

# XII ACNE VULGARIS AND ROSACEA

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Acne vulgaris accounts for approximately 15% of visits to dermatology offices each year. Both sexes and all ethnicities are affected. The disorder characteristically involves the face, but truncal involvement is also relatively common, most often occurring concurrently with facial involvement. Multiple clinical presentations may be observed, with severity often progressing over time during adolescence. Because acne vulgaris typically starts around or shortly after puberty and often persists for several years, the disorder has a marked negative impact on mood, self-esteem, and other quality-of-life parameters, regardless of severity. Severe forms of acne vulgaris can be especially disfiguring and debilitating and are more likely to lead to permanent scarring, but scarring may sometimes occur as a sequelae of moderate or mild disease. Therapeutic options are chosen primarily on the basis of clinical severity, with adjustments in treatment made on the basis of response or disease progression.

Unlike acne vulgaris, rosacea begins in adulthood, usually in the third decade of life or later. The disorder predominantly affects the central face in fair-skinned people, mostly those of northern European ancestry, although individuals of any race may be affected. Rosacea is a chronic disorder characterized by periods of exacerbation and remission; it may present as one or more of a variety of clinical subtypes. Fortunately, rosacea is not associated with scarring, although a subset of patients may develop localized proliferations of sebaceous and fibrous tissue called a phyma. Like acne vulgaris, rosacea may also adversely impact quality of life.

## Acne Vulgaris

### EPIDEMIOLOGY AND ETIOLOGY

Acne vulgaris is the most common dermatologic problem of adolescent years. Age of onset and severity of disease are affected by sex and genetics. Acne often subsides after the teenage years, but the disease can remain a problem for adults in the third and fourth decades and beyond. A subset of acne patients consists of women who present after the teenage years. Many women experience perimenstrual flares of acne; this phenomenon may be more common during late adolescence and afterward.<sup>1</sup>

Genetic factors clearly play a role in acne severity. A family history of severe acne can often be elicited from affected patients. Although externally applied agents such as cosmetics (acne cosmetica), or garments causing friction (acne mechanica) may cause acneiform lesions or exacerbate current acne vulgaris, these precipitating factors are relatively uncommon. Certain medications (e.g., corticosteroids, adrenocorticotrophic hormone, phenytoin, isoniazid, lithium, progestins, potassium iodide, bromides, and actinomycin D) can cause acnelike lesions (acne medicamentosa) [see 2:VI Cutaneous Adverse Drug Reactions].

### PATHOGENESIS

Multiple factors contribute to the development of acne in susceptible persons. The most significant are androgenic stimulation, follicular hyperkeratinization, accumulation of sebum, and stimulation of inflammation.

Hyperkeratinization of the follicular infundibulum leads to a proliferation of keratinocytes, which causes obstruction of the follicular orifice. When not visible, the noninflamed obstructed follicle is called a microcomedo; when visible, it is referred to as a comedo.

Sebaceous glands are often larger and sebum production is greater in persons affected with acne vulgaris as compared with unaffected persons.<sup>2</sup> In addition, sebum in patients with acne vulgaris contains decreased concentrations of linoleic acid.<sup>3</sup> Inflammation in acne has also been attributed to the commensal anaerobic diphtheroid *Propionibacterium acnes*. The presence and proliferation of *P. acnes* correlates with the occurrence of acne vulgaris in adolescents.<sup>4</sup> The microbe's role in inflammation has been attributed to lipases, proteases, hyaluronidases, and chemotactic factors, as well as direct stimulation of innate immune response through interaction with Toll-like receptor-2 (TLR-2).<sup>5</sup>

Androgens play a pivotal role in the development of acne vulgaris. This is evidenced by increased levels of dehydroepiandrosterone sulfate (DHEAS) in peripubertal girls with acne vulgaris<sup>6</sup> and an association of the disorder with endocrinopathies characterized by increased levels of circulating androgens. Endocrine disorders associated with the development of acne lesions include polycystic ovary disease, congenital adrenal hyperplasias, and some ovarian and adrenal tumors. Exogenous administration of androgens may also cause an acneiform eruption. Androgens act to increase sebum production and enlarge sebaceous glands; they appear to be at least partially involved in the stimulation of the follicular hyperkeratinization that leads to formation of the primary acne lesion, the microcomedo. However, serum androgen levels are usually within the normal range in patients with acne vulgaris, including women with adult-onset or adult-persistent disease. Some researchers have postulated that local production or increased sensitivity to androgens contributes to the formation of acne lesions. Skin biopsies from patients with acne vulgaris demonstrate increases in 5 $\alpha$ -reductase activity.<sup>7</sup> This increased androgenic activity may result in the conversion of testosterone to dihydrotestosterone in the skin, leading to the development of acne lesions.

### DIAGNOSIS

#### Clinical Features

The characteristic skin lesions of acne include open and closed comedos, erythematous papules, pustules, nodules, cysts, and scars. The most commonly affected site is the face, although the trunk is also involved in approximately 50% of patients.

