ACNE AND ROSACEA

Christopher G. Nelson, M.D.
Affiliate Professor, University of South Florida
Director Emeritus, Clinical Research Unit
Potential Conflicts of Interest

• Consultant/Speakers Bureau
  – Fougera (Pharmaderm)
  – Celgene

• Clinical Trials
  – Amgen
  – Abbvie
  – Galderma
  – Eli Lilly
  – Maruho
  – Regeneron
  – Celgene
  – Genentech

I have no financial interest in any of them
<table>
<thead>
<tr>
<th>Acne</th>
<th>Rosacea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comedones</td>
<td>No comedones</td>
</tr>
<tr>
<td>No telangiectasia</td>
<td>Telangiectasia</td>
</tr>
<tr>
<td>No erythema</td>
<td>Erythema (deep, diffuse)</td>
</tr>
<tr>
<td>Peak onset: adolescence</td>
<td>Peak onset: 30 - 50 years</td>
</tr>
<tr>
<td>Affects face, back, chest</td>
<td>Affects central face</td>
</tr>
</tbody>
</table>

Kligman’s ‘Follicular Filament’
PATHOPHYSIOLOGY AND RATIONALE FOR TREATMENT

- Hyperkeratinization and comedo formation
- Sebum Overproduction
- Bacterial Proliferation
- Inflammation
Matching the Treatment to Type of Acne

<table>
<thead>
<tr>
<th>Comedonal acne</th>
<th>Mixed comedonal + inflammatory acne</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Topical retinoid</td>
<td>✓</td>
</tr>
<tr>
<td>Other topicals (antibiotic, BPO)</td>
<td>✓</td>
</tr>
<tr>
<td>Systemic antibiotic</td>
<td></td>
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<tr>
<td>Isotretinoin</td>
<td></td>
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Topical Retinoids: Mechanism of Action and Impact on Pathophysiology

- **P. acnes-Induced Inflammation**
  - Inhibition of TLR-2 Receptor
  - Reduction in Inflammation

- **Retinoic Acid Receptors (RAR-gamma)**
  - Reduced Formation of Hyperproliferative Keratins (K6, K16)
  - Reduction in Microcomedo Formation

- **Matrix Metalloproteinases (MMPs)**
  - Inhibition of AP-1 Pathway
  - Reduction in Inflammation and Scarring (?)
HYPERKERATINIZATION

- Topical retinoids
  - Tretinoin (Retin-A™)
  - Adapalene (Differin™)
  - Tazarotene (Tazorac™)
- Azaleic Acid (Finacea™ Azalex™)
- Alpha Hydroxy Acids (Glycolic, Lactic, etc.)
- Beta Hydroxy Acid - Salicylic Acid
- Oral Isotretinoin
Retinoids

- Mainstay of treatment
  - Unplug follicles
  - Anti-inflammatory
  - May help prevent scarring
- Tretinoin
  - Photolabile – use at night
- Adapalene (Differin™) – now 0.1% gel is OTC
- Tazarotene (Tazorac™)
TRETINOIN

- All trans-retinoic acid
- RAR α, β, and γ, weakly with all RXR’s
- Retin-A® and various generics
  - Cream(less drying) or gel
- .025% to .1%
- Safe around the eyes
- Apply at bedtime
- Unstable in UV light (except for Retin-A Micro™)
- Unstable with some topicals
- Side effects: Scaling, drying, irritation
ADAPALINE

- Differin® cream or gel .1% or 0.3% gel
- Naphthoic acid derivative with retinoid properties
- Specific for RAR β and γ, weak for α
- Apply once a day
- Photostable (can be used in AM)
- Stable with other topicals
- Side effects: Scaling, dryness, irritation
TAZAROTENE

- Tazorac™ cream or gel .05% or .1%
- True retinoid – more potent than adapaline
- Specific for RAR β and γ, weak for α
- Apply once daily
- Photostable (can be used in AM)
- Stable with other topicals
- Pro-drug – may use over or under other topicals
- Side effects: Scaling, dryness
- Pregnancy category X
Azaleic Acid

- Finacea™ Gel 15%
- Azelex™ Cream 20%

- Decrease P. acnes counts
- Increase desquamation
- Decrease hyperpigmentation
- Use once or twice a day
KERATOLYTICS

• Alpha Hydroxy Acids (glycolic, lactic)
  – Exfoliate
• Beta Hydroxy – Salicylic Acid
  – Keratolytic
    – Penetrates follicle
    – Anti-inflammatory
• Available in washes, lotions, etc.
SEBUM OVERPRODUCTION

