Acne

Acne is the most common skin condition in the United States.

About 40 to 50 million Americans have acne at any one time.

Most people who have acne are teenagers or young adults, but acne can occur at any age.

- Without treatment, long lasting dark spots and permanent scars can appear on the skin as acne clears.
- Treating acne often boosts a person’s self-esteem
Four Primary Components of Acne

- Subclinical skin inflammation
- Excess sebum, or oil gland, production (Androgens contribute to acne flares by overstimulating the oil glands and altering the development of skin cells that line hair follicles in the skin)
- Skin cells that shed become abnormally sticky and accumulate, or clog up, in the hair follicle
- Increased number of \( P.\ acnes \).
What causes inflammation in acne?

- It is thought that acne begins with subclinical inflammation.
- Non lesional skin biopsies show excess inflammatory markers, perhaps to a type IV hypersensitivity.
- Inflammation leads to skin cell death. Normally, dead skin cells rise to surface and shed.
- With excess sebum, dead skin cells stick together and become trapped inside the pore.
- The bacteria, *p. acnes*, lives on our skin and inside the pore.
- The skin again becomes inflamed due to the *p. acnes*.
- If the inflammation cycle continues, an acne cyst or nodule appears.

Schlosser, MD, PhD, FAAD; [www.aad.org](http://www.aad.org), Mar 2012
Acne Grading Scales

- Clinicians may find it helpful to use a consistent grading/classification scale (encompassing the numbers and types of acne lesions as well as disease severity, anatomical sites, and scarring) to facilitate therapeutic decisions and assess response to treatment.

- Currently, no universal acne grading/classifying system can be recommended.
Lesion Progression in Acne

- Subclinical inflammation
  - $P. acnes$
  - Monocyte
  - Neutrophil
  - T cell
  - Inflammatory mediators

- Microcomedone formation
  - Sebum accumulates
  - Follicle enlarges
  - Keratinous material builds up
  - $P. acnes$ proliferates and generates inflammatory mediators
  - Immune reactions

- Inflammatory lesion

References:
Acne Scar Evolution

- Upregulation of TLR2 happens early in lesion development
- Downstream upregulation of MMPs, breakdown of collagen, and increased pro-collagen may contribute to scarring
- “Scarrers” have increased T helper cells in peri-lesional infiltrate relative to “non-scarrers”
  - More specific, but less effective, immune response in patients who scar
  - Altered inflammatory response
  - Possible Type IV hypersensitivity to *P. acnes*

Holland et al, 2004 *Br J Dermatol*
Holland et al, 2005 *Semin Cutan Med Surg*
Acne Scarring Treatments

- Dermabrasion
- Laser Resurfacing
- Surgery/electrodissection
- Fillers
- Collagen-induction (needling)
- Prevention is the best cure
Acne Therapies

- Retinoids and retinoid-like drugs
- Benzoyl peroxide
- Topical antibiotics
- Topical Dapsone
- Salicylic/Azelaic Acid
- Combinations of topical agents
Acne Therapies

Topical retinoids are vitamin A derivatives that are prescription agents. Retinoids are the core of topical therapy for acne because they are comedolytic, resolve the precursor microcomedone lesion, and are anti-inflammatory.

- tretinoin (0.025-0.1% in cream, gel, or microsphere gel vehicles),
- adapalene (0.1%, 0.3% cream, or 0.1% lotion)
- tazarotene (0.05%, 0.1% cream, gel or foam).
- Each retinoid binds to a different set of retinoic acid receptors thereby causing slight differences in activity, tolerability, and efficacy.
Acne Therapies

Benzoyl peroxide (BPO)

- BPO is an antibacterial agent that kills P acnes through the release of free oxygen radicals and is also mildly comedolytic.
- No resistance to this agent has been reported, and the addition of BPO to regimens of antibiotic therapy enhances results and may reduce resistance development.
- BPO is available as topical washes, foams, creams, or gels, and can used as leave-on or wash-off agents.
- BP therapy is limited by concentration-dependent irritation, staining and bleaching of fabric, and uncommon contact allergy.
- Total skin contact time and formulation can also affect efficacy.
Topical Therapies

Salicylic acid

Comedolytic agent that is available over the counter in 0.5% to 2% strengths for the therapy of AV.