**Comedonal acne lesions** Comedos are characterized by follicular hyperkeratinization and may be open or closed; individual patients may have either or both types of lesions. Open comedos (blackheads) are black papules measuring 0.1 to 2 mm that are easily extruded with gentle pressure. The material that is removed is greasy and has a gray-white color. Contrary to popular belief, the dark color of open comedos is caused by melanin, not by dirt or oxidized fatty acids. Closed comedos (whiteheads) consist of white papules measuring 0.1 to 2 mm; unless extracted, they persist somewhat longer than open comedos, often for weeks to months.



**Figure 1** Inflammatory acne is characterized by erythematous papules and pustules.

**Inflammatory acne lesions** Erythematous papules, pustules, nodules, and cysts are the predominant lesions in inflammatory acne [see Figure 1]. Superficial inflammatory lesions (i.e., papules and pustules) range in size from 3 to 5 mm, eventually resolving as an erythematous macule, normal skin, or occasionally as an atrophic or pitted scar. In patients with dark complexions, postinflammatory hyperpigmentation is a common sequelae that is often slow to fade [see 2:XV Disorders of Pigmentation]. Nodules, which are 1 cm or larger, are erythematous and tender. They can be firm at onset, typically becoming fluctuant over time. A fluctuant acne nodule is often erroneously referred to as an acne cyst, which is a misnomer in that the lesion does not have an epithelial lining. In severely affected individuals, these lesions may form fluctuant sinuses that can open to the surface through multiple tracts. Scarring is a common sequelae of deep inflammatory (nodular) acne vulgaris.

*Clinical Variants of Acne*

**Acne conglobata** Acne conglobata is a severe, scarring form of acne in which large nodules and abscesses become confluent to form draining sinus tracts. Scarring is often severe. Topical acne therapy and oral antibiotics are frequently ineffective; patients may require treatment with oral isotretinoin [see Treatment, below]. Intralesional injection of corticosteroids and drainage of abscesses are temporarily helpful.

**Acne cosmetica** A persistent, low-grade form of acne can result from the use of comedogenic cosmetics, moisturizers, and sunscreens. Women are most commonly affected.

**Acne excoriée** Picking of minor acne lesions can cause large ulcers and erosions that heal with scarring. Young women are most typically affected.

**Acne mechanica** An acneiform eruption can result from repeated trauma associated with the wearing of sports helmets, shoulder pads, and bras and from the chin rests of violins and violas (fiddler's neck).

**Pomade acne** A form of acne may result from the use of thick oil-based products on skin or in the hair. Comedones, papules,

and pustules are usually found close to the hairline. Black men and women are most commonly affected.

**Acne in neonates and children** Neonatal acne has been attributed to maternal androgens, as well as androgens secreted by the neonatal adrenal gland. Erythematous papules and pustules may last for 2 to 3 months after birth but usually resolve earlier spontaneously.

Infantile acne develops between 3 and 6 months after birth. This condition is characterized by inflamed papules and pustules; it signals early secretion of androgens by the gonads, particularly in boys. This condition may last until age 5 years. It has been suggested that affected infants may be predisposed to severe acne vulgaris later in life.

*Laboratory Tests*

The clinical features of acne are so readily recognized that laboratory investigation is usually not necessary. Laboratory tests should be considered, however, for female patients who have other signs of hyperandrogenism, such as hirsutism or irregular menses. Serum for determining levels of DHEAS and free testosterone and the ratio of luteinizing hormone to follicle-stimulating hormone should be obtained 2 weeks before the onset of menses [see Table 1]. Tests should also be undertaken in patients whose conditions do not respond to adequate doses of isotretinoin or who exhibit early or frequent recurrences [see Treatment, below].

**DIFFERENTIAL DIAGNOSIS**

Clinical features of acne vulgaris are sufficiently distinctive that diagnosis is usually made accurately on the basis of clinical examination alone. An important diagnostic feature of acne vulgaris is polymorphism—that is, the presence of multiple lesion types in different stages. Nevertheless, a number of disorders can be mistaken for acne.

**Folliculitis** The follicular pustules of folliculitis can be distinguished from the lesions of acne by their distribution. Folliculitis can affect the trunk and extremities and is usually not limited to the usual sites of acne (i.e., the face, back, and chest). Bacterial folliculitis produces papules and pustules; however, comedonal lesions are not observed. *Malassezia* folliculitis is characterized by pruritic erythematous papules or pustules that do not respond to typical acne therapies. Gram stain of pus from the lesions reveals gram-positive budding yeast [see 2:VII Fungal, Bacterial, and Viral Infections of the Skin].

