Chapter 15: Acne Vulgaris

INTRODUCTION

- *Acne* is a chronic skin disease characterized by open or closed comedones and inflammatory lesions, including papules, pustules, and nodules (cysts).

PATHOPHYSIOLOGY

- Acne usually begins during prepuberty and progresses as androgen production and sebaceous gland activity increase with gonad development.
- Acne progresses through four stages: (1) increased sebum production by sebaceous glands, (2) *Propionibacterium acnes* (renamed *Cutibacterium acnes*) follicular colonization (and bacterial lipolysis of sebum triglycerides to free fatty acids), (3) release of inflammatory mediators, and (4) increased follicular keratinization.
- Circulating androgens cause sebaceous glands to increase their size and activity. There is increased keratinization of epidermal cells and development of an obstructed sebaceous follicle, called a *microcomedone*. Cells adhere to each other, forming a dense keratinous plug. Sebum, produced in increasing amounts, becomes trapped behind the keratin plug and solidifies, contributing to open or closed comedone formation.
- Pooling of sebum in the follicle facilitates proliferation of the anaerobic bacterium *P. acnes*, which generates a T-cell response resulting in inflammation. *P. acnes* produces a lipase that hydrolyzes sebum triglycerides into free fatty acids that may increase keratinization and lead to microcomedone formation.
- *Noninflammatory acne* lesions include closed comedones (whiteheads) and open comedones (blackheads). Closed comedones are the first visible lesion in acne; they are almost completely obstructed to drainage and have a tendency to rupture. Open comedones are formed as the plug extends to the upper canal and dilates its opening.
- *Inflammatory acne* lesions include papules, pustules, and nodules. Pus formation occurs due to recruitment of neutrophils into the follicle during the inflammatory process and release of *P. acnes*–generated chemokines. *P. acnes* also produces enzymes that increase permeability of the follicular wall, causing it to rupture, thereby releasing keratin, lipids, and irritating free fatty acids into the dermis.

CLINICAL PRESENTATION

- Lesions usually occur on the face, back, neck, shoulders, and chest and may extend to the buttocks or extremities. One or more anatomic areas may be involved; once present, the pattern of involvement tends to remain constant. The skin, scalp, and hair are frequently oily.
- Lesions may take months to heal completely. Nodules and deep lesions may result in scarring. Resolution of inflammatory lesions may leave erythematous or pigmented macules (hyperpigmentation) that persist for months or longer, especially in dark-skinned individuals.

DIAGNOSIS

- Diagnosis is established by patient assessment, which includes observation of lesions and excluding other potential causes (eg, drug-induced acne). Several different systems are in use to grade acne severity.

TREATMENT

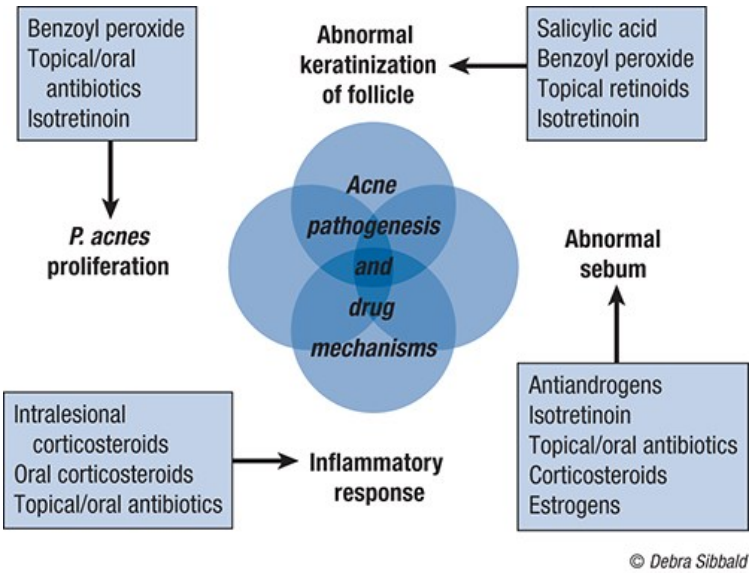
- Goals of Treatment: Reduce the number and severity of lesions, improve appearance, slow progression, limit duration and recurrence, prevent disfigurement from scarring and hyperpigmentation, and avoid psychologic suffering.

