeated application of moderate to high potency topical corticosteroids
- As with periorificial dermatitis, reducing the strength of the topical corticosteroid as well as the frequency of application (rather than an abrupt discontinuation) is advisable to reduce a rebound flare.
- Systemic doxycycline, tetracycline, minocycline, azithromycin or erythromycin may also be required for 4 to 8 weeks.
- •

Rosaceiform dermatitis is a term usually employed to describe a cutaneous reaction to a drug that clinically resembles rosacea.

- It is due primarily to topical or systemic corticosteroids and topical calcineurin inhibitors and is characterized by facial erythema plus small papules and numerous pustules.
- The distribution on the face is usually widespread, although there are exceptions.
- Abundant Demodex mites have been found on the facial skin of some of these patients, possibly the result of the immunomodulating effects of the inciting medications.
- This term is also used by some clinicians to describe patients with features of both rosacea and facial dermatitis

Acneiform papulopustular eruption due to growth factor receptor (EGFR) inhibitors

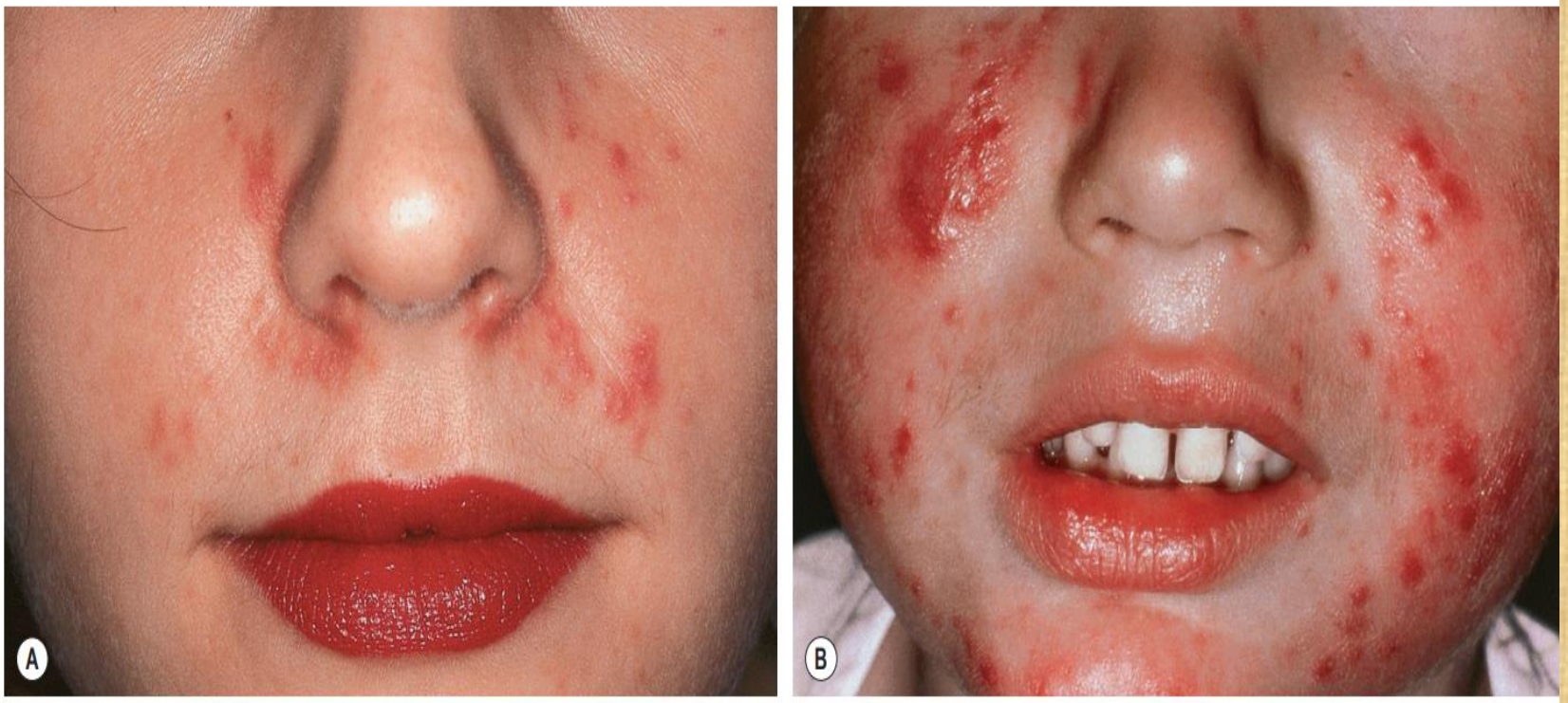


Fig. 37.14 Steroid rosacea. A Milder disease in an adult with scattered erythematous papules and papulopustules of the central face. **B** Severe disease in a chil with confluence of erythematous papulopustules. *A, Courtesy, Kalman Watsky, MD.*

Idiopathic facial aseptic granuloma (IFAG) usually presents with a single erythematous nodule on the cheek of a child which persists for several months then spontaneously resolves.

