

A SUPPLEMENT TO

Skin & Allergy News®

# CHANGING THE FACE OF ROSACEA MANAGEMENT



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● **Emerging Concepts in Rosacea  
Etiology, Pathophysiology,  
and Diagnosis**

● **Do Antibiotics Still Have a Role  
in Rosacea?**

● **Treating the Many Faces  
of Rosacea: A Systematic  
Approach to Developing  
Individualized Regimens**



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# CHANGING THE FACE OF ROSACEA MANAGEMENT

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## TARGET AUDIENCE

This activity has been developed for dermatologists and other health care practitioners who manage patients with the signs and symptoms of rosacea.

## EDUCATIONAL NEEDS

Rosacea, which affects approximately 14 million Americans, is a dermatosis of the central part of the face that is characterized by abnormalities in the cutaneous microcirculation. The resulting clinical signs may include persistent erythema, telangiectases, papules and pustules, and ocular involvement. The underlying etiology is unknown, but the failure to demonstrate the presence of pathogens on the skin, and histopathologic findings such as perivascular and follicular leukocytic infiltrates support an inflammatory rather than an infectious process. The appearance of patients with rosacea may be severely affected, resulting in problems with interpersonal interactions and occupational difficulties. Research efforts regarding etiology and treatment options have yielded a significant body of information in the recent medical literature. Among the treatment options that will be discussed are topical agents (metronidazole, sodium sulfacetamide/sulfur, and azelaic acid, as well as some medications that are used which have not been approved by the US Food and Drug Administration), oral medications (including tetracyclines, macrolides, metronidazole, and isotretinoin), and laser and light therapies. This supplement addresses this information in a succinct presentation that will bring practitioners up to date on the most clinically relevant aspects of this topic.

## LEARNING OBJECTIVES

After reading and studying this supplement, participants should be able to:

- describe the epidemiology, natural history, and diagnosis of rosacea.
- discuss the most recent research findings regarding the etiology of rosacea.
- explain the growing public health concerns associated with the use of oral antibiotics, the traditional treatment for rosacea.
- discuss topical and oral treatment options for rosacea and the patient selection factors that should be considered in choosing a regimen.

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## INTRODUCTION

**D**ermatologists commonly see patients with rosacea—an estimated 14 million individuals in the United States have the condition. Although rosacea certainly is not a life-threatening disease, it very often adversely affects quality of life. Patients with rosacea typically are self-conscious about their appearance. Often they must contend with papules and pustules, lesions they thought they had left behind after adolescence. Facial erythema is just as problematic, forcing patients to explain that they are not embarrassed by a conversation, do not suffer from uncontrolled hypertension, or did not stay in the sun too long. Ocular rosacea can look like an infectious eye disease. Phymatous changes can become severely disfiguring.

Highly effective strategies now are available that completely clear or dramatically improve acne-like lesions. In addition, triggers that exacerbate “flushing and blushing”—and which are avoidable—have been identified, cosmetics now are marketed that help patients (including those with sensitive skin) improve their appearance, and procedures such as laser and light modalities have been developed that are used successfully to treat facial erythema and resculpt the nose and other facial features affected by phymatous processes.

Our panel of experts offers updates on rosacea etiology and pathophysiology, as well as medical therapy and other management strategies, including laser and surgical procedures, that will help improve the comfort and quality of life of our patients who have this disease.

*Henry H. Roenigk, Jr., MD, Chair*



## EMERGING CONCEPTS IN ROSACEA ETIOLOGY, PATHOPHYSIOLOGY, AND DIAGNOSIS

*Diane S. Berson, MD*



**R**osacea is a common skin disease that affects both men and women of all skin types and all age groups; however, rosacea is most frequently seen in individuals with fair skin who are older than 30 years of age. An estimated 14 million Americans have the condition.<sup>1</sup> The most recent estimate of prevalence is based on a Swedish epidemiologic study published in 1989.<sup>2</sup> One possible reason for the lack of epidemiologic data concerns the difficulty, until recently, of defining the clinical parameters and features of rosacea, which has variable morphology and presentations.

### ETIOLOGY AND PATHOPHYSIOLOGY

No cause of rosacea has been established to date, although etiologic theories abound. Crawford and colleagues<sup>3</sup> note that the proposed causative mechanisms

can be grouped in the categories of vasculature, climatic exposures, matrix degeneration, chemicals and ingested agents, pilosebaceous unit abnormalities, and microbial organisms.

One of these categories, microbial organisms, probably can be eliminated. For many years, the mite species *Demodex* was considered the probable cause of rosacea. However, this presumption was proved incorrect when it became apparent that treatment to eliminate *Demodex sp* from the skin had no effect on rosacea signs and symptoms. Later, *Helicobacter pylori* was proposed as a possible cause, based on the observation that some individuals with gastric ulcers associated with *H. pylori* infection also had rosacea signs and symptoms.

