State of the Art in Dermatology August 2021

Update on Acne: 2021

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Disclosures

Novartis
Galderma (past)
Cassiopea (past)
Foamix (past)

Topics

- AAD guidelines
- Hormonal therapies and acne
  - Spironolactone adolescent females
  - Long term use of spironolactone
- New drugs
  - Sarecycline
  - Minocycline foam
  - Trifarotene- truncal acne
  - Clascoterone

AAD Guidelines for Treatment of Acne 2016

Zaenglein A *et al.* J Am Acad Dermatol 2016;74:945-73

Recommendations for topical antibiotics

- Benzoyl peroxide or combinations with erythromycin or clindamycin are effective acne treatments and are recommended as monotherapy for mild acne, or in conjunction with a topical retinoid, or systemic antibiotic therapy for moderate to severe acne
- Benzoyl peroxide is effective in the prevention of bacterial resistance and is recommended for patients on topical or systemic antibiotic therapy
- Topical antibiotics (eg, erythromycin and clindamycin) are effective acne treatments, but are not recommended as monotherapy because of the risk of bacterial resistance.

Zaenglein A *et al*. J Am Acad Dermatol 2016;74:945-73

Recommendations for systemic antibiotics

- Systemic antibiotics are recommended in the management of moderate and severe acne and forms of inflammatory acne that are resistant to topical treatments
- Doxycycline and minocycline are more effective than tetracycline, but neither is superior to each other
- Although oral erythromycin and azithromycin can be effective in treating acne, its use should be limited to those who cannot use the tetracyclines (ie, pregnant women or children<8 years of age)
- Erythromycin use should be restricted because of its increased risk of bacterial resistance

Zaenglein A *et al*. J Am Acad Dermatol 2016;74:945-73

Recommendations for systemic antibiotics

- Systemic antibiotic use should be limited to the shortest possible duration.
- Re-evaluate at 3-4 months to minimize the development of bacterial resistance.
- Concomitant topical therapy with benzoyl peroxide or a retinoid should be used with systemic antibiotics and for maintenance after completion of systemic antibiotic therapy

Zaenglein A *et al.* J Am Acad Dermatol 2016;74:945-73

Is antibiotic resistance something we need to worry about?

Why worry?

- In 2015, WHO declared the global emergence of antibiotic-resistant strains of bacteria as an urgent crisis
- Epidemiologic evidence of association of antibiotic use with upper respiratory infection, pharyngitis, inflammatory bowel disease, colon and breast cancer (tetracycline class)

World Health Organization. Global Action Plan on Antimicrobial Resistance. Geneva: WHO, 2015.

Pilot study of microbiome changes with systemic minocycline therapy for acne

- In this study of 4 women with acne, there was a significant decrease in the relative abundance of *Cutibacterium acnes* concurrent with a significant increase in the relative abundance of *Pseudomonas* species across participants following 4 weeks of treatment with oral minocycline.
- After 8 weeks following antibiotic treatment withdrawal, *C. acnes* levels recovered, while *Streptococcus* species significantly increased and *Lactobacillus* species significantly decreased from baseline.

Chien, A et al . *JAMA Dermatol.* 2019;155(4):425-434.

What are the risks of using antibiotics for acne long term?

Potential risks of antibiotics

- In addition to resistance among *C. acnes*, the use of oral antibiotics is associated with disruption of the normal flora, bacterial resistance among other organisms, and increased rates of upper respiratory infection and pharyngitis.
- Antibiotic use might also be associated with inflammatory bowel disease and collagen vascular disease.
- There might be an association between the use of oral tetracycline class antibiotics and risk for breast and colon cancer.

Barbieri JS et al. J Am Acad Dermatol 2019;80:538-49.

Is there an association between long-term antibiotics for acne and subsequent infection sequelae and antimicrobial resistance? A systematic review protocol

- The overall aim of this systematic review is to elucidate what is known about oral antibiotics for acne contributing to antibiotic treatment failure and antimicrobial resistance.

Bhate K, Lin L-Y, Barbieri J, *et al*. *BMJ Open* 2020;10:e033662. doi:10.1136/bmjopen 2019-033662

What is the ideal duration for antibiotics in the management of acne?

