Chapter 2

Acne Vulgaris

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Additional information is available at the end of the chapter

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Abstract

Acne vulgaris is a multifactorial disorder of the pilosebaceous unit. The clinical picture can range from mild comedones to fulminant, scarring cases. Approximately 83–100% of all adolescents experience acne vulgaris at some point of their lives. Although acne often tends to resolve following the adolescent period, many men and women continue to suffer from either active acne or postinflammatory scars into their twenties and thirties. Most patients with acne vulgaris are in the complicated adolescence period and thus carry a distinctive psychosocial burden. They possess a disease stigma on their skin for the external world to criticize every day. For all these reasons, acne is a disease which should be treated promptly and efficiently in all age groups. This chapter will provide a comprehensive and up-to-date review of pathophysiology of acne vulgaris, new molecular mechanisms on the evolving acne lesions, epidemiology of the disease, and latest treatment options. The molecular biology of acne lesions, novel treatment options including cosmetic approaches, their role in acne pathogenesis, pathophysiology, and mechanism of actions of the drugs, safety, and efficacy issues, and various treatment regimens will be discussed along with novel discoveries and areas in which further research is needed.

Keywords: acne vulgaris, acne vulgaris pathophysiology, treatment of acne vulgaris, systemic treatment of acne vulgaris

1. Introduction

Acne vulgaris is a disease of the pilosebaceous unit. The disorder has a very broad spectrum of clinical picture, from mild comedones to deep inflamed nodules with systemic findings. Acne vulgaris is mainly observed during the adolescent period. Although all age groups may be affected, being primarily a disorder of adolescence, it has a big psychosocial effect leading to low self-esteem, social isolation, and major depression [1].

2. History

The source of the word acne is controversial. It may be derived from the Greek *achne*, a word meaning efflorescence, or the Greek *acme* (Latin acme), which implies a summit or peak. Others have pointed to a hieroglyphic for the word AKU-T as the first written record referring to acne, a symbol interpreted to mean "boils," "pustules," or "a painful swelling" [2]. In the sixth century AD, the term "acne" was first used by the Emperor Justinian's physician, Aetius Amidenus [3]. Its use became obsolete by the 1800s, when "acne" regained a place in medical dictionaries. In 1842, Erasmus Wilson separated acne simplex (acne vulgaris) from acne rosacea [4].

3. Epidemiology

Between 30 and 50% of adolescents experience psychological difficulties associated with acne, including body image concerns, embarrassment, social impairment, anxiety, frustration, anger, depression, and poor self-esteem [5]. The prevalence of body dysmorphic disorder among acne patients has been measured to be as high as 21% in some office settings [6], and these patients are more likely to report dissatisfaction with dermatologic treatment, attempt suicide, and threaten health-care providers both legally and physically [7, 8].

Acne vulgaris affects approximately 40–50 million individuals each year in the USA, with an estimated cost of $2.5 billion annually. The disease affects approximately 85% of young people between 12 and 24 years of age and often tends to continue into the adulthood. In a survey-based study, 35% of women and 20% of men reported having acne in their thirties, while 26% of women and 12% of men were still affected in their forties [9]. Males of Caucasian origin have a tendency to have more severe nodulocystic disease than other groups. Individuals with XYY karyotype or endocrine disorders such as polycystic ovarian syndrome, hyperandrogenism, hypercortisolism, and precocious puberty are at increased risk for acne development, with a more resistant clinical course.

4. Pathogenesis

The development of acne involves a complex interaction of multiple factors within the pilosebaceous gland. Understanding the anatomy and physiology of this unique structure is vital to understanding the pathogenesis of acne and important for formulating effective treatment regimens.

Acne vulgaris is a disease of pilosebaceous units. Major hypotheses on its pathophysiology include the following [10, 11]:

1. Altered follicular keratinization (hyperkeratinization) of the pilosebaceous unit [12]
2. *Propionibacterium acnes* (*P. acnes*) follicular colonization and activity [13]
3. Hormonal influence [14, 15]

4. Sebum production [16]

5. Release of inflammatory mediators [13, 17]

4.1. Genetic factors

The pathogenesis of acne is multifactorial, and the precise role of genetic predisposition is uncertain. The number, size, and activity of sebaceous glands are inherited. In addition, the concordance rate for the prevalence and severity of acne among identical twins is very high. Variable studies have shown strong association between moderate to severe acne and family history [18]. However, because of the high prevalence of acne, it is difficult to attribute its presence only to genetic factors.

4.2. Sebum production

The sebaceous gland is controlled primarily by hormonal stimulation. After the first 6 months of life (when sebum production is relatively high), the rate decreases and remains stable throughout childhood. At adrenarche, sebum production dramatically increases. Although the overall composition of sebum is the same in persons with or without acne, those with acne have variable seborrhea [19].

The sebaceous glands exude lipids by disintegration of entire cells, a process known as *holocrine secretion*. The life span of a sebocyte from cell division to holocrine secretion is approximately 21–25 days [20]. Human sebum, as it leaves the sebaceous gland, contains squalene, cholesterol, cholesterol esters, wax esters, and triglycerides. During passage of sebum through the hair canal, bacterial lipases from *P. acnes* hydrolyze some of the triglycerides, so that the lipid mixture reaching the skin surface contains free fatty acids (FFA) and small proportions of mono- and diglycerides in addition to the original components. The precise function of sebum in humans is unknown. Cunliffe and Shuster proposed that sebum's solitary role is to cause acne [21]. Another theory suggests that sebum reduces water loss from the skin's surface and functions to keep skin soft and smooth. The sebaceous gland-deficient mouse (Asebia) model provides evidence that glycerol derived from triglyceride hydrolysis in sebum is critical for maintaining stratum corneum hydration [22], but there is no evidence for this in humans as stratum corneum hydration is normal during periods, such as, childhood when the gland is quiescent. Similarly, vitamin E delivery to the upper layers of the skin protects the skin and its surface lipids from oxidation; thus, sebum flow to the surface of the skin may provide the transit mechanism necessary for vitamin E to function [23]. Recent evidence suggests that sebaceous glands and sebum play a role in the skin's innate immunity. Sebum is known to have mild antibacterial action, presumably due to the presence of immunoglobulin A [24]. Recent studies show that FFA in human sebum is bactericidal against Gram-positive organisms as a result of its ability to increase antimicrobial peptide, b-defensin 2 (HBD2) expression [25]. Additional antimicrobial peptides including cathelicidin, psoriasin, b-defensin 1, and b-defensin 2 are expressed within the sebaceous gland. Functional cathelicidin peptides have direct antimicrobial activity against *P. acnes* but also initiate cytokine production and inflammation in the host organism [26, 27]. Innate immune Toll-like receptors 2 and 4 (TLR2, TLR4) and CD1d and CD14 molecules are also expressed in sebaceous glands [28]. All these findings

provide evidence that the sebaceous gland may play an important role in pathogen recognition and protection of the skin surface.

The exact mechanisms underlying the regulation of human sebum production are not fully defined. Results from a variety of experimental models clearly indicate that sebaceous glands are regulated by androgens and retinoids. Recent evidence suggests that peroxisome proliferator activated receptors, melanocortins, corticotropin-releasing hormone, and fibroblast growth factor receptors play a role as well.

The role of sebum in the pathogenesis of acne is closely associated with the activity of *P. acnes*. The microenvironment within the sebaceous gland is anaerobic and favors the survival of *P. acnes* bacteria over others (i.e., *Staphylococcus epidermidis*). The *P. acnes* bacterium relies on sebaceous lipids as a nutrient source and breaks down triglycerides into FFA, which can be irritating and contribute to the inflammatory response [29, 30]. Furthermore, it is demonstrated that *P. acnes* is capable of stimulating the production of both proinflammatory cytokines/chemokines and antimicrobial peptides from keratinocytes and cultured sebocytes, indicating that keratinocytes and sebocytes themselves may play a role in the inflammatory aspects of acne [31, 32].

4.3. Comedo formation

First step of acne production is the formation of microcomedo, which begins in the infundibulum, the keratinized lining of the upper portion of the follicle. The corneocytes are normally shed into the lumen of the follicle and extruded through the follicular ostium. When they are retained and accumulated, this leads to hyperkeratosis. Lamellar granules, cell membranes, epidermal lipids, and intercellular cementing substances all play a role in the increased adhesiveness of these cells. In addition to increased intercellular cohesiveness of the corneocytes, their production is also accelerated. In the proximal portion of the infundibulum, the infrainfundibulum, combination of increased cellular cohesion, and proliferation creates a bottleneck phenomenon and subsequent microcomedo formation. In the underlying follicular epithelium, keratohyaline granules are increased in size and number, whereas lamellar granules and tonofilaments are decreased. As the comedo expands, the sebaceous lobule undergoes regression. Because of the very narrow opening to the skin surface, there is initially an accumulation of loosely packed shed keratinocytes and sebum. With expansion of the comedo, the contents become closely packed, creating whorled lamellar concretions. With increased pressure, rupture of the comedo wall leads to extrusion of the immunogenic keratin and sebum, with resultant inflammation.

