

REVIEW

Approaches to limit systemic antibiotic use in acne: Systemic alternatives, emerging topical therapies, dietary modification, and laser and light-based treatments

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Acne is one of the most common diseases worldwide and affects ~50 million individuals in the United States. Oral antibiotics are the most common systemic agent prescribed for the treatment of acne. However, their use might be associated with a variety of adverse outcomes including bacterial resistance and disruption of the microbiome. As a result, multiple treatment guidelines call for limiting the use of oral antibiotics in the treatment of acne, although actual prescribing often does not follow these guidelines. In this review, the rationale for concerns regarding the use of oral antibiotics for the management of acne is reviewed. In addition, we will discuss our approach to complying with the intent of the guidelines, with a focus on novel topical agents, dietary modification, laser and light-based modalities, and systemic medications, such as spironolactone, combined oral contraceptives, and oral isotretinoin. (J Am Acad Dermatol <https://doi.org/10.1016/j.jaad.2018.09.055>.)

Key words: acne; antibiotics; antibiotic stewardship; diet; evidence-based medicine; guidelines; isotretinoin; laser; spironolactone.

Antibiotic resistance is a growing problem across medicine, and rates of antibiotic resistance, including to tetracycline-class antibiotics, among isolates of *Cutibacterium* (formerly *Propionibacterium*) *acnes* have been rising.¹⁻⁴ 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.⁵⁻⁸ Antibiotic use might also be associated with inflammatory bowel disease and collagen vascular disease.⁷⁻¹⁶ Last, there might be an association between the use of oral tetracycline-class antibiotics and risk for breast and colon cancer.^{17,18} As a result, there have been calls throughout

medicine to decrease overuse of antibiotics, and multiple recent acne guidelines recommend limiting their use.¹⁹⁻²⁵ However, in clinical practice, antibiotics are the most frequently prescribed systemic therapy for acne and are often used for longer durations than recommended in the guidelines.²⁶⁻²⁹ In fact, dermatologists prescribe more antibiotics per provider than any other specialty.³⁰ In this article, we will discuss alternative approaches to limit antibiotic use in the treatment of acne.

SPIRONOLACTONE

Given the crucial role of hormones in the pathogenesis of acne, therapies with antiandrogenic or antisebogenic properties are mechanistically enticing

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Abbreviations used:

COC:	combined oral contraceptive
HGLD:	high glycemic load diet
IGF-1:	insulin-like growth factor 1
IPL:	intense pulsed light
LGLD:	low glycemic load diet
PDT:	photodynamic therapy
PDL:	pulse dye laser
SCD1:	stearoyl coenzyme A desaturase 1

options.³¹⁻³⁵ Spironolactone is a synthetic 17-lactone steroid that has antagonistic effects on the androgen and progesterone receptors. Although its original clinical application was as a potassium-sparing diuretic, due to its effect on sebum production through inhibition of the androgen receptor on sebocytes, spironolactone has been used off-label in the treatment of acne for >30 years.³⁶⁻⁴⁴ It might also reduce synthesis of androgen precursors in the adrenal glands.^{45,46}

Although it was found in a 2009 Cochrane review that randomized trials evaluating spironolactone for the treatment of acne were too scarce and small to support its effectiveness, there have since been multiple large retrospective observational studies of several hundred patients supporting its effectiveness (Table I).⁴⁷⁻⁵⁴ Although use of spironolactone has increased substantially in recent years, oral antibiotics are still prescribed 3-5 times more frequently among women with acne.²⁷ As a result, increased use of spironolactone might represent an opportunity to improve antimicrobial stewardship and outcomes in patients with acne. Last, it is important to note that spironolactone might be effective for acne in women of all ages, and its use should not be limited only to adult women or women with prominent acne on the lower face or acne that flares with their menstrual cycle.^{49,52,55} In our practice, the starting dose is typically 100 mg/d in the evening (Table II).³⁵ Doses up to 200 mg/d can be used; however, side effects increase with higher doses.^{35,44,48} Several months of treatment is typically required to reach the full effectiveness of treatment.