To test the *H. pylori* hypothesis, Bamford and colleagues<sup>4</sup> conducted a 2-week, randomized, double-blind,

placebo-controlled trial of 44 patients with active rosacea who tested positive for *H. pylori* on both a rapid whole blood test and a urea breath test. The subjects were given either placebo or a treatment regimen consisting of clarithromycin (500 mg t.i.d.) plus omeprazole (40 mg once daily). Almost all of the patients showed improvement in rosacea by the end of the 2-week study period (although none were cured), and the difference between the active treatment and cohort groups was not statistically significant. The investigators concluded that the treatment for *H. pylori* infection had no effect on rosacea, and, therefore, this study did not support a causative link.

In all of the other categories, studies have neither proved nor disproved the proposed mechanisms. In fact, given the range of manifestations evident in the types of rosacea—

as described in the following section on diagnosis—it would not be unlikely that several etiologic mechanisms may be identified, and those mechanisms, alone or in combination, may be responsible for each of the rosacea subtypes.

Nevertheless, a factor that is common to most of the proposed etiologies is inflammation. Several authors, including Millikan,<sup>5</sup> have argued that the absence of causative microbial organisms plus some suggestive histopathologic findings support an inflammatory process—or processes—in rosacea. In addition, it has been demonstrated that the antibiotics—such as the tetracyclines—that have been clinically shown to be of benefit in controlling the primary signs of rosacea are agents that also suppress some inflammatory mediators that may be involved in the pathogenesis of this condition. These inflammatory mediators include tumor necrosis factor-alpha, interleukin (IL)-1, and IL-6, which, in turn, result in chemotaxis and activation of neutrophils. The neutrophils express nitric oxide, reactive oxygen species, and matrix metalloproteinases, products that are known to be involved in molecular and structural degradation of cutaneous cells and tissues.<sup>6</sup>

## DIAGNOSIS: GRADING AND CLASSIFYING ROSACEA

No laboratory tests—either histologic or serologic—have been developed to provide a definitive diagnosis of rosacea, so the diagnosis must be made clinically. To address the need for a standard method of classifying the types and grading the severity of rosacea, the National Rosacea Society (NRS) convened an Expert Committee on the Classification and Staging of Rosacea, which issued recommendations in 2002 for a standard classification system<sup>7</sup> and, in 2004, for a standard grading system.<sup>8</sup>

Most dermatologists recognize the features of rosacea (**Table 1**). Almost all of these affect the central face, primarily erythema, which may be

transient or persistent; non-comedonal papules and pustules; and/or telangiectases. Crawford and colleagues<sup>3</sup> propose that central facial erythema of at least 3 months' duration be considered the most important feature and the “sole requisite criterion for the diagnosis of rosacea.” They also propose that papules/pustules and telangiectases are “supportive characteristic findings, but not necessary for a diagnosis.”<sup>3</sup>

Other possible features include burning or stinging; plaques; the appearance of dryness; acute or chronic edema, which may or may not be pitting; ocular manifestations, which may include blepharitis, conjunctivitis, and watery, dry, or irritated eyes; phymatous changes, particularly on the nose (rhinophyma), but also seen on the chin, forehead, one or both ears, and/or the eyelids; and/or granulomatous changes.

**Table 1. Clinical Features of Rosacea**

### PRIMARY

- Erythema, transient (flushing)
- Erythema, nontransient (persistent)
- Papules and pustules
- Telangiectases

### SECONDARY

- Burning or stinging of facial skin
- Plaques (confluent areas of inflammation)
- Dry appearance
- Edema (acute or chronic; pitting or nonpitting)
- Ocular manifestations (see **Table 2**)
- Peripheral signs and symptoms (ie, not located on central face)
- Phymatous changes: rhinophyma (nose), gnatophyma (chin), metophyma (forehead), otophyma (one or both ears), eyelids (blepharophyma)

Source: Wilkin et al.<sup>8</sup> Used with permission.

The differential diagnosis includes a number of conditions that cause facial erythema or other signs that could be features of rosacea. The list includes—but is not limited to—polycythemia vera, seborrheic dermatitis, systemic lupus erythematosus or other connective tissue disease, acne vulgaris, lupus miliaris disseminatus faciei, basal cell carcinoma, and granulomatous eruptions such as granuloma faciale and sarcoid. Many of these conditions can be identified by the presence of systemic symptoms or cutaneous signs on areas other than the face.

The NRS Expert Committee noted that, until more is known about etiology and pathogenesis, morphologic features must suffice as the criteria by which diagnosis for clinical management can be made and as the standards for investigators to use in research so that results can be evaluated on the basis of comparable data. In grading rosacea, the NRS Expert Committee recommends that clinicians assess the primary features and secondary features (as shown in **Table 1**). Further details can be documented on each of the primary and secondary features, and suggestions for additional standardized scoring are offered in the NRS Expert Committee's paper published in 2004.<sup>8</sup> Such details are more likely to be useful to researchers rather than to clinicians.