General Approach

- Acne is a chronic disease that warrants early and aggressive treatment (**Fig. 15-1**). Maintenance therapy is often needed for optimal outcomes. Patient adherence to lengthy treatment regimens is crucial to long-term control.
- Eliminating follicular occlusion will arrest the acne cascade. Nondrug and pharmacologic measures should be directed toward cleansing, reducing triggers, and combination therapy targeting all four pathogenic mechanisms.
- Combination therapy is often more effective than single therapy and may decrease side effects and minimize resistance or tolerance to individual treatments.
- Topical therapy is standard treatment for mild-to-moderate acne, whereas systemic therapy is required for moderate-to-severe acne.
- First-, second-, and third-line therapies should be selected and altered as appropriate for the severity and staging of the disease. Treatment is directed at control, not cure. Regimens should be tapered over time, adjusting to response.
- Combine the smallest number of agents at the lowest possible dosages to ensure efficacy, safety, avoidance of resistance, and patient adherence. Once control is achieved, simplify the regimen but continue with some suppressive therapy.

FIGURE 15-1

Acne pathogenesis and drug mechanisms.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

Nonpharmacologic Therapy

- Encourage patients to avoid aggravating factors (eg, mechanical occlusion, cosmetics), maintain a balanced low-glycemic-load diet, and control stress.
- Patients should wash twice daily with a mild, nonfragranced opaque or glycerin soap or a soapless cleanser. Scrubbing should be minimized to prevent follicular rupture.

- Males using a safety razor for shaving should soften the beard with soap and warm water or shaving gel. Shaving should be done lightly and infrequently, using a sharp blade and being careful to avoid nicking lesions. Strokes should be in the direction of hair growth, shaving each area only once to minimize irritation.
- Comedone extraction results in immediate cosmetic improvement but has not been widely tested in clinical trials.
- Light therapies are believed to work by killing *P. acnes* and by damaging and shrinking sebaceous glands, reducing sebum output with few or temporary adverse effects. Light therapies may be used once or twice weekly over a course of 6–10 treatments, with each irradiation lasting 10–20 minutes. Home-use blue light therapy is now available.

Pharmacologic Therapy

- *Comedonal noninflammatory acne*: Select topical agents that target the increased keratinization by producing exfoliation. Topical retinoids (especially adapalene) or a fixed combination with a retinoid (eg, adapalene plus benzoyl peroxide) are drugs of choice. Benzoyl peroxide, azelaic acid, or salicylic acid are second-line alternatives.
- *Mild-to-moderate papulopustular inflammatory acne*: It is important to reduce the population of *P. acnes* in follicles. Either the fixed-dose combination of adapalene plus benzoyl peroxide or benzoyl peroxide, topical retinoid, or azelaic acid are recommended as first choice therapy. In moderate papulopustular inflammatory acne, the fixed-dose combination is preferred, with or without hormonal therapy and/or antibiotic, particularly if the trunk is involved. If there are limitations in use of first-choice agents, alternatives include blue light monotherapy, alternate combination therapy (such as fixed-dose combination of erythromycin plus tretinoin), or oral zinc. In cases of widespread disease, combining an oral antibiotic with topical benzoyl peroxide with or without adapalene can be considered.
- *Moderately severe or severe papulopustular or moderate nodular acne*: An oral antibiotic plus the fixed-dose topical combination is preferred. Alternatively, oral isotretinoin or oral hormonal therapy can be added. If there are limitations to use of these agents, consider oral antiandrogens in combination with oral antibiotics or topical treatments.
- *Nodular or conglobate acne*: Monotherapy with oral isotretinoin is first choice. As alternatives, a retinoid fixed combination or oral antibiotic can be recommended. For females, oral isotretinoin plus antiandrogenic hormonal therapy is preferred. Alternatively, a fixed combination retinoid with oral antibiotics and/or an oral antiandrogen can be recommended.
- *Maintenance acne therapy*: A topical retinoid alone or a retinoid plus benzoyl peroxide fixed-dose combination is most commonly recommended. Topical azelaic acid is an alternative. Maintenance is usually begun after a 12-week induction period and continues for 3–4 months. A longer duration may be necessary to prevent relapse upon discontinuation. Long-term therapy with antibiotics is not recommended to minimize antibiotic resistance.

