Acne Peer-to-Peer Educational Toolkit

A compilation of key content from select presentations at the 2020 South Beach Symposium and the Masters of Pediatric Dermatology

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Neonatal Acne

- 0-6 weeks of life
- Small erythematous papules
- Acne --- maybe neonatal cephalic pustulosis
- Neonatal acne represents a heterogeneous set of conditions
- Controversy Pityrosporum (Malassezzia) – sometimes present and sometimes not
- Usually resolves over a few months
- Distribution: Forehead, Cheeks, Nose
  Less commonly: neck, chest, back

Neonatal Acne - Consensus

- Neonates may have true acne
- Many self-limiting papulopustular eruptions that occur on neonate faces
- Systemic abnormalities noted (growth, precocity, virilization), then referral to pediatric endocrinology

Eichenfield, LF, et al. Pediatrics 2013;131;5163

Neonatal Acne - Treatment

- Ketoconazole cream 2%
- Gentle cleanser
- If there are true comedones consider acne medications that you would use in infantile acne
- Usually not scarring, so can also not treat
Infantile Acne

- 0-1 year; usually see around 3-6 months
- Boys>girls
- May predispose to worse acne in teenage years*
- Increased sebum production
- Look more like classic acne – will see comedones
- Face where cheeks are mainly affected, also chin
- Less on the chest and back
- Should treat – can cause scarring
- Look for signs of hormonal abnormalities


Infantile Acne - Consensus

- Most infantile acne is self-limited
- If there are signs of hormonal abnormalities, refer to pediatric endocrinologist


- Combine treatments
- Watch for products that are appropriate for a baby
  - Topical antibiotics/benzoyl peroxide
  - Adapalene cream/low strength tretinoin
  - Avoid washes so that wash doesn’t get into the eye
  - Oral erythromycin
  - Isotretinoin if severe, scarring
    - HOW YOUNG? I have seen case reports in the first months of life
    - DOSE 0.5mg/kg to 1mg/kg; cumulative dose 60-180mg/kg
Mid-childhood Acne

- Most likely time to have underlying hormonal abnormality
- Newer concept
- From 1-7(8) years of age
  - Androgens should be low and stable
  - Evaluate for Hyperandrogenism
  - Distribution – face, chest, back

Guide for Evaluation of Mid-Childhood Acne

- Bone age
- Growth Chart
  - Height crossing percentiles upward in androgen excess
  - Weight crossing percentiles upward and height downward in Cushing’s syndrome
- Hormone Levels

Acne Vulgaris Editors, Shalita, AR., Del Rosso, JQ, Webster, GF, 2011 Informa Healthcare. Pp188-190

Mid-childhood acne - consensus

- Acne in this age group is very uncommon
- Should warrant workup for cause of hyperandrogenism


Which Hormones to check (Mild childhood acne)

- DHEA(s)
- Testosterone
- Cortisol
- 17 hydroxyprogesterone
- Androstenedione
- LH/FSH
- Prolactin
- Pediatric Endocrinologist Referral – to ensure completeness
Pre-adolescent Acne

- **8-12 years of age**
- Treatments same as infantile/mid-childhood
- Adherence
- Once a day regimen
- Swallowing pills – use liquid forms
- Isotretinoin – uncommon but may need to repeat (early teen acne – young age they may need again)

Sometimes called Preteen acne

- Comedones
- Seborrhea
- Polycystic Ovarian Syndrome (PCOS) – can see at this age (8-12 years) in girls
- Distribution of acne:
  - Face (especially forehead)
  - Conchae of ears may be involved
  - Chest
  - Back

- Pelvic Ultrasound is **not considered useful** for diagnosis of PCOS because it is considered non-specific


Jonette E. Keri, M.D., Ph.D.
Acne Treatment Tips

**Mild Acne**
- Mild acne – topicals may suffice
- Benzoyl Peroxide or Retinoid
- Combination Products possibly including topical antibiotic

**Moderate Acne**
- Start with a combination therapy
- Use oral antibiotics
- Consider oral isotretinoin
- Hormonal therapy rarely