- Oral Contraceptives
- Antiandrogens
- Oral Isotretinoin
- Dietary manipulation
INFLUENCE OF DAIRY IN THE DIET

Nurses Health Study (NHS II)
- Started in 1989 - 116,671 married female nurses aged 25-42
- In 1989, asked about physician Dx’d severe acne
- In 1998, 47,355 provided dietary information
- Now growing up today (GUTS) is studying their offspring (9,039 girls and 7,843 boys)
FINDINGS - NHS II AND GTS

• Positive association of dairy intake and severe acne
• Skim milk seems worse than whole milk
• Also associated: instant breakfast drink, sherbet, cottage cheese, and cream cheese

SO, WHAT’S IN MILK?
Prolactin, somatostatin, Growth-Hormone-Releasing-Factor-like activity, Gonadotropin-Releasing Hormone, luteinizing hormone, thyroid-stimulating and thyrotropin-releasing hormones, numerous steroid hormones, insulin, epidermal growth factor (EGF), nerve growth factor (NGF), insulin-like growth (IGF) factors 1 and 2, transforming growth factors (TGF’s), vitamin D, transferrin, many prostaglandins including F2a, erythropoetin, bombesin, neurotensin, vasoactive intestinal peptide, various nucleotides, cyclic AMP and GMP, β-casomorphins and even relaxin
Young growing humans need milk from pregnant cows

Just as much as

Young growing cows need milk from pregnant humans

Danby, F William, American Academy of Dermatology, 2005
ORAL CONTRACEPTIVES

• Directly inhibit sebaceous glands

• Inhibit ovulation, preventing ovary from producing androgens

• Hepatic production of sex hormone binding globulin, which binds free testosterone
O.C. INGREDIENTS

• Estrogen component – ethinyl estradiol
• Progestin
  – Estranes – norithindrone, ethynodiol
  – Gonanes – norgestrel, levonorgestrel, norgestimate, desogestrel)
    • Less androgenic activity than estranes
  – Drospirenone (Angeliq, Gianvi, Loryna, Ocella, Syeda, Vestura, Yasmin, Yaz, Zarah)
    • Diuretic, anti-androgen activity
ANTIANDROGEN

- Spironolactone (Aldactone)
  - FDA approved diuretic and antihypertensive
  - Not approved for treatment of acne
  - Blocks androgen receptors

- Dose: 50 – 100mg/day in women with ↑DHEA

Follow potassium levels
BACTERIAL PROLIFERATION

- Benzoyl Peroxide
- Topical or Oral Antibiotic
- Azelaic Acid
- Tretinoin, Adapalene and Tazarotene
- Oral Isotretinoin
BENZOYL PEROXIDE

- Antibacterial against *Propionibacterium acnes*
- ↓ Lipids and free fatty acids
- ↑ Desquamation (drying and peeling)
- ↓ Comedones and acne lesions

- Washes or topical creams or gels
  - *Caution:* can bleach fabrics or surfaces
  - Use as a wash or topically at hs
  - BPO washes are now OTC
ANTIBIOTICS – TOPICAL

• Erythromycin
  – Resistance is a problem
  – Use with benzoyl peroxide

• Clindamycin Phosphate
  – Increasing resistance
  – Use with benzoyl peroxide

• Sodium sulfacetamide
ANTIBIOTICS – SYSTEMIC

• Tetracycline – 250mg – 1 gram/day
  – Minocycline 100mg – 200mg/day
  – Doxycycline 100mg – 200mg/day
  • Photosensitivity is dose related
• Erythromycin 250mg – 1 gram/day
• TMP/SMX (Septra-DS®; Bactrim-DS®) qd or BID
• Amoxicillin 250mg – 1 gram/day
• Taper to minimum dose; can even be intermittent. D/C if possible
MINOCYCLINE - PROBLEMS

- Vertigo – mainly in females
- Minocycline hyperpigmentation
- Staining of teeth
- Serum sickness like syndrome
- Lupus like syndrome
- Hypersensitivity syndrome
Dapsone Gel

- 7.5% Dapsone (Aczone™) once daily
- 5% generic use BID
- Provides anibacterial and anti-inflammatory activity
- Safe for G-6PD deficient patients
Photodynamic Therapy

• Photodynamic therapy (blue light with or without ALA)
  – Kills *Propionibacterium acnes*
  – Reduces the size and activity of sebaceous glands
ISOTRETINOIN