Patient and clinician global assessments complete the evaluation. In the first assessment, patients are asked to rate the severity of their condition. The clinician's assessment is the determination of the subtype of rosacea, according to symptoms (**Table 2**)—subtype 1, erythemotelangiectatic; subtype 2, papulopustular; subtype 3, phymatous; or subtype 4, ocular. A patient may have symptoms of more than one subtype, so the assessment should note that each subtype is absent, mild, moderate, or severe.

The NRS offers “scorecards” to clinicians for documenting these assessments for patients' charts. The one-page form is available for downloading, free of charge, at the NRS web site: [www.rosacea.org](http://www.rosacea.org).

## CONCLUSION

Rosacea is a common and chronic skin disease that often is frustrating for patients to live with and challenging for clinicians to treat. Fortunately, strategies have been developed that can help prevent flares and manage outbreaks

when they occur. Future breakthroughs in therapy will depend on further elucidation of the etiology and pathogenesis of rosacea. Meanwhile, the classification and grading systems developed by Wilkin and colleagues of the NRS

Expert Committee on the Classification and Staging of Rosacea serve as an excellent system for guiding clinical management and providing a common language for researchers to use in developing studies and reporting data. ■

**Table 2. Rosacea Subtypes**

Subtype	Principal Characteristics	Comments
1. Erythemotelangiectatic rosacea	Includes: <ul style="list-style-type: none"> <li>• Flushing</li> <li>• Persistent erythema of the central face</li> <li>• Telangiectases (common)</li> </ul>	<ul style="list-style-type: none"> <li>• Telangiectases are not necessary for the diagnosis of rosacea</li> </ul>
2. Papulopustular rosacea	Includes: <ul style="list-style-type: none"> <li>• Persistent erythema of the central face</li> <li>• Transient papules, pustules, or both in central facial distribution</li> </ul>	<ul style="list-style-type: none"> <li>• Burning and stinging also may be reported</li> </ul>
3. Phymatous rosacea	May include: <ul style="list-style-type: none"> <li>• Thickening skin</li> <li>• Irregular surface nodularities</li> <li>• Enlargement of affected area(s): nose, chin, forehead, cheeks, ears</li> <li>• Patulous, expressive follicles in phymatous areas</li> <li>• Telangiectases</li> </ul>	
4. Ocular rosacea	May include: <ul style="list-style-type: none"> <li>• Watery or bloodshot appearance (interpalpebral conjunctival hyperemia)</li> <li>• Foreign-body sensation</li> <li>• Burning or stinging</li> <li>• Dryness</li> <li>• Itching</li> <li>• Light sensitivity</li> <li>• Blurred vision</li> <li>• Telangiectasia of conjunctiva and lid margin</li> <li>• Lid and periocular erythema</li> <li>• Blepharitis</li> <li>• Conjunctivitis</li> <li>• Irregularity of eyelid margins</li> <li>• Meibomian gland dysfunction (presenting as chalazia)</li> <li>• Chronic infection manifested by hordeola (styes)</li> </ul>	<ul style="list-style-type: none"> <li>• Loss of vision may occur in some patients as a result of corneal complications: punctate keratitis, corneal infiltrates, ulcers, or marginal keratitis</li> <li>• Meibomian gland dysfunction and styes are common</li> </ul>

Source: Wilkin et al.<sup>8</sup> Used with permission.

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# DO ANTIBIOTICS STILL HAVE A ROLE IN ROSACEA?

Hilary E. Baldwin, MD



**T**he symptoms of rosacea vary from minor to severe, across a range of presentations. Despite these variations, patients have in common the desire to be treated without delay and to have their facial symptoms resolve immediately and permanently.

Oral antibiotic therapy has been the mainstay for many years, although rosacea was not an indication approved by the US Food and Drug Administration (FDA). The use of antibiotics originally was based on the assumption that rosacea has an infectious etiology, a hypothesis that was supported by the observation that oral antibiotic therapy is often highly effective in controlling the signs and symptoms of this condition. Years of investigation have not resulted in a determination of the etiology or pathogenesis of rosacea, but there is a growing consensus that bacterial infection probably is not the cause.

Meanwhile, it has also been clinically observed and proposed that antibiotics—particularly tetracyclines—given for acne vulgaris and for rosacea seem to have anti-inflammatory properties. Indeed, research has shown that some antibiotics that have demonstrated efficacy in rosacea act to suppress some important inflammatory mediators that are thought to play a role in this condition.<sup>1,2</sup>

## CONSEQUENCES OF ANTIBIOTIC THERAPY FOR ROSACEA

The observed benefit of oral antibiotic treatment in patients with rosacea makes both clinicians and patients reluctant to exclude these agents from the list of therapeutic options or, in fact, to downgrade antibiotics from their first-line status. However, two major issues must be addressed. The first is the side effects associated with long-term

antibiotic use, and the second, which has the potential for both individual health and far-reaching public health consequences, concerns the emergence of resistant strains of bacteria.

