

State of the Art September 9, 2022 20 min

What's New in Acne: 2022 ?



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Disclosures

Biofrontera	Consultant
Galderma	Clinical trials, consultant
Novartis	Consultant

Updates on:

- New drugs for acne
- Spironolactone
- Hormonal IUDs and acne
- Isotretinoin dosing
- Managing acne fulminans

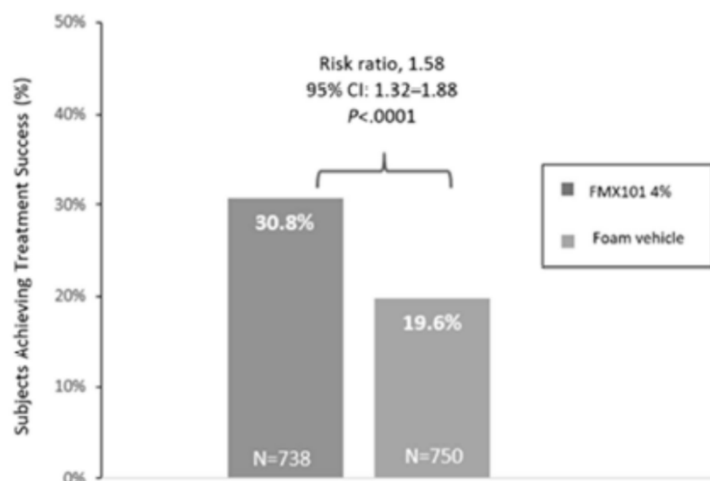
New Treatments for Acne

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

Raouf 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 including truncal acne

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

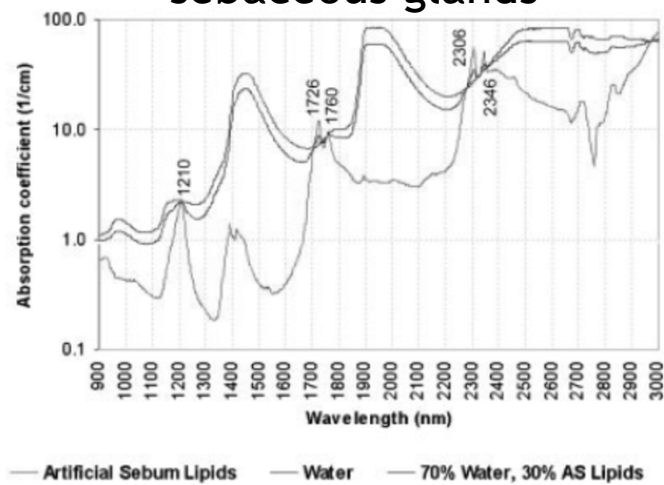
- Topical androgen receptor inhibitor
- Two phase 3 trial in 1440 males and females (>9yrs)
- Treatment success and absolute reduction in inflammatory and noninflammatory lesions was significantly greater in clascoterone group compared to vehicle
- FDA approved in Aug 2020