Changes in duration of antibiotic treatment

Study	Years	Data Source	Duration
Levy *et al*	2003	Dermatology clinic patients	Mean 11.5 mos (SD 18.7)
Barbieri *et al*	2004-2014	OptumInsight Clinformatics DataMart	Median 126 days
Lee *et al*	2008-2010	Market Scan	Median 99 days
Straight *et al*	2008-2010	Market Scan	Median 93 days

Levy RM, *et al. Arch Dermatol* 2003; **139**: 467-71.
Barbieri JS et al. *J Am Acad Dermatol* 2017; **77**: 456-63 e4.
Lee YH, *et al. J Am Acad Dermatol* 2014; **71**: 70-6.
Straight CE, *et al. J Am Acad Dermatol* 2015; **72**: 822-7.

Dermatologist prescriptions 2004-2013 (OptumInsight Clinformatics)

# courses/ 100 patients	2004	2013	Change
Spironolactone (females)	2.08	8.13	291% increase
OCPs	34.3	30.74	↓
Antibiotics	26.24	27.08	↑
Isotretinon	5.43	5.35	↓

Barbieri J, James W, Margolis D. J Am Acad Dermatol 2017;77:456-63

Trends in antibiotic prescribing among dermatologists

- 2004-2013: the number of courses of oral antibiotics prescribed per 100 patients with acne increased from 26.24 to 27.08
- 2008 -2016 overall antibiotic prescribing among dermatologists decreased 36.6%, most of the decrease occurred among extended courses for acne and rosacea
- There was an increase in short-term Abx for surgical procedures and cysts

Barbieri JS et al. *J Am Acad Dermatol* 2017; 77: 456-63 e4.

Barbieri J et al. *JAMA Dermatol* 2019.

Patient awareness of antibiotic resistance and antibiotic use in acne

- An online survey assessed antibiotic resistance awareness in adults with acne (n=809) and the parents of adolescents with acne (n=210).
- More than 80 percent of subjects said that they were “somewhat familiar” or “very familiar” with antibiotic resistance
- Among subjects who might have been prescribed antibiotic treatment for their acne, including individuals that reported antibiotic treatment and individuals that were not sure, 76.9 percent reported that they would be very or extremely likely to use effective antibiotic-free options if given the opportunity.

DelRosso JQ *et al. J Clin Aesthetic Dermatol.* 2019;12(6):30–41

Strategies to mitigate antibiotic resistance

Potential strategies

- Maintenance Rx with topicals
- Spironolactone
- OCPs
- Isotretinoin
- Subantimicrobial dosing of doxycycline

Modified release 40mg doxy vs 100mg

	Doxycycline	Placebo (n=222)	Significance
Inflammatory Lesion Reduction:			
MR 40 mg (n=216)	16.1	12.6	yes
100 mg daily (n=224)	12.9	12.6	no
IGA Success: Clear or Almost Clear 2 grade reduction			
MR 40 mg	14.4	7.7	yes
100 mg daily	13.8	7.7	yes

Moore A *et al*. J Drugs in Dermatol 2015; 14(6): 581-586

Long-term use of spironolactone

- 403 females (Univ. of PA)
  - mean age 26 (IQR 22-29.5)
  - 7.9% had PCOS
- The majority of patients (n=403) were initially prescribed spironolactone as part of a combination therapy, including:
  - 274 (68.0%) patients who were concurrently prescribed a topical retinoid with spironolactone.
  - Nine (2.2%) were concurrently treated with an oral antibiotic
  - 154 (40.7%) were concurrently taking a combined oral contraceptive
- Mean days on spironolactone = 470