Adverse effects and monitoring

The most common side effect in patients taking spironolactone is menstrual irregularities, which occur in 15%-30% of patients. This side effect is dose dependent, with a relative risk of 4.12 (95% confidence interval 3.27-5.19) in women receiving a dose of 200 mg/d compared with those receiving lower doses. The concomitant use of combined oral contraceptives (COCs) or a hormonal intrauterine device can minimize the

incidence of this side effect.^{44,56} Other side effects include breast tenderness (3%-5%), dizziness (3%-4%), nausea (2%-4%), headache (2%), polyuria (1%-2%), and fatigue (1%-2%).⁴⁴ Spironolactone is pregnancy category C. However, when administered in high doses to rats, it has been found to cause feminization of the male fetus, and there are no well-controlled human studies of its use in pregnancy.⁵⁷ Therefore, patients should be counseled to avoid becoming pregnant while on spironolactone.

Because spironolactone is a potassium-sparing diuretic, hyperkalemia is a potential complication, which has been observed in patients with renal insufficiency or severe heart failure taking high drug doses.⁵⁸ However, in young, healthy women being treated for acne who do not have heart disease, hypertension, or renal disease and are not taking potentially interacting medications, such as angiotensin converting enzyme inhibitors, there is no evidence of increased rates of hyperkalemia when compared with control patients not taking spironolactone.⁵⁹ In addition, spironolactone appears safe in patients who are receiving concomitant therapy with a drospirenone-containing COC.^{55,60} Hence, potassium monitoring in young, healthy women is not required but should be followed in the uncommon woman with acne who also has risk factors for hyperkalemia.¹⁹

Due to evidence of tumorigenicity in animal studies in which doses >100 times greater than those used in clinical practice were used, spironolactone has a black box warning recommending against off-label and unnecessary use of spironolactone.⁵⁸ However, several large cohort studies with >30 million person-years of combined follow-up have not confirmed such a risk when used in typical clinical practice.⁶¹⁻⁶⁴ In a study of women treated for acne with spironolactone, which included 200 person-years of spironolactone exposure and 506 person-years of follow-up, no cases of serious illnesses attributable to spironolactone were observed.⁶¹ In our practice, for patients with a family history of breast or ovarian cancer, we will still consider its use after a thorough discussion of the black box warning.

ORAL CONTRACEPTIVES

COCs containing estrogen and progestin (Table III) address the hormonal pathogenesis of acne, decreasing free testosterone by 40%-50% on average.^{65,66} Estrogen also reduces the conversion of testosterone to dihydrotestosterone in the pilosebaceous unit, further decreasing sebum production.

Table I. Summary of recent observational studies supporting the efficacy of spironolactone for the treatment of women with acne

Study	Study size	Key findings
Charny, 2017 ⁴⁹	110	84% of those treated with spironolactone 100 mg/d showed initial improvement, with 40% clearing completely. An additional 32 patients improved or cleared by increasing the dose to 150 mg/d and another 13 improved or cleared at 200 mg/d.
Grandhi, 2017 ⁵⁰	400	86% of patients reported improvement, with only 4% experiencing any side effects.
Isvy-Joubert, 2017 ⁵¹	70	In a population in which 60% had previously relapsed after treatment with isotretinoin, 71% of patients had a good clinical response to spironolactone, with a median time to response of 6 months.
Park, 2018 ⁵³	672	The mean cumulative antibiotic treatment duration for women who received either a combined oral contraceptive or spironolactone was 83.4 fewer days than those who did not receive either therapy, after controlling for age and acne type.
Barbieri, 2018 ⁵⁴	38,298	The rate of switching to another systemic agent within the first year of therapy was similar between those who initially received spironolactone (14.4%) and those who initially received antibiotics (13.4%), suggesting that spironolactone might have similar clinical effectiveness to oral antibiotics for women with acne.