4.4. Inflammatory responses

Inflammation is not always a result of comedo rupture and can also be observed in early acne lesions. Prior to hyperkeratinization, the number of CD4+ T cells and levels of interleukin-1 (IL-1) have been shown to be increased perifollicularly, especially in acne-prone sites [33]. If neutrophils predominate (typical of early lesions) in the lesion, a suppurative pustule is formed. Neutrophils also promote the inflammatory response by releasing lysosomal enzymes and generating reactive oxygen species, which directly correspond with acne

severity [34]. Influx of lymphocytes (predominately T-helper cells) and foreign body-type giant cells, together with neutrophils result in inflamed papules, nodules, and cysts. Genetics are likely to play a role as not all patients with inflammatory acne will scar and patients often report that their parents also have severe scarring from acne in their youths. Data suggest that the likelihood of scarring is associated with the type of inflammatory response. Early, nonspecific inflammation results in less scarring whereas delayed and specific inflammatory response lead to permanent scar tissue [35]. Holland et al. observed that in inflammatory lesions from patients who have less scarring, there is a brisk inflammatory cellular infiltrate composed of T-helper lymphocytes, macrophages, and Langerhans cells, with accompanying angiogenesis that quickly resolves compared with patients who are prone to scarring, where the inflammation and angiogenesis start slowly but is maintained over a longer period. It is speculated that the prolonged inflammatory response in patients prone to scarring is a delayed-type hypersensitivity reaction to persistent antigenic stimulus that they were initially unable to eliminate [36]. As there is no tool to predict who will develop this delayed-type reaction, treating early inflammation is the best approach to prevent acne scarring.

4.5. *Propionibacterium acnes* and the innate immune system

These Gram-positive, non-motile rods which contributes significantly to the pathogenesis of acne are found deep within the sebaceous follicle, along with *Propionibacterium granulosum* and, rarely, *Propionibacterium parvum*. They are anaerobic/microaerophilic and naturally produce porphyrins (primarily coproporphyrin III) that fluoresce with Wood's lamp illumination. These microorganisms release enzymes contributing to comedo rupture, lipases and chemotactic factors, and stimulate host response by inflammatory cells and keratinocytes leading to production of proinflammatory mediators and reactive oxygen species. In acne patients, the number of *P*. acnes cases is increased, but their numbers do not correlate with clinical severity [37]. Different strains of *P. acnes* have been shown to induce varying degrees of sebocyte differentiation and proinflammatory cytokine/chemokine responses [32].

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 such as monocytes, macrophages, and neutrophils as well as by keratinocytes. TLR2 is found on the surface of macrophages surrounding acne follicles, and *P. acnes* has been found to increase expression of TLR2 and TLR4 on keratinocytes. *P. acnes* has been shown to stimulate the release of proinflammatory mediators (e.g. IL-1α, IL-8, IL-12, tumor necrosis factor-α [TNF-α], matrix metalloproteinases) through the TLR2 pathway [38–40]. IL-8 results in neutrophil recruitment, the release of lysosomal enzymes and subsequent disruption of the follicular epithelium, whereas IL-12 promotes Th1 responses. The degree to which IL-8, IL-12, and interferon-γ production is augmented does not appear to depend upon the strain of *P. acnes* that is present [40, 41]. In contrast, certain strains of *P. acnes* may have an increased propensity, to upregulate expression of human β-defensin-2 by the pilosebaceous unit via a TLR-dependent mechanism [42]. Beta-defensin-2 cathelicidins and other antimicrobial peptides such as psoriasin work synergistically to protect the pilosebaceous unit from *P. acnes* [26, 43]. Histone H4, which is secreted in a holocrine manner by sebocytes, also directly kills *P. acnes*

and may function together with free fatty acids to augment innate immune defenses [44]. Lastly, *P. acnes* can induce monocytes to differentiate into two distinct innate immune cell subsets: (1) CD209+ macrophages (development of which is promoted by tretinoin) that more effectively phagocytose and kill *P. acnes* and (2) CD1b+ dendritic cells that activate T cells and release proinflammatory cytokines [45].

All these new findings about the role of innate immunity on acne formation build upon traditionally known pathogenetic factors can be summed up as follows;

1. Inflammatory events mediated by interleukin-1 precede hyperkeratinization
2. *P. acnes* activates the innate immune system via Toll-like receptors
3. *P. acnes* induces matrix metalloproteinase and antimicrobial peptide production
4. Sebaceous gland lipids influence the innate immune system.

4.6. Hormonal influences

Sebum secretion is under direct influence of hormonal factors. Androgens are produced primarily from the gonads and adrenal glands but also locally via the enzymes of 3β-hydroxysteroid 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). DHT is the principal androgen mediating sebum production and has a 5–10-fold greater affinity than testosterone for the androgen receptor. The role of androgens in sebaceous gland activity begins during the neonatal period. With the onset of adrenarche (typically at 7–8 years of age, usually heralding menarche by several years), circulating levels of DHEAS begin to rise due to adrenal production. 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 the initial development of comedonal acne [46]. The exact mechanism of how estrogens modulate sebum production is not known. Any estrogen given systemically in sufficient amounts will decrease sebum production. However, the dose of estrogen required to suppress sebum production is greater than the dose required to suppress ovulation. Although acne may respond to treatment with lower-dose oral contraceptives containing 0.035–0.050 mg of ethinyl estradiol or its esters, higher doses of estrogen are often required to demonstrate a reduction in sebum secretion [47]. Estrogens may inhibit the effects of androgens locally within the sebaceous gland or via a negative feedback loop whereby pituitary gonadotropin release is inhibited.

4.7. Dietary factors

It has long been posited that diet has no impact on acne, but recent clinical trials have suggested that a relationship does indeed exist. The relationship between diet and acne has always been controversial. The association between glycemic load and acne is especially convincing. Prospective studies have documented a link between a high glycemic-load diet and acne risk [48]. Further clinical trials among a wider patient base could better define recommendations

for modifying carbohydrate intake, but until then, it is appropriate for dermatologists to recommend a lower glycemic load diet among patients with acne.

Although the link between dairy and acne is less convincing than high glycemic load diet, a recent case control study showed a positive association between low-fat/skim milk consumption and acne [49]. The exact mechanism by which dairy may impact acne, whether it is via a hormonal pathway or upregulated IGF-1, remains to be further clarified. If physicians choose to counsel their patients that dairy consumption may indeed exacerbate their acne, it is reasonable to simultaneously advise patients to supplement their diets with vitamin D and calcium. The role of o-3 fatty acids, antioxidants, zinc, vitamin A, and iodine in acne vulgaris remains to be elucidated. Given the level of evidence available if a particular patient notes an association between a certain dietary factor and acne severity, it is best to support that patient's dietary supplementation or restriction and to encourage the patient to keep a food diary to test his or her hypothesis.

5. Clinical features

Acne is mostly observed on the facial area and upper trunk, areas with increased number of sebaceous glands (**Figure 1**). Comedones constitute non-inflammatory lesions of acne.