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

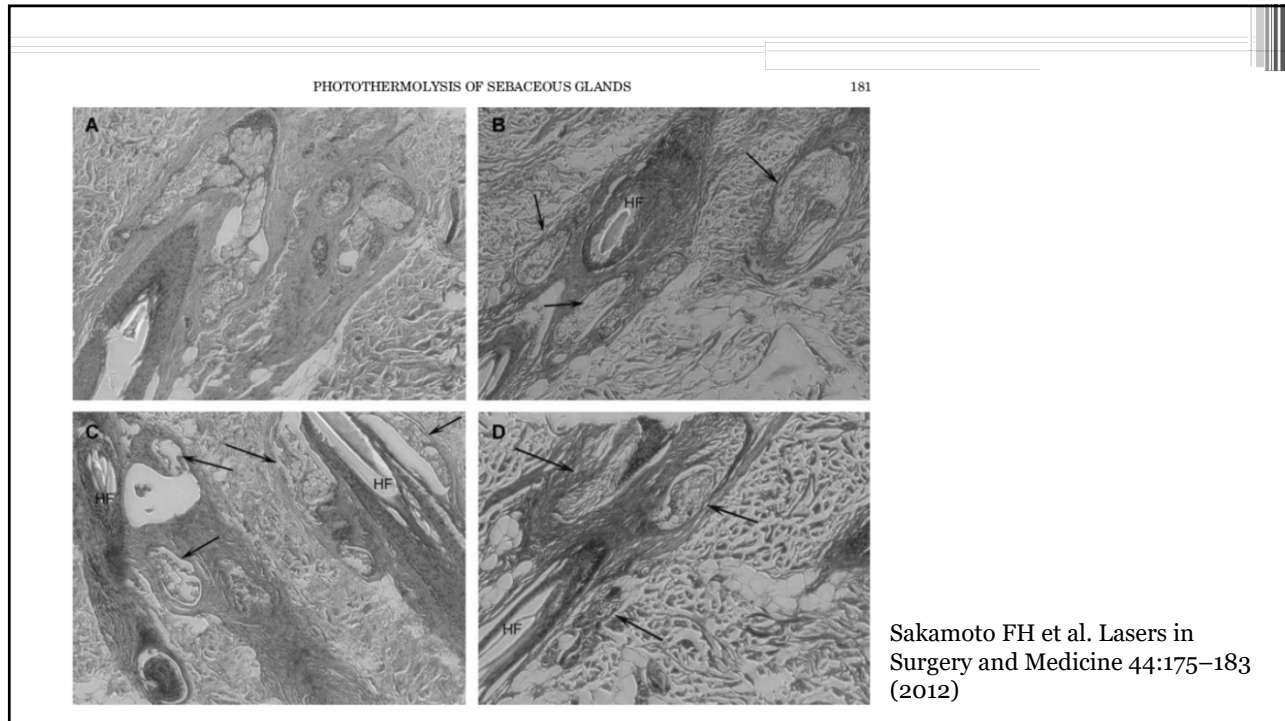
1726 nM lasers for acne

- Accure laser CE mark approved in Europe May 7, 2020
- Cutera Aviclear FDA approved for acne March 28, 2022

1726 nM laser- selective photothermolysis of sebaceous glands



Sakamoto FH et al. Lasers in Surgery and Medicine 44:175–183 (2012)



Spirolonactone

Spirolactone

- Blocks the androgen receptor and 5α -reductase
- Dose: 25-100 mg. Twice daily
- Frequent side effects:
 - Breast tenderness
 - Menstrual irregularity
- Avoid pregnancy

Trends in spironolactone prescribing patterns

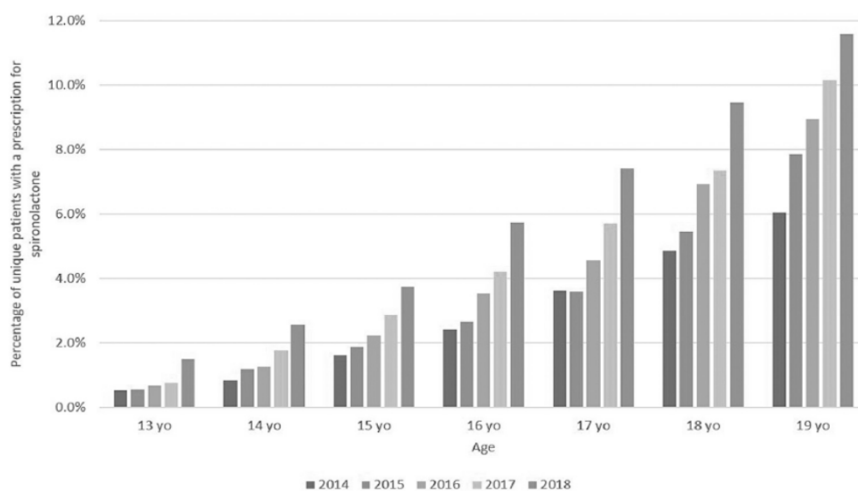


Fig 1. Trend in spironolactone prescriptions for patients with acne by age group. *yo*, Years of age.
HoriSSian M, Maczuga, S, Barbieri J, Zaenglein A. J Am Acad Dermatol <https://doi.org/10.1016/j.jaad.2021.12.005>

Trends in prescribing patterns of spironolactone for acne and hidradenitis suppurativa

- During this period, there were 2- to 3-fold increases in the use of spironolactone for acne and HS across all age groups
- The use of spironolactone increased with age and was used approximately 10 times more frequently in 19 year old women vs. 13 year old girls
- With the increase in its use in younger patients, safety is a concern that needs to be addressed. Importantly, spironolactone's antiandrogen effects on endocrine development in early adolescence, before full pubertal development is attained, are not known.

Horissian M, Maczuga, S, Barbieri J, Zaenglein A. J Am Acad Dermatol <https://doi.org/10.1016/j.jaad.2021.12.005>

Spironolactone and Cancer Risk

Black box warning

- Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Precautions*).
- Spironolactone should be used only in those conditions described under *Indications and Usage*.
- Unnecessary use of this drug should be avoided.