Table II. Suggested dosing, contraindications, side effects, monitoring, and pregnancy and lactation information for spironolactone

Category	Description
Dosing	25-200 mg/d, typically starting 100 mg/d in the evening
Contraindications	Significant renal impairment, hyperkalemia or medications known to increase serum potassium level (eg, trimethoprim or angiotensin-converting enzyme inhibitors), Addison disease
Side effects	Menstrual irregularities, breast tenderness, dizziness, nausea, headache, polyuria, fatigue
Monitoring	Routine monitoring is not required in young women without hypertension, renal, or cardiac disease.
Pregnancy category	C
Nursing	Compatible with breastfeeding; risk to infant is minimal

In a Cochrane review, the effectiveness of all COCs for the treatment of acne in women was supported, and a few preparations have been approved specifically for acne.^{35,67-70} In trials in which drospirenone-containing COCs were compared with other COCs, the drospirenone-containing COC have generally been favored.⁷⁰⁻⁷⁵ In contrast, progestin-only contraceptives and long-acting reversible contraceptives are associated with worsening of acne.⁷⁵ A course of 3-6 months of therapy is typically required for patients to experience the full benefit of treatment with a COC.⁷⁶

Adverse effects and monitoring

The most common side effect in patients taking COCs is breakthrough bleeding, which is often associated with missed pills. Other common side effects include nausea and breast tenderness. All of these side effects have a tendency to resolve over the first 2-3 cycles of use.^{35,77} More serious adverse effects associated with COCs are thromboembolic events. Although, the risk for venous

thromboembolism in reproductive age non-COC users is ~2/10,000 person-years, this rate increases to ~6/10,000 person-years for those on COCs and to ~9/10,000 person-years for drospirenone-containing COCs.^{78,79} Because of these risks, the labelling for drospirenone-containing COCs includes a warning to limit use to those who also desire a COC for birth control.⁸⁰ However, when counseling patients, it is important to keep in mind that the attributable risk for venous thromboembolism is low; in fact, the risk for venous thromboembolism is higher with pregnancy than COC use.⁷⁹ Likewise, the attributable risk for cardiovascular events (~2/10,000 person-years) and ischemic stroke (~1/25,000 person-years) are low in otherwise healthy women. In addition, women who take a COC are not at increased risk for cardiovascular disease later in life.⁸¹⁻⁸⁸

Although there is conflicting data on the potential association between COCs and breast cancer, there is compelling evidence that COCs are associated with a significantly reduced risk for colon cancer, uterine

Table III. Suggested dosing, contraindications, side effects, monitoring, and pregnancy and lactation information for combined oral contraceptives used in acne

Category	Description
Dosing	Quick start (preferred): begin on the day prescription is given (as long as pregnancy is reasonably excluded); Sunday start: begin on the first Sunday after period; combined oral contraceptives approved for acne: ethinyl estradiol 20/30/35 mcg/norethindrone 1 mg, ethinyl estradiol 35 mcg/norgestimate 180/215/250 mcg, and ethinyl estradiol 20 mcg/drospirenone 3 mg
Contraindications	Pregnancy, age >35 years and smoking >15 cigarettes/d, multiple risk factors for coronary artery disease, hypertension (>160 mmHg systolic or >100 mmHg diastolic), venous thromboembolism, known thrombogenic mutations, history of stroke, complicated valvular heart disease, systemic lupus erythematosus, migraine with aura at any age, breast cancer, cirrhosis, hepatocellular adenoma or malignant hepatoma, renal insufficiency or hepatic dysfunction for drospirenone-containing combined oral contraceptives
Side effects	Breakthrough bleeding, nausea, breast tenderness, increased risk for thromboembolic events (attributable risk low), increased risk for breast cancer (decreased risk for gynecologic malignancies overall)
Monitoring	Blood pressure, routine gynecologic screening
Pregnancy category	X
Nursing	Compatible with breastfeeding (American Academy of Pediatrics)

cancer, and ovarian cancer. Overall, COCs are associated with a net decrease in cancer risk, including a 29% decreased risk for gynecologic malignancies.^{89,90}