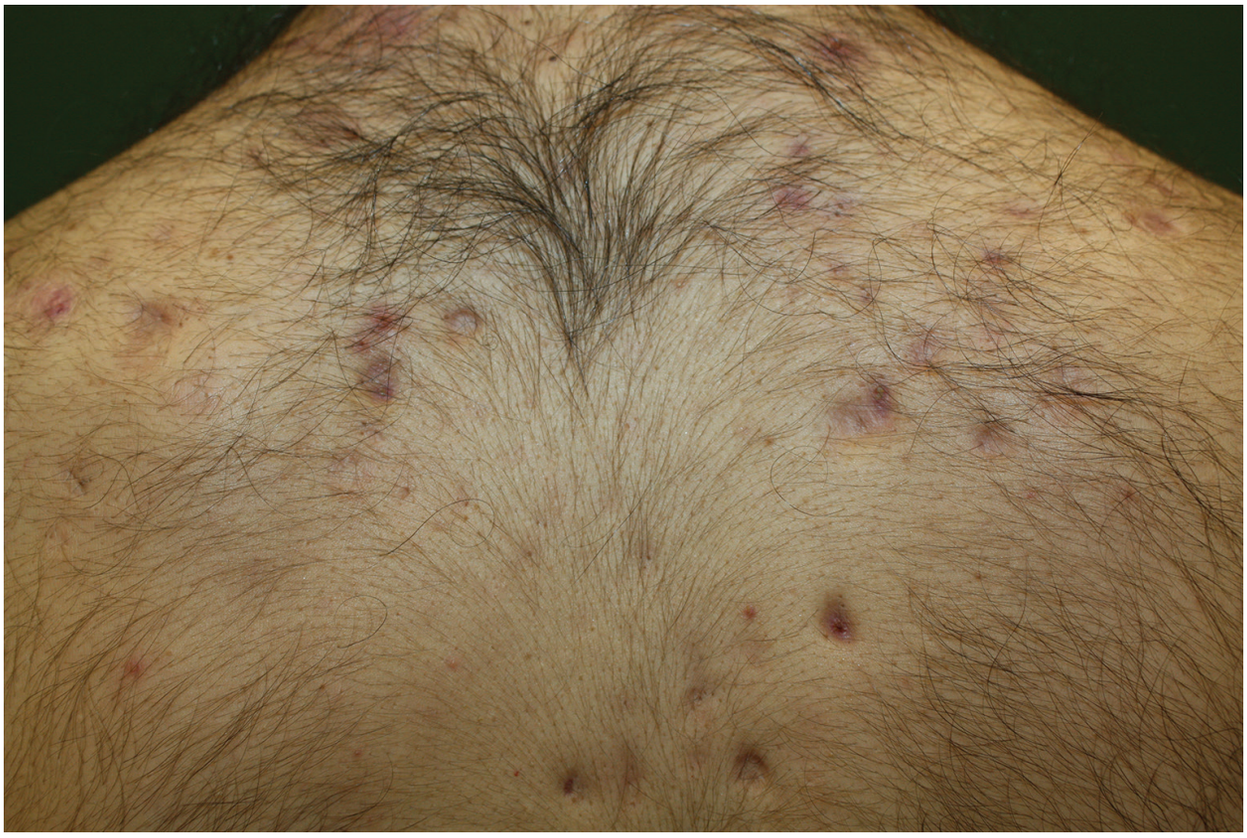

Figure 1. Acne lesions and scars are seen on the back of the patients.

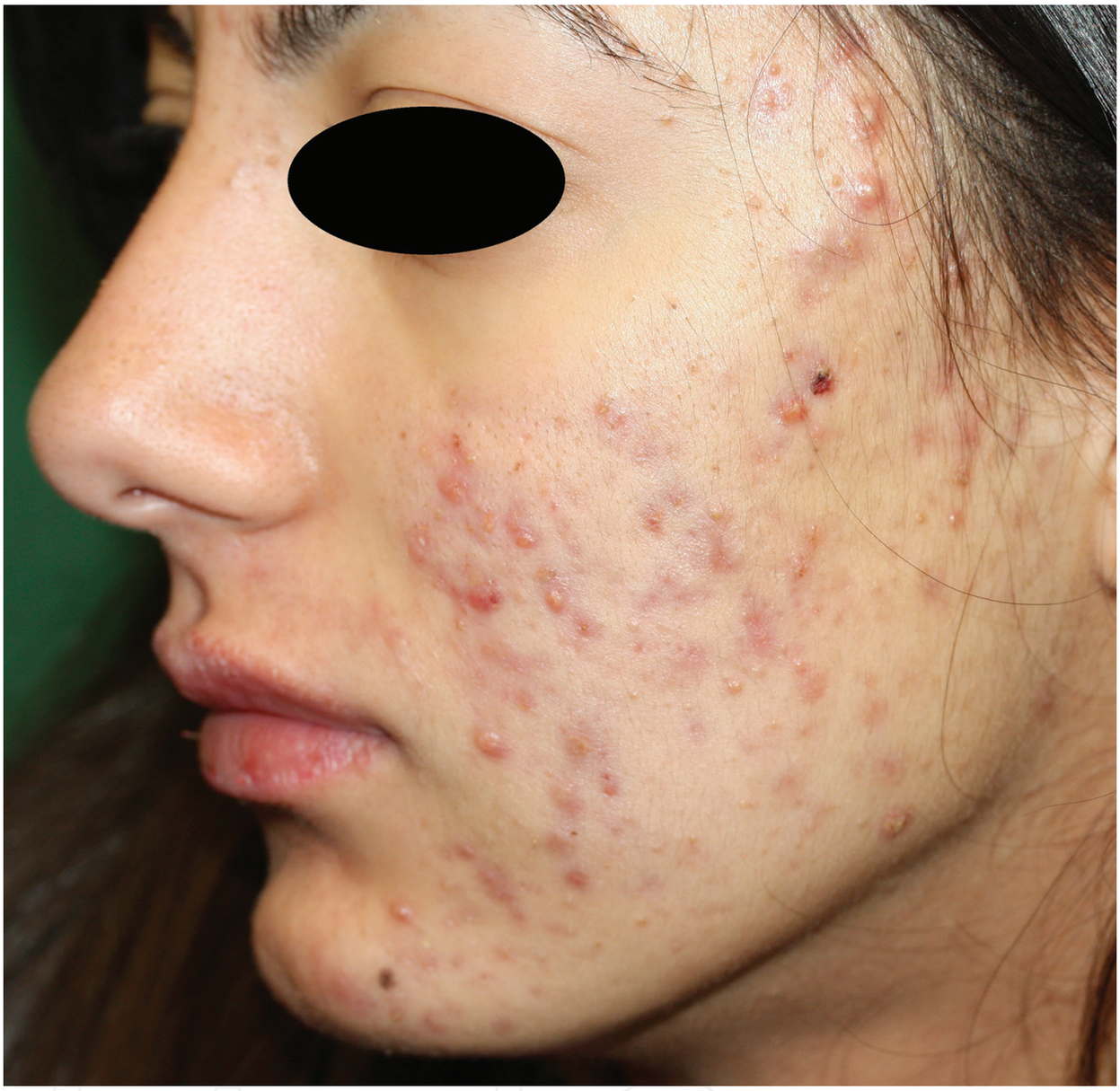

Figure 2. Marked papules, pustules, and comedones are noticed.

Closed comedones are small skin-colored papules with no apparent follicular opening. These lesions may be subtle and best diagnosed via palpation, stretching or side-lighting of the skin. Open comedones, on the other hand, mostly referred as blackheads, are dome-shaped papules with dilated follicular openings filled shed keratin. Black coloration is due to melanin deposition and lipid oxidation within the debris. Inflammatory acne also originates with comedo formation, followed by the development of papules, pustules, nodules, and cysts (**Figure 2**).

Erythematous papules typically range from 1 to 5 mm in diameter. Pustules tend to be approximately equal in size and are filled with white pus and normal flora. As the severity of lesions progresses, nodules form and become markedly inflamed, indurated, and tender.

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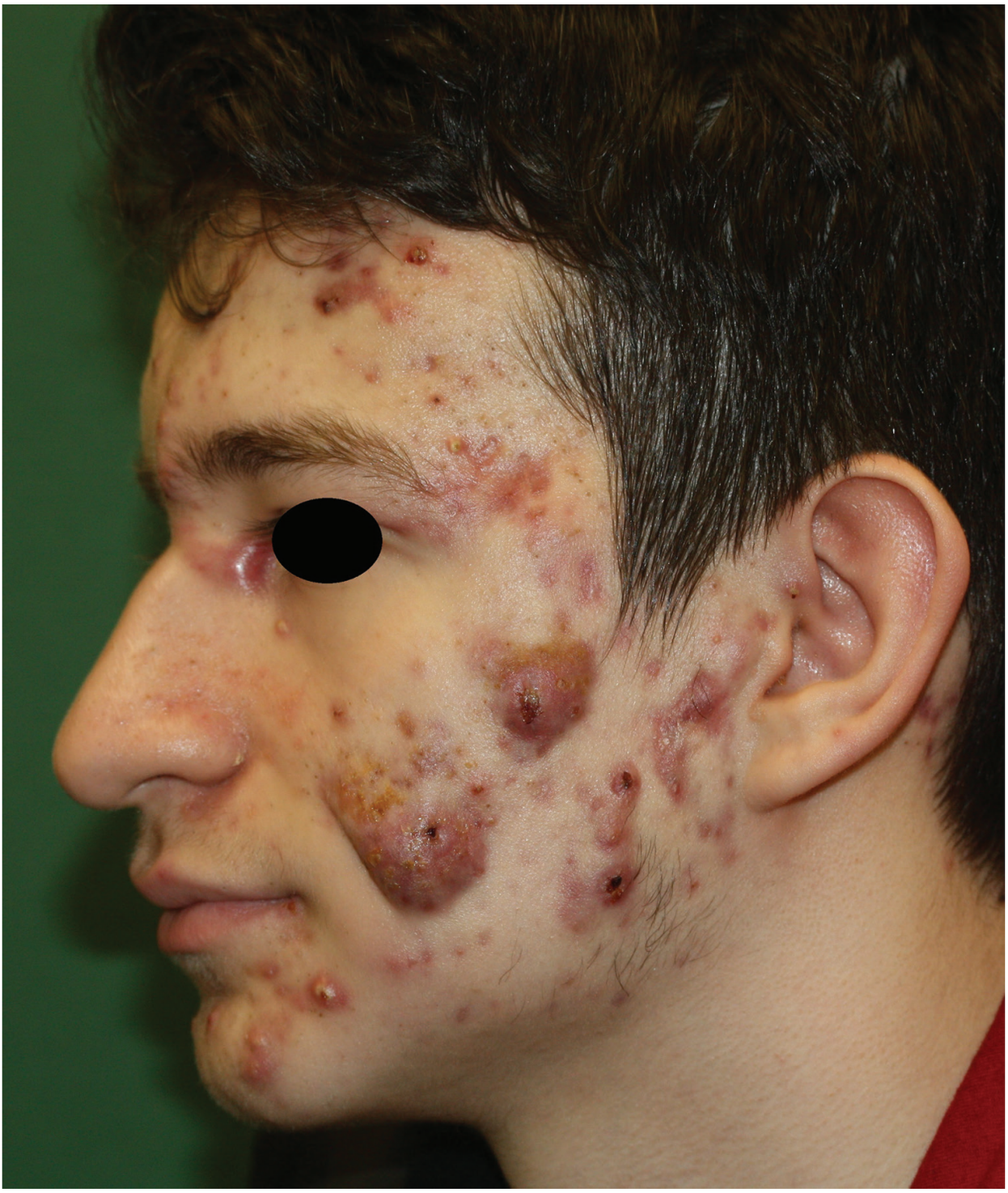