Exfoliants (Peeling Agents)

- Exfoliants induce continuous mild drying and peeling by irritation, damaging superficial skin layers and inciting inflammation. This stimulates mitosis, thickening the epidermis and increasing horny cells, scaling, and erythema. Decreased sweating results in a dry, less oily surface and may resolve pustular lesions.
- **Resorcinol** is less keratolytic than salicylic acid and, when used alone, is classified by the Food and Drug Administration (FDA) as category II (not generally recognized as safe and effective). The FDA considers resorcinol 2% and resorcinol monoacetate 3% to be safe and effective when used in combination with sulfur 3%–8%. Resorcinol is an irritant and sensitizer and should not be applied to large areas or on broken skin. It produces a reversible dark brown scale on some dark-skinned individuals.
- **Salicylic acid** is a comedolytic agent available over the counter in 0.5%–2% strengths; concentrations between 3% and 6% are keratolytic, softening the horny layer and producing shedding of scales. It has mild antibacterial activity against *P. acnes* and offers slight anti-inflammatory activity at concentrations up to 5%. Salicylic acid is recognized by the FDA as safe and effective, but it offers no advantages over benzoyl peroxide or topical retinoids. Salicylic acid products are often used as first-line therapy for mild acne because of their availability without a prescription in alcohol–detergent impregnated pads, washes, bars, and semisolid vehicles. Both wash-off and leave-on preparations are well tolerated. Lower concentrations are sometimes combined with sulfur to produce an additive keratolytic effect. Concentrations of 5%–10% can also be used by

prescription, beginning with a low concentration and increasing as tolerance develops to the irritation. Salicylic acid is often used when patients cannot tolerate topical retinoids because of skin irritation.

- **Sulfur** is keratolytic and has antibacterial activity. It can quickly resolve pustules and papules, mask lesions, and produce irritation that leads to skin peeling. Sulfur is used in the precipitated or colloidal form in concentrations of 2%–10%. Although it is often combined with salicylic acid or resorcinol to increase effect, use is limited by offensive odor and availability of more effective agents.

Topical Retinoids

- Retinoids reduce obstruction within the follicle and are useful for both comedonal and inflammatory acne. They reverse abnormal keratinocyte desquamation and are active keratolytics. They inhibit microcomedone formation, decreasing the number of mature comedones and inflammatory lesions.
- Topical retinoids are safe, effective, and economical for treating all but the most severe cases of acne. They should be the first step in moderate acne, alone or with antibiotics and benzoyl peroxide, reverting to retinoids alone for maintenance once adequate results are achieved. Combination products containing benzoyl peroxide or topical antimicrobials are available.
- Retinoids can produce extended periods of remission if accompanying irritation does not impede patient adherence. Side effects of dryness, peeling, erythema, and irritation can be mitigated by reduced frequency of application.
- Retinoids should be applied at night, a half hour after cleansing, starting with every other night for 1–2 weeks to adjust to irritation. Doses can be increased only after 4–6 weeks of the lowest concentration and least irritating vehicle. Gels and creams are less irritating than solutions.
- **Tretinoin** (retinoic acid, vitamin A acid) is available in various strengths in creams, gels, and pumps. Tretinoin should not be used in pregnant women because of risk to the fetus.
- **Adapalene** (Differin) is the topical retinoid of first choice for both treatment and maintenance therapy because it is as effective but less irritating than other topical retinoids. Adapalene is available as 0.1% gel (nonprescription for once-daily application by patients age 12 years and older), cream, solution, lotion, and pads. A 0.3% gel is also available. It is also available in fixed-dose combinations with benzoyl peroxide to increase efficacy over monotherapies.
- **Tazarotene** (Tazorac) is as effective as adapalene in reducing noninflammatory and inflammatory lesion counts when applied half as frequently. Compared with tretinoin, it is as effective for comedonal and more effective for inflammatory lesions when applied once daily. The product is available as a 0.05% and 0.1% cream or gel and a 0.1% foam. Tazarotene is contraindicated in pregnancy.
- **Trifarotene** (Aklief) was approved in the United States in late 2019 for treatment of acne in patients age 9 years and older. The product is available as a 0.005% cream for application once daily in the evening.

Topical Antibacterial Agents

- **Benzoyl peroxide** is bactericidal to *P. acnes* and is also mildly comedolytic. It suppresses sebum production and reduces free fatty acids, which are comedogenic and trigger inflammation. No resistance has been reported, and addition of benzoyl peroxide to antibiotic therapy improves efficacy and may reduce resistance development.

