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

John S. Barbieri, MD, MBA[#1], **Natalie Spaccarelli, MD**[#1], **David J. Margolis, MD, PhD**[1,2], and **William D. James, MD**[1]

[1)]Department of Dermatology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, 19104, USA

[2)]Department of Biostatistics and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, 19104, USA

[#] These authors contributed equally to this work.

Abstract

Acne is one of the most common diseases worldwide and affects approximately 50 million individuals in the United States. Oral antibiotics are the most common systemic agent prescribed for the treatment of acne. However, their use may 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.

Antibiotic resistance is a growing problem across medicine and rates of antibiotic resistance among isolates of *Cutibacterium* (formerly *Propionibacterium*) *acnes* have been rising, including to tetracycline-class antibiotics.[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 may also be associated with inflammatory bowel disease and collagen vascular disease.[7–16] Finally, there may be an association between the use of oral tetracycline-class antibiotics and risk of breast and colon cancer.[17,18] As a result, there have

Corresponding author: John Barbieri, 2 Maloney, 3600 Spruce Street, Philadelphia, PA 19104, USA, Phone: 215-662-2737; Fax: 215-349-8839, john.barbieri@uphs.upenn.edu.

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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 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 impact on sebum production through inhibition of the androgen receptor on sebocytes, spironolactone has been used off-label in the treatment of acne for over 30 years.[36–44] It is also may reduce synthesis of androgen precursors in the adrenal glands.[45,46]

While a 2009 Cochrane review found 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 1).[47–54] Although use of spironolactone has increased substantially in recent years, oral antibiotics are still prescribed three to five times more frequently among women with acne.[27] As a result, increased use of spironolactone may represent an opportunity to improve antimicrobial stewardship and outcomes in patients with acne. Finally, it is important to note that spironolactone may 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 100mg/day in the evening (Table 2).[35] Doses up to 200mg/day 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% CI 3.27-5.19) in women receiving a dose of 200mg/day compared to those receiving lower doses. The concomitant use of a COC or 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.

Since spironolactone is a potassium-sparing diuretic, hyperkalemia is a potential complication, which has been observed at high-doses in patients with renal insufficiency or

severe heart failure.[58] However, in young healthy women being treated for acne who do not have heart disease, hypertension, or renal disease, and who are not taking potentially interacting medications such as angiotensin converting enzyme inhibitors, there is no evidence of increased rates of hyperkalemia when compared to 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] As a result, 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 using doses over 100 times greater than those used in clinical practice, spironolactone has a black box warning recommending against off-label and unnecessary use of spironolactone.[58] However, several large cohort studies with over 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 or 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

Combined oral contraceptives (COCs, Table 3) containing estrogen and progestin 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.

A Cochrane review supports the effectiveness of all COCs for the treatment of acne in women and a few preparations have been approved specifically for acne.[35,67–70] Trials comparing drospirenone containing COCs to other COCs have generally favored the drospirenone containing COC.[70–75] In contrast, progestin only contraceptives and long-acting reversible contraceptives are associated with worsening of acne.[75] A course of three to six 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. While the risk of venous thromboembolism in reproductive age non-COC users is approximately 2 per 10,000 person years, this rate increases to approximately 6 per 10,000 person years for those on COCs and to approximately 9 per 10,000 person years for drospirenone containing COCs.[78,79] Due to 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 of venous

thromboembolism is higher with pregnancy than COC use.[79] Similarly, the attributable risk for cardiovascular events (approximately 2 per 10,000 person-years) and ischemic stroke (approximately 1 per 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]

While 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 of colon cancer, uterine cancer, and ovarian cancer. Overall, COCs are associated with a net decrease in cancer risk, including a 29% decreased risk of gynecologic malignancies.[89,90]

Since drospirenone containing COCs have a mild potassium-sparing diuretic effect, there have been concerns about hyperkalemia with these agents. However, multiple, large retrospective cohort studies of patients prescribed a drospirenone containing COC have found no increased risk of hyperkalemia compared to patients prescribed other COCs.[60,91,92] In addition, a retrospective study of 5,752 patients taking both spironolactone and drospirenone containing COCs concomitantly found no significant increased risk for hyperkalemia.[60]

ISOTRETINOIN

Isotretinoin is typically started at 0.5mg/kg/day and uptitrated to 1mg/kg/day as tolerated (Table 4).[19]Several alternative dosing approaches have also been proposed. Low dose isotretinoin (e.g. 0.2 to 0.4mg/kg/day) has been demonstrated to have similar effectiveness and reduced side-effects when compared to higher dose regimens, 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. A prospective study of 180 patients with severe acne found that the relapse rate at 1 year was 26.6% among those who received >220mg/kg cumulative dose compared to 43.8% among those treated with lower doses.[97] In addition, there have been suggestions that continuing treatment for at least two months after achieving no evidence of activity results in a decreased frequency of relapse.[95,98]

While isotretinoin is the only acne medication that alters the course of the disease, many patients will have some degree of relapse following discontinuation of treatment, with most relapses occurring within the first 3 years.[99–101] Younger age at initial treatment and male gender are associated with an increased risk of relapse, with those under 16 years of age having approximately a 25% increased rate of relapse.[101] One cohort study found that among those under 16 years of age treated with a course of 120-150mg/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] Xeropthalmia, conjunctivitis, and other ocular complications can occasionally be observed; patients with conditions that can impair corneal wetting (e.g. contact lenses) should be

counseled about these potential side-effects and primary prevention with ocular lubricants should be considered.[103–107] A randomized trial of 118 patients found omega-3 1g/day 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 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]

