Acne Vulgaris:
“Guidelines to Clinical Practice”

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Objectives

• Be able to describe the epidemiologic presentation of acne vulgaris
• Be able to understand and verbalize the four pathogenic mechanisms of acne
• Be able to recognize and differentiate the clinical stages of acne
• Be able to discuss where the pharmacological agents work on the four mechanisms involved in the pathogenesis of acne
• Be able to determine the benefits and risks of using topical or systemic drug therapy and support there use in the various clinical stages of acne
• Be able to design and support a therapeutic plan including drugs, dosages, routes of administration, monitoring parameters, and adverse events
• Describe the prescribing and dispensing regulations surrounding systemic retinoids and verbalize the rationale for there adoption
Introduction

• Acne Vulgaris
  – Epidemiology
    • ~40-50 million people in the United States
  – Etiology
    • “the 4 factors”
  – Pathophysiology
    • Disease of the pilosebaceous unit
  – Treatment Options
    • Topical Vs Systemic agents

• Review/Questions??
Epidemiology

- Affects 40 to 50 million people in the US
  - Most common dermatologic physician office visit
- Approximately 90% of all adolescents
  - Age 14-19 years most affected
    - Age 12-25 years of age = 80% of the population
- Incidence: Females = Males
  - No race or ethnicity prevalence
Acne Myths

- Diet
- Psychological stress
- Cleanliness
- Sexual activity

NOT ASSOCIATED WITH ACNE FORMATION!!!
Etiology

• Endogenous Factors
  – Increased sebum production
  – Sloughing of keratinocytes
  – Bacterial growth and colonization
  – Inflammation and immune response
Increased Sebum Production

• Androgen stimulation enhanced at puberty
  – Testosterone increased
    • Androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate

• Androgenic activity drives sebum production in the sebaceous gland
  – Minimal endocrine abnormalities

• Acne affected pilosebaceous units are hyperresponsive to circulating androgens
Sloughing of Keratinocytes

- ↑ Keratinocyte proliferation
- ↑ Horny cell accumulation in sebaceous follicle
  - Plugging of the sebaceous follicle
    - Closed comedone
    - Open comedone
Bacterial Colonization

• Propionibacterium
  – Resident partial anaerobic organism
• Proliferates in excessive sebum within follicular cells
  – P. acnes $\rightarrow$ proteases $\rightarrow$ free fatty acids
• Antigenic
  – Immune complex complement activation
    • Vascular leakage, mast cell degranulation, leukocyte chemotaxis and cytokine release
  – Higher levels of antibodies to P. acnes in severe acne vs. normal controls
Immune Mediated Inflammatory Reactions

Closed comedone

↑ Sebum production  Mechanical pressure

Follicular wall rupture

Inflammatory Response

Lymphocytes  Monocytes
macrophages  Cytokines: Interleukin, TNF
Genetic Predisposition

• Enhanced CYP P450 1A1 activity
  – Reduced levels of protective endogenous retinoids
Pathophysiology: Acne Vulgaris

• Common, self limiting disease
• Characterized by the appearance of lesions on the face, back, and/or upper arms
  – Noninflammatory follicular papules or comedones
  – Inflammatory papules, pustules, and nodules
Noninflammatory lesions: Comedones

- Open comedo
  - “Blackhead”

- Closed comedo
  - “Whitehead”
Inflammatory Lesions

• Papules
  – Elevated, palpable, distinct area of skin generally less than 1cm in diameter involving the epidermis and/or dermis

• Pustules
  – Elevated, distinct, superficial cavity filled with purulent fluid, typically surrounding a hair follicle

• Nodules
  – Elevated, firm, distinct, palpable, round or oval lesion up to 1cm in diameter which occurs in the dermis or hypodermis
Common Acne Variants

• Neonatal
  – Onset:
    • Birth - 3 wks of age
  – Incidence:
    • 20% of neonates
    • Males > Females
  – Affected Area:
    • Around the face
    • cheeks and scalp
  – Etiology
    • lingering of maternal hormones after birth

• Adult
  – Onset:
    • mid 20’s
  – Incidence:
    • Female > Male
  – Affected Area:
    • Lower facial area
    • Mouth, chin, & jaw line
  – Etiology:
    • Fluctuating hormone levels
Severe Acne Variants

• Acne fulminans
  – Acute febrile ulcerative acne

• Acne conglobata
  – Keloidal and atrophic interconnecting abscesses and scars
Rosacea

- Formerly acne rosacea
- Characterized by facial erythema, telangiectasia, and papules
- Affects T-zone: forehead, nose, chin
  - Can causes burning, tingling, itching of affected areas
- Occurs later in life
  - Mean age at onset is 42 years
Cosmetics