**Acne and Signs of Hyperandrogenism**

<i>Finding</i>	<i>Suspected Condition</i>
DHEAS 4,000–8,000 ng/ml > 8,000 ng/ml	Congenital adrenal hyperplasia Adrenal tumor
LH:FSH ratio > 2.0	Polycystic ovary disease
Testosterone (unbound) 20–40 yr, > 107.5 pmol/L 41–60 yr, > 86.7 pmol/L 61–80 yr, > 69.3 pmol/L	Polycystic ovary disease; ovarian tumor Polycystic ovary disease; ovarian tumor Polycystic ovary disease; ovarian tumor

DHEAS—dehydroepiandrosterone sulfate FSH—follicle-stimulating hormone  
LH—luteinizing hormone

**Gram-negative folliculitis** In patients on long-term antibiotic therapy, superficial pustules or nodules can develop. Lesions are often located on the face, often predominantly in the perinasal and perioral regions. This condition may respond to oral antibiotics that provide broad-spectrum gram-negative coverage, such as amoxicillin-clavulanate, oral cephalosporins (e.g., cefdinir), or quinolones; however, oral isotretinoin is the treatment of choice.<sup>8</sup>

**Milia** Milia are white pinpoint epidermal cysts that resemble closed comedos. They frequently occur around the eyes but can develop anywhere on the face. If untreated, they last for months or years. Milia are unrelated to acne vulgaris; they can be carefully opened and their contents extracted with a small surgical blade.

**Perioral dermatitis** Long-term use of topical corticosteroids on the face can result in acneiform, erythematous, inflamed pink individual or coalescent small papules on the chin and cheeks. Despite the name, the area immediately around the mouth is typically spared in perioral dermatitis (perivermillion sparing). A similar eruption can occur in persons who have not used corticosteroids; it is most commonly observed in young female patients.

**Chloracne** Cysts and closed comedos that resemble acne lesions can be caused by exposure to halogenated hydrocarbons.

**Hidradenitis suppurativa** Hidradenitis suppurativa is a chronic condition in which inflamed cysts in the axillae and groin form fluctuant sinuses with draining tracts.

**Favre-Racouchot disease** Numerous open and closed comedos can appear around the eyes of elderly patients, especially men who have worked outdoors for much of their lives. This condition has been attributed to a lifetime of sun exposure.

#### TREATMENT

Treatment of acne depends on the type and severity of lesions and on the patient's response to particular measures. Comedonal acne lesions are usually best managed with topical retinoids and acne surgery; superficial inflammatory acne lesions are treated with a range of topical therapies, including benzoyl peroxide, topical antibiotics (e.g., clindamycin or erythromycin), topical retinoids, azelaic acid, and sulfacetamide with or without sulfur. When superficial inflammatory acne is more severe or when there is a significant presence of deep inflammatory acne, oral antibiotic therapy is usually required. Because nodules are more likely than comedos to cause scarring, they are initially treated more aggressively, with the combination of a topical regimen and an oral antibiotic such as minocycline or doxycycline plus, if necessary, oral isotretinoin (see below). Intralesional corticosteroid injection administered by a dermatologist produces a rapid response and can prevent scarring, although local skin atrophy may result. Unroofing of sinus tracts (marsupialization) and other surgical procedures are best performed by physicians with expertise in dermatologic surgery [see Table 2]. Scars are not responsive to medical therapies, warranting treatment with a physical modality such as dermabrasion or laser abrasion. The appearance of depressed scars may be improved by ceratin chemical peels, punch excision, and resurfacing procedures, as well as by the injection of filler substances.<sup>9</sup>

**Table 2** Surgical Treatments for Acne Lesions and Acne Scars

Lesions	Extraction of comedos
	Drainage of pustules and cysts
	Intralesional injection of corticosteroids in cysts
	Excision and unroofing of sinus tracts and cysts
Scars	Dermabrasion
	Laser abrasion
	Acid peels
	Injection of filling materials (e.g., collagen)
	Excision
	Punch autografts

Numerous over-the-counter cleansing agents are available to help patients remove seborrhea and oily debris from the skin, resulting in subjective improvements. However, many over-the-counter products are abrasive and irritating to skin, leading to reduced tolerability when acne medications are applied. Self-manipulation of acne lesions by picking, squeezing, or excessive washing can lead to exacerbation of lesions, dyschromia, and even scarring.

Topical skin care preparations, including sunscreens, cleansers, moisturizers, and cosmetics, should be oil-free and non-comedogenic. Many over-the-counter oil-free, noncomedogenic moisturizers are available and can be used to prevent or lessen the dryness, redness, and peeling that may occur with topical acne treatment.

There is no clearly defined role for dietary manipulation in the management of acne. Previous beliefs that chocolate or oily foods cause acne have not been substantiated.