• 0.5-2.0 mg/kg/day for 20 weeks with food
• For truncal acne – 2mg/kg
• Total dose 135-150 mg/kg.
• Patient selection, education and follow-up, including laboratory parameters.
• iPledge program
INFLAMMATION

• Topical retinoids
• Topical or oral antibiotics
• Azaleic acid
• Intralesional Corticosteroids
  – Triamcinolone 2.5 - 5mg/cc
  – Inject directly into inflamed cyst
  – Dilute with non-paraben preserved NS
  – Warn about atrophy – it is temporary
• Systemic Corticosteroids
  – Prednisone as a single AM dose
  – Dexamethasone 0.75mg at hs for two weeks only in females
RECOMMENDATIONS

• Use keratolytics, benzoyl peroxide and topical retinoids as the mainstay of treatment
• Do not use a systemic antibiotic when a topical medication will suffice
• Always use benzoyl peroxide with topical antibiotics to avoid resistant strains
• D/C systemic antibiotics when control is achieved and maintain with topicals; restart if necessary, using the same drug if possible
• Use intervening courses of benzoyl peroxide to eliminate resistant strains
• If adequate control not achieved after 90 days of antibiotics, consider isotretinoin.
MY REGIMEN

• Evaluate aggravating factors (football equipment, ingestion of large amounts of dairy, whey protein supplements, etc.)
• Retinoid in the morning (except tretinoin)
• Topical antibiotic or antibiotic-BPO combo. at bedtime
• Benzoyl peroxide wash to suit skin type
• Systemic antibiotic if necessary
  – I start with doxycycline 100 BID for 7 days, then 100mg daily. Taper as tolerated.
• Return 1 month and adjust regimen as needed
ROSACEA

THE UNINVITED GUEST
CLINICAL DESCRIPTION

• Chronic inflammatory dermatosis
• Predisposition to affect central regions of the face
• Frequently presents with flushing and erythema with an intermittent acneiform eruption
• 16 million Americans have rosacea, yet only 18% are receiving treatment
Co-morbidities

• Increased incidence of other systemic inflammatory diseases, CVD, GI disease, and certain cancers.
• Higher incidence of migraine in women, and people over 50.
• Impact on QOL, social and professional interactions, and self esteem.

Rosacea Subtypes

- Erythematotelangiectatic
- Papulopustular
- Phymatous
- Ocular
Etiology of Rosacea

• UNKNOWN!
• Papulopustular rosacea may be associated with:
  • Overpopulation of Demodex mites
    – Rx with topical ivermectin (Soolantra™)
• H. pylori infection
  – Titers are unreliable
  – Treat empirically if suspected
OCULAR ROSACEA

• Up to 58% of rosacea patients – 20% precede rosacea
• Correlation between degree of ocular involvement and tendency to flush
• May be associated with:
  - Blepharitis
  - Conjunctivitis
  - Episcleritis
  - Iritis
  - Keratitis

Rx: Baby shampoo scrubs 30 sec. BID, followed by erythromycin ophthalmic ointment; oral doxycycline
GRANULOMATOUS (LEWANDOWSKY’S) ROSACEA

- Variant of papular rosacea
- Histology significant for granuloma formation
- Clinically: yellow-brown nodules on the lateral surfaces of the face and neck
  - Extrafacial lesions reported in 15% of patients with Lewandowsky’s rosacea
- Treatment is same for typical rosacea
PERIORAL DERMATITIS

• Small erythematous papules, zone of sparing around mouth
• Preponderance of females
• Often precipitated by fluorinated topical steroids
• Rx: Oral doxycycline, topical calcineurin inhibitor (off label), or WEAK topical steroid (HC; desonide)
ROSACEA – STEROID INDUCED

Etiology: Fluorinated or other potent topical steroids

Rx: D/C offending agent. Oral doxycycline. Topical pimecrolimus (*off label*), *WEAK* topical steroid, or none

Expect flares; fewer and further between
ROSACEA FULMINANS

- Sudden onset
- Preponderance of females
- Previous history of flushing
- Rx:
  - Systemic antibiotics (tetracycline, doxycycline or minocycline)
  - Intralesional steroids
  - Systemic steroids
TREATMENT

• Trigger Avoidance

• Proper Skin Care

• Therapeutic Intervention
Potential Triggers

- Sun exposure
- Stress
  - Emotional
  - Physiologic
- Hot weather
- Alcohol
- Spicy foods
- Wind
- Hot baths, saunas
- Exercise
- Cold weather
- Hot drinks
- Skin-care products