  ✔ Benzoyl peroxide is useful for both noninflammatory and inflammatory acne. It has a rapid onset and may decrease the number of inflamed lesions within 5 days. Used alone or in combination, benzoyl peroxide is the standard of care for mild-to-moderate papulopustular acne. It is an agent of first choice when combined with adapalene for most patients with mild-to-moderate inflammatory acne and a second-line choice for patients with noninflammatory comedonal acne. It is often combined with a topical retinoid or antibiotic. For maintenance therapy, benzoyl peroxide can be added to a topical retinoid.

  ✔ Topical washes, foams, creams, or gels can be used as leave-on or wash-off agents. Strengths available range from 2.5% to 10%. All single-agent preparations are available without prescription.

✔ Therapy should be initiated with the weakest concentration (2.5%) in a water-based formulation in the evening. Once tolerance is achieved, the strength may be increased to 5% or the base changed to the acetone or alcohol gels, or to paste. It is important to wash the product off in the morning. A sunscreen should be applied during the day.

✔ Side effects of benzoyl peroxide include dryness, irritation, and, rarely, allergic contact dermatitis. It may bleach hair, clothing, and towels.

- **Topical clindamycin** and **erythromycin** are macrolide antibiotics that are effective and well-tolerated acne treatments. They are recommended for use in combination with topical benzoyl peroxide (wash-off or leave-on) or retinoids, which increases efficacy and decreases development of resistant organisms. Clindamycin is preferred over erythromycin because of better efficacy and lack of systemic absorption; it is available as a single-ingredient topical preparation or in combination with benzoyl peroxide. Erythromycin is available alone and in combination with retinoic acid or benzoyl peroxide, but it is seldom used in practice.

- **Azelaic acid** has antibacterial, anti-inflammatory, and comedolytic activity. It is used for mild-to-moderate inflammatory acne but has limited efficacy compared with other therapies. It is an alternative to first-choice therapy for comedonal and inflammatory acne, particularly in combination. It is also an alternative to topical retinoids for maintenance therapy. Azelaic acid is well tolerated, with adverse effects of pruritus, burning, stinging, and tingling occurring in 1%–5% of patients. Erythema, dryness, peeling, and irritation occur in fewer than 1% of patients. Azelaic acid is available in 20% cream (Azelex) and 15% gel (Finacea) formulations, which are usually applied twice daily (morning and evening) on clean, dry skin. Most patients experience improvement within 4 weeks, but treatment may be continued over several months if necessary.

- **Dapsone** (Aczone) is a sulfone that has antibacterial and anti-inflammatory properties and improves both inflammatory and noninflammatory acne. It may be particularly useful for patients with sensitivities or intolerance to conventional antiacne agents and may be used in sulfonamide-allergic patients. Dapsone 5% topical gel is applied twice daily; the 7.5% gel is applied once daily. Combination therapy with topical retinoids may be indicated if comedonal lesions are present. Topical dapsone 5% gel has also been used in combination with adapalene or benzoyl peroxide.

Oral Antibacterials

- Use of oral antibiotics is reserved for patients with moderate-to-severe inflammatory acne. Tetracyclines (**minocycline** and **doxycycline)** have both antibacterial and anti-inflammatory effects and are considered first-line therapy. Macrolides (**erythromycin**, **azithromycin**) and **trimethoprim/sulfamethoxazole** are acceptable alternative agents. Because of bacterial resistance, erythromycin should be limited to patients who cannot use a tetracycline (eg, pregnant women and children <8 years old).

- **Ciprofloxacin** and **trimethoprim** alone may be effective in cases where other antibiotics cannot be used or are ineffective.

- **Sarecycline** (Seysara) is a narrow-spectrum tetracycline derivative with anti-inflammatory properties approved for treatment of inflammatory lesions of non-nodular moderate-to-severe acne vulgaris in patients 9 years of age or older.

- Oral antibiotics should be accompanied by early use of combination therapy with retinoids. In such cases, the antibiotic may often be discontinued after 3–6 months of therapy.

- The incidence of significant adverse effects with oral antibiotic use is low. Vaginal candidiasis may complicate use of all oral antibiotics. Minocycline has been associated with pigment deposition in the skin, mucous membranes, and teeth; it may also cause dose-related dizziness, urticaria, hypersensitivity syndrome, autoimmune hepatitis, a systemic lupus erythematosus–like syndrome, and serum sickness–like reactions. Doxycycline is a photosensitizer, especially at higher doses.