**...research has shown that some antibiotics that have demonstrated efficacy in rosacea act to suppress some important inflammatory mediators that are thought to play a role in this condition.<sup>1,2</sup>**

The antibiotics most frequently used for the treatment of rosacea are those in the tetracycline class, especially minocycline and doxycycline. The widespread use of these agents, along with their decades-long track record of safety and efficacy, should not lead either clinicians or patients to underestimate these drugs. They are potent antimicrobial agents that are extremely effective in eradicating a range of bacterial pathogens and, at the same time, they have the potential for significant side effects.

### Side Effects

A common side effect of doxycycline treatment is gastrointestinal distress, and gastrointestinal ulcers are a risk. Minocycline has been associated with vertigo, hyperpigmentation, hypersensitivity syndromes, lupus-like reactions, and hepatitis. Photosensitivity may occur with any of the agents in this class, so patients must be cautioned to avoid sun exposure during treatment to prevent serious reactions. The tetracyclines also cause changes in normal bacteria microflora that can cause gram-negative folliculitis and *Candida* vaginitis.

### Antibiotic Resistance

The issue of antibiotic resistance is one that has caused increasing concern. In the dermatology literature, for example, reports abound concerning the

resistance of *Propionibacterium acnes* to erythromycin and the tetracyclines, including the emergence of resistance to minocycline.<sup>3</sup> Antimicrobial resistance and cross-resistance of dermatologic infectious organisms such as *P. acnes* has been growing and has worldwide implications.

As early as 1993, Eady and colleagues<sup>4</sup> noted the resistance of *P. acnes* to erythromycin in patients with acne vulgaris, and reported the development of erythromycin-resistant strains that were cross-resistant to clindamycin, as well as tetracycline-resistant strains that were cross-resistant to doxycycline. Other patients had strains of *P. acnes* that were resistant to trimethoprim, and a number of patients carried *P. acnes* strains that were resistant to two or more antibiotics. The investigators urged the development of policies to modify how antibiotics are used, including using topical agents whenever possible rather than oral antibiotics, and treating only as long as necessary to achieve the treatment goal.

In 2001, Levy<sup>5</sup> showed an increased prevalence of antibiotic-resistant strains of *P. acnes* with resistance rates of up to 60%. Such resistance means that patients with either acne vulgaris or rosacea will not respond as well to previously effective antibiotics. However, the consequence of resistance is more significant than the problem of a reduced effect on individual patients.

That same year, Dreno and colleagues<sup>6</sup> reported the first French study of patients with mild-to-moderate acne, documenting erythromycin resistance to *P. acnes* in France. In addition to a 52% prevalence of bacterial resistance to *P. acnes* strains, the investigators showed a 95% prevalence of erythromycin-resistant *Staphylococcus epidermidis* in their study population of patients with mild-to-moderate acne. The authors note

that their findings confirm the reports of such resistance from other countries. Furthermore, 42% of patients who had never used erythromycin carried erythromycin-resistant strains of *P. acnes*.

In 2003, Levy and colleagues<sup>7</sup> evaluated 105 patients who had used tetracycline for at least 6 months and compared them with a group of subjects who had not used antibiotics. The investigators found that 85% of tetracycline users had positive cultures for tetracycline-resistant *Streptococcus pyogenes* in the oropharynx, whereas only 20% of subjects in the control population carried these organisms.

Clearly, the issue of existing and emerging resistance of a wide range of organisms to common, safe, and effective antibiotics is a critically important one. Mounting evidence shows that rosacea is an inflammatory rather than a bacterial condition, so using antimicrobial therapy—despite its anti-inflammatory efficacy—only adds to the problem of antimicrobial resistance.

## SUBANTIMICROBIAL ANTIBIOTIC DOSING

In clinical trials, it was shown that a 40-mg, controlled-release dose of doxycycline falls below the drug's threshold of antibiotic activity, yet is sufficient to provide the anti-inflammatory effect associated with this drug. In addition, compared with placebo and with antimicrobial doses of the tetracyclines in general and doxycycline specifically, anti-inflammatory doxycycline is associated with a greatly reduced risk for side effects.<sup>8</sup> In 2006, the FDA approved a 40-mg, time-release formulation of doxycycline monohydrate.

Del Rosso and Bikowski,<sup>8</sup> the lead authors on the paper detailing the results of a multicenter, double-blind, randomized, parallel-group trial, reported on the efficacy and safety of 40-mg doxycycline monohydrate, controlled-release capsules (30-mg, immediate release and 10-mg, delayed release) in adult patients with moderate-to-severe rosacea. Two 16-week pivotal trials identified as Study 301 (n=121 patients in the active treatment group, n=124 in the placebo group) and Study 302 (n=142 in the active treatment group, n=144 in the placebo

**Table. Antibiotics and Rosacea: Summary of Major Points**

**Most effective:** Tetracycline class (tetracycline and second-generation tetracyclines, doxycycline and minocycline), ciprofloxacin, TMP/SMX

**Active against *Demodex* sp:** None

**Active against *Propionibacterium acnes*:** All

**Direct anti-inflammatory activity (antichemotactic, anti-PKC, antigranuloma):** All

PKC = protein kinase C; TMP/SMX = trimethoprim/sulfamethoxazole.

group) showed statistically significant differences between doxycycline and placebo on multiple efficacy end points. The end points included lesion counts (papules, pustules, and nodules), erythema (on a Clinician's Erythema Assessment scale), and a five-point Investigator's Global Assessment (0=clear, 1=near clear, 2=mild, 3=moderate, and 4=severe).