**Severe Acne**
- Use combination therapy AND systemic medications (oral antibiotics and/or hormonal therapy, rarely)
- Consider Isotretinoin

Jonette E. Keri, M.D., Ph.D.
TOPICAL RETINOIDS

Tretinoin 0.05% Lotion in Acne Vulgaris
Once Daily – 12-Week Phase III Monotherapy Studies

>9 Years of Age with Facial Acne (N=1640)

Moderate to Severe Acne at Baseline

Two Randomized (1:1) Controlled Studies

Greater Improvements in Skin Oiliness, Patient Satisfaction and QoL with active vs vehicle (Week 12 vs Baseline)

Del Rosso JQ, Pariser D, et al. Poster presentation, SCALE Meeting, Nashville, TN, May 2018

WEEK 12
Mean % Reduction Inflammatory Lesions 50.9% - 53.4%
(Tretinoin) vs 40.4% - 41.5%
(Vehicle)

Mean % Reduction Comedonal Lesions 47.5% - 45.6%
(Tretinoin) vs 27.3% - 31.9%
(Vehicle)

All Comparisons P<0.001
TOPICAL RETINOIDS
POST HOC ANALYSES FROM PIVOTAL TRIALS

ASIAN POPULATION (N=69)
AGE 12-48 YRS
EFFICACY AND TOLERABILITY CONFIRMED

PREADOLESCENT POPULATION (N=154)
AGE ≤13 YRS
EFFICACY AND TOLERABILITY CONFIRMED

TRETINOIN 0.05% LOTION
ONCE DAILY
MODERATE-SEVERE ACNE

HISPANIC POPULATION (N=766)
AGE 11-50 YRS
EFFICACY AND TOLERABILITY CONFIRMED

ADULT AND ADOLESCENT FEMALE POPULATION (N=909)
AGE 9-58 YRS
EFFICACY AND TOLERABILITY CONFIRMED
TOPICAL RETINOIDS

**Trifarotene Cream**

**Phase 3 Studies in Moderate Facial AND Truncal Acne**

- Trifarotene is a RARγ-selective topical retinoid in a cream (50 μg/g)
- Development program evaluated efficacy and safety in both FACIAL and TRUNCAL ACNE
- Two 12-week, double-blinded, multicenter, vehicle-controlled studies
  - Once daily trifarotene cream (n=1209) or vehicle cream (n=1183)
  - Randomization pattern 1:1

<table>
<thead>
<tr>
<th>TRUNCAL ACNE (Data at 12 Weeks)</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean % Change Inflammatory Lesions</td>
<td>57.4% vs 50.0%</td>
<td>65.4% vs 51.1%</td>
</tr>
<tr>
<td>Mean % Change Non-Inflammatory Lesions</td>
<td>49.1% vs 40.3%</td>
<td>55.2% vs 45.1%</td>
</tr>
</tbody>
</table>

Majority of adverse events local tolerability reactions early in therapy
- Consistent with topical retinoid therapy – managed with proper skin care
- Fewer reactions on trunk

TOPICAL CLASCOTERONE

Clascoterone Targets Multiple Pathways Operative in Acne Pathophysiology

- **CLASCOTERONE** Reduces
  - Sebum secretion\(^1\)
  - Follicle cell keratinization\(^2\)
  - Inflammation\(^1\)

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TOPICAL CLASCOTERONE

Topical Clascoterone Phase I/II Studies
Top Line Outcomes

First topical anti-androgen + anti-inflammatory properties
New Chemical Entity ~ New Mode of Action
Previously referred to as CB-03-01 and/or cortexolone 17-α propionate
Safety profile similar to vehicle (>1300 exposed in Phase I/II studies)
Statistical significance in Phase II primary end-points

35.7% Total Lesion Count reduction vs 13% with vehicle
Clinically superior / better tolerated than topical tretinoin (Phase IIa trial) 22%
IGA improvement vs 11.5%, 66% Total Lesion Count reduction vs 52%
Anticipate use in combination with other acne therapies
Cannabidiol (CBD) [BTX 1503]

