

ACNE PHARMACOLOGY AND
MANAGEMENT THROUGH THE
LIFESPAN

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Objectives

- Explain the mechanism of action of keratolytics
- Give one rationale for oral antibiotic choice
- Identify the choice of topical medications for acne rosacea

Acne Treatment Goals

- Normalize hyperkeratinization and follicular desquamation
- Decrease inflammation
- Decrease *P acnes*
- Decrease sebum
- Prevent scarring

Myths vs Truths

- **Myth:** Blackheads are caused by dirt.
- **Fact:** They are black because of oxidized melanin. Blackheads, or open comedones, are collections of sebum and keratin that form within follicular openings. When exposed to air, they become oxidized and turn black.
- **Myth:** Acne should disappear by the end of adolescence.
- **Fact:** Some women have acne that persists well past adolescence. Others have an initial episode in their 20s or 30s.
- **Myth:** Acne is caused or worsened by certain foods, such as chocolate, sweets, and greasy junk food.
- **Fact:** Despite occasional personal anecdotes and persistent cultural myths, acne is probably not significantly influenced by diet.
- **Myth:** A dirty face exacerbates acne; therefore, scrubbing the face daily helps clear it up.
- **Fact:** Scrubbing and rubbing a face that has acne, particularly inflammatory acne, will only serve to irritate and redden an already inflamed complexion. Instead, the face should be washed with a gentle cleanser.
- **Myth:** Frequent facials are beneficial.
- **Fact:** Professional facials and at-home scrubs, astringents, and masks are generally not recommended because they tend to aggravate acne.

• Goodhear

DRUGS THAT INDUCE OR AGGRAVATE ACNE

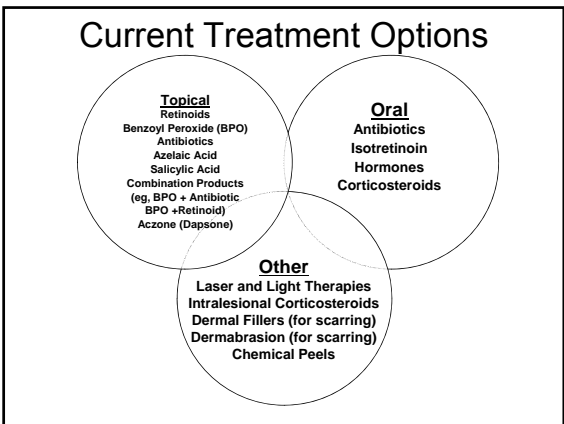
- Androgens
- Adrenocorticotrophic hormone (ACTH)
- Bromides
- Glucocorticoids
- Oral/fluorinated topical corticosteroids
- Hydantoins
- Iodides
- Isoniazid
- Lithium
- Phenobarbital
- Phenytoin
- Rifampin
- Trimethadione

Causes of Acne

- Increased keratinization within the follicle
- Increased sebum production
- Proliferation of *Propionibacterium acnes*
- Inflammation

- Skin cells in acne patients do not desquamate
- Keratinocytes (epidermal cells) produce the protein keratin
 - Hyper-keratinization causes comedones
- Creates buildup of surface debris that traps oil and *P.acnes* in a deoxygenated environment, causing anerobic bacteria to proliferate

- ### ACNE MEDICATIONS
- Keratolytics
 - Antibiotics
 - Antibacterials
 - Hormones
 - Accutane



BENZOYL PEROXIDE

- Benzac: 2.5%, 5%, 10% gel
- Benzagel 5%, 10% gel
- Desquam-X: 5%, 10%
- Neobenz 2.5%, 5%, 8%, 10%
- Persa-gel 5%, 10%
- Zoderm: 4.5%, 6.5%, 8.5%

Benzoyl Peroxide (BPO)

- Anti-bacterial
 - Reduce *P. acnes*
- Comedolytic activity
- Some formulations are available over the counter, some are available by prescription
- May bleach hair, clothes, and bed linen
- May cause irritation

Bershad SV, *Mil. Signal. J. Med.* 2001;68:279-286

Benzoyl Peroxide Mechanism of Action

- Potent antibacterial agents
- Improve both inflammatory and noninflammatory lesions (comedones).
- Dry and peel the skin
- Help clear blocked follicles.
- May be used alone to treat mild acne
- For more severe cases, it should be used in conjunction with topical retinoids, as well as topical or systemic antibiotics

