The Pathophysiology of Acne Vulgaris in Children and Adolescents, Part 2: Tailoring Treatment

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Various pathophysiologic factors are involved in the development of acne lesions, microcomedones, comedones, and inflammatory lesions. These factors include follicular hyperkeratosis, increased colonization of follicles by Propionibacterium acnes*, increased sebum production, and inflammatory mediators. Optimal treatment of acne involves the use of agents that address these various underlying pathogenetic factors.*

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Various pathophysiologic factors contribute to the development of acne. The disorder begins with increased prepubertal androgen production and is followed by abnormal pilosebaceous follicular keratinization and desquamation; increased proliferation of sebocytes, enlarged sebaceous glands, and augmented secretion of sebum; obstruction of sebaceous follicles; colonization of pilosebaceous units by *Propionibacterium acnes*; and perifollicular inflammation.[1-9] Androgen production is involved in follicular hyperkeratinization, sebocytic hyperplasia, and seborrhea.[10-12]

Therapeutic options for acne target the follicular hyperkeratosis and abnormal desquamation of epithelial cells in sebaceous follicles, the excess production of sebum, the proliferation of *P acnes*, and the inflammatory response generated by this bacterium (Table 1).[4-6,11,13-14] Treatment recommendations and algorithms have been developed based on the nature and severity of acne lesions.[3,4,6,8,9,15-22] One of the most recent algorithms was developed by the Global Alliance to Improve Outcomes in Acne (Table 2).[22] For predominantly comedonal acne or low-grade inflammatory acne, either alone or in combination, topical retinoids are the treatment of choice. In the presence of mild papular/pustular inflammatory acne, most researchers suggest adding a topical antibiotic. However, it should be noted that newer retinoids, such as tazarotene (a receptor-selective retinoid)[23] and adapalene (a retinoidlike agent with a different retinoid receptor–binding profile)[21] have demonstrated significant anti-inflammatory and immunomodulatory effects in clinical trials[14] and also are useful for treating mild papular/pustular inflammatory acne. For moderate papular/pustular inflammatory acne and nodular inflammatory acne, a topical retinoid in combination with an oral antibiotic with or without benzoyl peroxide is suggested. Antiandrogenic oral contraceptives that contain norgestimate or desogestrel may be useful as adjunctive therapy for adolescent girls. These agents reduce androgen levels by increasing sex hormone–binding globulin, thereby decreasing the availability of biologically active free testosterone. Other hormonal therapies such as androgen receptor blockers and 5 α-reductase inhibitors are usually reserved for adult women.[24] In severe inflammatory acne (nodular/conglobate), isotretinoin is the treatment of choice. After discontinuing isotretinoin, maintenance therapy usually consists of only a topical retinoid.

Role of Topical Retinoids

Retinoids and retinoid analogs reverse abnormal follicular keratinization and slow the process of keratinocyte desquamation, producing a comedolytic effect and thereby decreasing the number of microcomedones.[20,21] Because these agents inhibit the formation of the microcomedone—the precursor lesion—they prevent the formation of comedones and inflammatory lesions. They also appear to exert direct immunomodulatory and

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anti-inflammatory effects and enhance the penetration of other antiacne agents by altering the follicular microenvironment.

Tretinoin is the best-known topical retinoid. Adapalene has the same clinical efficacy on inflammatory and noninflammatory acne lesions as tretinoin, but offers better tolerability with initial use and therefore offers potentially better compliance.[13,22] Tazarotene may be more irritating than other topical retinoids. Topical agents, particularly benzoyl peroxide and retinoids, are used for maintenance therapy. The ideal agent for maintenance therapy should prevent or limit microcomedone formation and be well tolerated to permit application over a wide epidermal surface for control of microcomedones. Relatively nonirritating topical agents include benzoyl peroxide in low concentrations, retinoids such as adapalene, and tretinoin applied with the new Microsponge® delivery system. Use of a cream rather than a gel formulation, alternative-dosing regimens (such as alternate-day application or short-contact therapy), or combination therapy can reduce the skin irritation that occurs with tazarotene, most commonly during the first 1 to 2 weeks of treatment.[23]

Adolescents and Pregnancy

Each year in the United States, 800,000 to 900,000 adolescent girls 19 years or younger become pregnant.[25] The number of pregnancies among 13- and 14-year-old girls in 1997—the most recent year for which such data are available—was 23,700 (pregnancy rate of 0.64%); among girls aged 15 to 17 years, the number of pregnancies was 321,300 (pregnancy rate of 5.71%). Isotretinoin is a known human teratogen that can cause multiple major malformations in an embryo or a fetus.[26] Its teratogenicity has led to severe restrictions on the use of isotretinoin by young women,[26] but isotretinoin-exposed pregnancies occur.[27] Although the number of reproductive-aged adolescents taking isotretinoin in the United States is unknown, approximately 900 pregnancies occurred among adolescent girls and women who

Table 1.

Mechanisms of Action of Antiacne Drugs[4-6,11,13,14]

Mechanism of Action	Topical Agents	Oral Agents
Anticomedonal	Tretinoin Adapalene Tazarotene Salicylic acid Isotretinoin Azelaic acid	Isotretinoin
Antiseborrheic	None established	Estrogens Antiandrogens Spironolactone Isotretinoin
Antibacterial	Erythromycin Clindamycin Benzoyl peroxide Azelaic acid	Tetracycline Erythromycin Minocycline Doxycycline Clindamycin
Anti-inflammatory	Adapalene Tazarotene Tretinoin Intralesional corticosteroids	Corticosteroids Isotretinoin Certain antibiotics (erythromycin, clindamycin)

Table not available online

had enrolled voluntarily in the Boston University Accutane Survey.[26] Anomalies among exposed neonates may include complex congenital heart disease, hydrocephalus, facial dysmorphism, and neural tube closure defects. Accordingly, isotretinoin has a US Food and Drug Administration pregnancy category X rating (ie, studies in animals or humans show fetal abnormalities; adverse reaction reports indicate evidence of fetal risk that clearly outweighs any potential benefit from using the drug in pregnant women, regardless of trimester).[27,28] Tazarotene also has a pregnancy category X rating, despite the fact that systemic absorption is minimal.[29] Tretinoin and adapalene have a pregnancy category C rating (risk cannot be ruled out, human studies are lacking, and animal studies are either positive for fetal risk or lacking; however, potential benefits may justify the potential risk).

Conclusion

Increasing levels of circulating androgens of adrenal and gonadal origin during childhood and adolescence seem to trigger acne. The pathophysiology of acne includes, in a somewhat sequential manner, retention hyperkeratosis, colonization by *P acnes*, and perifollicular inflammation. The goal of therapy is to reverse these pathogenetic events

and thereby minimize or prevent acne lesions. To achieve these clinical objectives, acne therapeutic regimens that address as many of the underlying pathogenic factors as possible should be chosen.

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