Both wash-off and leave-on preparations are well tolerated.

Clinical trials demonstrating the efficacy of salicylic acid in acne are limited.
Topical Therapies

Azelaic Acid 20%

- Mildly effective as a comedolytic, antibacterial, and antiinflammatory agent.
- The agent has use in patients with sensitive skin or of Fitzpatrick skin types IV or greater because of the lightening effect of the product on dyspigmentation.
- Azelaic acid is category B in pregnancy
Topical Therapies

Clindamycin 1% topical

- Currently the preferred topical antibiotic for acne therapy
- Topical antibiotics for acne accumulate in the follicle and have been postulated to work through anti-inflammatory mechanisms and via antibacterial effects.
- Use in combination with BPO (wash-off or leave-on), to increases efficacy and decrease the development of resistant bacterial strains.
- Monotherapy with topical antibiotics in the management of acne is not recommended because of the development of antibiotic resistance.
Topical Therapies

Dapsone 5% gel, is available as a twice-daily agent for the therapy of AV. In clinical trials, topical dapsone showed modest to moderate efficacy, primarily in the reduction of inflammatory lesions.

Combination with topical retinoids may be indicated if comedonal components are present. The mechanism of action is poorly understood, and its ability to kill *P acnes* has been poorly studied. It is generally thought to work as an antiinflammatory agent. The benefit in women seems to exceed the benefit in male and adolescent patients.

Topical dapsone may be oxidized by the coapplication of BP, causing orange-brown coloration of the skin which can be brushed or washed off.

Topical dapsone 5% gel is pregnancy category C and has efficacy and safety data down to patients 12 years of age.
BPO + Retinoids

- Comedolytic/keratolytic effects of BPO and Retinoids
- Decreasing Inflammation
  - Action of Retinoids on immune and inflammatory responses, including:
    - ↓ TLR2 (greater impact with inc. lesions?)
    - ↓ cytokine production
    - ↓ AP-1
    - ↓ neutrophil chemotaxis
    - ↓ MMPs
    - ↓ antimicrobial peptides (when combined with BPO)

BPO + Retinoids

- Bactericidal action of BPO
  - Against *P. acnes*
  - Potent antimicrobial agent with no evidence of bacterial resistance

- Retinoids inhibit hyperkeratinization (anticomedogenic)
  - Abnormal keratinization may be a trigger or response to inflammation
  - Ex vivo evidence for synergistic effect of adapalene and BPO on normalization of keratinocyte proliferation

Czernielewski et al, 2001 *JEADV*, Tenaud et al, 2007 *Exp Dermatol*
Rosacea

- Rosacea is a common chronic relapsing inflammatory skin condition which mostly affects the central face.
- The pathophysiology is not completely understood.
- Dysregulation of the immune system, as well as changes in the nervous and the vascular system have been identified.
- Microbes that are part of the normal skin flora, and specifically in the pilo-sebaceous unit – including *Demodex* mites and *Staphylococcus epidermidis* – may also play a role as triggers of rosacea.
Rosacea

- Usual age of onset is 30 to 50 years
- Affects approximately 16 million Americans
- 2x to 3x higher in women than men
- Can occur in any race or ethnic background
  - Typical patient is fair-skinned and of northern European descent
  - May be challenging to detect in dark-skinned patients
- High emotional impact
Rosacea

- Flushing and redness in the center of the face
- Visible broken blood vessels (spider veins)
- Swollen skin
- Skin may be very sensitive
- Skin may sting and burn
- Dry skin, roughness or scaling
- Have a tendency to flush or blush more easily than other people
ROSACEA

Four Distinct Subtypes

A. Erythematotelangietatic
B. Papulopustular
C. Rhinophymatous
D. Occular
Rosacea Features

Multiple rosacea features may overlap and present themselves on a single patient, who should be treated accordingly.