Figure 3. Severe nodules and cysts on the face.

The cysts of acne are deeper and filled with a combination of pus and serosanguineous fluid. In patients with severe nodulocystic acne (**Figure 3**), 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. Pigmentary changes usually fade away in months whereas pitted or hypertrophic scars are often permanent.

5.1. Acne variants

5.1.1. Postadolescent acne

This form of acne mostly affects women older than 25 years of age with signs of hyperandrogenism and increases in severity prior to menstruation. The lesions consist of tender, deep-seated papulonodules on the lower third of the face, jawline, and neck [50]. Hormonal therapy is often effective regardless of androgen levels.

5.1.2. Acne fulminans

It is the most severe form of acne and is characterized by nodular and suppurative acne lesions with systemic manifestations. It primarily affects adolescent boys who typically have mild to moderate acne prior to the onset of acne fulminans. Numerous microcomedones suddenly erupt and become markedly inflamed. Most commonly affected areas are the face, neck, chest, back, and arms. 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. Systemic manifestations include fever, arthralgias, myalgias, hepatosplenomegaly, and severe malaise. The related *s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis and *o*steitis can be seen and is defined as SAPHO syndrome. Erythema nodosum may also arise in association with acne fulminans. An elevated ESR, proteinuria, leukocytosis, and anemia mostly accompanies and may be related with the clinical course and response to therapy.

Treatment of acne fulminans usually includes initial oral corticosteroid treatment, followed by systemic isotretinoin, after the acute inflammation subsides. During the first few weeks of isotretinoin therapy, acne fulminans-like flares can be observed [51]. Oral antibiotics, TNF-α inhibitors, and immunosuppressive agents (e.g. azathioprine) can also be used. Acne fulminans associated with erythema nodosum responds well to dapsone therapy [52].

5.1.3. Acne conglobata and associated conditions

Acne conglobata is also a severe form of nodulocystic acne that may have a sudden onset but without systemic manifestations. The nodules are usually found on the chest, shoulders, back, buttocks, upper arms, thighs, and face (**Figure 4**). It is a part of the follicular occlusion tetrad, along with dissecting cellulitis of the scalp, hidradenitis suppurativa, and pilonidal cysts. The association of sterile *p*yogenic *a*rthritis, *p*yoderma gangrenosum, and *a*cne conglobata can occur in the context of an autosomal dominant autoinflammatory disorder referred to as PAPA syndrome [53]. This syndrome is caused by mutations in the gene that encodes *p*roline–*s*erine–*t*hreonine *p*hosphatase *i*nteracting *p*rotein 1 (PSTPIP1) which leads to the disruption of the physiologic signaling required for maintenance of a proper inflammatory response [53].

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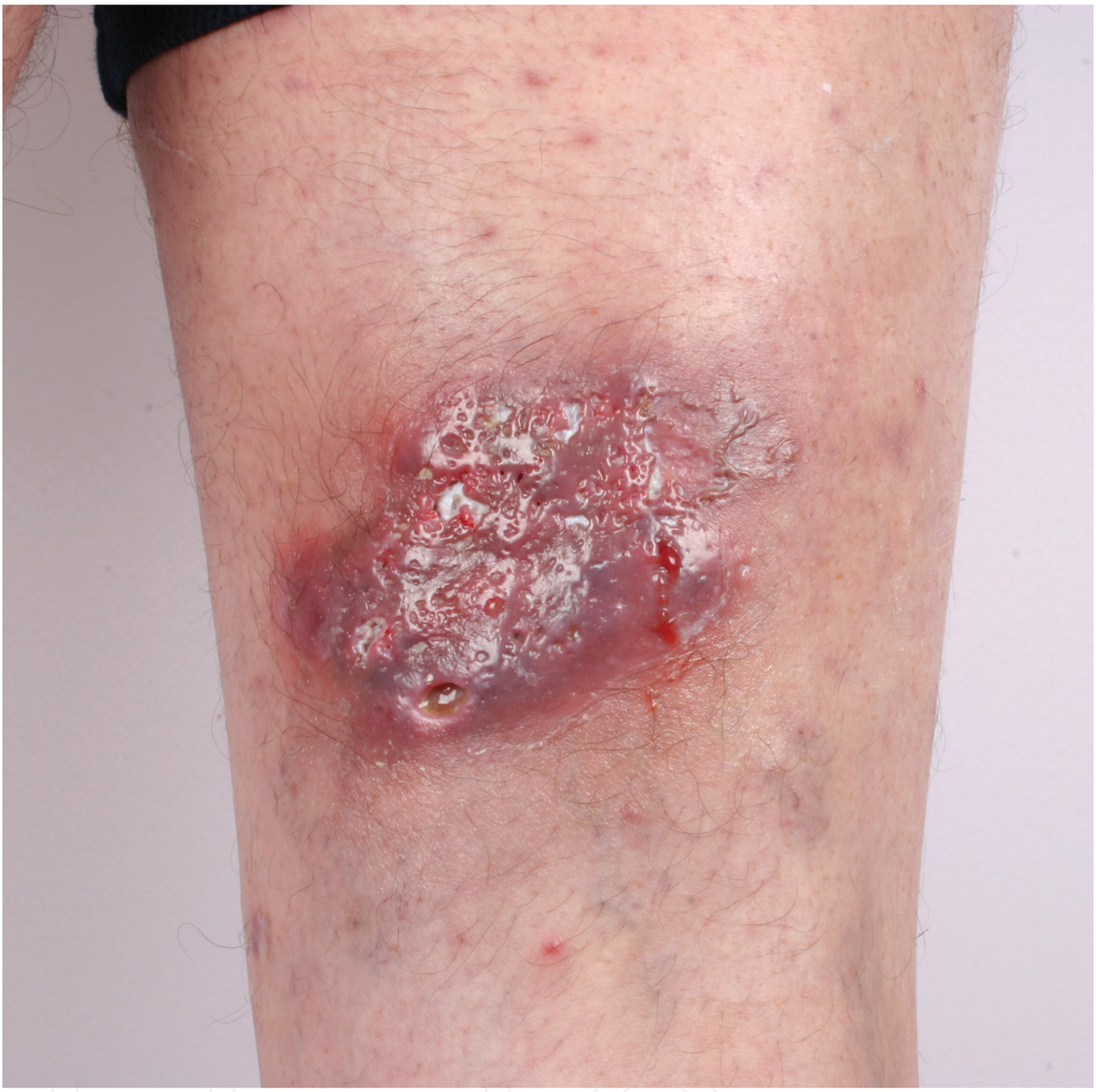

Figure 4. A closer view of draining sinuses and nodules on the lower extremity.

5.1.4. Solid facial edema

An unusual and disfiguring complication of acne vulgaris is solid facial edema (Morbihan's disease). Clinically, there is a distortion of the midline face and cheeks due to soft tissue swelling and accompanying erythema. Due to chronic inflammation and mast cell activation, lymphatic drainage is impaired resulting in fibrosis. Similar changes have been described in patients with rosacea and Melkersson-Rosenthal syndrome. The degree of the edema may change but solid facial edema does not usually resolve spontaneously. Treatment options include systemic isotretinoin alone or together with ketotifen or systemic corticosteroids [54, 55].