- The choice of antibiotic should be determined based on the side effect profile, resistance, cost, and consensus guidelines.

Intralesional Corticosteroids

- Intralesional **triamcinolone acetonide** injections are effective for large individual inflammatory nodules. Intralesional injections may produce rapid improvement and decreased pain but may also be associated with local skin atrophy.

Antisebum Agents

- **Isotretinoin** is a metabolite of vitamin A that decreases sebum production, inhibits *P. acnes* growth, and reduces inflammation. It is approved for treatment of severe recalcitrant nodular acne in non-pregnant patients 12 years of age and older with multiple inflammatory nodules with a diameter of 5 mm or greater. It has also been used for moderate acne that is treatment resistant, relapses quickly after discontinuation of oral antibiotic therapy, or produces physical scarring or significant psychosocial distress. Isotretinoin is the only drug treatment for acne that produces prolonged remission.

  ✔ The approved isotretinoin dose range is 0.5–2 mg/kg/day, usually given over a 20-week course. Drug absorption is greater when taken with food.

  ✔ Guidelines recommend initiation at 0.5 mg/kg/day when appropriate, subsequently increasing to 1 mg/kg/day after the first month as tolerated, with a goal cumulative dose between 120 and 150 mg/kg.

  ✔ Side effects include those of the mucocutaneous (most common), musculoskeletal, and ophthalmic systems, as well as headaches and central nervous system effects. Most adverse effects, such as cheilitis and dry nose, eyes, and mouth, are temporary and resolve after discontinuation. Laboratory monitoring during therapy should include triglycerides, cholesterol, transaminases, and complete blood counts. Mood disorders, depression, suicidal ideation, and suicides have been reported sporadically, but a causal relationship has not been established. The issue is complex because depression and suicidal ideation occur with severe acne in the absence of isotretinoin.

  ✔ Because of teratogenicity, two different forms of contraception must be started in female patients of childbearing potential beginning 1 month before therapy, continuing throughout treatment, and for up to 4 months after discontinuation of therapy. All patients receiving isotretinoin must participate in the iPLEDGE program, which requires pregnancy tests and assurances by prescribers and pharmacists that they will follow required procedures.

- **Oral contraceptives** containing estrogen can be useful for acne in some women because of their antiandrogenic properties. Agents with FDA approval for acne in women who also desire contraception include **norgestimate with ethinyl estradiol** and **norethindrone acetate with ethinyl estradiol**; other estrogen-containing products may also be effective. They may be used alone or in combination with other acne treatments.

- **Spironolactone** in higher doses is an antiandrogen. Doses of 50–200 mg have been shown to be effective for acne in select women.

- **Cyproterone acetate** is an antiandrogen that may be effective for acne in females when combined with ethinyl estradiol (in the form of an oral contraceptive). No cyproterone/estrogen–containing oral contraceptives are available in the United States.

- **Oral corticosteroids** in high doses used for short courses may provide temporary benefit in patients with severe inflammatory acne. Low-dose **prednisone** (5–15 mg daily) given alone or with high estrogen-containing combination oral contraceptives has shown efficacy for acne and seborrhea. Long-term adverse effects preclude oral corticosteroid use as a primary therapy for acne.

EVALUATION OF THERAPEUTIC OUTCOMES

- Provide patients with acne with a monitoring framework that includes specific parameters and frequency of monitoring. Have them record the objective response to treatment in a diary. Contact patients within 2–3 weeks after the start of therapy to assess progress and then every 4–8 weeks thereafter.

- Good adherence to therapy is the key to treatment success.

- Lesion counts should decrease by 10%–15% within 4–8 weeks or by more than 50% within 2–4 months. Inflammatory lesions should resolve within a few weeks, and comedones should resolve by 3–4 months. If anxiety or depression is present at the outset, control or improvement should be achieved within 2–4 months.

- Long-term parameters should include no progression of severity, lengthening of acne-free periods throughout therapy, and no further scarring or pigmentation throughout therapy.

- Monitor patients regularly for adverse treatment effects with appropriate dose reduction, alternative therapy, preventative measures, or drug

discontinuation as appropriate.

See Chapter 113, Acne Vulgaris, authored by Debra J. Sibbald, for a more detailed discussion of this topic.