Principles of Oral Acne Therapy

Systemic antibiotics still play a key role in the care of many acne patients. Proper prescribing, patient education, and effective use of adjunctive topical therapy ensure good outcomes.

By Joseph Bikowski, MD

Topical acne therapy is appropriate for the management of mild to moderate acne vulgaris and is indicated as monotherapy or adjunctive therapy for the vast majority of patients affected by the disease. Topical treatment is generally effective and well-tolerated. Given the variety of formulations that exist, treatment can be matched to the patient's presentation, skin type, and lifestyle. Nonetheless, oral acne therapy is as relevant as ever, and systemic antibiotics continue to play a key role in the care of many patients in the pediatrician's or the dermatologist's office. Patients with moderate acne that does not adequately respond to topical therapy, who have a history of recurrence, or who have a significant inflammatory component to acne may be candidates for systemic therapy. Oral antibiotics are also beneficial for truncal acne when topical interventions present a treatment challenge, due to difficulties in application. Systemic antibiotics confer general anti-inflammatory effects and act specifically to reduce Propionibacterium acnes. Treatment success requires proper prescribing, patient education, and the effective use of adjunctive topical therapy.

Understanding Oral Acne Therapy

In efforts to diminish dependence on oral antibiotics and thus limit risk of developing resistance, the latest guidelines in acne management emphasize topical antimicrobials and retinoids as well as shortened courses of systemic antibiotics. As such, the guiding principle of oral antibiotic therapy for acne is to always accompany systemic agents with a topical benzoyl peroxide-containing product and possibly a retinoid. This strategy is shown to reduce the development of bacterial resistance, a growing concern across all areas of medicine. A topical retinoid is of primary value in acne management, as retinoids primarily function to regulate hyperkeratinization, preventing the formation of microcomedones and encouraging resolution of clinically apparent comedones. They also confer anti-inflammatory effects, i.e. reducing and preventing erythematous papules and pustules.

The Problem of Resistance. The dermatology community has been aware of the risks of antibiotic resistance since the 1980s, when the first documented reports of P. acnes resistance to antibiotics emerged. Subsequent studies documented the phenomenon of subsequent studies documented the phenomenon of

Take-Home Tips. Patients with moderate acne that does not adequately respond to topical therapy, who have a history of recurrence, or who have a significant inflammatory component to acne may be candidates for systemic therapy. Oral antibiotics are also beneficial for truncal acne when topical interventions present a treatment challenge, due to difficulties in application. Systemic antibiotics confer general anti-inflammatory effects and reduce Propionibacterium acnes. Treatment success requires proper prescribing, patient education, and the effective use of adjunctive topical therapy; benzoyl peroxide is indicated every time a patient is treated with oral antibiotics for acne.
antibiotic resistant acne and resultant treatment failure. Studies have found *P. acnes* resistance rates as high as 60 percent in some patient populations.

Among acne patients, development of resistance is not limited to *P. acnes*. Researchers have identified resistant strains of *Staphylococcus epidermidis* among acne patients treated with oral erythromycin and shown that systemic antibiotic therapy is associated with *Streptococcus pyogenes* colonization and resistance in the oropharynx.

MRSA (Methicillin-resistant *Staphylococcus aureus*) is, of course, an issue of concern that has increased public awareness of resistance risks. Concern about long-term antibiotic use and subsequent resistance risk is especially high in light of the increase in reports of community-acquired MRSA skin and soft-tissue infections. Price, et al. report that MRSA accounted for just 1.5 percent of all strains of *S. aureus* at select dermatology outpatient clinics in 1988. A decade later at these same clinics, 11.9 percent of all *S. aureus* strains were Methicillin-resistant.

**Mechanisms of Action.** Despite these valid concerns, the judicious use of systemic antibiotics for acne vulgaris continues. Both doxycycline and minocycline have anti-*P. acnes* action and are considered first-line systemic antibiotic therapy for moderate to severe presentations. However, the utility of oral antibiotics in acne care extends beyond *P. acnes* reduction. In fact, there is growing consensus that “antibiotic” is something of a misnomer; it refers to one of several activities of these molecules but does not accurately define the class.

A molecule may have more than one activity. While there is a tendency to rank those activities as primary or secondary mechanisms of action, such categorization is not always accurate. It should be noted that about a decade after Fleming’s discovery of penicillin, “antibiotic” was adopted in use as a noun to describe agents under investigation for their ability to inhibit bacterial growth in culture (see sidebar).

We have since learned that the designation of “antibiotic” overlooks important characteristic of this class of drugs. Molecules in this class have long been recognized for conferring anti-inflammatory effects, which have been under clinical investigation for at least three decades. One method to isolate the anti-inflammatory effects of tetracyclines is through modification of the molecule so that the dimethylamino group from carbon-4 position (the side-chain required for antimicrobial activity) is removed. These chemically modified tetracycline (CMT) analogues have current or investigational uses in disease like periodontitis, arthritis, osteoporosis, and cancer. CMT analogues reduce inflammatory enzymes and lead to decreased expression of cytokines, including TNF, IL-1, and IL-6.