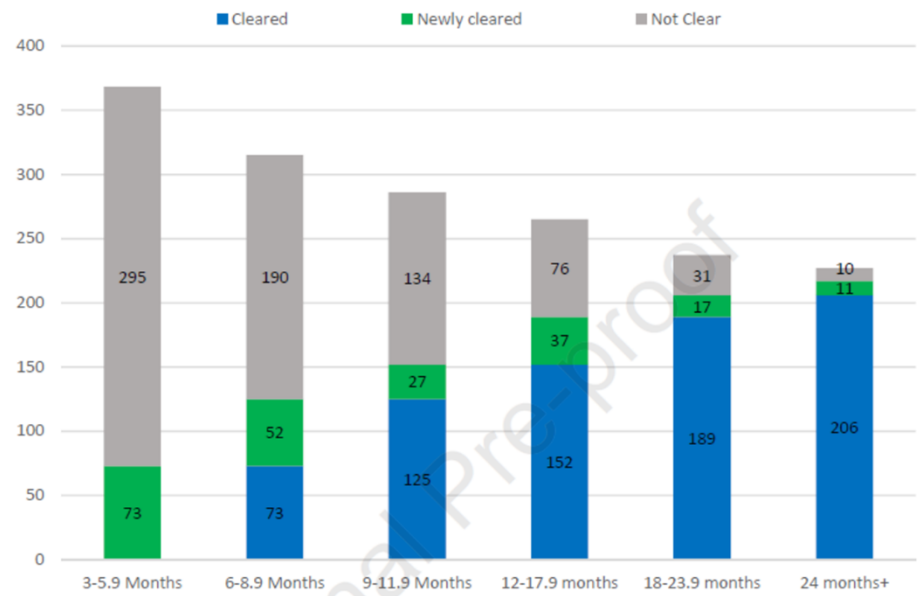
Garg V, Choi JK, James WD, Barbieri JS, *J Am Acad Dermatol* (2021), doi: https://doi.org/10.1016/j.jaad.2020.12.071.

Long- term use of spironolactone for acne

	Face	Chest	Back
	N=269	N=106	N=106
Cleared	95 (35.3%)	82 (77.4%)	72 (67.9%)
Improved	108 (40.2%)	7 (6.6%)	13 (12.3%)
Unchanged	59 (21.9%)	13 (12.3%)	16 (15.1%)
Worsened	7 (2.6%)	4 (3.8%)	5 (4.7%)
Clear = CASS global assessment score of "0"; Improved or worsened = a 1 grade change in CASS; Unchanged=no change in CASS score			

Garg V, Choi JK, James WD, Barbieri JS, *J Am Acad Dermatol* (2021), doi: https://doi.org/10.1016/j.jaad.2020.12.071.

Figure 1. Clearance rates at follow-up visits among those available for follow-up



Garg V, Choi JK, James WD, Barbieri JS, *J Am Acad Dermatol* (2021), doi: https://doi.org/10.1016/j.jaad.2020.12.071.

Use of spironolactone in adolescent females

TABLE 1 Characteristics of 80 adolescent patients with ≥3 mo of spironolactone treatment

Characteristics	Value[a]
Age, median (range), y	19 (14-20)
History of PCOS	3 (3.8)
Acne located on jawline	54 (67.5)
Cyclic flares	57 (71.3)
Initial acne European severity classification,[b] mean, grade	3
Acne unresponsive to other oral treatments before spironolactone[c]	75 (93.8)
Background of OCP use	
No OCP	32 (40.0)
OCP	48 (60.0)
OCP started >6 mo before spironolactone initiation	38 (47.5)
OCP started ≤6 mo before spironolactone initiation	10 (12.5)
OCP started after spironolactone initiation	5 (6.3)

Roberts EE, Nowsheen S, Davis DMR, Hand JL, Tollefson MM, Wetter DA. *Pediatr Dermatol.* 2021;38:72–76.

Spironolactone use in adolescent females

Therapy		
Spironolactone monotherapy	46 (71.9)	9 (56.3)
Oral antibiotics and spironolactone	9 (14.1)	1 (6.3)
OCP and spironolactone[d]	9 (14.1)	5 (31.3)
Antibiotics, OCP, and spironolactone	0 (0.0)	1 (6.3)

Roberts EE, Nowsheen S, Davis DMR, Hand JL, Tollefson MM, Wetter DA. *Pediatr Dermatol.* 2021;38:72–76.

Spironolactone use in adolescent females

Spironolactone dose, median (range), mg	100 (25-200)
Time receiving spironolactone, mo	
Mean (SD)	11.2 (10.0)
Median (range)	7 (3-45)
Follow-up time, mo	
Mean (SD)	16.0 (16.8)
Median (range)	11 (3-110)
Response rate[a]	
Improvement with therapy	64 (80.0)
CR (≥90%)	18 (22.5)
PR (>50%)	29 (36.3)
PR (≤50%)	17 (21.3)
NR	16 (20.0)
NR and subsequently treated with isotretinoin	16 (20.0)

Roberts EE, Nowsheen S, Davis DMR, Hand JL, Tollefson MM, Wetter DA. *Pediatr Dermatol.* 2021;38:72–76.