Teach patient to anticipate flares
SKIN CARE

• Wash with lukewarm water

• Use a mild, non-soap cleanser

• Use fingertips, not washcloth

• Blot dry, don’t rub
COSMETIC THERAPY

• Precautions to avoid irritants

• Green makeup neutralizes red

• Order of application
  1. Medication
  2. Sunscreen
  3. Cosmetics
COSMETIC CAVEATS

• Avoid irritants – alcohol, witch hazel, etc.
• Avoid iridescent makeup – contains mica
• Look for a good base that won’t separate
• Throw out make up after three months
• Use a matte finish
• Use setting gel or powder to prevent migration
• White or light powders are less irritating
Pharmacologic Therapy: Topical Agents

• Primary¹
  – Metronidazole
  – Azelaic acid
  – Sodium sulfacetamide with or without sulfur
  – Ivermectin (Soolantra™)

• Secondary*
  – Clindamycin – use with benzoyl peroxide
  – Erythromycin – use with benzoyl peroxide
  – Benzoyl peroxide
  – Other agents (e.g., tretinoin, tacrolimus, pimecrolimus) have been used on a case-by-case basis

*Not approved for the treatment of rosacea

New For Erythema

- Mirvaso© (bromidine) gel 0.33%
- Alpha adrenergic agonist – vasoconstrictor
- Apply as needed – action peaks at 6 hours and lasts 12 hours
- Minimally absorbed: $C_{\text{max}} \ 46 \pm 62 \ \text{pgm/ml}$
- Contraindicated in vascular insufficiency
- Rare rebound
New For Erythema

• Rhofade™ (oxymetazoline 1% cream)

• Apply once a day - vasoconstrictor

• Caution in CVD or Raynauds
Compounding For Rosacea

• Have a compounding pharmacist add phenylephrine 0.05% to metronidazole cream, gel or lotion.
Clinical Considerations With Topical Agents

• Not capable of treating all subtypes or severity levels of rosacea\textsuperscript{1}
  – Patients with more severe disease typically require addition of oral antibiotics
• Effect is temporary\textsuperscript{2}
  – 25\% of patients relapse 1 month after discontinuation
  – 66\% of patients relapse 6 months after discontinuation
• Can cause contact, irritant, or allergic dermatitis


SYSTEMIC THERAPY

Systemic antibiotics – 2 to 6 weeks to see results

• First line
  – Tetracyclines
  – Doxycycline 100mg BID and taper
    • Oracea® 40mg sustained release
  – Minocycline 100mg BID and taper

• Second line
  – Erythromycin 250mg – 1 gram daily and taper
  – Amoxicillin 250mg – 1 gram daily and taper

• Third line
  – TMP/SMX-DS 1 - 2 tablets daily
  – Metronidazole 250mg – 1 gram daily
Antibiotics for Rosacea?

• Most experts agree that rosacea is an inflammatory condition.

• No bacterial pathogen has been identified.

• Doxycycline is a broad spectrum antibiotic.

• According to the PI, there is a wide range of bacteria throughout the body susceptible to doxycycline.
Anti-inflammatory Dose Doxycycline

- Or — when is an “antibiotic” not an antimicrobial?
- Periostat™ 20mg BID
- Oracea™ 40mg daily
  - 30mg immediate release + 10 mg timed release
- Cut the generic 100mg doxycycline tablet into quarters, and take ¼ BID
PHYSICAL INTERVENTIONS

• Electrosurgery
  – Rhinophyma
  – Telangiectasias

• Laser surgery
  – Rhinophyma
  – Telangiectasias
  – Destroy deep vascular beds to help control the disease

• Intense pulsed light
  – Erythema
  – Telangiectasias

• Photodynamic therapy (blue light with or without ALA)
  – Kills *Propionibacterium acnes*
  – Reduces the size and activity of sebaceous glands
RECOMMENDATIONS

• Patient education
  – Trigger avoidance
  – Correct cosmetic use
• Mild cleansing techniques
• Topical medications
  – Metronidazole
  – Azaleic acid
  – Ivermectin if Demodex suspected
  – Sodium sulfacetamide
  – Avoid topical steroids if possible – use topical calcineurin inhibitors (off label) if anti-inflammatory needed
  – Vasoconstrictor for erythema
• Because of its favorable safety profile, subantimicrobial doxycycline may be instituted as part of first line therapy