Because drospirenone-containing COCs have a mild potassium-sparing diuretic effect, there have been concerns about hyperkalemia with these agents. However, in multiple, large retrospective cohort studies, no increased risk was found for hyperkalemia among patients prescribed a drospirenone-containing COC compared with those prescribed other COCs.^{60,91,92} In addition, a retrospective study of 5752 patients taking both spironolactone and drospirenone-containing COCs concomitantly, no significant increased risk for hyperkalemia was found.⁶⁰

ISOTRETINOIN

Isotretinoin is typically started at 0.5 mg/kg/d and uptitrated to 1 mg/kg/d as tolerated (Table IV).¹⁹ Several alternative dosing approaches have also been proposed. Compared with higher dose regimens, low-dose isotretinoin (eg, 0.2-0.4 mg/kg/d) has been demonstrated to have similar effectiveness and reduced side effects, although these studies have been in patients with mild-to-moderate acne with limited follow-up.⁹³⁻⁹⁶ There is evidence that higher cumulative doses of isotretinoin are associated with decreased rates of relapse. In a prospective study of 180 patients with severe acne, the relapse rate at 1 year was 26.6% among those who received >220 mg/kg cumulative dose and 43.8% among those treated with lower doses.⁹⁷ In addition, there

have been suggestions that continuing treatment for at least 2 months after achieving no evidence of activity results in a decreased frequency of relapse.^{95,98}

Although isotretinoin is the only acne medication that alters the course of the disease, many patients will have some degree of relapse after discontinuation of treatment, with most relapses occurring within the first 3 years.⁹⁹⁻¹⁰¹ Younger age at initial treatment and male sex are associated with an increased risk for relapse, with those <16 years of age having approximately a 25% increased rate of relapse.¹⁰¹ In 1 cohort study, among those <16 years of age treated with a course of 120-150 mg/kg of isotretinoin, nearly 80% of patients required a second course of therapy within 2 years after completing the first course of isotretinoin.¹⁰²

Adverse effects and monitoring

Almost all patients treated with isotretinoin will experience mucocutaneous dryness, which can typically be managed with liberal emollient use or topical steroids (if needed).¹⁰³⁻¹⁰⁵ Xerophthalmia, conjunctivitis, and other ocular complications are occasionally observed; patients with conditions that can impair corneal wetting (eg, contact lenses) should be counseled about these potential side effects, and primary prevention with ocular lubricants should be considered.¹⁰³⁻¹⁰⁷ In a randomized trial of 118 patients, it was found that 1 g/d omega-3 reduces mucocutaneous side effects from isotretinoin.¹⁰⁸ Myalgias can be reported in up to a quarter of patients receiving high-dose isotretinoin. Importantly, these myalgias

Table IV. Suggested dosing, contraindications, side effects, monitoring, and pregnancy and lactation information for isotretinoin

Category	Description
Dosing	0.2-1.0 mg/kg/d, typically starting at 40 mg/d if more mild-to-moderate facial disease and 20 mg/d if severe truncal disease to help avoid flares; increase dose monthly as patient tolerates side effects
Contraindications	Pregnancy, prior hypersensitivity reaction
Side effects	Cheilitis, epistaxis, ocular complaints, photosensitivity, muscle aches, skin fragility, fatigue, mood changes, periungual granulomas, increased triglycerides, liver abnormalities
Monitoring	Pregnancy testing every 30 d (for women), liver function testing and triglycerides at baseline and at 2 months if no other clinical reasons. Consider more frequent monitoring with dose changes and in those at risk for complications. Routine complete blood count monitoring is unwarranted. Engage patient's family or friends to assist patient in monitoring for depression.
Pregnancy category	X, patients must be enrolled in iPLEDGE
Nursing	Not yet determined

are not associated with decreases in muscle strength or performance.^{103,104,109}

Retinoid embryopathy is a serious and well-documented complication of systemic retinoid exposure during pregnancy, and patients must be enrolled in the iPLEDGE program during treatment.¹¹⁰

Although some early reports suggested there might be an association between isotretinoin use and the development of inflammatory bowel disease, subsequent studies controlling for potential confounders, such as oral antibiotic use, and a recent meta-analysis of 6 prior studies have not confirmed such a risk.¹¹¹⁻¹¹⁶ The relationship between depression and the use of isotretinoin is uncertain. In a recent meta-analysis, no association was found between isotretinoin and an increased risk for depression, and depressive symptoms overall are decreased after treatment.¹¹⁷⁻¹¹⁹ However, there are reports of patients who experience mood changes during treatment with positive dechallenge and rechallenge responses.^{120,121} Although isotretinoin is associated with improved mood for the majority of patients as their acne improves, it is sensible to educate the patient and family about depression and to monitor for concerning symptoms during treatment.