RETINOIDS

- Azelaic acid 20%: antibacterial/keratolytic
(Azelex, Finacea)
- Adapalene: 0.1% gel, 0.3% gel, .05%cream, 0.1% lotion (Differin)
- Tretinoin: .025% cream, .05% cream, 0.1% cream
 - .01%, .025 gel
 - .04%, 1% aqueous gel (Retin A Micro)
 - Atralin: .05% tretinoin
 - Ziana: .05% tretinoin/5%Clindamycin
- Tazarotene: .05%, .1% aqueous gel, cream (Tazorac)

Retinoids Mechanism of Action

- Target microcomedones – precursors for all other acne lesions
- Increases turnover of follicular epithelial cells, causing extrusion of comedones
- Help normalize hyperkeratinization and abnormal desquamation
 - Help prevent formation of both comedones and inflammatory lesions
- Improve follicular microclimate
- Reduce inflammation
- Enhance follicular penetration by other drugs
- Important for:
 - Maintaining clear skin (prevent new lesions forming)
 - Clearing both comedonal and inflammatory acne
- All retinoids cause sun-sensitivity

Gollnick H. et al. / J Am Acad Dermatol. 2003;49:S1-S37

- Tretinoin: Vasodilation
- Azelaic Acid: Vasoconstriction
- Adapalene: No effect

TOPICAL ANTIBIOTICS

- Clindamycin: solution, lotion, gel, pledgettes, foam
- Erythromycin: solution, lotion, pledgetts
- Sulfa: lotion, cream

Topical Antibiotics

- Antibacterial and anti-inflammatory effects
- Indirect effect on comedogenesis (by reducing *P. acnes*, which would otherwise activate the immune system and intensify comedogenesis)
- Should not generally be used as monotherapy
 - Strains of *P. acnes* may develop that are resistant to the antibiotic
 - This can be prevented by using in combination with BPO

1. Bershad SV. *Mt Sinai J Med.* 2001;68:279-286. 2. Layton AM. *Am J Clin Dermatol.* 2001;2:135-141. 3. Toyoda M, Morohashi M. *Dermatology.* 1998;196:130-134

Topical Antibiotics

- Preparations that contain the topical antibiotics clindamycin and erythromycin are active against *P. acnes*.
- Antibacterial action
- Anti-inflammatory action (papules and pustules).
- Drug resistance has been reported with these antibiotics.

BPO Combination Products

- Benzamycin: Erythromycin 3%, benzoyl peroxide 5%
- Benzaclin/Duac: Clindamycin, benzoyl peroxide 5%
- Acanya: Clincamycin, benzoyl peroxide 2.5%
- Epiduo: Adapalene 1%Gel, benzoyl peroxide 5%

Combination Products

- The combination of erythromycin and clindamycin with benzoyl peroxide helps prevent bacterial resistance
- There appears to be a synergistic effect: the combination appears to be more effective than either drug used alone

Aczone (Dapsone)

- Mechanism of action: Anti-inflammatory
- Co-administration with TMP/SMX caused increased levels of dapsone and its metabolites
- Co-administration with topical BPO caused temporary yellow/orange discoloration of skin and facial hair

INFLAMMATORY ACNE

- Deeper lesions that develop in the lower portion of the follicle create warm, tender nodulocystic lesions
- Results in scars and pits
- Inflammatory reactions to sebum, fatty acids, and *P.acnes* bacteria distends the follicle
- Often resolve with hyperpigmentation

ORAL ANTIBIOTICS

- Decrease inflammation
- Decrease *P.acnes* and free fatty acids
- Treat four to six weeks for improvement
- Treatment may continue for months

Systemic Therapies

- Moderate to severe acne that is unresponsive to topical treatment
- Acne that tends to scar
- Truncal acne does not respond to topical therapy as readily as does facial acne
 - **Significant acne on the chest and back often requires systemic therapy**
- Systemic therapy has a more rapid onset of improvement, which may enhance patient compliance.

Oral Antibiotics

- Erythromycin 250-500mg BID
- Tetracycline 250-500mg BID
- Doxycycline 50-100mg BID
 - Doryx 50mg, 100mg, 150mg
- Minocycline 50-100mg BID
 - Adoxa 50mg, 100mg, 150mg
 - Solodyn 45mg, 65mg, 80mg, 90mg, 115mg, 135mg
- Less Common:
 - Clindamycin, Cephalosporins, Ampicillins, Trimethoprim/Sulfamethoxazole

Oral Antibiotic Method of Action

- Inhibit the growth of *P. acnes* and bacterial protein synthesis
- Decreases free fatty acid production and pustule formation
- Significant anti-inflammatory action as a result of their inhibition of the chemotactic response of neutrophils.