The authors noted that patients receiving the 40-mg/day dosage of doxycycline monohydrate showed a significant reduction in inflammatory lesions within the first 3 weeks of the studies, and progressive reductions continued over the next 13 weeks. Erythema was reduced in both active-treatment groups and, to a lesser extent, in both placebo groups. The differences between the active-treatment and placebo groups did not reach statistical significance. The safety analysis demonstrated that both doxycycline and placebo were well tolerated, with "no major safety issues or concerns identified during the course of either study."

According to minimum inhibitory concentration evaluations of bacterial strains that are susceptible to the tetracyclines, an antimicrobial dose of these antibiotics is one that is greater than 40 mg. The 40-mg, controlled-release formulation of doxycycline monohydrate is below the antimicrobial threshold, and, therefore, does not produce selection pressure for the susceptible microbes. This is based on minimum inhibitory concentration evaluations of susceptible strains. The 40-mg, controlled-release formulation is not antimicrobial, and, therefore, does not produce selection pressure for the susceptible microbes.

As an anti-inflammatory agent, doxycycline has both extracellular and

intracellular mechanisms of action. Extracellularly, the drug has anti-chemotactic activity, including scavenging reactive oxygen species and inhibiting matrix metalloproteinases. Intracellularly, doxycycline down-regulates cytokines, inhibits nitric oxide activity, and suppresses the arachidonic acid pathways. All of these mechanisms, as well as other biologic effects detailed in the results of the Del Rosso and Bikowski report, are anti-inflammatory. In addition, the study showed that doxycycline has effects on collagenase, which is thought to be one cause of the connective tissue decrease seen in rosacea.

## CONCLUSION

Antibiotic therapy has been a mainstay of rosacea therapy for almost 4 decades, with demonstrated efficacy in treating inflammatory lesions and reducing erythema. In recent years, evidence began to accumulate showing that rosacea is an inflammatory rather than a bacterial process, and antibiotic agents such as those in the tetracycline class improve rosacea as a result of their anti-inflammatory activity rather than anti-activity. The issue of existing and emerging organisms resistant to antimicrobial agents has implications for both individual patients and public health in general. The use of anti-inflammatory dosage of antibiotic agents provides anti-inflammatory benefits and a reduced risk for side effects. A once-daily, 40-mg, controlled-release formulation of doxycycline monohydrate is an anti-inflammatory drug that has been shown effective and safe in the treatment of rosacea, and the 40-mg, controlled-release dose is below the drug's threshold of antibiotic activity. ■

*References continued on page 11*

# TREATING THE MANY FACES OF ROSACEA: A SYSTEMATIC APPROACH TO DEVELOPING INDIVIDUALIZED REGIMENS

*Diane M. Thiboutot, MD*



**G**iven that the underlying etiology of rosacea has not yet been established, the condition currently is not curable. However, effective strategies for controlling symptoms and improving appearance have been developed. Some of these strategies apply to all patients with rosacea; others apply to patients with specific subtypes of the disease.

## TREATMENT EXPECTATIONS

An issue in treatment not to be overlooked is the patient's expectation of cosmetic improvement. The majority of patients with rosacea present with background erythema and, in fact, many initially seek treatment for their disease because of their concern about their appearance.

The medical treatments now available are highly effective in managing rosacea-associated papules and pustules. The medications with anti-inflammatory properties do reduce erythema in most patients, but they are not universally effective for this problem and patient response is variable. Thus, in counseling patients, it is important to let them know that they can expect complete or almost complete clearance of papulopustular lesions. Even if the first medication tried does not yield optimum results, other monotherapy or combination regimens can be used, and a successful treatment plan is likely to be found. For background erythema and telangiectases that either do not improve or do not resolve sufficiently on topical or oral medications, laser and light therapies—especially pulsed dye laser and intense pulsed light treatment—have shown benefit.

## ROUTINE SKIN CARE

A major concern of all patients with rosacea is how to take care of their skin. Although some patients are not particularly sensitive to various ingredients in skin care products, many individuals with rosacea—both men and women—experience burning, stinging, and erythema on exposure to certain cleansers, astringents, toners, sunscreens, and fragrance products.

**...individuals with rosacea must be particularly careful [to use sunscreen] because exposure to ultraviolet radiation is a common trigger for acute flare-up of the disease.**

In general, patients should be instructed about mild cleansing techniques and should be guided toward cleansing products that not only will be nonirritating, but also may improve the signs and symptoms of rosacea. Cleansers that contain sodium sulfacetamide are a good example. Patients should be cautioned to read labels carefully and to avoid cleansers, astringents, and toners that contain alcohol as well as other harsh ingredients.