- One theory is that it represents a form of childhood granulomatous roseacea.

Pityriasis folliculorum is a poorly recognized disorder that primarily affects women in the 20- to 40-year age group who rarely allow water to contact their face and who instead often apply moisturizing and cleansing creams as well as cosmetic preparations.

- There is a roughened whitish scaling skin surface (referred to as “frosty”) on a background of faint erythema, along with some scattered fine papules and pustules that are not limited to the central face.
- The patient usually complains of “sensitive” facial skin and burning stinging sensations.
- Gentle scraping of the skin surface with a glass slide reveals the presence of multiple dead and some live Demodex mites.
- Application of topical sulfur or permethrin 5% cream at night for 4 to 6 weeks is usually effective when combined with a facial washing routine; it is possible that topical ivermectin may also be effective.

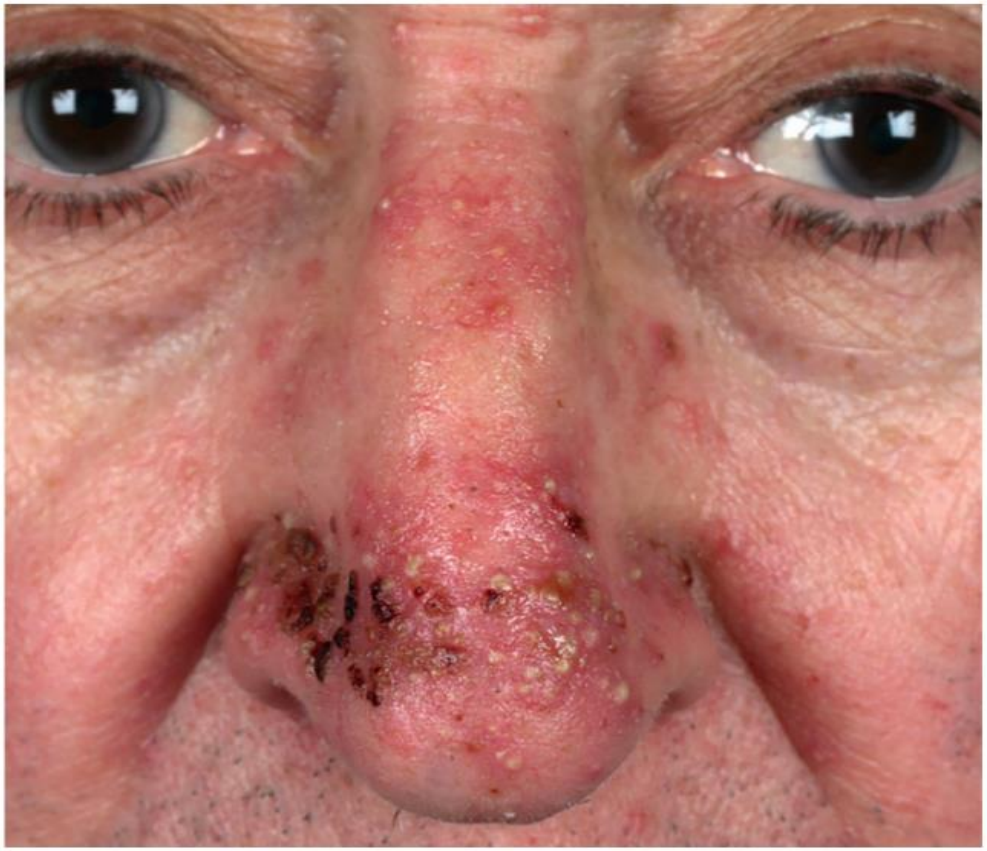


Fig. 37.15 Papulopustular eruption due to an epidermal growth factor receptor (EGFR) inhibitor. There is a resemblance to rosacea but the onset is more abrupt.

- Morbihan disease is a rare facial disorder characterized by a progressive and persistent, asymptomatic, non-pitting swelling of the central upper face that is associated with fixed facial erythema

- Lymphedema in this location can result from a number of initiating factors, from injuries to contact allergy to acne vulgaris.

- Some authors believe that rosacea represents an additional trigger while others, including the authors of this chapter, think any true relationship to rosacea is doubtful.

- Histologically, it may be indistinguishable from other forms of rosacea, including presenting with granulomatous features.

- Lymphedema can also be seen.

- There is no consistently effective therapy, but prolonged courses of antihistamines and low-dose oral isotretinoin have been reported as helpful in individual patients.

- Patients with Haber syndrome, currently viewed as a subtype of Dowling–Degos disease with comedones of the trunk and pitted scars, can also have early-onset, rosacea-like facial erythema.

Fig. 37.16 Morbihan disease. Erythematous, firm, non-pitting, asymptomatic swelling of the upper midface. Areas of greatest involvement can acquire a "peau d'orange" appearance.