HORMONAL THERAPY

- Estrogens
- Spironolactone
- Suppress androgenic stimulation of sebum production
- Beneficial to females

Hormonal Therapy

- Aims to reduce effect of androgens on the:
 - Sebaceous glands
 - Follicular keratinocytes
- Other aspects of acne pathophysiology unaffected, so additional agents usually needed
- May be warranted in females with:
 - Severe seborrhea
 - Clinically apparent androgenic alopecia
 - Seborrhea/acne/hirsutism/alopecia (SAHA) syndrome
 - Late-onset acne

Gollnick H. et al. J Am Acad Dermatol. 2003;49:S1-S37.

Hormonal Therapy

- Androgen receptor blockers
 - Spironolactone
 - Drospirenone
 - Desogestrel
 - Flutamide
- Reduce ovarian + adrenal androgen production
 - Estrogens
 - Oral contraceptives
 - Cyproterone acetate
 - Gonadotropin-releasing hormone agonists
 - Low-dose glucocorticoids

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Oral Contraceptives

- Mechanism
 - Reduce androgen formation, circulating testosterone, and subsequent sebum production
- Clinical utility
 - $\geq 50\%$ improvement with some preparations
- Safety
 - Cardiovascular risks (less with low-estrogen preparations)

1. Shaw JC. Am J Clin Dermatol. 2002;3:571-578. 2. Lemay A, Lajoie PG. Skin Ther Lett. 2002;7:1-5.

Oral Contraceptives

- Decrease serum testosterone concentrations:
 - Suppress gonadotropins
 - Reduce ovarian androgen secretion
 - Increase sex hormone-binding globulin levels
- Estrogens block the androgenic stimulation of sebaceous glands
 - Act as androgen receptor blockers.

- Birth control patch and ring have an unpredictable effect on acne
 - can provoke acne
 - Depo-Provera can also worsen or trigger acne at times.
- Premenstrual flares: increased dosage of oral antibiotics 5 to 7 days before next menstrual period (Azithromycin)

Spironolactone

- Mechanism
 - Blocks androgen receptors
 - Inhibitor of 5 α -reductase
- Clinical utility
 - Women with therapy-resistant acne (not FDA approved for acne)
- Safety
 - Menstrual irregularities, breast tenderness/enlargement, lethargy, headache
 - Menstrual irregularities prevented when taken with oral contraceptive
 - There could be a risk of feminization of a male fetus if taken by a pregnant woman

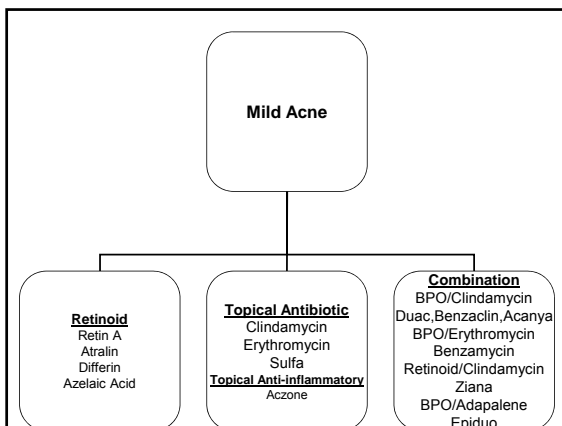
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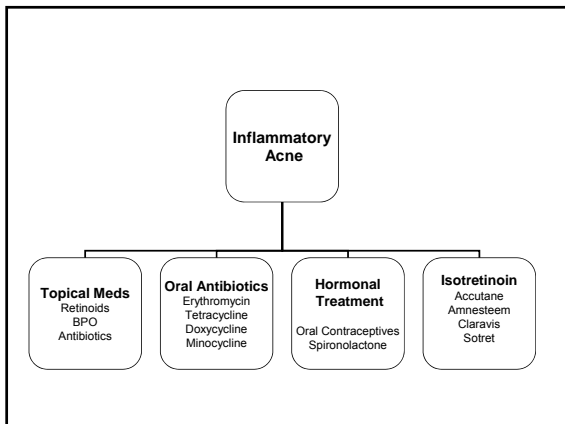
Oral Isotretinoin

- Indicated for severe recalcitrant nodular acne
- Teratogenic
- High Response Rate
- Careful Monitoring of CBC and hepatic/renal function
- HCG in females monthly
- Mechanisms
 - Suppresses sebum production
 - Promotes shedding of keratinocytes
 - Reduces *P. acnes* colonization
 - Decreases inflammation