• Contribute to the development of acne
  – Pomades
    • Thick oily product is comedogenic
    • Apply to hair tip only - avoid contact with scalp
  – Moisturizers
    • Oil and water components

• Trial and error
  – Individual response to cosmetic products
Occupational & Environmental Exposure

• Occupational
  – Skin irritation
    • Halogenated compounds, UV light, and dioxin
  – Comedogenic
    • Oily products
      – Animal fats or petroleum derivatives

• Environmental
  – Hot & humid weather
    • Stimulate sweating which worsens acne
  – Dry sunny weather
    • Improve acne appearance
Mechanical Irritation

• Skin irritation

• Culprits
  – Headbands, hats, chin straps, backpacks, or shoulder straps
  – Tight synthetic fabrics most common
    • Prevent skin breathability
Complications of Acne

• Scarring
  – “ice pick” pitting with disfigurement
  – Exacerbated by tissue excoriation
    • Picking or squeezing lesions

• Psychological distress
  – Anxiety
  – Depression

• ↑ unemployment rates
Goals of Therapy

- Relieve Discomfort
- Improve skin appearance
- Prevent pitting or scarring
- Alleviate psychological distress and social rejection
Clinical Presentation/Diagnostics

• Duration: onset and peak of severity
  – Seasonal variation
  – Family history, including severity
  – Females: relation to menstrual periods, pregnancy status, scalp hair thinning, and contraceptive method (if used)

• Location & distribution

• Present and past treatments
  – Topical vs. systemic
  – Rx vs. OTC

• Other skin disorders or medical problems

• Medications and drug allergies

• Occupational exposure to chemicals or oils

• Use of cosmetics, moisturizers, hairstyling products (pomades)

• Areas of skin friction or irritation
Treatment Expectations

• Prevention
  – Resolution of 20%, 60%, and 80% of lesions expected in 2, 6, 8 months respectively

• Therapy modification
  – No more often than every 1-2 months
Nonpharmacologic Therapy

• Non-moisturizing soap, mild
  – Twice daily cleansing
  – Avoid abrasive cleansers and aggressive scrubbing, squeezing, or picking

• Dermabrasion, cryotherapy, surgical comedone extraction
  – Occasionally used as adjunct therapy with medication for severe, treatment refractory acne

• CO2 laser therapy, iontophoresis, recollagenation
  – Acne scarring treatments
  – Requires further safety and comparative efficacy analysis
Pharmacotherapy: Drug Selection Criteria

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<th>Moderate</th>
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<td>Systemic therapy</td>
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Acne Grading Scales

- Clinical Practice
  - Mild
    - Few lesions, little or no inflammation
  - Moderate
    - Many lesions, significant inflammation
  - Severe
    - Numerous lesions, extreme inflammation and/or cysts, presence of scarring

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Comedones</td>
</tr>
<tr>
<td>II</td>
<td>Comedones + papules</td>
</tr>
<tr>
<td>III</td>
<td>Pustules</td>
</tr>
<tr>
<td>IV</td>
<td>Nodulocystic acne</td>
</tr>
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</table>
Mild Comedonal

- **First Choice**
  - Topical retinoid
- **Alternative**
  - TR or salicylic acid or azelaic acid
- **Alternatives for females**
  - TR
- **Maintenance**
  - TR
Retinoids - topical

- Vitamin A analogs
- US Commercial Products
  - Tretinoin (Retin-A, Retin-A micro), adapalene (Differin), Tazarotene (Tazorac)
    - Skin irritation: solution > gel > cream
- Comedolytic → stimulate epidermal cell turnover
  - Decreases stratum corneum from 14 to 5 layers
- BPO and tretinoin = additive/synergistic effects
- Adverse effects: Irritation, erythema, and peeling limit successful therapy.
  - Application techniques ↑ adherence and continuation
Salicylic Acid

• ß - hydroxy acid
• MOA:
  – Follicular activity
    • Solubilization of intracellular cement of keratin cells in the stratum corneum
• Conflicting evidence
  – Efficacy: limited quality studies
  – Possibly less effective than benzoyl peroxide or tretinoin
• Application to a large body surface area can lead to increased absorption
  – Salicylism
Azelaic Acid 20%

Dicarboxylic acid structure
- Reduced bacterial colonization
  - Suppresses P. acnes
    - Interferes with DNA synthesis by inhibiting thioredoxin reductase
  - Follicular activity
    - Normalizes keratinization

- Equally effective as oral antibiotics or topical tretinoin
  - Less skin irritation
  - Significant reduction of inflammatory lesions at 1 months and non-inflammatory lesions at 2 months

- AE: erythema, burning, pruritus
- Applied to affected areas twice daily to clean dry skin
Mild Papular Pustular