#### Topical Therapy

**Comedonal acne** Topical retinoids—tretinoin, adapalene and tazarotene—are among the most effective therapies for comedonal and inflammatory acne; these preparations reduce follicular hyperkeratinization, which reduces microcomedo formation, and also allow for increased penetration of topical antibiotics and benzoyl peroxide. In addition, retinoids exhibit direct anti-inflammatory activity, at least partially through downregulation of TLR-2 expression. As a component of an acne treatment regimen, retinoids can be used in combination with topical and oral antibacterial agents.<sup>10</sup>

Topical retinoids may be irritating to skin, especially during the first few weeks of use. Patients can reduce irritation by use of a moisturizer and a gentle skin cleanser or by temporarily reducing the frequency of application. Visible improvement is usually not evident for 6 to 8 weeks but can continue for 3 to 4 months and beyond.

Newer formulations of retinoids that are reported to be less irritating include a tretinoin microsphere vehicle and adapalene.<sup>11,12</sup> Tazarotene is less irritating in a cream formulation than in its gel vehicle. Tazarotene gel can also be used in a short-contact method, in which it is applied for seconds to minutes.<sup>13</sup>

**Inflammatory acne** Topical antibiotics may be used in combination with benzoyl peroxide and a topical retinoid for inflammatory acne. Topical antibiotics used for acne treatment include clindamycin, erythromycin, and sulfacetamide. Evaluations in clinical trials indicate that clindamycin has sustained its therapeutic efficacy over time, whereas response to topical erythromy-

Table 3 Topical Therapies for Acne

Medication	Formulation	Frequency of Application	Primary Mechanism of Action	Adverse Effects
Azelaic acid	20% cream	b.i.d.	Anticomedonal, antibacterial	Stinging, irritation
Benzoyl peroxide	2.5%, 5%, 10% creams, gels, lotions, washes	b.i.d.	Antibacterial	Dryness, irritation, allergic contact dermatitis
Antibiotics				
Clindamycin	1% solutions, lotions, gels	b.i.d.	Antibacterial	Antibiotic resistance
Erythromycin	2% solutions, creams, gels, pledgets, wipes	b.i.d.	Antibacterial	Antibiotic resistance
Erythromycin–benzoyl peroxide	3% erythromycin–5% benzoyl peroxide gel	b.i.d.	Antibacterial	Dryness, irritation, allergic contact dermatitis; deteriorates if not refrigerated
Sodium sulfacetamide–sulfur	10% sodium sulfacetamide, 5% sulfur lotions	b.i.d.	Antibacterial	Dryness, irritation, allergic contact dermatitis
Retinoids				
Adapalene	0.1% gels	q.d.	Comedolytic	Dryness, irritation, photosensitivity
Tazarotene	0.05%, 0.1% gels	q.d.	Comedolytic	Dryness, irritation, photosensitivity
Tretinoin	0.025%, 0.05%, 0.1% creams; 0.01%, 0.025% gels; 0.05% solutions	q.d.	Comedolytic	Dryness, irritation, photosensitivity
Sulfur and resorcinol	2% resorcinol, 8% sulfur lotions, creams	q.d., b.i.d.	Comedolytic	Dryness, peeling, allergic contact dermatitis
Salicylic acid	0.5%–2% gels, pads, soaps	q.d., b.i.d.	Comedolytic	Dryness, irritation

cin has waned. Resistance of *P. acnes* to antibiotics has been documented and may potentially threaten the efficacy of antibiotic treatment in some patients.<sup>14,15</sup> It is therefore useful to prescribe antibiotics in combination with benzoyl peroxide, which does not induce resistance and has been shown to reduce the emergence of resistant *P. acnes* strains. A combined formulation of clindamycin 1% and benzoyl peroxide 5% has been found to produce faster and greater reductions in *P. acnes* than formulations containing clindamycin alone.<sup>16</sup> Moreover, the combination of benzoyl peroxide and clindamycin resulted in greater improvement in acne than either of its individual components alone.<sup>17</sup> A 1% foam formulation of topical clindamycin, which is highly adaptable for widespread application because of easy spreadability and lack of residue or bleaching of fabric, may be used in combination with a benzoyl peroxide wash for mild or moderate truncal acne vulgaris; severe truncal involvement warrants the addition of an oral antibiotic to the topical regimen. In one commonly used regimen, a gel consisting of a combination of an antibiotic and benzoyl peroxide is applied in the morning, and a topical retinoid is used in the evening.

Azelaic acid, an anticomedonal and antibacterial agent, offers yet another choice for the topical treatment of acne. It can be used in combination with a topical retinoid, benzoyl peroxide, a topical antibiotic, and oral antibiotic therapy.<sup>18</sup>

Salicylic acid plays a minor role in the treatment of acne. Over-the-counter formulations of salicylic acid offer only limited efficacy for acne, because of their low concentration [see Table 3].

#### Systemic Therapy

Systemic therapy is warranted for patients with nodular acne or inflammatory acne that is not responsive to topical therapy alone. Agents used for systemic therapy include antibiotics; isotretinoin; and, in selected female patients, hormonal agents.