Another approach to isolate the anti-inflammatory action of tetracyclines is through the administration of sub-antimicrobial or sub-minimal inhibitory concentration (sub-MIC) doses; plasma levels of drug are not sufficient to affect bacteria. Sub-MIC doses of tetracycline, declomycin and erythromycin all inhibited levels of inflammatory by-products of *P. acnes*. Subsequent in vitro investigations have shown similar
reductions in levels of inflammatory by-products and expression of inflammatory mediators associated with P. acnes\textsuperscript{27,28} P. granulosum and coagulase-negative staphylococcus (CNS).\textsuperscript{28}

Studies have shown that minocycline has roughly 12-times the anti-inflammatory effect of tetracycline, and doxycycline has 33-times the effect.\textsuperscript{23}

**Treatment Selection**

Minocycline and doxycycline are first-line oral antibiotics for the treatment of acne vulgaris. Both agents are generally considered safe with a low rate of significant adverse events. Nonetheless, a risk for certain well-known side effects exists. A review of case reports published between 1966 and 2003 found a somewhat lower rate of adverse events with doxycycline than with minocycline,\textsuperscript{29} although proper patient evaluation, treatment selection, patient education, and monitoring should minimize risks associated with the use of either agent by adolescents.

A newer, extended-release minocycline formulation (Solodyn, Medicis) has been shown to significantly reduce inflammatory acne lesions while decreasing the rate of dose-dependent acute vestibular adverse events associated with minocycline.\textsuperscript{30} A slow-release formulation featuring enteric-coated doxycycline hyclate pellets encased in capsules (Doryx, Warner-Chilcott) is associated with significantly less nausea, vomiting, and abdominal discomfort compared to uncoated doxycycline hyclate powder encased in capsules.\textsuperscript{31,32} Of note, these tablets can be broken and even crushed and sprinkled over applesauce without impeding the slow-release mechanism.\textsuperscript{33} (To learn more about these formulations and the risks and benefits of oral antibiotic formulations, see the supplement to this edition of Practical Dermatology for Pediatrics.)

The selection of an adjunctive topical antimicrobial and retinoid depends on the prescriber’s preference, the patient’s presentation, and the likelihood of adherence. Generally, a combination benzoyl peroxide/clindamycin fixed combination formulation is prescribed for application each morning, while topical tretinoin, adapalene, or tazarotene will be prescribed for nighttime application. If a once-a-day regimen is desired, fixed combination formulations of clindamycin/tretinoin (Veltin, Stiefel/GlaxoSmithKline or Ziana, Medicis) or benzoyl peroxide/adapalene (EpiDuo, Galderma) are available. For more on topical therapy selection, please see the May/June issue of Practical Dermatology for Pediatrics online at PracticalDermatologyPeds.com).

Typically, a six- to 12-week course of oral antibiotics will provide notable clearing of acne. Lack of response to a three-month trial may indicate a misdiagnosis, a lack of therapeutic adherence, or the need for alternative therapy, such as isotretinoin. It is important to educate patients about proper administration of oral antibiotics, including the need to take all of their medication.

Educating patients about the rationale for topical therapy is also important. Because many patients will have unsuccessfully self-treated with an OTC topical therapy, there may be a false perception that prescription-only oral therapy is somehow superior to a topical agent, even a prescription-only one. Others may assume it is unnecessary and not cost-effective to apply a topical antimicrobial and/or retinoid (tretinoin, adapalene, or tazarotene) along with an oral antibiotic. Simply explain to the patient that the combination approach

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<th>Table 2. Acne Therapies and Their Actions</th>
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will reduce the long-term need for oral medication (and associated treatment costs). Discuss how the topical retinoid provides a different mechanism of action than the antimicrobials. Finally, acknowledge that the patient should develop the habit of applying topical therapy now because it will become the basis for long-term maintenance.

Preserving an Important Treatment Option

Despite the efficacy of topical acne therapies, many patients have moderate to severe acne that requires treatment with oral antibiotics. In order to preserve the continued efficacy of these agents and ensure the short- and long-term health of patients, prescribers must use oral antibiotics judiciously. Adjunctive topical therapy with benzoyl peroxide is indicated every time a patient is treated with oral antibiotics for acne.

Data suggest that clinicians are already changing their prescribing habits for acne due to concerns about resistance. Investigators examined the National Ambulatory Medical Care Survey database for acne patients and noted declines in the use of erythromycin and isotretinoin for acne by all physicians and increases in tetracyclines and BPO/clindamycin combination topical treatments. However, while topical retinoid use increased among dermatologists, it appeared to be on the decline among non-dermatologists. Topical retinoids target several key steps in the pathogenesis of acne and are appropriate for the vast majority of—if not all—acne patients. They are excellent, rational adjutants to topical and/or oral antimicrobials.

Dr. Bikowski has served on the speaker's bureau or advisory board or is a shareholder or consultant to Allergan, Coria, Galderma, Stiefel/GlaxoSmithKline, Intendis, Medicis, Promius, Quinova, Ranbaxy, and Warner-Chilcott. 1. Ochsendorf F. Systemic antibiotic therapy of acne vulgaris. J Dtsch Dermatol Ges. 2006;4:828-839.