While some early reports suggested there may 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 six prior studies have not confirmed such a risk.[111–116] The relationship between depression and the use of isotretinoin is uncertain. A recent meta-analysis found no association between isotretinoin and increased risk of depression and depressive symptoms overall are decreased following treatment.[117–119] However, there are reports of patients who experience mood changes during treatment with positive dechallenge and rechallenge responses.[120,121] While 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 two 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, a recent systematic review found insufficient evidence to support delaying procedures other than mechanical dermabrasion and fully ablative laser treatments.[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 (FDA) approved topical therapies for acne are needed.[19,126] Topical medications aiming to suppress sebum production are one emerging approach.[127] The enzyme stearoyl-CoA 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 (α-MSH) has demonstrated a sebotrophic effect in mice and an α-MSH mimetic compound is being tested in subjects with acne in a phase 2 study.[127,128]

Nitiric-oxide (NO) 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] Two phase 2 studies of the topical NO-releasing drug SB204 found that it significantly reduced non-inflammatory and inflammatory lesion counts in patients with mild, moderate, and severe acne compared to vehicle alone.[128,130,131]

Finally, a phase 2 study of the anti-androgen cream (cortexolone 17α-propionate 1%) found improved total and inflammatory lesions counts compared to 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 (ALA) or methyl aminolevulinate (MAL) to the skin, each of which are preferentially absorbed by the pilosebaceous unit.[133] Blue light, red light, pulse dye laser (PDL), or intense pulsed light 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]

A recent randomized trial evaluating 46 patients treated with either ALA-PDT followed by adapalene 0.1% gel or oral doxycycline 100 mg/daily plus adapalene gel found a greater reduction of inflammatory and total lesion counts in the PDT group at 12 weeks.[136] However, additional high-quality trials are needed, since most studies of PDT are small, unblinded, and observational with varying treatment protocols.[19,137]

Other light-based and laser treatments

Since photoexciting porphyrins produced by *C. acnes* could release singlet oxygen species that kill bacteria, devices that emit blue and/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] Intense pulsed light (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] Several small trials assessing the utility of IPL in acne have concluded that IPL (alone or in combination with photopneumatic therapy) may be effective in reducing acne.[144–146] A number of limited studies have supported the efficacy of the pulsed dye laser (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. While a gold-coated silica microparticle suspension is currently marketed in Europe, it is not available in the United

States and two recent trials of a topical silver photoparticle compound in conjunction with 810 nm and 1064 nm lasers did not achieve the primary efficacy endpoints.[160,161]

DIET AND ACNE

Glycemic index

Since high glycemic-load diets (HGLDs) may increase levels of insulin-like growth factor 1 (IGF-1) activity and activation, thereby inducing proliferation of both keratinocytes and sebocytes as well as simulating androgen production, some have proposed that HGLDs might be pathogenic in acne.[162–169] Observational studies have found conflicting results regarding the influence of HGLD and acne.[170–177] While individual randomized trials have found that a low glycemic-load diet (LGLD) decreases sebum production and reduces acne lesion counts compared to HGLD, a 2015 Cochrane review found insufficient evidence to support LGLD for the management of acne.[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, 5α-pregnanedione, and 5α-androstanedione that may promote acne.[166,183,184]

Several retrospective and prospective observational studies have suggested a potential association between dairy consumption and acne.[185–187] A recent meta-analysis of 14 observational studies found a positive relationship between acne and total milk, low-fat milk, and skim milk intake.[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.

Finally, 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 about 6g of whey protein, whereas bodybuilders may consume 40-80g of whey daily (equivalent of 6-12 liters 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, combined oral contraceptives, 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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Table 1:

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 100mg/day showed initial improvement, with 40% clearing completely. An additional 32 patients improved or cleared by increasing the dose to 150mg/day and another 13 improved or cleared at 200mg/day.
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 duration for women who received either a combined oral contraceptive or spironolactone was 83.4 fewer days than for 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 may have similar clinical effectiveness to oral antibiotics for women with acne.

Table 2:

Suggested dosing, contraindications, side-effects, monitoring, and pregnancy and lactation information for spironolactone

Dosing	**25-200mg daily, typically starting 100mg daily in the evening**
Contraindications	Significant renal impairment, hyperkalemia (or medications known to increase serum potassium such as trimethoprim or ACE 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

Table 3:

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

Dosing	Quick start (preferred): Begin on the day given prescription (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 per day, multiple risk factors for CAD, hypertension (>160mmHg systolic or >100mmHg diastolic), VTE, 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 of thromboembolic events (attributable risk low), increased risk of breast cancer (decreased risk of gynecologic malignancies overall)
Monitoring	Blood pressure, routine gynecologic screening
Pregnancy category	X
Nursing	Compatible with breastfeeding (American Academy of Pediatrics)

Table 4:

Suggested dosing, contraindications, side-effects, monitoring, and pregnancy and lactation information for isotretinoin

Dosing	0.2-1.0mg/kg/day, typically starting at 40mg/day if more mild to moderate facial disease. Starting at 20mg/day if severe truncal disease may avoid flares. Increase the dose monthly as patient tolerates with respect to side-effects.
Contraindications	Pregnancy, prior hypersensitivity reaction.
Side-effects	Chelitis, epistaxis, ocular complaints, photosensitivity, muscle aches, skin fragility, fatigue, mood changes, periungual granulomas, increased triglycerides, liver abnormalities.
Monitoring	Pregnancy testing every 30 days (for women). Liver function testing and triglycerides at baseline and at 2 months if no other clinical reasons. More frequent monitoring should be considered with dose changes and in those at risk of complications. Routine CBC 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