• First Choice
  – TR + topical antibiotic

• Alternatives
  – TA + alternate TR or AA

• Alternatives for females
  – TR + TA

• Maintenance
  – TR
Topical Antibiotics

- **Erythromycin**
  - MOA: Reduce P. acnes
- **Combination Therapy**
  - Zinc: may enhance erythromycin into the pilosebaceous unit
  - BPO: reduced Abx resistance
    - $E + BPO > E + TR$
- Applied twice daily to clean dry skin
- AE: erythema, pruritis

- **Clindamycin**
  - MOA: reduce P. acnes
- **Combination Therapy**
  - BPO: increased efficacy
- Applied twice daily to clean dry skin
- AE: erythema, pruritis
  - Pseudomembranous colitis (rare)
Antiandrogens

• Cyproterone
  – Orphan drug in US/used widely in Europe

• SpiranoLactone
  – Antiandrogen properties
    • Inhibitor of 5α-reductase
    • Reduces sebum production

• Males: not used due to development of gynecomastia

• Women: often used in combination with estrogens to prevent menstrual irregularities

• AE: (dose dependant) hyperkalemia, irregular menses, breast tenderness, HA, fatigue
Papulur Pustular Acne

• First Choice
  – Oral antibiotic + TR ± BPO

• Alternatives
  – OA + alternate TR ± benzoyl peroxide

• Alternatives for females
  – Oral antiandrogen + TR/AA ± TA

• Maintenance
  – TR ± BPO
Systemic Antibiotics

• Bacterial Colonization
  – Decrease P. acnes
  – Prevent sebaceous fatty acid metabolic byproducts
    • Indirectly reduce inflammatory reactions

• Numerous antibiotic choices
  – Cost, prior response, AE, pregnancy status, and/or age

• Resistance
  – Erythromycin ~ 60% > Tetracycline > Minocycline ~ 1%
    • Topical benzoyl peroxide or oral isotretinoin prevent clinically significant P. acnes resistance
Macrolide Abx

- **Erythromycin**
  - Reserved for patient who failed TCN
  - 1 gram daily with food
  - AE: gastrointestinal symptoms

- **Azithromycin**
  - Increased adherence: T-QIW
  - No clinical resistance noted

- **Clindamycin**
  - Pseudomembranous colitis limits long term use
Tetracyclines

• Tetracycline
  – Drawbacks:
    • Suprainfection: vaginal candidiasis
    • Intracranial hypertension (rare)
    • C/I
      – children < 10 years: tooth discolorization
      – Pregnant women: inhibition of skeletal growth
    • Phototoxicity

• Minocycline is associated with the most AE
  – Vestibular toxicity, discoloration of the skin, drug-induced lupus erythematosus, interstitial nephritis/hepatic failure/systemic eosinophilia
Benzoyl Peroxide

• Dryness and irritation common
  – Begin with a low potency
  – Increase potency or frequency over time

• Formulation
  – Gels usually more potent
    • Alcohol base can lead to increased dryness
  – Lotions and soaps weaker potency

• Fair and moist skin more sensitive to irritation
  – Apply to dry skin at least 30 min. prior to washing

• May bleach fabrics (pillowcase, washcloth)
• Applied to affected area twice daily as tolerated
Benzoyl Peroxide

• Bacterial Colonization
  – Decomposition on the skin by cysteine liberates free oxygen radicals which oxidize bacterial proteins
    • Daily application of 10% solution reduces free fatty acids by 50% and P. acnes by 98%
    • 50% to 75% reduction of inflammatory lesions in 8 to 12 weeks
    • Efficacy enhanced when combined with topical antibiotic (i.e. erythromycin)

• Follicular Activity
  – Increases epithelial cell sloughing & loosens follicular plug structure
Moderate Nodular Acne

• First Choice
  – OA + TR ± BPO

• Alternatives
  – Oral isotretinoin or
  – Alternate OA + alternate TR ± BPO/AA

• Alternative for females
  – AN + TR ± OA ± alternate TA

• Maintenance
  – TR ± BPO ± OA
Severe Nodular Acne

• First Choice
  – Oral isotretinoin

• Alternative
  – OA + TR + BPO

• Alternative for females
  – AN + TR ± alternate TA

• Maintenance
  – TR ± BPO
Retinoids - systemic

- Isotretinoin
  - 16-week course produces a greater than 70% success rate followed by a prolonged remission of more than 20 months.
    - Repeat courses required in 15 to 20% of patients
    - Rarely, patients may require 3 to 5 courses
  - 0.5 to 1.0 mg/kg per day with success attributed to cumulative doses of 120 to 150 mg/kg.
  - Major adverse reactions include mucocutaneous effects, teratogenicity, and depression/suicide.
## Isotretinoin Adverse Effects