5.1.5. Acne mechanica

This form occurs secondary to repeated mechanical and frictional trauma causing obstruction of the pilosebaceous outlet. Rubbing by helmets, chin straps, suspenders or collars can be responsible for acne mechanica. Linear and geometrically distributed comedones are characteristic.

5.1.6. Acne excoriée des jeunes filles

Typical comedones and inflammatory papules are systematically excoriated, leaving crusted and linear erosions (**Figure 5**). An underlying psychiatric component should be considered.

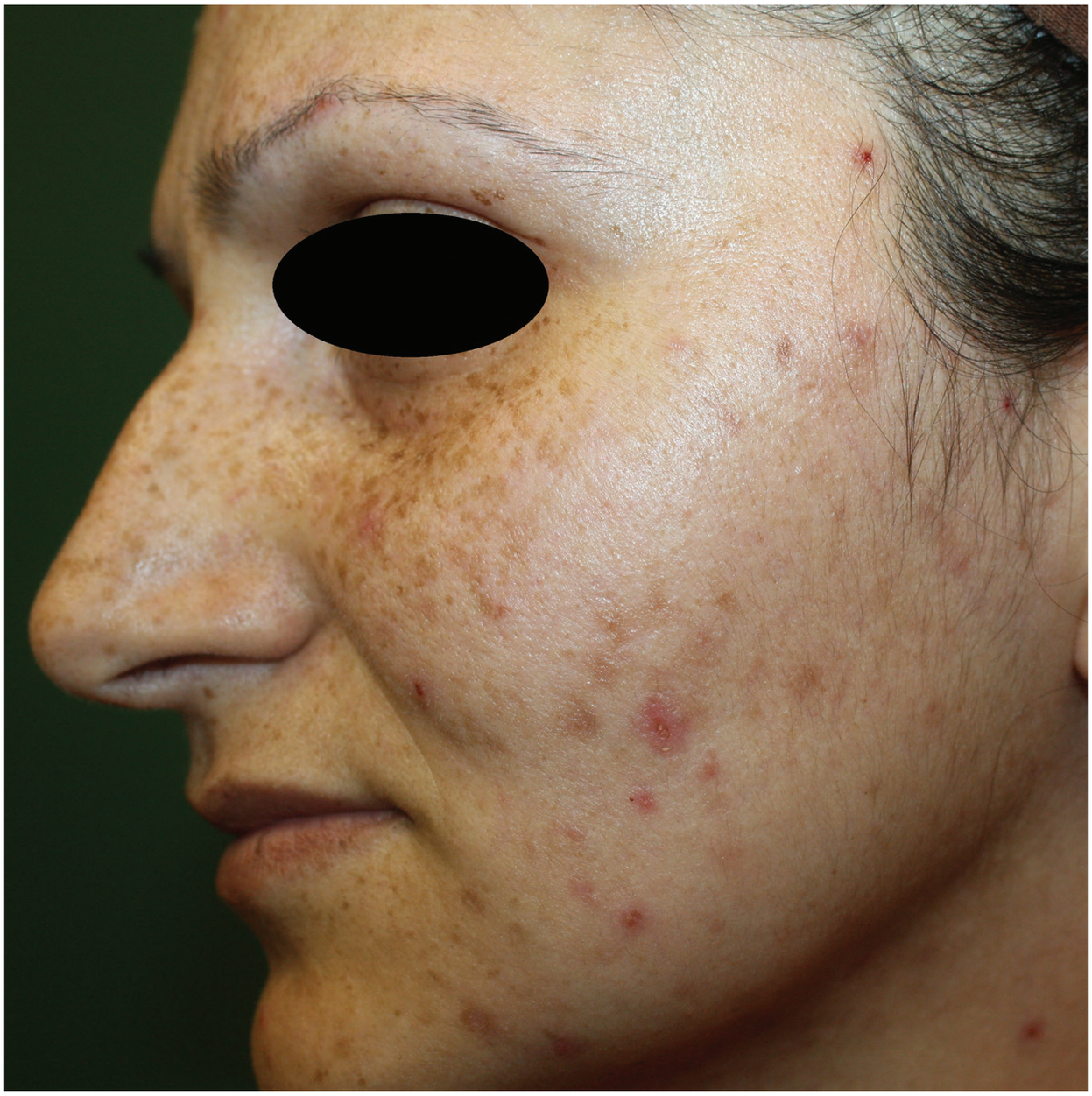

Figure 5. Excoriated inflammatory lesions are seen.

Individuals with an anxiety disorder, obsessive–compulsive disorder or personality disorder are particularly at risk.

5.1.7. Drug-induced acne

Acne or eruptive acneiform lesions can be seen as a side effect of certain drugs. Characteristically abrupt, mono morphous eruption of inflammatory papules and pustules are observed. 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 postwithdrawal.

5.1.8. Occupational acne, acne cosmetica

Occupational acne results from exposure to insoluble, follicle-occluding substances. Cutting oils, petroleum-based products, chlorinated aromatic hydrocarbons, and coal tar derivatives can be responsible. Comedones together with papules, pustules, and cystic lesions distributed in exposed as well as typically covered areas. *Acne cosmetica* is mostly seen as closed comedones, due to chronic occlusion of follicles with the use of cosmetics.

5.1.9. Chloracne

It is caused several weeks after the exposure to chlorinated aromatic hydrocarbons. Most commonly affected areas are the malar, retroauricular, and mandibular regions of the head and neck, axillae, and scrotum. Small cystic papules and nodules are seen and healing with scar tissue formation is not uncommon. 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.

5.1.10. Neonatal acne (neonatal cephalic pustulosis)

Neonatal acne can be observed in more than 20% of healthy newborns. Lesions usually start appearing 2 weeks after birth and generally resolve within the first 3 months of life. Small, inflamed papulopustules without comedones on the cheeks and nasal bridge are typical for neonatal acne. The disease responds well to topical imidazoles, and this also supports the inflammatory response to *Malassezia* spp. as a pathogenetic mechanism. The active sebaceous glands and high sebum excretion rate in neonates 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.

5.1.11. Infantile acne

Infantile acne occurs after 3 months of age and usually persists until the end of first year. In contrast to neonatal acne, comedo formation is prominent and pitted scarring can develop.

Deep cystic lesions and suppurative nodules are occasionally seen. Androgen production due to elevated levels of LH stimulating testicular production of testosterone in boys and elevated levels of DHEA produced by the infantile adrenal gland in both boys and girls is responsible from acne formation. These androgen levels normally decrease substantially by 12 months of age and remain at low levels until adrenarche. Thus infantile acne typically resolves within 1–2 years and remains quiescent until around puberty. 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 cases [56].

5.1.12. Endocrinologic abnormalities

Hyperandrogenism should be suspected in female patients with hirsutism or irregular menstrual periods, as well as in children who develop acne between 2 and 7 years of age. Hyperandrogenism-originated acne is often severe and resistant to therapy. Other signs and symptoms of hyperandrogenism in women and children include 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. Initial laboratory tests of serum levels of total and free testosterone, DHEAS, and 17-hydroxyprogesterone can give an idea about the source of excess androgens. An elevated serum DHEAS or 17-hydroxyprogesterone level indicates an adrenal problem such as congenital adrenal hyperplasia or an adrenal tumor. 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 level.

6. Pathology

Histopathologic stages of acne lesions show a parallel course with the clinical findings. In early lesions, microcomedones are seen. A mildly distended follicle with a narrowed follicular opening is impacted by shed keratinocytes. In closed comedones, the degree of follicular distension is increased and a compact cystic structure with eosinophilic keratinaceous debris, hair, and numerous bacteria is formed. Open comedones have broad, expanded follicular ostia and overall an increased follicular distension. Perivascular mononuclear cell infiltrate circles the expanding follicle. As the follicular epithelium distends, highly immunogenic cystic contents rupture into the dermis, inducing a marked inflammatory response. Neutrophils first appear, creating a pustule. As the lesion matures, scarring due to foreign body granulomatous inflammation can be seen.

7. Differential diagnosis

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 similar dermatoses including sebaceous hyperplasia and miliaria rubra. Predominantly comedonal acne vulgaris needs to be differentiated from comedonal eruptions caused by follicular occlusion or friction, including pomade and occupational acne, acne cosmetica and acne mechanica. Multiple open comedones are clustered in the lateral malar region in Favre-Racouchot disease or appear in a linear array in nevus comedonicus. Angiofibromas and appendageal tumors of follicular origin like trichoepitheliomas, trichodiscomas, and fibrofolliculomas, often present as multiple noninflammatory facial papules. Steatocystoma multiplex is also characterized by noninflammatory, closed cystic papules and nodules on the central chest and back. 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. Folliculitis lesions are typically monomorphous and comedones are not present. Acne vulgaris treated with oral antibiotics for a prolonged period can complicate with Gram-negative folliculitis. The papular component of rosacea favors the malar region, chin, and forehead; the presence of telangiectasias, absence of comedones and a history of easy flushing can lead to diagnosis. 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.