Mechanism of Action in Acne
BTX 1503 (Cannabidiol) Effects on Acne Pathophysiologic Factors

PRIMARY FACTORS IN ACNE PATHOPHYSIOLOGY:

- Excess sebum production
- Follicular hyperkeratinization (microcomedo)
- *C. acnes* (formerly *P. acnes*) colonization
- Perifollicular inflammation

CBD SHOWN TO:

- Suppress sebocyte proliferation
- Inhibit human keratinocyte proliferation, through a of the follicle non-CB1/CBs mechanism
- Have potent anti-microbial activity against gram-positive bacteria
- Have anti-inflammatory effects on human sebocytes

TOPICAL MINOCYCLINE FORMULATIONS

% INFLAMMATORY LESION REDUCTION
Baseline to Week 12
2% vs 1% vs Vehicle

- 58.5% lesion reduction at Week 12 (2% dose)
- 43.3% lesion reduction at Week 4 (2% dose)
- 25% with ≥2-grade reduction in IGA + Clear or Almost Clear (2% dose)
- 25% lesion reduction at Week 4 (Time to Onset)
- Statistically significant lesion reduction (P=0.0256)

25% IGA “SUCCESS”
MINOCYCLINE 4% FOAM ONCE DAILY

PHASE 3 12-WEEK STUDIES – MODERATE/SEVERE ACNE
>9 YEARS OF AGE – CHANGE IN INFLAMMATORY LESIONS (ILs)

**Study 22 - IL Count % Change**

- **N = 1507**
- Baseline total lesions ~80
- ANCOVA, Intent to Treat (ITT) Population, Observed Cases
  *P ≤ .0001; †P ≤ .001; ‡P ≤ .01.

**Study 05 - IL Count % Change**

- **N = 495**
- Baseline total lesions ~81-83
- ANCOVA, Intent to Treat (ITT) Population, Observed Cases
  *P ≤ .0001; †P ≤ .001; ‡P ≤ .01.

TOPICAL VS ORAL ANTIBIOTIC USE

IMPLICATIONS FOR MINOCYCLINE 4% FOAM

![Graph showing competitive release of resistance and probability of resistant mutation based on drug pressure.]

<table>
<thead>
<tr>
<th></th>
<th>Plasma $C_{\text{max}}$</th>
<th>Skin (epidermis) $C_{\text{max}}$</th>
<th>Skin/Plasma Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMX101 4%</td>
<td>1.3 ng/mL</td>
<td>560,000 ng/g</td>
<td>&gt;400,000</td>
</tr>
<tr>
<td>Oral Minocycline</td>
<td>1000 ng/mL</td>
<td>8000 ng/g</td>
<td>8</td>
</tr>
</tbody>
</table>

JAMES Q. DEL ROSSO, DO
Therapeutic options for Moderate to Severe Acne

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy</td>
<td>Oral antibiotics + topical retinoids ± BPO</td>
</tr>
<tr>
<td></td>
<td>First line</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>Women with moderate to severe acne, especially if contraception is desirable</td>
</tr>
<tr>
<td></td>
<td>Used in combination with other modalities</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Severe and/or recalcitrant acne</td>
</tr>
<tr>
<td></td>
<td>Teratogenic; stringently regulated for women with childbearing potential</td>
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</table>
# Acne Treatment Algorithm

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comedonal</strong></td>
<td>Topical retinoid</td>
<td>Topical retinoid + topical antimicrobial</td>
<td>Oral antibiotic + topical retinoid +/- BPO</td>
</tr>
<tr>
<td><strong>Papular/pustular</strong></td>
<td>Oral antibiotic + topical retinoid +/- BPO</td>
<td>Oral antibiotic + topical retinoid +/- BPO</td>
<td>Oral isotretinoin^4</td>
</tr>
<tr>
<td><strong>First choice</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alternatives</strong></td>
<td>Azelaic acid or salicylic acid</td>
<td>All topical antimicrobial agent + all topical retinoid or azelaic acid^5</td>
<td>Oral isotretinoin or all oral antibiotic + all topical retinoid +/- BPO + BPO</td>
</tr>
<tr>
<td><strong>Alternatives for females</strong></td>
<td>See first choice</td>
<td>See first choice</td>
<td>Oral anti-androgen^11 + topical retinoid + azelaic acid^5 +/- BPO</td>
</tr>
<tr>
<td><strong>Maintenance therapy</strong></td>
<td>Topical retinoid</td>
<td>Topical retinoid +/- BPO</td>
<td></td>
</tr>
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</table>