**Antibiotic therapy** Oral antibiotics, used in combination with a topical regimen, are usually the first line of systemic treat-

ment; a trial of at least 8 to 12 weeks is warranted to assess responsiveness. Antibiotics have both antibacterial and anti-inflammatory effects that are beneficial in treating acne. The oral antibiotics most commonly used for acne therapy are doxycycline, minocycline, and trimethoprim-sulfamethoxazole [see Table 4]. Although tetracycline and erythromycin are still used, therapeutic response to these agents has lessened overall, presumably because of a greater prevalence of resistant strains of *P. acnes*.<sup>19</sup> An extended-release formulation of minocycline is now approved by the Food and Drug Administration for treatment of acne vulgaris, at a dosage of 1 mg/kg/day. This formulation and dosage regimen has been shown to reduce the vestibular side effects of minocycline. Trimethoprim-sulfamethoxazole is sometimes effective in cases of acne vulgaris exhibiting limited response to other oral antibiotics. It is important to recognize potentially serious side effects of trimethoprim-sulfamethoxazole, such as toxic epidermal necrolysis. Ultimately, the duration of treatment with any oral antibiotic depends on patient response.

In one study, azithromycin, given at a dosage of 500 mg/day for 4 days and repeated at 10-day intervals for four cycles, demonstrated efficacy comparable to minocycline, 100 mg/day for 6 weeks.<sup>20</sup> Further refinements of regimens with newer antibiotics and additional clinical trials need to be performed before these approaches achieve more widespread usage.

Doxycycline, especially at a dosage of 100 mg a day or greater, may be associated with photosensitivity. Minocycline is not associated with photosensitivity but may cause various forms of skin and mucosal hyperpigmentation and also can induce drug hypersensitivity syndrome, which may be associated with hepatitis and pneumonitis. A lupuslike syndrome has been reported with oral minocycline, usually in female patients on long-term therapy. Synovitis, the presence of antinuclear antibodies, and elevations in hepatic transaminase levels (hepatitis) have been reported, but renal disease and central nervous system disease do not appear to occur.<sup>21</sup> These syndromes resolve upon discontinuance of minocycline, but they recur with retreatment.

Controversy about the long-term use of antibiotics for the treatment of acne was raised by a study published in 2004 that suggested a positive correlation between antibiotic use for any diagnosis and breast cancer risk. The study found that an increase in the cumulative number of days of antibiotic use was associated with greater breast cancer risk.<sup>22</sup> The results of this study have been questioned, because of methodology and other potential shortcomings. Additional research is needed before definitive conclusions and recommendations can be made.

**Isotretinoin** Oral isotretinoin, used primarily in cases of refractory deep inflammatory acne vulgaris, is the most effective agent available. Over 16 to 20 weeks of treatment, oral isotretinoin therapy results in long-lasting remissions or cures in the majority of patients. Because of its potential for adverse effects, especially teratogenesis, oral isotretinoin is not generally used as first-line therapy; instead, this agent has generally been reserved for patients whose acne is refractory to a reasonable trial of other systemic therapies. Isotretinoin may be used as initial therapy in patients with particularly severe acne to prevent scarring, in cases where scarring is already evident, and in patients with a history of antibiotic intolerance.

Most of the side effects of isotretinoin are dose related and affect a majority of patients treated. For example, cheilitis uniformly occurs in patients treated with therapeutic doses. Myalgias, dryness of mucous membranes, and xerotic skin changes frequently occur during treatment. Hyperlipidemia, especially hypertriglyceridemia, may develop. In most cases, hyperlipidemia is modest and not problematic; rarely, however, triglyceride levels may rise sufficiently to cause pancreatitis.

Teratogenicity has been reported to occur with the administration of even a single dose of isotretinoin to pregnant women. For that reason, birth control counseling is an essential part of the management of women for whom isotretinoin is prescribed, and the use of two forms of contraception is mandatory in all patients of child-bearing potential. Despite major educational efforts, pregnancies in patients receiving isotretinoin do occur, resulting in severe birth defects.<sup>23</sup> With the introduction of generic isotretinoin, concern over teratogenicity increased. In response, the manufacturers of isotretinoin started a program in which physicians and pharmacists must register and agree to require that patients receiving isotretinoin undergo pregnancy testing on a regular basis.<sup>24</sup> Unfortunately, this program failed to eliminate pregnancies in women treated with isotretinoin. Attempts to enforce previous guidelines on the safe use of isotretinoin (i.e., the SMART [System to Manage Accutane Related Teratogenicity] program)<sup>25</sup> have been deemed inadequate. As a result, the federal government has instituted more stringent mandatory requirements for prescribing oral isotretinoin, the iPledge program, which is intended to reduce pregnancy exposures.<sup>26</sup> Use of oral isotretinoin in female patients now requires physician, patient, and pharmacy enrollment in the iPledge program (<https://www.ipledgeprogram.com>).