8. Treatment

Acne can have devastating physical as well as emotional effects and the treatment course of acne vulgaris requires a high degree of compliance. Thus it is critical that the patient be made aware of the nature of the disease process and what is to be expected from the treatment regimen prescribed. A complete history and physical examination are key to developing an appropriate and effective treatment plan. A review of all prescription and over-the counter medications used for acne or other conditions, and clinical responsiveness to them, together with 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. On physical examination, careful note should be taken of lesion morphology, including the presence of comedones, inflammatory lesions, nodules, and cysts. Secondary changes such as scarring and postinflammatory pigmentary changes are also important clinical findings. The patient's skin color and type can also influence the chosen formulation of a topical medication.

8.1. Topical treatments

8.1.1. Topical retinoids

Topical retinoids used for the treatment of acne vulgaris will be discussed in elsewhere.

8.1.2. Benzoyl peroxide and other topical antibacterial agents

Benzoyl peroxide (BPO) is still the gold standard for mild-to-moderate acne. It is the leading over the counter anti-acne agent in the United States. Different preparations including bar soaps, washes, gels, lotions, creams, foams, and pads with concentrations ranging from 2.5

to 10% are available as well as products which combine benzoyl peroxide with clindamycin, erythromycin, or adapalene. BPO is a bleaching agent, thus whitening of clothing and bedding can occur. İrritant or allergic contact dermatitis can develop to benzoyl peroxide, presenting with marked erythema. BPO 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.

The mechanism of action is presumably due to its strong oxidizing property. The release of free oxygen radical causes oxidation of bacterial proteins and the development of oxygen creates a milieu in the follicle, where anaerobic bacteria like *P. acnes* cannot survive [57–60]. BPO has a broad-spectrum and rapid activity against Gram-positive and Gram-negative bacteria, yeasts, and various fungi [58]. Significant and fast reduction in the number of propionibacteria from the skin surface and follicular casts can be achieved with topical use of BPO, starting within days after the initiation of the therapy. However, long-term use of the agent does not provide further decrease in the bacterial population [61–63].

Unlike common antibiotics, BPO is effective and can be readily used against antibiotic-resistant propionibacteria strains [60]. This agent shows its antibacterial action via powerful oxidation. This nonspecific mode of antibacterial action does not lead to the development of resistant strains and thus makes long-term use of the drug possible [62]. Therefore, in order to sustain long-lasting efficacy in acne therapy, broad-spectrum antibacterial agents such as BPO can be used concomitantly or sequentially with antibiotics. Unlike bacterial burden, BPO has a lack of direct effect on sebum production and does not reduce skin surface lipids, but it is effective in reducing the free fatty acids, known as comedogenic agents, and triggers of inflammation in sebum [64, 65]. BPO is thought to have weak comedolytic activity [66].

Another supplementary benefit of BPO in acne therapy is its anti-inflammatory action. BPO, however, does not have significant direct *in vivo* anti-inflammatory potency. A potential explanation for the anti-inflammatory effects of BPO could be the mediation by the antibacterial or oxidizing action of BPO. Following the decrease in the population of *P. acnes* in the follicles and the reduction of free oxygen radicals, one source of inflammation is cut and therefore inflammatory reactions are suppressed. The anti-inflammatory benefit of BPO, regardless of being direct or indirect, is reflected in several studies [67].

BPO products are indicated for mild-to-moderate acne with occurrence of predominantly inflamed lesions. One study tested different BPO formulations with different concentrations and at the end of 4 weeks treatment, they were all shown to decrease the number of papules and pustules and, to a smaller degree, the number of comedones [68]. Not only efficacy in mild-to-moderate acne but also a rapid onset of action can be observed after BPO application, which accompanies the quick antibacterial action within the first week of therapy [69].

8.1.3. Topical antibiotics

Topical antibiotics have been an integral component of the topical acne treatment. Over time, the most common topical antibiotics used for acne treatment have been erythromycin and clindamycin, with the latter being favored over the past several years, primarily

due to widespread emergence globally of *P. acnes* strains resistant to erythromycin [70]. Sulfacetamide with or without sulfur has also been used topically for treatment of acne vulgaris but data regarding the efficacy of these agents are limited. It is thought to restrict the growth of *P. acnes* through competitive inhibition of the condensation of para-aminobenzoic acid with pteridine precursors.

The principal mechanism of action of topical antibiotics appears to be through reduction in *P. acnes* organisms, which reduces the subsequent triggering of inflammatory activities [71, 72]. The use of benzoyl peroxide in combination with erythromycin or clindamycin augments reduction in *P. acnes*, reduces the emergence of resistant *P. acnes* strains, and may improve efficacy over use of either agent alone [71].

Concerns regarding emergence of clinically significant antibiotic-resistant bacteria primarily focus on systemic antibiotic use but topical antibiotic use can also change the cutaneous flora as application of topical antibiotics for treatment of acne is usually continued over several months to years [73, 74]. Thus, progressive emergence of normal bacterial flora that are less antibiotic sensitive such as macrolide-resistant *Staphylococcus epidermidis* and erythromycin- and tetracycline-resistant *P. acnes* strains has an estimated prevalence of 40% globally over approximately three decades [74]. Additionally, antibiotic-resistant *P. acnes* strains have been demonstrated on skin of untreated contacts of acne patients treated with topical antibiotic therapy, supporting interpersonal spread [75]. The clinically relevant effects of these changes in normal bacterial flora secondary to antibiotic use are not entirely clear. However, there is evidence for a correlation between antibiotic-resistant *P. acnes* and a reduction in efficacy with antibiotic therapy [73, 74]. Potential issues of concern that have been raised in this manner include increased prevalence of *P. acnes* strains less responsive to antibiotics, alterations in cutaneous flora, decreased therapeutic responsiveness to antibiotic therapy, and promotion of other clinical infections among treated patients and/or their close contacts. Apart from these, pharyngeal colonization with *Streptococcus pyogenes* and a possible increased risk of an upper respiratory tract infection have been associated with chronic use of antibiotics for acne, including topical agents [76, 77].

A report analyzing several monotherapy studies using either topical erythromycin or topical clindamycin for acne vulgaris demonstrated that the efficacy of topical erythromycin in reducing acne lesions has markedly decreased over time; however, the efficacy of topical clindamycin has not diminished on the basis of the same parameters of acne lesion reduction [78].

Topical antibiotics remain an important part of acne treatment and are recommended as a component of combination topical therapy; monotherapy with a topical antibiotic for acne is not recommended. At present, topical clindamycin remains the predominant topical antibiotic used for acne treatment; however, other agents such as erythromycin, sulfacetamide with or without sulfur, and azelaic acid are also options. Overall, the tolerability and safety profiles of topical antibiotics used for the treatment of acne vulgaris, are very favorable.

8.1.4. Azelaic acid

Azelaic acid is a naturally occurring dicarboxylic acid found in cereal grains. It is available as a topical 20% cream formulation, which has been shown to be effective in inflammatory and

comedonal acne [10]. 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. Overall, the position of azelaic acid in the treatment algorithm of acne vulgaris has been as an alternative to other topical agents. Initial improvement in acne with topical azelaic acid has been reported to be observed in 4–8 weeks, with maximum benefit generally noted after approximately 16 weeks of use [79]. 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.

8.1.5. Salicylic acid

Salicylic acid (SA) is a comedolytic and mild anti-inflammatory agent, widely used as a topical therapeutic agent for a variety of skin diseases, including acne, psoriasis, dandruff, and ichthyosis. Concentrations ranging from 0.5 to 10% have been recommended for acne, in numerous delivery formulations, including gels, creams, lotions, foams, solutions, and washes. The action of SA may occur due to the reduced cohesion between corneocytes, resulting in the shedding of epidermal cells, rather than "lysing" of keratin [80]. The antibacterial action of SA against *P. acnes* has also been demonstrated in both *in vitro* and *in vivo* studies. Side effects of topical salicylic acid include erythema and scaling.