Recent evidence suggests that routine monitoring of complete blood count is unwarranted.^{122,123} Mild increases in triglycerides are observed in about a quarter of patients treated with isotretinoin, but severe abnormalities are infrequent and subsequent changes to lipid levels are uncommon once a stable dose has been achieved. A reasonable approach is to check triglycerides and liver enzymes at baseline and 2 months into treatment, with more frequent monitoring with dose changes or as otherwise clinically indicated.^{123,124}

With respect to the timing of procedural interventions, insufficient evidence to support delaying procedures other than mechanical dermabrasion and fully ablative laser treatments was found in a recent systematic review.¹²⁵

EMERGING TOPICAL THERAPIES

Topical retinoids, benzoyl peroxide, and topical antibiotics have been a mainstay of the topical management of acne for decades. Novel Food and Drug Administration–approved topical therapies for acne are needed.^{19,126} Topical medications aiming to suppress sebum production are an emerging approach.¹²⁷ The enzyme stearoyl coenzyme A desaturase 1 (SCD1) is a potential target for reducing sebum production. Inhibition of SCD1 has been shown to reduce the synthesis of monounsaturated fatty acids and the number of sebaceous glands in mouse skin. Several clinical trials of topical formulations of SCD1 are ongoing. Melanocortin peptide α melanocyte–stimulating hormone has demonstrated a sebostrophic effect in mice, and an α melanocyte–stimulating hormone mimetic compound is being tested in patients with acne in a phase 2 study.^{127,128}

Nitric oxide–releasing particles are under investigation due to their potential to suppress the release of multiple cytokines from human monocytes and keratinocytes and to prevent *C. acnes* induced inflammation.¹²⁹ In two phase 2 studies of the topical nitric oxide–releasing drug SB204, the drug significantly reduced noninflammatory and inflammatory lesion counts in patients with mild, moderate, and severe acne compared with vehicle alone.^{128,130,131}

Last, in a phase 2 study, an anti-androgen cream (cortexolone 17 α -propionate 1%) was found to improve total and inflammatory lesions counts

compared with placebo after 8 weeks of therapy.¹³² Phase 3 studies are ongoing.¹²⁸

LASER AND LIGHT-BASED THERAPIES

Photodynamic therapy

Photodynamic therapy (PDT) is an off-label treatment for acne that involves first applying 5-aminolevulinic acid or methyl aminolevulinate to the skin, each of which are preferentially absorbed by the pilosebaceous unit.¹³⁵ Blue light, red light, pulse dye laser (PDL), or intense pulsed light (IPL) is then used to activate the topical agent to produce photosensitizing porphyrins, which generate free radicals and reactive oxygen species that damage sebaceous glands and result in the destruction of *C. acnes*.^{134,135}

In a recent randomized trial evaluating 46 patients treated with either 5-aminolevulinic acid–PDT followed by adapalene 0.1% gel or oral doxycycline 100 mg/d plus adapalene gel, a greater reduction of inflammatory and total lesion counts was found in the PDT group at 12 weeks.¹³⁶ However, additional high-quality trials are needed because most studies of PDT are small, unblinded, and observational with varying treatment protocols.^{19,137}