Sarecycline vs Placebo in Acne Vulgaris Inflammatory Lesion Count Reduction (%)

Sarecycline 1.5 mg/kg/day QD (n=1002) vs Placebo – 12-Weeks
Age Range 9-45 Years / ~25% Non-White Skin / 85% Moderate Severity

Mean Percent Change in Inflammatory Lesion Count from Baseline to Week 12

- Mean absolute reduction in lesion count was statistically significant at Week 12 and as early as Week 3


MAY BE TAKEN WITH OR WITHOUT FOOD
Practical Considerations with Sarecycline

Concept of Narrow Spectrum Tetracycline

POTENTIAL CONSIDERATIONS RELEVANT TO CLINICAL PRACTICE

EFFICACY FOR ACNE VULGARIS
Inflammatory AND Comedonal Lesions
Face & Trunk

ADVERSE REACTION PROFILE
GI Side Effects / Photosensitivity /
Vaginal Candidiasis

ANTIMICROBIAL SPECTRUM
Reduced Risk of Antibiotic Resistance vs Some
Organisms (especially Gram - )

REDUCE SELECTION OF GRAM (-) BACTERIA AND MULTI-DRUG RESISTANCE

A continued work in progress
Most data available with tetracyclines – “dual mechanisms”

Use in combination with maximized topical regimen
Incorporate benzoyl peroxide AND topical retinoid in regimen
AVOID antibiotic monotherapy or “unopposed” antibiotic use

Limit duration of oral antibiotic therapy *as best as possible*
Assess every 3 months
“Maximum” suggested (“hoped for”) duration: 3 - 6 months

Consensus agreement: “…a subset of patients for whom alternative therapies are inappropriate and who may require a longer course of antibiotics even while taking topical medications.”

Adult Female Acne

**Trigger Factors**

**Internal factors**
- Hormones
- Genetic background
- Endocrinopathies: POC

**External factors**
- Cosmetics, Stress
- Smoking
- Sun
- Medications (eg, benzodiazepin)

Patient Factors to Consider when Treating Adult Female Acne

Clinical aspects: lesions type
Potential slow response to treatment
Maintenance therapy
Likelihood of high adherence
Emotional/psychological impact
Child-bearing potential

Potential of older skin to irritation
Cosmetic use
Photoaging/damage
Skin type
Ethnicity
Smoking

Adult Female Acne

**Topical Treatments**

- **Retinoids** – first line, many formulations
  - photodamage, PIH

- **Benzoyl peroxide** – no resistance
  - inflammatory lesions

- **Sulfone (Dapsone)** – anti-inflammatory
  - vehicle

- **Azelaic acid** – antimicrobial
  - anti-tyrosinase (PIH)

- **Antibiotics** – fixed combinations
  - synergistic effects

- **Sodim sulfacetamide, sulfur**
Adult Female Acne

Oral Treatments
- Antibiotics – anti-inflammatory
- Isotretinoin
- Hormonal therapies

Spironolactone
- Perimenstrual flares
- Treatment resistant acne in women
- Augment OCP for “hormonal” acne
- Hirsutism, androgenic alopecia
Use of combination therapy is pathogenetically warranted, especially for patients who are genetically prone to the formation of post-acne scarring.

A 650 microsecond 1064nm laser is effective at stimulating neocollagenesis without the risk of excessive heating of the skin or pain.

Pathological scarring in acne was not observed. Improvement of preexisting acne scars was noticeable.

Combination therapy of a 650 microsecond 1064nm laser and isotretinoin at a low dosage (0.2-0.3 mg/kg/day) is safe, effective, and tolerable.