Association of Spironolactone with Risk of Cancer

- Systematic review and meta-analysis of studies that reported the occurrence of cancers in men and women 18 years and older who were exposed to spironolactone.
- Collected information on number of malignant tumors and effect measures reported (RRs, odds ratios, or hazard ratios [HRs])
- Risk of bias was assessed using the Newcastle-Ottawa Scale
- Data were combined when statistically homogeneous and expressed as RRs with their associated 95% CIs.
- The strength of the evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach

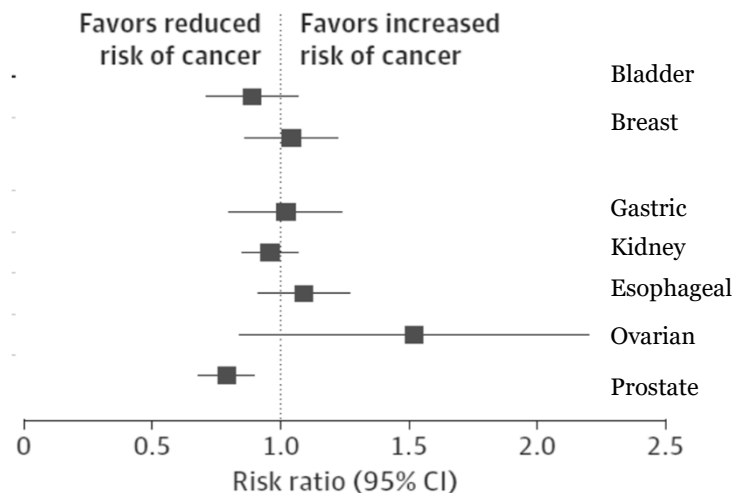
Bommareddy K et al *JAMA Dermatol*doi:10.1001/jamadermatol.2021.5866 Published online February 9, 2022.

Association of Spironolactone with Risk of Cancer

- Seven studies met eligibility criteria, with sample sizes ranging from 18,035 to 2.3 million with a total population of 4, 528, 332 individuals in the studies identified
- All studies were considered to be of low risk of bias
- Because of the heterogeneity of the studies and the conversions of the effect estimates needed for the analyses, certainty of the evidence was low or very low for each study

Bommareddy K et al *JAMA Dermatol* doi:10.1001/jamadermatol.2021.5866 Published online February 9, 2022.

Association of Spironolactone with Risk of Cancer



Bommareddy K et al *JAMA Dermatol* doi:10.1001/jamadermatol.2021.5866 Published online February 9, 2022.

Association of Spironolactone with Risk of Cancer

- In this systematic review and meta-analysis, spironolactone use was not associated with a substantial increased risk of cancer and was associated with a decreased risk of prostate cancer.
- However, the certainty of the evidence was low and future studies are needed, including among diverse populations such as younger individuals and those with acne or hirsutism.

Bommareddy K et al *JAMA Dermatol* doi:10.1001/jamadermatol.2021.5866 Published online February 9, 2022.

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 were initially prescribed spironolactone as part of a combination therapy, including:
 - 274 patients who were concurrently prescribed a topical retinoid with spironolactone.
 - Nine were concurrently treated with an oral antibiotic
 - 154 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>.

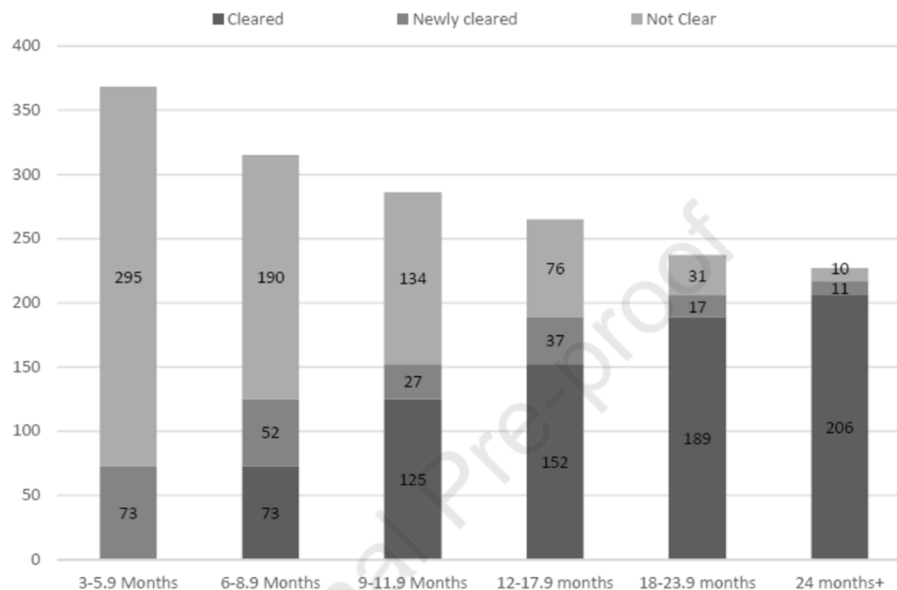
Long- term use of spironolactone for acne

	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>.