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Effect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common, Pharmacologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive</td>
<td>Teratogenic (birth defects, premature birth, neonatal death)</td>
<td>Avoid pregnancy</td>
</tr>
<tr>
<td>Skin</td>
<td>Dryness, peeling, pruritus, photosensitivity</td>
<td>Moisturizers or emollients, sunscreens, protective clothing</td>
</tr>
<tr>
<td>Hair, nails</td>
<td>Alopecia, nail fragility</td>
<td>None, discontinue drug if severe</td>
</tr>
<tr>
<td>Mucous membranes</td>
<td>Cheilitis (dry mouth, nose, eyes), blepharoconjunctivitis</td>
<td>Lip balms, sugarless gum/candy, saline nasal spray, artificial tears or ophthalmic ointment, decrease dose if severe or bothersome</td>
</tr>
<tr>
<td><strong>Uncommon, Toxic</strong></td>
<td></td>
<td></td>
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<tr>
<td>Liver</td>
<td>Increased transaminases; hepatitis</td>
<td>Monitor if mild elevation. Avoid in patients with previous liver dysfunction. Discontinue drug if hepatitis occurs.</td>
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<tr>
<td>Bones</td>
<td>Pain</td>
<td>Monitor at each visit</td>
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<tr>
<td></td>
<td>Bone loss (osteopenia)</td>
<td>Routine monitoring is not recommended</td>
</tr>
<tr>
<td>Muscle, ligaments</td>
<td>Pain, calcifications</td>
<td>Monitor, discontinue if severe</td>
</tr>
<tr>
<td>Eyes</td>
<td>Decreased night vision</td>
<td>Patients should use caution when driving</td>
</tr>
<tr>
<td>Metabolic</td>
<td>↑triglycerides, ↑cholesterol, ↑VLDL, ↑LDL</td>
<td>Reduce eliminate alcohol; low-fat diet, consider dosage reduction or drug discontinuation.</td>
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<tr>
<td>Psychiatric</td>
<td>Depression, suicide</td>
<td>Monitor for depressed mood and suicidal thoughts</td>
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Isotretinoin: Prescribing & Dispensing Regulations

• iPledge Program
  – Strengthened risk management program
    • Registration of prescriber, pharmacy, and patient
  – Goals of the program
    • Ensure no female starts isotretinoin therapy if pregnant
    • Ensure no female become pregnant while on isotretinoin therapy
  – Only wholesalers registered will be able to obtain isotretinoin from manufacturers
  – Only pharmacies registered will be able to obtain isotretinoin from registered wholesalers
    • Pharmacies must obtain authorization from the iPLEDGE system prior to dispensing any isotretinoin prescription
    • iPLEDGE authorization dependent on registration of patient, prescriber, and 2 documented negative pregnancy test if female of childbearing age
      – Then monthly pregnancy tests for WCBP (2 documented forms of contraception)
    • iPLEDGE prescribers assume the responsibility of pregnancy counseling
Oral Contraceptives

• Estrogen/Progestin combinations
  – Estrogen increases concentrations of sex hormone-binding globulin
    • Decreases free endogenous testosterone
  – Progestin has little or no antiandrogenic properties
    • Androgenic activity: norgestrel & levonorgestrel
      – May worsen acne
    • Acceptable progestins:
      – Norgestimate, desogestrel, & norethindrone
  – Ortho Tri-Cyclen has an FDA approved indication for treatment of moderate acne in females 15 years of age or older who are unresponsive to topical agents.
Corticosteroids

- Implicated in acne formation
  - When used long term
- Intrallesional triamcinolone 1.25-5mg/mL
  - Improve severe inflammatory acne
  - Used in combination with isotretinoin
    - Decrease the inflammatory response
- “Prom pack”
  - 7 day prednisone course (20mg/day)
  - Quickly and dramatically improve acne for important life events (prom, wedding, reunion)
- Topical corticosteroids are not effective
Drug Induced Acne

• Antiepileptics
  – Phenytoin
  – Phenobarbital
    • 80% of females experienced acne versus 30% of age-matched controls
  – Divalproic Acid
Pharmacist Role

• Patient Counseling
  – Realistic treatment goals and expectations
  – Drug administration and application technique
  – Adverse reaction management

• Identification of drug induced acne
  – Options for discontinuing offending agent

• Know when to refer
Questions ??


Updated November 2007
# Acne Classification/Drug Selection

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- **Isotretinoin**
- **Topical/systemic antibiotics**
- **Topical retinoids**
- **Benzoyl peroxide**
- **Azelaic acid**

**Benzoyl peroxide** and **Azelaic acid** can also be used as **Topical therapy if localized to face, if treatment resistant consider combination therapy**. If covering face, back, chest, arms use systemic therapy.**
# Drug Mechanism Classification

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<th>Mechanism</th>
<th>Drug Product</th>
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<tr>
<td>Follicular Activity</td>
<td>Normalize follicular keratinization</td>
<td>Retinoids</td>
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