It has been suggested that oral isotretinoin is associated with an increased risk of depression and suicidal tendency.<sup>27,28</sup> However, teenagers with severe acne are prone to depression and may be at increased risk for suicide regardless of the treatment they are using. A study compared the risk of depression, psychotic symptoms, suicide, and attempted suicide in acne patients receiving isotretinoin with the risk in acne patients being

*Table 4* Commonly Prescribed Systemic Therapies for Acne

<i>Medication</i>	<i>Dosage</i>	<i>Advantages</i>	<i>Adverse Effects</i>
<i>Antibiotics</i>			
Doxycycline	50–100 mg p.o., b.i.d.	Inexpensive	Photosensitivity, GI symptoms, candidiasis
Erythromycin	250–500 mg p.o., b.i.d.	Alternative to tetracyclines	GI symptoms, candidiasis
Minocycline	50 mg p.o., q.d.–100 mg p.o., b.i.d.	Highly effective; antibiotic resistance rare at 200 mg/day	GI symptoms, candidiasis, vertigo, lupuslike syndrome (rare), autoimmune hepatitis (rare)
Tetracycline	250 mg p.o., q.d.–500 mg p.o., q.i.d. (b.i.d. dosing preferred)	Inexpensive	Photosensitivity, GI symptoms, candidiasis
Trimethoprim-sulfamethoxazole	160 mg trimethoprim–800 mg sulfamethoxazole b.i.d.	Alternative to tetracyclines and erythromycin	Bone marrow suppression, drug eruption
<i>Other Agents</i>			
Isotretinoin	0.5–2.0 mg/kg/day, in two divided doses	Most effective treatment; long-lasting remissions	Teratogenicity, hyperlipidemia, cheilitis, alopecia, pyogenic granulomas, dry eyes, epistaxis, rare pseudotumor cerebri (especially with concomitant antibiotics)
Norgestimate–ethinyl estradiol	0.18 mg norgestimate, 0.035 mg ethinyl estradiol p.o., q.d., for 21 days; repeat every 4 wk	Alternative to antibiotics and isotretinoin; less androgenic activity than progestins in other contraceptives	Thromboembolic disorders; ?antibiotic interaction; ?increased breast carcinoma; gallbladder disease; reduced glucose tolerance; headache; fluid retention; hypertension; breakthrough bleeding; breast swelling and tenderness
Drospirenone–ethinyl estradiol	3 mg drospirenone and 0.3 mg ethinyl estradiol p.o., q.d., for 21 days, followed by 7 days of inert pills; repeat monthly	Alternative to antibiotics and isotretinoin; less androgenic activity than progestins in other contraceptives	Thromboembolic disorders; ?antibiotic interaction; ?increased breast carcinoma; gallbladder disease; reduced glucose tolerance; headache; fluid retention; hypertension; breakthrough bleeding; breast swelling and tenderness
Estrophasic contraceptive	1 mg norethindrone acetate and increasing doses of ethinyl estradiol: 20 µg, days 1–5; 30 µg, days 6–12; 35 µg, days 13–21; then 1 wk of inert tablet; repeat cycle every 4 wk	Alternative to antibiotics and isotretinoin; less androgenic activity than progestins in other contraceptives	Thromboembolic disorders; ?antibiotic interaction; ?increased breast carcinoma; gallbladder disease; reduced glucose tolerance; headache; fluid retention; hypertension; breakthrough bleeding; breast swelling and tenderness

treated with oral antibiotics. The relative risk of depression or psychosis for isotretinoin-treated patients was 1.0, and the relative risk of suicide and attempted suicide was 0.9, suggesting that isotretinoin is not associated with an increased risk of depression.<sup>29</sup> A study of pharmacy prescriptions yielded similar results. Prescriptions for antidepressants were quantified in 2,821 patients who filled oral isotretinoin prescriptions for the first time, and they were again quantified for patients filling isotretinoin prescriptions for a second time. The ratio of antidepressant use with the first prescription of isotretinoin to antidepressant use with the second prescription was not significantly different from 1.0—a finding that does not support an association between the use of isotretinoin and the onset of depression.<sup>30</sup>

Pseudotumor cerebri is a rare side effect of isotretinoin. It may be more likely to occur in patients who are concomitantly ingesting oral tetracycline antibiotics, although confirmatory data on this association are limited.

Patient counseling and monitoring—including serum chemistry panels and, in females, pregnancy testing—should be done before treatment with isotretinoin and should continue at monthly intervals during treatment. Depending on patient response, 0.5 to 1.0 mg/kg/day should be administered until a cumulative dose of 120 to 150 mg/kg is reached. Some clinicians have continued low-dose isotretinoin therapy for more than 6 months in selected cases. Rarely, a second course of therapy is indicated if deep inflammatory acne recurs.