Spironolactone: Do we need to monitor K+ ?

Low usefulness of K+ monitoring in young healthy women on spironolactone

- Analyzed rates of hyperkalemia
 - **974** healthy young women taking spironolactone for acne
 - **1165** healthy young women not taking spironolactone
- The rate of hyperkalemia in healthy young women taking spironolactone for acne is equivalent to the baseline rate of hyperkalemia in this population.
- Routine potassium monitoring is unnecessary for healthy women taking spironolactone for acne.

Plovanich M; Weng QY; Mostaghimi A, *JAMA Dermatol.* 2015;151(9):941-944.

Hormonal IUDs and development of acne

Association of Acne and Hormonal IUDs

- This study aimed to evaluate associations between hormonal IUDs and adverse dermatologic events using the TriNetX database of patients at the University of Iowa (2010-2020)
- Retrospective cohort study was designed using women who used levonorgesterol IUDs vs copper IUDs who developed acne, rosacea, androgenetic alopecia or hirsutism within one year of implantation (2010-2020)
- 1224 women (18-60) were included

Munjal A et al JAAD pre-proof Accepted Jan 19, 2022 <https://doi.org/10.1016/j.jaad.2022.01.023>

Association of Acne and Levonorgestrel IUDs

Group	Odds ratio	95% CI Lower Bound	95% CI Upper Bound	P-value
Overall	2.514	1.865	3.388	<0.0001
Age 19-29	4.193	1.547	11.365	0.0048
Age 30-39	3.576	2.177	5.874	<0.0001
Age 40 and over	1.725	1.149	2.59	0.0086

Munjal A et al JAAD pre-proof Accepted Jan 19, 2022 <https://doi.org/10.1016/j.jaad.2022.01.023>

Isotretinoin dosing?: Still discussing after 35+ years!

Isotretinoin dosing: An opportunity to study further

- What is the ideal daily dose of isotretinoin?
- What is the ideal cumulative dose of isotretinoin to minimize relapse of acne?
- What is the ideal duration of isotretinoin therapy?
- How do you define relapse?

Trends in dosing since isotretinoin approval

- 1 mg/kg/day
- Reduced first month dosing 0.5 mg/kg/day
- Low dosing
- Intermittent dosing
- High dosing

Which factors predict the need for retreatment?

- The dose of isotretinoin is important.
- Strauss et al. 1984 demonstrated relapse rates
 - 42% in patients treated with 0.1 mg/kg daily
 - 20% in patients treated with 0.5 mg/kg daily
 - 10% in patients treated with 1.0 mg/kg daily
- Similarly, we found more relapses in the 0.5 mg/kg group vs. those treated with 1-0 mg/kg.
- Factors contributing to the need for further courses of treatment included lower dose regimens (0.1 and 0.5 mg/kg), the presence of severe acne, being a female over the age of 25 at the onset of therapy, and having a prolonged history of acne.

Stainforth JM et al. British Journal of Dermatology (1993)129,297-301

Could higher doses of isotretinoin reduce the frequency of treatment failure in patients with acne?

- Of 102 patients in a retrospective chart review, 45.1% required further treatment (ie, relapsed) and 15.7% received a second course of isotretinoin.
- Analysis of the cumulative dose (mg/kg), follow-up period, treatment duration, and daily dose during the last month of treatment revealed that none of these characteristics were significantly different between the group that relapsed and the group that did not.

Coloe J, Du H, Morrell DS. J Am Acad Dermatol. 2011 Aug;65(2):422-423

Could higher doses of isotretinoin reduce the frequency of treatment failure in patients with acne?

- Our results show that while the cumulative dose of isotretinoin did not significantly impact acne relapse, patients who received a higher cumulative dose were less likely to require a second course of treatment.
- Female patients had a higher risk of needing retreatment regardless of their cumulative dose.
- Prescribing a higher dose per weight may result in less severe acne recurrences and the need for further isotretinoin therapy.

