Rosacea: Choosing Among the Topical and Systemic Therapeutic Options

As the field of therapies available for rosacea has expanded, clinicians must weigh the topical and oral treatment options on a case-by-case basis.

By Mark Bechtel, MD and Ann Bechtel, BSN

The management of rosacea can be challenging. Heat, sun exposure, environmental factors and specific foods can trigger flares in rosacea. The exact etiology of rosacea remains unknown, but is likely multifactorial. Infectious agents, such as Demodex, have been hypothesized as causative agents. In one recent study, staphylococcus epidermidis was felt to play a role in pustular and ocular rosacea. Vascular instability and pilosebaceous unit abnormalities may also be contributing factors.

The role of inflammation in rosacea has recently been given greater attention. Cathelicidins, which are antimicrobial peptides, are an important component of the innate immune system. Cathelicidins and related peptides trigger inflammation and promote angiogenesis. They have been noted to be increased in rosacea. One of the active inflammatory components of cathelicidin is LL-37, which is cleaved off a precursor molecule by serine proteases. Patients with rosacea produce an excessive serine protease, kallikrein 5, which generates increased LL-37. This may increase inflammation and angiogenesis.

Rosacea can be classified into four subtypes. These include erythematotelangiectatic, papulopustular, phymatous, and ocular variants. Proper classification of the rosacea subtype can make the management of rosacea more specific and focused.

Erythematotelangiectatic and Papulopustular Rosacea

The erythematotelangiectatic rosacea (ETR) subtype is challenging to manage. Patients report flushing episodes lasting more than 10 minutes, often accompanied by a burning or stinging sensation. Over time, the flushing becomes more longlasting and eventually permanent. Telangiectasias become prominent, especially with cumulative photodamage. Few to no inflammatory lesions are noted. Topical management is often unsuccessful, and patients report a lower threshold for irritation from topically applied substances. Dysesthesia of the skin can become prominent and a significant component of disability.

Take-Home Tips. The management of rosacea can be challenging, given incomplete understanding of its etiology, the influence of triggers, and lack of a one-size-fits-all therapy. The etiology of rosacea is likely multifactorial and may involve infectious agents. Vascular instability and pilosebaceous unit abnormalities may also be contributing factors. The role of inflammation in rosacea has recently been given greater attention. Cathelicidins and related peptides trigger inflammation and promote angiogenesis. They have been noted to be increased in rosacea. Rosacea can be classified into four subtypes (erythematotelangiectatic, papulopustular, phymatous, and ocular). Proper classification of the rosacea subtype can make the management of rosacea more specific and focused.
In the erythematotelangiectatic variant, it is important to avoid foods that may induce flushing. This includes cayenne pepper, hot coffee and tea, chocolate, red wine, and liquor. Heat, exertion, anger, stress, strong winds, and hot flashes may exacerbate the situation. Drugs, such as nicotinic acid, calcium channel blockers, tamoxifen, and erectile dysfunction drugs can stimulate flushing. In this variant of rosacea, it is especially important to avoid astringents, skin irritants, and harsh cosmetics. Topical rosacea therapies are sometimes irritating and ineffective. Cosmetic camouflage of the erythema and telangiectasias with green tint can be helpful, along with sunscreen use. The dysesthesia can be very disturbing for many patients and improved with amytriptyline or gabapentin.

Pharmacologic management of rosacea flushing is often disappointing, but may provide some benefit. Clonidine 0.05mg twice a day did not suppress flushing reactions provoked by water at 60°C, red wine, and chocolate. Nadolol 40mg daily had no effect on provoked flushing, but there was a trend towards improvement in patient reported spontaneous flushing. Treatment of rosacea with intense pulsed light resulted in a 75 percent reduction in flushing in one study. Pulsed dye laser treatment of rosacea has been shown to decrease telangiectasias, erythema, flushing, and burning and stinging. Oxymetazoline hydrochloride 0.05% solution, a selective alpha 1-adrenergic receptor agonist, has been used successfully to reduce erythema and flushing of rosacea when applied topically. Oxymetazoline hydrochloride reduced facial erythema within one hour and lasted throughout the day.

Inflammatory papulopustular rosacea (PPR) is a subset of rosacea with more effective therapies available. Metronidazole cream and gel are safe and effective in the treatment of PPR. There is no apparent clinical difference between once- and twice-a-day therapy. Azelaic acid cream and gel are safe and effective in treating rosacea. In a comparison double-blind trial of 15% azelaic acid and 0.75% metronidazole gel in the treatment of