**Hormonal therapy** Estrogens in the form of oral contraceptives can be beneficial for female patients with acne vulgaris, especially after adolescence; progestins, however, can exacerbate the condition. The newer progestins—desogestrel, norgestimate, and gestodene—have less androgenic activity and therefore are theoretically less likely to exacerbate acne. The mechanism of action of oral contraceptives appears to be related to increased serum levels of sex hormone-binding globulin, which effectively reduces free levels of circulating androgens, primarily testosterone. A combination of ethinyl estradiol and norgestimate has been shown to be beneficial in the treatment of acne vulgaris.<sup>31</sup> An oral contraceptive containing ethinyl estradiol in graduated doses, along with stable doses of norethindrone acetate, has been shown to have minimal androgenic activity and is also used for the treatment of acne.<sup>32</sup> A combined oral contraceptive containing ethinyl estradiol and drospirenone has also been found to ef-

fectively treat acne.<sup>33</sup> These agents are ideal for women who are seeking birth control methods and for women who are not candidates for, or who have not responded to, oral antibiotics or oral isotretinoin. Oral contraceptives can be particularly helpful in women with polycystic ovary syndrome. It is noteworthy that the beneficial effects of combined oral contraceptives are often diminished in patients who are obese.<sup>34</sup>

Concerns have been raised about the concomitant use of oral antibiotics and oral contraceptives because some antibiotics have the potential to interfere with contraceptive efficacy. Reviews of large numbers of patients treated concomitantly with oral contraceptives and antibiotics have not substantiated these concerns; risk of pregnancy was not significantly higher than the failure rate reported with oral contraceptives used alone.<sup>35</sup> Nevertheless, in view of the suggestions of a potential interaction in the published literature and antibiotic product labeling, caution is advisable when a patient uses an antibiotic and an oral contraceptive together.

Spirolactone, a weak potassium-sparing diuretic, exhibits moderate peripheral antiandrogenic activity.<sup>36</sup> It is often very effective in treating women with acne that persists after the teenage years or starts in postadolescence. Spirolactone is initiated at a dosage of 50 mg daily and may be increased to up to 200 mg daily, as warranted; however, the vast majority of patients respond favorably to 100 mg daily.

Overall, monitoring of serum potassium levels is not necessary for patients receiving spironolactone, but significant hyperkalemia is more likely to occur in patients with renal disease or in those taking potassium supplements, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Spirolactone should not be administered to patients using lithium carbonate, because of the potential for inducing marked rises in serum lithium levels and lithium toxicity.

Menstrual irregularity and painful gynecomastia may occur with spironolactone use, especially with higher doses (> 100 mg daily). These adverse effects do not occur when spironolactone is used in combination with an estrogen-containing oral contraceptive. This combination approach also appears to augment therapeutic benefit in postadolescent women with acne vulgaris.

#### *Phototherapy and Laser Therapies*

A number of light sources have been tested for the treatment of acne. Photodynamic therapy using topical aminolevulinic acid (ALA-PDT) has demonstrated efficacy for acne vulgaris.<sup>37</sup> Thorough reviews of the use of light and laser therapies of acne vulgaris have been published, including a summary of a consensus conference on the use of these modalities.<sup>38-40</sup> A blue light administered twice weekly for 4 consecutive weeks demonstrated efficacy for acne vulgaris exclusive of nodular lesions.<sup>41</sup> The 1,064 nm Q-switched neodymium:yttrium-aluminum-garnet (Nd:YAG) laser has proved useful for the treatment of acne scarring.<sup>42</sup>

#### **Rosacea**

Rosacea is a common condition that usually begins after the second to third decade of life. Clinically, rosacea is characterized by central facial erythema that may wax and wane in intensity, erythematous papules, pustules, and telangiectasias<sup>43,44</sup> [see Figure 2]. Facial flushing is a common feature. The presence of telangiectasia and the occurrence of flushing help distinguish rosacea from acne, as does the absence of comedos. The clinical course of rosacea is chronic, with periods of exacerbation and re-



**Figure 2** Erythematous papules, pustules, telangiectasia, and flushing are features of rosacea.

mission. Common triggers of rosacea include alcohol, exercise, extremes of temperature, and hot or spicy foods.<sup>43,44</sup> Medications that produce vasodilation, such as niacin, can precipitate flushing and exacerbate rosacea.

#### CLINICAL SUBTYPES OF ROSACEA

Various subtypes of rosacea are recognized.<sup>44,45</sup>

**Papulopustular (inflammatory) rosacea** Papulopustular (inflammatory) rosacea is characterized by erythema (most commonly involving the cheeks, nose, inner forehead and chin), telangiectasias, and inflammatory lesions (papules and pustules).

**Erythematotelangiectatic rosacea** Erythematotelangiectatic rosacea is characterized by diffuse erythema and telangiectasia with no or very few inflammatory lesions.