Sunscreen use is crucial for everyone to prevent long-term actinic skin damage. However, individuals with rosacea must be particularly careful because exposure to ultraviolet radiation is a common trigger for acute flare-up of the disease. The availability of moisturizers that contain sunscreens is likely to improve compliance with daily sunscreen use; patients should use a product with a sun protection factor of at least 15.

Patients who are concerned about how background facial erythema affects their appearance should be advised about the use of green-tinted cosmetics. These products, available in powder and cream cover-up forms, mask the redness of rosacea. The green-tinted product is put on first, then a skin-colored foundation is applied.

For patients with ocular rosacea, routine care includes the regular use of artificial tears and/or lubricating drops. Some patients with ocular rosacea also have seborrheic blepharitis, with an accumulation of scale and crusting on the eyelashes. These patients should follow a regular regimen of eye hygiene, cleansing their eyelashes once or twice daily with a very mild soap such as no-tear baby shampoo or with pre-packaged, one-use towelettes made especially for lid cleansing.

Patients with large-pored, seborrheic skin usually benefit from daily use of sodium sulfacetamide cleansers.

## TOPICAL TREATMENTS

Mild-to-moderate outbreaks of papules and pustules are often successfully managed with one of the three topical medications that have been approved by the US Food and Drug Administration (FDA) for the treatment of rosacea. These are metronidazole in 0.75% and 1.0% concentrations; several topical formulations of cleansers, creams, and lotions, and a color-correcting gel containing 10% sodium sulfacetamide with 5% sulfur; and a 15% concentration of azelaic acid gel (the 20% formulation is approved for the treatment of inflammatory acne vulgaris).

Topical retinoids have been proposed for use in rosacea, and improvement can be seen after 3 to 6 months of treatment.

Because of the long duration of onset of improvement, topical retinoid therapy may be combined with another agent such as an oral medication—an anti-inflammatory, subantimicrobial formulation of doxycycline monohydrate has recently been approved by the FDA for the treatment of rosacea. The rationale for topical retinoid use in rosacea is that it promotes connective tissue remodeling and reduces dermal inflammation. In addition, topical retinoids decrease abnormal levels of elastin and vascular endothelial growth factor, as well as increasing collagen and glucosaminoglycan production. All of these effects are beneficial in rosacea.

During initiation of treatment with topical retinoids, some patients may experience irritation. However, a low starting dosage with the use of a silicone-based moisturizer under the medication usually increases tolerance.

## ORAL MEDICATIONS

### Flushing Antagonists

Several oral agents have been used in an attempt to suppress flushing and, thus, reduce rosacea-associated erythema. These include  $\beta$ -blockers (such as propranolol), clonidine, and, more recently, selective serotonin reuptake inhibitors.

For severe flushing and blushing (transient erythema), clonidine at 0.05 mg b.i.d. reduces peripheral vasoconstriction yet does not have an effect on blood pressure.

Craige and Cohen<sup>1</sup> studied propranolol in patients with flushing and blushing. These investigators started patients on 10 mg t.i.d. of the drug and increased the dosage as tolerated. The lowest dosage of 10 mg t.i.d. failed to have any beneficial effect; 20 to 40 mg b.i.d. effected complete control of the transient erythema, but three patients had side effects at those dosages, and two of them experienced dizziness to such a degree that they stopped treatment. Other potential side effects

of propranolol used long term include fatigue, somnolence, and sexual dysfunction. Nevertheless, for patients with transient erythema who tolerate the  $\beta$ -blocker, this treatment can be quite effective at sufficient dosages.

**Table. FDA-Approved Medications for Rosacea**

#### TOPICAL

- Metronidazole, 0.75% and 1.0%
- 10% sodium sulfacetamide/5% sulfur (color-correcting gel, creams, lotions, cleansers)
- Azelaic acid gel, 15%

#### ORAL

- Doxycycline, 40-mg controlled-release (subantimicrobial dosage)

### Isotretinoin

Isotretinoin has a delayed onset of action compared to oral antibiotics, but with continued use, this agent does reduce the number of papules and pustules and has some benefit in reducing rosacea-associated erythema. Isotretinoin also has been shown to decrease the number and size of sebaceous glands. This results in a slight reduction in volume of phymatous tissue in preexisting phymata, but the main benefit is the slowing of the continuously accelerating process of phymatous tissue formation.

Isotretinoin also improves ocular symptoms, and—as in patients with acne vulgaris—low doses of this drug, even when given long term, are associated with few side effects; however, the serious concern regarding teratogenicity should always be kept in mind. Effective March 2006, any prescriber, female patient, pharmacy, and other distributors of isotretinoin must register for and meet the requirements of the iPLEDGE™ program.