Rational for Rosacea Combination Therapy

Ivermectin and doxycycline target the inflammation cycle of rosacea

Demodex

Ivermectin = I 
Doxycycline = D

I = Ivermectin 
M = Metronidazol 
A = Azelaic acid

Inflammation Cycle + Inflammasomes

1β, Interleukin 1 beta; LL-37, Cathelicidin Antimicrobial Peptide; MMP, Matrix Metalloproteinases; PGE2, Prostaglandin E2; ROS, Reactive Oxygen Species; TNF, Tumor Necrosis Factor; UV, Ultraviolet

KLK-5 and Cathelicidin Model

The pathophysiology of rosacea is not completely understood,

Dysregulation of the innate immune detection/response system plays a role in the inflammatory and vascular responses

Cathelicidin functions in the skin, acting as an innate antibiotic and as an immunomodulator. The protease kallikrein 5 (KLK5) controls enzymatic processing of the cathelicidin precursor in the skin.
Proposed Rosacea pathophysiology

- Microbes (e.g., Demodex)
- UV Light
- TLR2 Activation
- KLKS
- Prolytic Cleavage
- Active Cathelicidin
- CAP18 (Inactive Cathelicidin)

Cytokines
Angiogenesis
Chemotaxis

Farah A. Moustafa, Laura F. Sandoval, Steven R. Feldman; Drugs 2014
In rosacea, KLK5 levels are increased, leading to increased levels of Cathelicidin and its fragments. In addition to their increased abundance, these peptides also differ from those found in normal individuals.

Unlike normal Cathelicidin peptide fragments, these abnormal peptides control functions, such as leukocyte chemotaxis, angiogenesis, and expression of extracellular matrix components.

Their role in rosacea was confirmed by injecting these peptides into mouse skin, which led to the inflammatory response similar to that seen in rosacea.
Rosacea Triggers

Foods
● Liver
● Yogurt
● Sour cream
● Cheese (except cottage cheese)
● Chocolate
● Vanilla
● Soy sauce
● Yeast extract (bread is OK)
● Vinegar
● Eggplant
● Avocados
● Spinach
● Broad-leaf beans and pods (lima, navy or pea)
● Citrus fruits, tomatoes, bananas, red plums, raisins or figs
● Spicy and the temperature hot foods
● Foods high in histamine

Dr. Jonathan Wilkin, National Rosacea Society
Rosacea Triggers

Beverages

- Alcohol, especially red wine, beer, bourbon, gin, vodka or champagne
- Hot drinks, including hot cider, hot chocolate, coffee or tea

Dr. Jonathan Wilkin, National Rosacea Society
Rosacea Triggers

Medical conditions

- Frequent flushing
- Menopause
- Chronic cough
- Caffeine withdrawal syndrome
Rosacea Triggers

Weather
- Sun
- Strong winds
- Cold
- Humidity

Drugs
- Vasodilators
- Topical steroids

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Rosacea Triggers

Emotional influences

- Stress
- Anxiety

Physical exertion

- Exercise
- "Lift and load" jobs

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Rosacea Triggers

Skin care products

- Some cosmetics and hair sprays, containing alcohol, witch hazel or fragrances
- Hydro-alcoholic or acetone substances
- Any substance that causes redness or stinging

Dr. Jonathan Wilkin, National Rosacea Society
Rosacea Triggers

Temperature Related

- Saunas
- Hot baths
- Simple overheating
- Excessively warm environments
Demodex
The Role of Antibiotics

Rosacea, unlike acne, does not have an associated bacterial component. Antibiotics are therefore used for their anti-inflammatary component.

Doxycycline is the only antibiotic that has the demonstrated ability to be used in sub microbial doses as an anti-inflammatary.

All other currently tested oral antibiotics reach the MIC prior to exhibiting an anti-inflammatary effect.
Ivermectin

- Ivermectin, a semisynthetic, anthelmintic agent for oral administration.
- Now used in either oral or a topical formulation for the treatment of Rosacea. It has a dual mechanism of action, having both anti-inflammatory and acaricidal activity against *Demodex* mites.
- Ivermectin was derived from the avermectins, a class of highly active broad-spectrum, anti-parasitic agents isolated from the fermentation products of *Streptomyces avermitilis* found in the soil of Japan in the early 1970’s.
Anti-inflammatory Effects of Ivermectin

- Direct anti-inflammatory actions
- Reduce pro-inflammatory cytokines and chemokines
- Inhibit accumulation of leukocytes
- Indirect anti-inflammatory actions via cathelicidin pathway
- Modulates rosacea specific genes, kallikrein 5 (KLK5), and LL-37

Sulfur

- Anti Inflammatory
- Clogs respiratory system in mites, including Demodex
- Requires masking fragrances due to odor