Spironolactone use in adolescent females

Time to initial response, mo[b]	
Mean (SD)	4.0 (3.0)
Median (range)	3 (1-15)
Time to maximal response, mo[b]	
Mean (SD)	5.4 (3.2)
Median (range)	5 (2-15)
Had adverse effects[c]	3 (3.8)
Discontinued treatment because of adverse effects[c]	3 (3.8)

Roberts EE, Nowsheen S, Davis DMR, Hand JL, Tollefson MM, Wetter DA. *Pediatr Dermatol.* 2021;38:72–76.

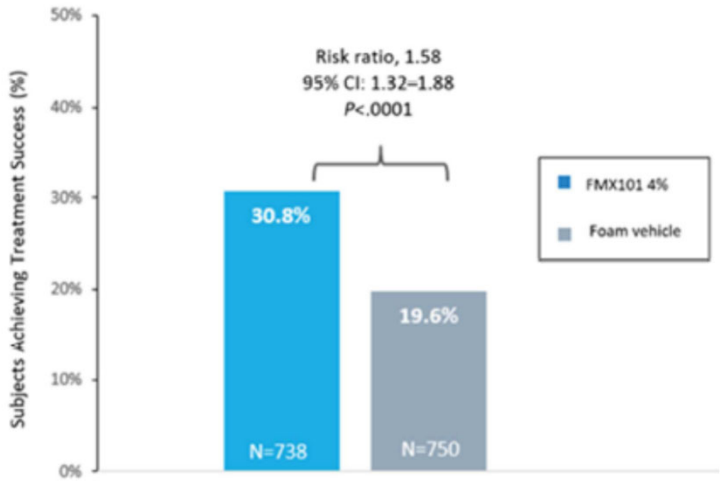
New Treatments for Acne

Sarecycline

- Novel, narrow spectrum tetracycline class antibiotic activity against *C. acnes, S. aureus* and *S. epidermidis*
- Limited activity against enteric G (-) bacteria which may lead to less disruption of the GI microbiome compared to doxycycline or minocycline
- FDA approved for acne October 2018 for acne in patients 9 yrs of age and older with inflammatory non-nodular moderate to severe acne

Moore A *et al* J Drugs Dermatol 17: 987-996, 2018

Minocycline Foam: IGA treatment success at week 12



4% foam FDA approved for acne in 2019

1.5% foam FDA approved for rosacea in 2020

Raoof TJ, et al , *J Am Acad Dermatol* (2019), doi: https://doi.org/10.1016/j.jaad.2019

Trifarotene 0.005% cream

- Two phase III studies of once-daily trifarotene cream versus vehicle in subjects aged 9 years or older
- In both studies, at week 12 the facial success rates according to the Investigator's Global Assessment and truncal Physician's Global Assessment and change in inflammatory and noninflammatory lesion counts were all highly significant (P<.001) in favor of trifarotene when compared with the vehicle.
- FDA approved for acne 2019

Tan J, Thiboutot D, Popp G, Gooderham M, Lynde C,Del Rosso J,et al. J Am Acad Dermatol 2019;80:1691-9

Clascoterone 1% cream

- Topical androgen receptor inhibitor
- Two phase 3 trial in 1440 males and females (>9yrs)
- Treatment success and absolute reduction in inflammatory and noninflammatory lesions was significantly greater in clascoterone group compared to vehicle
- FDA approved in Aug 2020

Hebert A, Thiboutot D, Stein Gold L, Cartwright M, Gerloni M, Fragasso E, Mazzetti A. JAMA Dermatol 2020;156(6):621-630

Take home points

- Alternatives to long-term antibiotic use in acne are key
- These include use of benzoyl peroxide, topical retinoids, hormonal therapy for women (OCP, spironolactone) and behavioral strategies
- New antibiotic agents demonstrate efficacy but should be used for limited periods of time and in regimens containing benzoyl peroxide