### Antimicrobial and Subantimicrobial Doses of Antibiotic Agents

Oral antibiotics have been used to treat rosacea for more than 40 years—

usually tetracycline or the second-generation drugs in the tetracycline class (doxycycline or minocycline). The disadvantages of antibiotic use in rosacea are the potential for side effects and, with longer-term use, the contribution that these drugs make to the development of resistant microbes.

Recently, studies have been done with the anti-inflammatory dosage of doxycycline, a 40-mg, controlled-release formulation that was recently approved by the FDA for the treatment of rosacea. With this formulation, antibiotic resistance is less of a concern, the risk for side effects is greatly reduced, and the likelihood of compliance—because it is an oral medication with once-daily dosing—is increased. Men, in particular, have difficulty complying with a regimen that requires application of topical medications.

## LASER AND LIGHT-BASED THERAPY

Phymata—that is, rhinophyma (nose), gnatophyma (chin), metophyma (forehead), otophyma (one or both ears), and/or blepharophyma (eyelids)—do not respond to the treatments used for other subtypes of rosacea. Instead, the treatments of choice for patients with phymatous changes are isotretinoin and surgical resculpting of the affected areas.<sup>2</sup> To restore the normal contours of the head and neck, modalities such as the carbon dioxide laser, the cauterizing Shaw scalpel, and dermabrasion—either as monotherapy or in combination—may be used.

Vascular and ablative lasers have been shown to be helpful for severe erythema and telangiectases and for removing or preventing the advancement of phymata. Vascular laser therapy reduces vascular dilation without causing collateral tissue damage, so it is effective and nonscarring.

Photodynamic therapy with either a monochromatic or a polychromatic light source and a photosensitizer

(most commonly, aminolevulinic acid [ALA]) produces reactive oxygen species that are toxic to tissues. ALA is strongly absorbed by the sebaceous glands, so the connective tissue is remodeled. In addition, photodynamic therapy may clear papules and pustules and improve telangiectases.

## COMBINATION THERAPY

Successful treatment of rosacea may require the use of more than one modality. Although data are not yet available about using the subantimicrobial dose of doxycycline with other therapies—such as topical agents—it seems reasonable that the anti-inflammatory properties of this low-dose agent may be helpful in combination with agents that have other mechanisms of action.

Patients with ocular rosacea often are treated with tetracyclines to control conjunctivitis and blepharitis. Again, studies are not yet available assessing the potential benefits of subantimicrobial doses of antibiotic agents, but since ocular symptoms likely result from inflammation, such treatment may be helpful.

## CONCLUSION

A number of treatments now are available for managing the signs and symptoms of rosacea. Improvements have been made in routine skin care products, including sodium sulfacetamide cleansers and moisturizers containing sunscreens. In addition, the new formulation of anti-inflammatory doxycycline provides the benefit of this drug's anti-inflammatory activity

without antimicrobial activity, thus reducing the risk of side effects and avoiding adding to the selective pressure for resistant organisms to emerge. It is hoped that future research focusing on persistent, chronic erythema will result in the development of improved treatments for this problem. ■

## REFERENCES

1. Craigie H, Cohen JB. Symptomatic treatment of idiopathic and rosacea-associated cutaneous flushing with propranolol. *J Am Acad Dermatol.* 2005;53:881-884.
2. Jansen T, Plewig G. Clinical and histological variants of rhinophyma, including nonsurgical treatment modalities. *Facial Plast Surg.* 1998; 14:241-253.

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## EMERGING CONCEPTS IN ROSACEA ETIOLOGY, PATHOPHYSIOLOGY, AND DIAGNOSIS *Continued from page 6*

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### REFERENCES

1. National Rosacea Society. Available at <http://www.rosacea.org>. Accessed July 2, 2006.
2. Berg M, Liden S. An epidemiological study of rosacea. *Acta Derm Venereol.* 1989; 69:419-423.
3. Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol.* 2004;51:327-341.
4. Bamford JT, Tilden RL, Blankush JL, Gangeness DE. Effect of treatment of *Helicobacter pylori* infection on rosacea. *Arch Dermatol.* 1999; 135:659-663.
5. Millikan L. The proposed inflammatory pathophysiology of rosacea: Implications for treatment. *Skinmed.* 2003;2:43-47.
6. Attur MG, Dave MN, Mohandas N, et al. Regulation of inflammatory mediators by tetracyclines. In: Nelson M, Hillen W, Greenwald RA, eds. *Tetracyclines in Biology, Chemistry and Medicine.* Basel, Switzerland: Birkhauser Verlag; 2001:295-310.
7. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol.* 2002;46:584-587.
8. Wilkin J, Dahl M, Detmar M, et al. Standard grading system for rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol.* 2004;50:907-912.