Many clinical studies have proven the anti-acne efficacy of SA-containing products. SA can induce a more rapid effect on noninflamed lesions, when compared to inflamed lesions, which strengthens the suggestion that it has a primary effect on comedogenesis [81]. According to cross-over studies, SA is slightly more effective than BPO for the treatment of comedonal acne, as well as inflammatory lesions [82, 83]. The observed superiority of SA might be due to its mode of action. Since the primary lesion of acne is the microcomedo, a treatment that is effective in preventing its formation will be effective in preventing inflammatory lesions into which the microcomedo can progress. As the action of SA is mainly keratolytic, it interferes in an earlier stage than BPO, and in consequence it seems to be superior in acting against later steps, the inflamed lesions.

8.1.6. Topical dapsone

Topical *dapsone* 5% gel is approved for the treatment of acne vulgaris. Of note, a temporary yellow-orange staining of the skin and hair occasionally occurs with concomitant use of topical dapsone and benzoyl peroxide.

8.2. Oral treatments

8.2.1. Antibiotics

Current basic clinical research including identification of the *P. acnes* genome, analysis of innate-immune response in acne inflammation, evaluation of the role of inflammation in comedogenesis, and microbiologic studies correlating *P. acnes* with specific treatments and therapeutic benefit, all support the goal of *P. acnes* suppression with antimicrobial therapy as

a component of acne management [72]. In addition to *P. acnes* suppression, some antibiotics such as the tetracycline derivatives also exhibit anti-inflammatory properties that appear to contribute to their therapeutic benefit in acne vulgaris [84].

Conventionally, the predominant oral antibiotics used for treatment of acne vulgaris in most countries have been tetracycline, doxycycline, minocycline, erythromycin, azithromycin, and rarely trimethoprim. Doxycycline and minocycline are used more frequently than tetracycline and erythromycin due to resistance issues but over time there has been a trend toward an increase in *P. acnes* strains becoming less sensitive to doxycycline and minocycline as well [74, 85, 86] (**Table 1**).The greatest decrease in *P. acnes* colony counts has been demonstrated with minocycline, followed in order of magnitude by doxycycline, tetracycline, trimethoprim-sulfamethoxazole, and erythromycin [87]. The clinical efficacy of oral antibiotic therapy for acne vulgaris is well established and recognized as a conventional component of rational acne treatment.

The main indication for oral antibiotic therapy in acne vulgaris is moderate-to-severe inflammatory involvement on the face and/or trunk [72]. Antibiotic monotherapy should be avoided due to promotion of antibiotic-resistant bacterial strains, with oral antibiotic therapy best utilized in combination with a topical regimen, namely benzoyl peroxide or a topical retinoid [88]. It has also been suggested that a short course of benzoyl peroxide therapy prior to initiating antibiotic therapy assists in the eradication of antibiotic-resistant *P. acnes* strains, thus enhancing the overall efficacy of antibiotic treatment. The combination therapy may also allow for better ability to discontinue the oral antibiotic at some point based on response to treatment, and hopefully allow the topical regimen alone to maintain control of acne.

If not enterically coated, doxycline, especially the hyclate salt, is best administered with food and a large glass of water when the patient is upright and not prior to anticipated reclining for at least a few hours, to reduce the risk of gastrointestinal side effects such as esophagitis. Concomitant administration of doxycycline and minocycline with iron supplements and metal ions may decrease absorption of both agents. Azithromycin, on the other hand, does not as commonly cause gastrointestinal side effects, and is best taken on an empty stomach to maximize absorption.

In case of resistance challenges, it is important to recognize that a direct correlation between prevalence of *P. acnes* resistance and poor therapeutic response to antibiotic therapy has not always been consistent [74]. Factors potentially associated with a reduced response to antibiotic therapy may include pre-existing antibiotic resistance, the quantity of antibiotic-resistant

Drug	Usual dosage range
Minocycline (immediate release)	50–100 mg once or twice daily
Minocycline (extended release)	1 mg/kg/day (45–135 mg once daily)
Doxycycline	75–100 mg once or twice daily 150 mg once daily

Table 1. The recommended dosing schedule is seen.

P. acnes strains in the individual patient, resistance to multiple antibiotics, use of antibiotics without concomitant use of benzoyl peroxide, repeated courses of antibiotic therapy especially without concomitant use of benzoyl peroxide, unnecessary switching of oral antibiotic agents despite previous efficacy, individual drug characteristics such as GI absorption and lipophilicity, relative effects on serum and tissue levels due to interference of GI absorption by co-administered chelating metal ions, and existence of *P. acnes* in a protective extracellular biofilm *in vivo*.

When oral antibiotic therapy is incorporated with a topical regimen for acne, it has been suggested that it be administered over a minimum period of 6–8 weeks and a maximum of 12 weeks–6 months. In the initial follow-up 6–8 weeks after the start of therapy, if a substantial lack of efficacy is observed despite adequate compliance, a change in oral antibiotic therapy is reasonable [72, 74, 89]. If partial improvement is observed, it may be reasonable to continue with the current therapy for an additional 6–8 weeks to evaluate if further progress is achieved. Changing a regimen too frequently often results in suboptimal outcomes as a given regimen is never afforded a true opportunity to initiate its therapeutic effect. Once control of acne is felt to be stable, which is usually achieved over a duration of 3–6 months assuming compliance is adequate, discontinuation of the oral antibiotic therapy may be suggested, with continuation of the topical regimen for long-term maintenance. Stabilized control of acne does not necessarily imply complete clearance but may be defined as the observation that new inflammatory lesions have stopped or markedly decreased. Despite the alleged use of a topical maintenance regimen, some patients return with an acne flare within a few weeks to months after discontinuation of the oral antibiotic. In such cases, it is suggested to reinitiate therapy with the same oral antibiotic that was previously effective.

Use of systemic antibiotics may cause some adverse reactions. Doxycycline is associated with dose-related phototoxicity, whereas minocycline causes acute vestibular adverse events, lupus-like syndrome, together with cutaneous and/or mucosal hyperpigmentation, including brown, gray, or blue pigmentation of skin and/or mucosa and blue discoloration of acne scars. There are no specific recommendations to routinely perform baseline or periodic laboratory testing with oral antibiotics used to treat acne vulgaris; however, medical history of the individual patient may prompt the clinician to avoid use of a specific oral antibiotic or to incorporate baseline and/or periodic laboratory monitoring.

Overall, the efficacy and safety of conventional oral antibiotic therapy used for acne have been very favorable based on available studies and extensive clinical experience over many years.

8.2.2. 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. Hormonal therapies are most effective in adult women with inflammatory papules and nodules of the lower face and neck that tend to flare prior to menstruation. These lesions are usually resistant to oral antibiotherapies, thus hormonal therapy with oral contraceptives to block both ovarian and adrenal production of androgens can be initiated. Due to potential long-term risks associated with oral contraceptive use consultation with a gynecologist is recommended. Most oral contraceptive formulations combine an estrogen with a progestin in

order to minimize the risk of endometrial cancer, which is known to occur with unopposed estrogen administration. Second-generation progestins with low intrinsic androgenic activity such as ethynodiol diacetate, norethindrone, and levonorgestrel are preferred in the combinations. Newer, third-generation progestins like desogestrel, norgestimate, and gestodene have even less androgenic activity and other progestins like drospirenone, cyproterone acetate, and dienogest have *anti*androgenic 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 [90]. Side effects of 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 [91–93]. The progestational antiandrogen cyproterone acetate primarily makes androgen receptor blockade. The standard formulation combines cyproterone acetate (2 mg) with ethinyl estradiol (35 or 50 mcg) in an oral contraceptive formulation, which is the treatment of choice for sexually active women with hormonally responsive acne [94].

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 [95]. Side effects are dose-related and include potential hyperkalemia, irregular menstrual periods, breast tenderness, headache, and fatigue. However, hyperkalemia is rare in young healthy patients. Because it is an antiandrogen, there is a risk of feminization of a male fetus if a pregnant woman takes this medication. The potential risk to a fetus and the symptoms of irregular menstrual bleeding can be alleviated by combining spironolactone with an oral contraceptive. Side effects can also be minimized if therapy is initiated with 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 that is approved by the FDA for the treatment of prostate cancer, can also be an effective treatment for acne in women at doses of 62.5–500 mg/day. In addition to side effects similar to those of other antiandrogens severe dose-related hepatotoxicity occasionally occurs.

8.2.3. Isotretinoin

Currently, isotretinoin (13-*cis*-retinoic acid) is the drug of choice for the management of severe, treatment-resistant acne vulgaris. Treatment with isotretinoin can lead to both marked improvement and long-lasting remission. It was not until 1979 when Peck et al. conducted an open-label trial for treatment-resistant cystic and conglobate acne with isotretinoin [96] and shortly thereafter the Food and Drug Administration (FDA) approved isotretinoin for the treatment of severe nodulocystic acne. Isotretinoin, though a vitamin A derivative, is a relatively water-soluble molecule. Peak plasma levels are achieved between 1 and 4 hours [97].