Coloe J, Du H, Morrell DS. *J Am Acad Dermatol.* 2011 Aug;65(2):422-423

High-Dose Isotretinoin Treatment and the Rate of Retreatment, Relapse, and Adverse Effects

- 116 patients treated to clearance with dosing at discretion of provider
- Relapse defined as subsequent treatment with an oral or topical agent
- In the lower-dose treatment group (<220mg/kg, mean =170mg/kg), the relapse rate was 47.4% compared with 26.9% in the high-dose (>220 mg/kg) group ($P = .03$).
- Almost 100% of the patients in both treatment groups developed cheilitis and xerosis during treatment.
- Retinoid dermatitis was significantly more common in the high-dose treatment group (53.8% vs 31.6%; $P = .02$).
- None of the other adverse effects was significantly different between the 2 groups.

Blasiak RC *et al. JAMA Dermatol.* 2013;149(12):1392-1398

Isotretinoin relapse: Review of 1453 patients in a single practice

- Defined relapse as need for a second course of isotretinoin.
- Neither daily nor cumulative dosages influenced relapse of acne vulgaris in patients treated with varying doses of isotretinoin as long as treatment was continued for ≥ 2 months after the acne had completely resolved.

Rademaker M International Journal of Dermatology 2016, 55, 518–523

Evidence for isotretinoin cumulative dose recommendations

- The current evidence underpinning the 120-150 mg/kg cumulative threshold-dosing regimen is equivocal and is based on 2 low grade studies.
- Cumulative ISO doses required for clearance appear lower for acne of mild to moderate severity and higher for more severe acne.
- Future investigations should use clinically relevant endpoints as end of treatment criteria and define treatment success in acne accurately.

Tan J *et al.* Journal of Cutaneous Medicine and Surgery 2016, Vol. 20(1) 13–20

Variables to consider in selection of daily dose

- Presence of intense inflammation, cysts, nodules
- Potential difference in side effect profiles with ethnicity
- An individual's degree of side effects and their level of comfort

Guidelines: Classification, management and prevention of acne fulminans (AF)

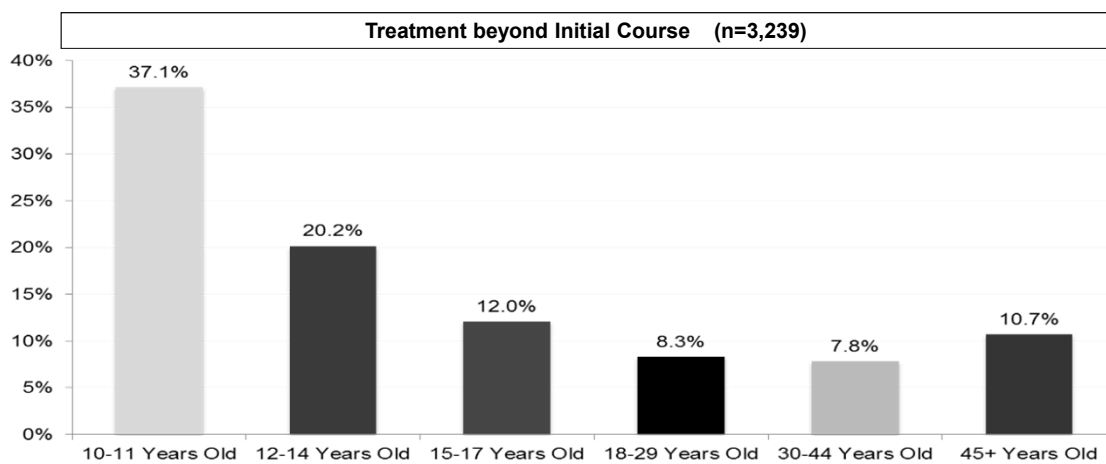
- Isotretinoin can induce acne fulminans
- Should be started at a lower dose +/- inclusion of prednisone

Greywal T *et al.* J Am Acad Dermatol 2017;77:109-17

Variables affecting duration of response to isotretinoin

- Age at treatment
 - Earlier age of onset of acne
 - Adult female acne
- Cumulative dose
- Presence of truncal acne

All Patients requiring retreatment with isotretinoin



Tortoise

Pros

- Minimize side effects
- Avoid cystic flare

Cons

- Longer treatment period
- More visits
- Prolonged drug exposure in patients who can get pregnant

Hare

Pros

- Shorter treatment duration
- Potential cost savings

Cons

- Increased side effects
- Risk of cystic flare

General agreement: Treat until clear and ~2 months longer

Take home points

- New drugs are available for acne but comparative efficacy data is needed
- Spironolactone use is increasing
 - Evidence does not support association with cancer in humans
 - Efficacy has been demonstrated with long-term use
- The cumulative dose of isotretinoin needed to prevent relapse is unknown
- Limited evidence for use of doses $> 1\text{mg/kg/day}$
- General recommendation is to treat patients with isotretinoin until clear and for an additional 2 months