Other light-based and laser treatments

Because photoexciting porphyrins produced by *C. acnes* can release singlet oxygen species that kill bacteria, devices that emit blue or red light (including at-home light-emitting diode–based devices) have been explored as therapeutic modalities, although the quality of evidence is low to support their efficacy.^{133,134,138–141} IPL has been explored due to its potential to destroy *C. acnes* and induce thermolysis of blood vessels supplying the sebaceous glands, thereby reducing sebum production.^{142,143} In several small trials assessing the utility of IPL in acne, it was concluded that IPL (alone or in combination with photopneumatic therapy) might be effective in reducing acne.^{144–146} A number of limited studies have supported the efficacy of PDL for treating acne.^{147–152} As PDL preferentially targets oxyhemoglobin and induces photothermolysis of blood vessels, some believe it should be particularly effective in treating inflammatory acne lesions.¹⁵³ Several studies have found the 1450-nm diode laser can improve acne, and it has been shown to cause sebaceous gland destruction in a rabbit ear model and in ex vivo human skin.^{154–159}

To improve efficacy and reduce side effects of laser-based treatments, attempts have been made to concentrate the thermal injury to the sebaceous glands while sparing surrounding structures using gold-coated silica and silver microparticles. Although a gold-coated silica microparticle

suspension is currently marketed in Europe, it is not available in the United States, and in two recent trials of a topical silver photoparticle compound in conjunction with 810-nm and 1064-nm lasers, the primary efficacy endpoints were not achieved.^{160,161}

DIET AND ACNE

Glycemic index

Because high glycemic load diets (HGLDs) might increase levels of insulin-like growth factor 1 (IGF-1) activity and activation, thereby inducing proliferation of both keratinocytes and sebocytes as well as stimulating androgen production, some have proposed that HGLDs might be pathogenic in acne.^{162–169} In observational studies, conflicting results were found regarding the influence of HGLD and acne.^{170–177} Although individual randomized trials have found that a low glycemic load diet (LGLD) decreases sebum production and reduces acne lesion counts compared with HGLD, in a 2015 Cochrane review insufficient evidence to support LGLD for the management of acne was found.^{178–182} Additional evidence is needed regarding the impact of LGLD on acne; however, given the low risk and potential health benefits of LGLD (many of the patients in the above trials also experienced weight loss), we feel the practitioner should consider recommending LGLDs as a helpful adjuvant for the treatment of acne.

Milk

Milk consumption, like HGLDs, has been suggested to play a potential role in the pathogenesis of acne by increasing insulin and IGF-1 levels.¹⁶⁴ In addition, it has been noted that milk contains bovine IGF-1, which is able to bind to the human IGF-1 receptor and contains dihydrotestosterone precursors including placenta-derived progesterone, 5 α -pregnanedione, and 5 α -androstanedione that might promote acne.^{166,183,184}

Results from several retrospective and prospective observational studies have suggested a potential association between dairy consumption and acne.^{185–187} In a recent meta-analysis of 14 observational studies, a positive relationship between acne and total milk, low-fat milk, and skim milk intake was found.¹⁸⁸ This relationship was stronger with low-fat milk and skim milk than whole milk. It has been suggested that the fat-reducing process could enhance the insulin and IGF-1-promoting elements of milk.

Last, given that whey protein constitutes 20% of protein in cow's milk, its insulin-promoting component could help to explain the possible link between milk and acne.^{164,166,189} A case report of 5 men who developed acne in the setting of whey protein

supplement consumption that improved upon discontinuation of the supplement supports this potential association.¹⁸⁹ Of note, a liter of milk contains only ~6 g of whey protein, whereas bodybuilders potentially consume 40–80 g of whey daily (equivalent of 6–12 L of milk).¹⁹⁰ Given how commonly whey protein is used as a nutritional supplement, it is an important exacerbating factor to consider in those with acne. We recommend screening for whey protein supplements and stopping them when acne occurs in those consuming it.

CONCLUSIONS

Although oral antibiotics are the most frequently prescribed agent for moderate-to-severe acne, their use can be associated with a variety of adverse effects, and multiple guidelines recommend limiting their use. Emerging topical therapies, laser and light-based modalities, dietary modification, spironolactone, COCs, and isotretinoin can all be effective therapeutic alternatives in the appropriate clinical context. Careful consideration of these options is an important opportunity to improve antibiotic stewardship and outcomes in patients with acne.

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