Importantly, the magnitude of this peak level is increased by co-administration with lipids. Thus, patients are instructed to take their doses with a small, fatty meal. Given the half-life of 10–20 hours, it is best to take isotretinoin twice a day [97, 98]. Isotretinoin is metabolized in the liver, where it is oxidized to 4-oxo-isotretinoin via CYP450 3A4 substrate and then excreted in urine and feces.

The primary mechanism of isotretinoin is its effect on sebaceous glands, inhibiting sebaceous gland activity, proliferation, differentiation, function, and production of sebum. *In vitro* studies conclude that isotretinoin induces apoptosis and cell cycle arrest of human sebocytes [99]. This effect seems to persist indefinitely upon completion of a full course (120–150 mg/kg) of isotretinoin, and this is thought to be the mode by which treatment with isotretinoin can cure acne. Unlike other retinoids used in dermatology, isotretinoin does not bind retinoic acid receptors (RARs), but functions via an RAR/RXR-independent mechanism. Secondary mechanisms that contribute to the efficacy of isotretinoin include anti-inflammatory, antibacterial (secondary to sebum reduction/alteration), and antikeratinizing effects.

Isotretinoin is indicated for the treatment of severe recalcitrant nodular acne, and its use for less severe acne is often indicated provided such cases are treatment-resistant and especially if the disease is leading to scarring, whether physical or emotional. In only the severest cases should it be considered as initial therapy.

Isotretinoin should be dosed at 0.5–1 mg/kg/day divided BID. Commonly, an initial dose of 0.5 mg/kg/day for the first month is preferred to acclimate the patient to mucocutaneous xerosis, minimize initial inflammatory response, and monitor for any adverse effects. The dose should then be increased to approximately 1 mg/kg/day. In patients with severe acne in which explosive flares may occur, pre-treatment for one or two weeks with daily prednisone is advised. After this pretreatment, 0.5 mg/kg/day of isotretinoin is initiated-vwhile gradually decreasing the steroid dose. What is more important than the daily dose, is achieving a total cumulative dose of 120–150 mg/kg, ensuring the prolonged remission of acne [100].

Relapses can be observed after the completion of the therapy, especially in cases of younger patients, males, and truncal acne. However, acne that recurs after isotretinoin therapy is more responsive to less aggressive acne treatments such as topical agents or oral antibiotics. If still severe, a repeat course of isotretinoin can be tried with success rates similar to that of initial treatments. Purported relapse rates following treatment of acne with isotretinoin varies between 5.6 and 65.5% [101]. The most likely reasons for this large discrepancy are small sample size, short follow-up, retrospective design, and/or subtherapeutic cumulative dosage.

Absolute contraindications for isotretinoin use include pregnancy, breast-feeding, and hypersensitivity to parabens, soybean oil, or other retinoids. Relative contraindications include psychiatric disorders, skeletal disorders, seizure disorder, hyperlipidemia, pancreatitis history, diabetes mellitus, hyperuricemia, gout, and anorexia nervosa.

Concomitant use of isotretinoin and tetracycline can induce intracranial hypertension, leading to pseudotumor cerebri, via idiosyncratic reaction. Severe and persistent headaches with nausea, vomiting, and blurred vision can be signs of pseudotumor cerebri.

Treatment with isotretinoin can have various adverse effects since RARs are ubiquitous throughout the body. These side effects mimic the effects of hypervitaminosis A and almost all are reversible upon discontinuation of isotretinoin. The first, and essentially universal, side effect of isotretinoin is cheilitis and its absence is often considered a marker of noncompliance or insufficient dosage. Any mucocutaneous site can be affected including the skin, conjunctiva, oropharynx, nasopharynx, and genitalia. Treatment for mucocutaneous dryness consists of artificial tears for the eyes, emollients for the lips and body. Other rarely reported dermatological side effects of isotretinoin include photosensitivity, exuberant granulation tissue, abnormal wound healing, telogen effluvium, nail plate fragility, paronychia, and onycholysis.

Transient dyslipidemia is the second most common side effect after mucocutaneous xerosis. About 20% of acne patients treated with isotretinoin experience hypertriglyceridemia [102]. LDL may also be increased, while HDL may be decreased. These alterations typically occur early in treatment during the first month or two, stabilize, and then revert to pretreatment levels upon discontinuation of isotretinoin. Substantially increased triglyceride levels can have risks including pancreatitis and eruptive xanthomas. Since triglyceride elevations are dose related, one can decrease the dose of isotretinoin. If dose reduction is not sufficient, apart from lifestyle changes pharmacologic therapy is indicated. The drug of choice for isotretinoin-induced hypertryglyceridemia is gemfibrozil, 600 mg twice daily. For triglyceride levels greater than 800 mg/dL, discontinuation of isotretinoin is appropriate.

Increased transaminase levels are seen in some 11–15% of acne patients treated with isotretinoin, whereas development of severe hepatotoxicity is extremely rare [103].

Other occasionally reported adverse effects of isotretinoin include nausea, diarrhea, abdominal pain, gastritis, proctocolitis, flares of inflammatory bowel disease, decreased white blood cell count, hemoglobin, and platelets, arthralgias, or myalgias.

The most serious side effect of isotretinoin is teratogenicity. It affects organogenesis; therefore, its greatest risk to a fetus is early in pregnancy, during the first trimester. Even one dose is thought to be able to induce congenital defects or spontaneous abortion [104]. The rate of birth defects ranges from 18 to 28%, including craniofacial, cardiac, central nervous system, thymic, and various other abnormalities [104–106]. Female patients of childbearing potential must have at least one or two negative pregnancy tests before starting treatment and practice effective contraception for 1 month prior to, during, and for 1 month after completing therapy.

Long-term treatment with isotretinoin can decrease bone mineral density and cause hyperostosis and osteophytes. However, it is not clear if these effects apply to the short-term treatment of acne with a standard course of isotretinoin [107].

In case of psychological side effects, there is no evidence that there is a causal relationship between mood disturbances such as depression, anxiety, or suicidal ideation and the use of

isotretinoin. However, there are many studies demonstrating positive and negative correlation between isotretinoin use and increased risk of depression [108–112]. Nevertheless, given the serious nature of depression and suicidal ideation, close psychological monitoring of patients is recommended.

Before the initiation of isotretinoin therapy, fasting lipids and liver function tests should be checked at baseline, monthly for the first 2 months. If no abnormalities are found and the dose unchanged blood tests are done every 2 months.

8.3. Surgical treatment

Extraction of especially deep and persistent comedos can improve the cosmetic appearance of acne and aid in therapeutic responsiveness to topical comedolytic agents [113]. The keratinous contents of open comedones may be expressed via a comedo extractor. The Schamberg, Unna, and Saalfield types of comedo expressers are most commonly used. Nicking the surface of a closed comedo with an 18-gauge needle or a #11 blade allows easier expression. This procedure should be used in conjunction with a topical retinoid or other comedolytic treatment for maximum benefit. Comedo extraction should not be performed on inflamed comedones or pustules because of the risk of scarring. Light electrocautery, electrofulguration, and cryotherapy can also be effective treatments for comedones.

Photodynamic therapy utilizing topical 5-aminolevulinic acid together with various light sources (e.g., blue, red, intense pulsed) or lasers (e.g., pulsed dye, 635 nm red diode) have been successfully used to treat acne [114]. In addition, blue or intense pulsed light alone and lasers such as the pulsed dye, the 1320 nm neodymium:YAG and especially the 1450 nm diode may be of therapeutic benefit for inflammatory acne.

Intralesional injection of corticosteroid (triamcinolone acetonide 2–5 mg/ml) can quickly improve the appearance and tenderness of deep, inflamed nodules and cysts [115]. Larger cysts may require incision and drainage prior to injection. The maximal amount of corticosteroid used per lesion should not exceed 0.1 ml. The risks of corticosteroid injections include hypopigmentation (particularly in darkly pigmented skin), atrophy, telangiectasias, and needle tract scarring.

Low-concentration chemical peels are also beneficial for the reduction of comedones. The α-hydroxy acids (including glycolic acid), salicylic acid, and trichloroacetic acid are the most common peeling agents. Higher-concentration glycolic acid peels (20–70%, depending on the patient's skin type) and the less predictable phenol peel may also be performed in the office setting. Risks of chemical peels include irritation, pigmentary alteration, and scarring [116].

One of the most distressing consequences of acne vulgaris is scarring. Laser resurfacing (fractional as well as traditional), dermabrasion, and deeper chemical peels can be used in case of scarring [117]. Surgical subscision combined with filler substances is also a commonly used technique in the management of "ice-pick" acne scars. For larger hypertrophic scars, aggregated pitted scars, and sinus tracts, full-thickness surgical excision may result in improved scar placement and a better cosmetic appearance.

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