**Ocular rosacea** Ocular rosacea is common and can include blepharitis and conjunctival hyperemia or, less commonly, iritis, episcleritis, superficial punctuate keratopathy, and corneal neovascularization.<sup>46</sup>

**Phymatous rosacea** Phymatous rosacea is fortunately uncommon overall, occurring more frequently in males. It is characterized by localized sebaceous hyperplasia and fibrosis with development of bulbous and lobular proliferations of affected tissue. The nose (rhinophyma) is the most commonly affected anatomic site.

#### PATHOGENESIS

The pathogenesis of rosacea is poorly understood, although several associated mechanisms have been reported.<sup>43,44,47</sup> Proliferation of commensal *Demodex* mites may play a role, with papulopustular involvement through stimulation of inflammatory pathways, but it is not believed to be a major factor in many cases. It has been suggested that *Helicobacter pylori* may play a role in the pathogenesis of rosacea, although this theory remains controversial. There is no definitive evidence that any bacterium plays a role in the pathogenesis of rosacea. Several vascular inflammatory and tissue degradative mechanisms are believed to be operative, including increased facial blood flow, oral-thermal flushing, upregulation of reactive oxygen species (ROS) with reduced antioxidant reserve in skin, and upregulation of matrix metalloproteinase enzymes (MMPs) involved in dermal matrix degradation.

#### DIAGNOSIS

The diagnosis of rosacea is made on the basis of clinical evaluation.<sup>43,44</sup> There is no definitive diagnostic testing or histologic pattern that confirms the diagnosis.

#### TREATMENT

No curative therapy is available for rosacea, although treatment may effectively reduce severity of visible signs and symptoms and may control the intensity and frequency of rosacea flares. Therefore, it is important for the clinician to define treatment goals and set expectations with patients. It is also important to characterize the subtype of rosacea, because different clinical features respond differently to specific forms of therapy.<sup>44,45,47</sup> Optimal therapeutic results often require a combination of medical and physical treatment modalities.

Avoidance of triggers such as alcohol, hot or spicy foods, and heat is an important part of the therapeutic regimen offered to patients with rosacea.<sup>43,44</sup> Sunscreens are likewise useful to reduce erythema, decrease telangiectasia formation, reduce production of ROS, and decrease dermal matrix degradation.<sup>44,47</sup> Skin sensitivity increases in rosacea, as a result of an inherent increase in transepidermal water loss. Therefore, daily use of a gentle cleanser and a moisturizer is a vital component of the overall treatment program.<sup>44,47,48</sup> Proper skin care has been shown to augment the therapeutic benefit of topical medical treatment for rosacea.<sup>47,48</sup>

Several medications are helpful for the treatment of inflammatory lesions and perilesional erythema. Topical therapies that are effective for papulopustular rosacea of mild to moderate severity include sulfacetamide-sulfur, metronidazole, and azelaic acid.<sup>44</sup> Trials of topical therapy should be continued for 8 to 12 weeks to assess response. When successful, therapy markedly decreases inflammatory lesions and partially reduces erythema and disease-related symptoms (e.g., stinging and burning). Topical agents may be used in combination with systemic therapy in patients with more severe involvement.<sup>44</sup>

Systemic therapy for rosacea has conventionally utilized oral antibiotics, especially tetracycline derivatives (e.g., tetracycline, doxycycline, minocycline).<sup>44</sup> Although there is no definitive evidence that the antimicrobial action of these agents contributes to their efficacy against rosacea, tetracyclines have several anti-inflammatory effects unrelated to antimicrobial activity, such as downregulation of several MMPs,<sup>49</sup> and these anti-inflammatory effects may provide much of the therapeutic benefit in rosacea.<sup>44</sup> Doxycycline monohydrate in an anti-inflammatory dose, formulated as a 40 mg controlled-release capsule taken once daily, is approved by the FDA for the treatment of inflammatory rosacea, including long-term treatment.<sup>50</sup> This formulation differs from other available tetracycline formulations, including doxycycline, in that it results in blood levels below those required for antibiotic activity without loss of anti-inflammatory activity, as long as it is administered no more than once daily. Data for both short-term treatment (16 weeks' efficacy data) and long-term treatment (safety data over 9 months and microbiologic data up to 18 months) with doxycycline in an anti-inflammatory dose have indicated therapeutic benefit without production of antibiotic-resistant bacterial flora.<sup>50</sup> Microbiologic assessments have included evaluation of flora from the mouth, skin, gastrointestinal tract, and genitourinary tract. In large-scale pivotal clinical trials, no women treated with anti-inflammatory-dose doxycycline developed vaginal candidiasis.<sup>50</sup>

Persistent diffuse facial erythema seen after adequate medical treatment of papulopustular rosacea, diffuse facial erythema seen with erythematotelangiectatic rosacea, telangiectasias, and phymas are poorly responsive to topical and systemic therapies. In such cases, physical modalities such as properly selected laser therapy, intense pulse light (IPL), or both are warranted.<sup>44</sup>

#### Additional Information

Additional information about acne and rosacea are available from the American Academy of Dermatology (<http://www.aad.org>).

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