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## DO ANTIBIOTICS STILL HAVE A ROLE IN ROSACEA? *Continued from page 8*

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### REFERENCES

1. Millikan L. The proposed inflammatory pathophysiology of rosacea: Implications for treatment. *Skinmed.* 2003;2:43-47.
2. Attur MG, Dave MN, Mohandas N, et al. Regulation of inflammatory mediators by tetracyclines. In: Nelson M, Hillen W, Greenwald RA, eds. *Tetracyclines in Biology, Chemistry and Medicine.* Basel, Switzerland: Birkhauser Verlag; 2001:295-310.
3. Thiboutot D. Acne: 1991-2001. *J Am Acad Dermatol.* 2002;47:109-117.
4. Eady EA, Jones CE, Tipper JL, Cove JH, Cunliffe WJ, Layton AM. Antibiotic resistant propionibacteria in acne: Need for policies to modify antibiotic usage. *BMJ.* 1993;306:555-556.
5. Levy SB. Antibiotic resistance: Consequences of inaction. *Clin Infect Dis.* 2001;15(33 suppl 3): S124-S129.
6. Dreno B, Reynaud A, Moyses D, Habert H, Richet H. Erythromycin-resistance of cutaneous bacterial flora in acne. *Eur J Dermatol.* 2001;11:549-553.
7. Levy RM, Huang EY, Roling D, Leyden JJ, Margolis DJ. Effect of antibiotics on the oropharyngeal flora in patients with acne. *Arch Dermatol.* 2003;139:467-471.
8. Del Rosso JQ, Bikowski JB. Multicenter, double-blind, randomized, placebo-controlled, parallel-group trial results evaluating the effects of 40 mg doxycycline monohydrate controlled-release capsules in the treatment of rosacea. Poster presented at: 64th American Academy of Dermatology Meeting; March 3-7, 2006; San Francisco, Calif.

CME POST-TEST AND EVALUATION

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Estimated Time to Complete This Activity: 1.5 hours

Please circle the most appropriate response. Six correct responses are required for credit.

1. The feature of rosacea that responds most readily and rapidly to pharmacologic therapy is:
  - a. Erythema
  - b. Papules and pustules
  - c. Phymatous changes
  - d. Seborrheic blepharitis
2. The dosage of doxycycline in a non-controlled-release formulation that has antimicrobial activity is:
  - a. ≤25 mg/day
  - b. ≤30 mg/day
  - c. ≤35 mg/day
  - d. ≥40 mg/day
3. In 1993, Eady and colleagues noted that, in patients with acne vulgaris, tetracycline-resistant strains of *Propionibacterium acnes* were cross-resistant to doxycycline, and erythromycin-resistant strains of *P. acnes* were cross-resistant to:
  - a. Clindamycin
  - b. Doxycycline
  - c. Minocycline
  - d. Tetracycline
4. One cause of the connective tissue decrease seen in patients with rosacea is:
  - a. Collagenase
  - b. Matrix metalloproteinase
  - c. Protein kinase
  - d. Reactive oxygen species
5. The most likely cause of rosacea is:
  - a. *Demodex follicularum*
  - b. *Helicobacter pylori*
  - c. Inflammatory processes
  - d. *Propionibacterium acnes*
6. Crawford and colleagues have proposed that the "sole requisite criterion" for diagnosing rosacea should be:
  - a. Central facial erythema lasting at least 3 months
  - b. Flushing and blushing
  - c. Papules and pustules
  - d. Telangiectases
7. The oral treatment of choice for patients with ocular rosacea is:
  - a. Clindamycin
  - b. Erythromycin
  - c. Isotretinoin
  - d. Tetracyclines
8. The definitive diagnosis of rosacea is made on the basis of:
  - a. Clinical findings
  - b. Microscopic examination of skin scrapings
  - c. Punch biopsy results
  - d. Serologic testing

Course Evaluation

Please evaluate the effectiveness of this activity by circling your choice on a scale of 1 to 5, with 1 the lowest and 5 the highest.

(All information is confidential.)

Please Print

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Please indicate if the following objectives were met.

Describe the epidemiology, natural history, and diagnosis of rosacea. 1 2 3 4 5

Discuss the most recent research findings regarding the etiology of rosacea. 1 2 3 4 5

Explain the growing public health concerns associated with the use of oral antibiotics, the traditional treatment for rosacea. 1 2 3 4 5

Discuss topical and oral treatment options for rosacea and the patient selection factors that should be considered in choosing a regimen. 1 2 3 4 5

How do you rate the overall quality of the activity? 1 2 3 4 5

How do you rate the educational content of the activity? 1 2 3 4 5

Was the information presented fair, objective, balanced, and free of bias in the discussion of any commercial product or service?  Yes  No

If not, please describe: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

After participation in this activity, have you decided to change one or more aspects in the treatment of your patients?  Yes  No

If yes, what changes will you make? \_\_\_\_\_  
 \_\_\_\_\_

If no, why? \_\_\_\_\_  
 \_\_\_\_\_

Would you be willing to participate in follow-up evaluations?  Yes  No

Suggested topics for future activities: \_\_\_\_\_  
 \_\_\_\_\_

Suggested authors for future activities: \_\_\_\_\_  
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