Table 1. Rosacea Subtypes, Signs/Symptoms, and Targeted Interventions

<table>
<thead>
<tr>
<th>Rosacea Subtypes</th>
<th>Signs/Symptoms</th>
<th>Targeted Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythematotelangiectatic</td>
<td>Dysesthesia</td>
<td>Amytriptyline, Gabapentin</td>
</tr>
<tr>
<td>Papulopustular</td>
<td>Flushing</td>
<td>Trigger avoidance, Avoid astringents, skin irritants, harsh cosmetics, Nadolol 40mg for spontaneous flushing, Laser; IPL</td>
</tr>
<tr>
<td>Phymatous</td>
<td>Erythema</td>
<td>Laser; IPL, Topical Oxymetazoline hydrochloride 0.05% solution (and flushing), Cosmetic camouflage (green tint)</td>
</tr>
<tr>
<td>Ocular</td>
<td>Papules, pustules, inflammation-related erythema</td>
<td>Metronidazole cream and gel, Azelaic acid gel, Topical erythromycin, clindamycin, and sulfa products, Oral tetracycline, doxycycline, minocycline, erythromycin, azithromycin, Anti-inflammatory dose doxycycline (40mg), Isotretinoin</td>
</tr>
<tr>
<td>Seborrheic dermatitis overlap</td>
<td></td>
<td>Topical sulfa products</td>
</tr>
<tr>
<td>Rhinophyma</td>
<td></td>
<td>Isotretinoin (no contour restoration), Laser: CO2, Nd:YAG, Er:YAG, Shaw scalpel</td>
</tr>
<tr>
<td>Ocular rosacea</td>
<td></td>
<td>Tear substitutes, Doxycycline, minocycline, and fucidic acid ophthalmic gel</td>
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</tbody>
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Rosacea involving 251 patients, azelaic acid was superior for reducing erythema and inflammatory lesions, while metronidazole was slightly better tolerated.\textsuperscript{11} Azelaic acid has been shown to down-regulate the production of cathelicidins and promote anti-inflammatory effects.\textsuperscript{4} The use of betadex in metronidazole 1\% gel allows a higher concentration of the active ingredient, relative to the original formulation on the market while maintaining a high water content. In addition, the presence of nicinamide in metronidazole 1\% gel may provide additional anti-inflammatory properties.\textsuperscript{12} Topical erythromycin, topical clindamycin, and topical sulfa products have shown clinical benefit in rosacea. Topical sulfa products may be helpful in patients with a seborrheic dermatitis/rosacea overlap.

Oral therapy can be very effective in patients with papulopustular rosacea. Antibiotics tetracycline, doxycycline, minocycline, erythromycin, azithromycin, and the retinoid isotretinoin have demonstrated clinical benefit in rosacea. Anti-inflammatory doses of doxycycline in a 40mg controlled release formulation deliver anti-inflammatory effects of doxycycline with peak plasma levels below the minimum inhibitory concentrations (M ICs) for susceptible organisms. This eliminates the risk of developing doxycycline resistant microorganisms. Doxycycline at 40mg, as compared to 100mg, was equally effective in reducing total inflammatory lesions and erythema.\textsuperscript{13} Anti-inflammatory dose doxycycline has been shown to be beneficial when combined with topical either metronidazole or azelaic acid.\textsuperscript{14} In tetracycline intolerant patients, azithromycin, ampicillin, and oral metronidazole can be considered. Azithromycin has been described in the literature to be beneficial in treating rosacea in two different dosing regimens. Azithromycin 500mg on day one followed by 250mg per day for four consecutive days, beginning on the first and fifteenth days of each month, has been reported.\textsuperscript{15} Azithromycin 250mg on Monday, Wednesday, and Friday has also been described.\textsuperscript{16} Systemic isotretinoin has been reported to be effective in the treatment of rosacea. In a randomized placebo-controlled study, isotretinoin at 0.2mg/kg, 0.3mg/kg, or 0.5mg/kg was compared to doxycycline 100mg daily for 15 days, then 50mg daily for a total of 12 weeks. Isotretinoin at 0.3mg/kg proved to be the most effective. There was a minimal difference in reduction in lesion count at 12 weeks with isotretinoin having a 90 percent reduction and doxycycline an 83 percent reduction.\textsuperscript{17}

Phymatous and Ocular Rosacea
Phymatous rosacea often does not respond to conventional or systemic rosacea therapy. Systemic isotretinoin (1mg/kg) can significantly reduce the bulk of rhinophyma, but it does not restore normal contour. Electrotherapy, carbon dioxide (CO\textsubscript{2}) laser, Nd:YAG laser, Erbium:YAG laser, and the Shaw scalpel have been noted to improve the cosmetic contour of the nose.

Ocular rosacea can be a source of significant discomfort and can be noted in up to 50 percent of rosacea patients. Patients complain of ocular dryness, tearing, pain, blurring of vision, styes, and corneal damage. Meibomian gland impaction leads to decreased lipid in tear film and greater tear evaporation. Metalloproteinase (MMP-9) is elevated in ocular rosacea tear fluid. Ocular rosacea can be treated with tear substitutes, doxycycline, minocycline, and fucidic acid ophthalmic gel (available in Europe).
**Individualized Therapy**

There have been many new developments in understanding the pathophysiology of rosacea and rendering treatment. Our scientific knowledge of this common disorder has expanded. It is important that therapy of rosacea be targeted based at clinical manifestations of the patient. Therapy should be individualized to improve efficacy and compliance.

**Ann Bechtel, RN, BSN** graduated from Indiana University with a BSN and worked for 25 years in dermatology and is now working independently in educational endeavors.

**Mark A. Bechtel, MD, FAAD** is Director of Dermatology at Ohio State University College of Medicine.


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**Rosacea Treatment Options**

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