Isotretinoin Mechanism of Action

- Reduces the size and output of sebaceous glands
- Limits the amount of sebum and thus the food supply of *P. acnes*
- Stabilizes keratinization
 - Keratinocytes produce the protein keratin
 - Less likely to produce comedones





Mechanisms of Action

	Normalize Keratinization	↓p. acnes	↓ Inflammation	↓ Sebum
Retinoids	X		X	
BPO	X	X		
Topical ABX		X	X	
Salicylic Acid	X			
Azaelic Acid	X	X		
Oral ABX		X	X	
Hormones				X
Isotretinoin	X	X	X	X

Rosacea

- Usually arises later in life: between 30 and 50 years of age
- Most commonly in fair-skinned people with an ethnic background from Great Britain (Scotland and Wales), Ireland, Germany, Scandinavia, and certain areas of Eastern Europe
- Women three times more likely to be affected than men
- Rare in all dark-skinned people, including Hispanic, African, and African-American populations

Rosacea

- Rosacea is not caused by drinking excessive amounts of alcohol—a serious misconception that has been around for ages and should be put to rest!
- Precipitating factors that may exacerbate rosacea include:
 - Sun exposure
 - Excessive washing of the face
 - Irritating cosmetics

Rosacea

- Lacks the comedones (“blackheads” or “whiteheads”) that are seen in acne.
- Does not appear to have any relationship to androgenic hormones.
- Does not scar or present with nodules or cysts, unless the patient has concomitant acne.
- May begin with erythema on the cheeks and forehead
- Spreads to the nose and chin (erythemotelangiectatic rosacea)
- Often, affected patients describe how they are inclined to flush and blush easily.
- As rosacea progresses, telangiectasias, papules, and sometimes, pustules begin to arise against a background of erythema
- Papules and pustules (papulopustular rosacea) tend to come and go in cycles, but the erythema and telangiectasias tend to remain

Rosacea

- **Distribution of Lesions**
 - Lesions are most typically seen on the central third of the face—the forehead, nose, cheeks, and chin (the so-called “flush/blush” areas)
 - Lesions tend to be bilaterally symmetric, but they may occur on only one side of the patient's face.
- **Clinical Manifestations**
 - Burning and flushing can be quite uncomfortable.
 - Patients may also have ocular involvement, which results most often in blepharconjunctivitis
 - Ocular rosacea may precede the skin manifestations in up to 20% of people

Rosacea Triggers

- **Sun exposure**
- **Excess alcohol ingestion.** Drinking habits have nothing to do with *causing* rosacea; however, it is accepted that the blushing and flushing of rosacea may flare up in the short term when some people drink alcohol—especially red wine. However, it is questionable that the drinking of alcoholic beverages causes a long-term worsening of the condition.
- **Spicy foods**
- **Smoking**
- **Caffeine**
- **Emotional stress**
- **Physical exertion**

Rosacea Treatment

- **Azelaic Acid:** Causes vasoconstriction, decreases inflammation and erythema
- **Metronidazole:** 0.75% cream, gel, lotion, 1% gel
- **Doxycycline** 50mg, 75mg, 100mg for papular/pustular lesions; anti-inflammatory
- **Oracea** 40mg (Doxycycline) (30mg immediate release, 10mg delayed release)

- Dermatologists at the University of California San Diego have developed a vaccine with *Propionibacterium acnes* which demonstrated efficacy in mouse models (Infect. Discord. Drug Targets 2008;8:160-5)

References

Bolognia, Jean L., et al. *Dermatology*. Mosby, 2003.
Cohen, Bernard JA. *Pediatric Dermatology*, Third Edition, Mosby, 2005.
Goodheart, Herbert P. *Photoguide to Common Skin Disorders*, Third Edition, Lippincott, 2009.
Habif, Thomas. *Clinical Dermatology*. Fourth Edition, Mosby, 2004.
Schachner, Lawrence A. & Hansen, Ronald C. *Pediatric Dermatology*, Third Edition, Mosby, 2003
Clinical & Aesthetic Dermatology: April 2010, Volume 3, No. 4
Cosmetic Dermatology: April 2010, Volume 23, No. 4
Cosmetic Dermatology: February 2010, Volume 23 No. 2
Cosmetic Dermatology: March 2008, Volume 21, No. 3
Cosmetic Dermatology: April 2008, Volume 21, No. 4
Dermatology Therapy: Treatment of Psychocutaneous Diseases:
January-February 2008, Volume 21, No. 1
