

Acne Vulgaris and Rosacea: Evaluation and Management

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Acne vulgaris, commonly termed acne, is an extremely common disease. It can be found in nearly all teenagers to some degree as well as in women in their 30s. Regardless of severity, acne often has a greater psychologic effect than cutaneous effect. Indeed, most patients overestimate the severity of their disease, while most physicians underestimate its impact on their patients. Studies have shown that people with severe acne as teens are less employable as adults and that self-esteem is low. When combined with other adolescent tensions, acne can be a difficult disease to treat. Rosacea, which usually starts in the late 20s, may affect the eyes as well as the skin. This article describes the pathogenesis of acne and rosacea and treatment approaches the primary care physician can use.

PATHOGENESIS OF ACNE VULGARIS

The pathogenesis of acne vulgaris is multifactorial, involving disturbances of keratinization, hormonal secretion, and immunity (**Table I**). The central defect involves the formation of the comedo, a plug in the follicle that results from aberrant desquamation of the follicular wall. Clinically, comedones are described as “open” if the pore is visible and “closed” if it is not. The black tip of an open comedo results from the oxidation of sebaceous lipid and melanin and is not dirt, contrary to advice from mothers throughout the world. The cause of comedo formation is not known. It is clear that comedones do not result from poor hygiene, diet, or use of brand-name cosmetics. In fact, major cosmetic companies test their products for acnegenicity.

In many patients acne remains for the most part in this first stage; in others it progresses to inflammatory lesions of varying severity (**Table II**). The target of inflammation is *Propionibacterium acnes*, an aerotolerant anaerobic member of the normal flora in sebaceous regions of the skin.

P acnes lives in the follicle and metabolizes sebaceous triglycerides into fatty acids and glycerol. It consumes the glycerol and casts off the fatty acids. In the past it was thought that the fatty acids in sebum were the cause of acne inflammation; however, research has shown that the organism itself is the target.

P acnes is highly inflammatory, activating complement, secreting neutrophil and monocyte chemotactic factors, activating lymphocytes, and inducing lysosomal enzyme release. The organism degrades slowly, resulting in a persistent follicular inflammatory response.

KEY POINT

The central defect in acne involves the formation of the comedo, a plug in the follicle that results from aberrant desquamation of the follicular wall.

TABLE I.

PATHOGENESIS OF ACNE

Follicular dyskeratinization → Comedo formation
 Androgen secretion → Sebum production → *Propionibacterium acnes* proliferation
 Hypersensitivity to *P acnes* → Increased severity of inflammation

TABLE II.

TYPES OF ACNE LESIONS

Comedo—Lesions may be “open” or “closed,” depending on the presence of a visible black tip resulting from defective keratinization.

Papule/pustule—Inflammatory lesions that if large or persistent may lead to permanent scarring.

Nodule—A deep inflammation, >5 mm in size, guaranteed to produce a scar. Lesions are erroneously termed “cysts.” In reality, they are abscesses with no cyst wall present.

Conglobate lesions—Grouped nodules connected by sinus tracts present in the severest forms of acne.

Because all individuals have a significant level of *P acnes* and some degree of follicular plugging, it is curious that we all do not have active acne. The explanation lies in the level of the immune response to the organism. Patients with excessive humoral and cellular immunity to *P acnes* mount a more destructive inflammatory response that produces clinical lesions. This response may represent a true hypersensitivity to *P acnes* in that the organism is a beneficial commensal and of minimal infectious potential.

day clinical setting. A practical approach is for the physician and patient to reach some consensus on how bad the acne is by looking at the severity of the actual lesions and the impact of the disease on the patient. Inflammatory acne lesions range in severity from superficial pustules to deep scarring nodules (Table II). Generally, patients will have a mixture of lesion types, and their acne should be graded based on the most severe lesions present; that is, a patient with 3 scarring nodules has more severe acne than a patient with 50 superficial pustules. The presence of acne on the chest or back also connotes a more severe and hard-to-treat disease.

The terms *inverse acne*, *triad acne*, and *hidradenitis suppurativa* all describe a follicular process that results in comedo formation and inflammation in the scalp, axilla, and groin. In the past this process was thought to be an apocrine disease, but recent thought holds it to be a disease of the hair follicle, like acne vulgaris. However, unlike acne vulgaris, *P acnes* plays little or no role in acne of nonsebaceous regions. Various bacteria, enterics, pseudomonads, and streptococci colonize these lesions and provoke inflammation and scarring. Sinus tract formation is common and results in disease that is often best treated surgically.

KEY POINT

A patient with 3 scarring nodules has more severe acne than a patient with 50 superficial pustules.

A minority of women have an endocrine aspect to their acne. Although not necessarily severe, their acne may be refractory. Such patients may have a history of irregular menses, be overweight, or have increased facial hair or androgenetic alopecia.

There are many acne grading systems. Those systems that involve pimple counting are useful in clinical trials but are too cumbersome in the every-

Treatment Approaches

The first step in the treatment of a patient with acne

TABLE III. TOPICAL ACNE THERAPY		
<i>Anticomedonal</i>	<i>Antibacterial</i>	<i>Anti-inflammatory</i>
<ul style="list-style-type: none"> ● Tretinoin ● Tazarotene ● Adapalene ● Salicylic acid 	<ul style="list-style-type: none"> ● Azelaic acid ● Benzoyl peroxide ● Erythromycin ● Clindamycin ● Benzoyl peroxide/erythromycin gel ● Benzoyl peroxide/clindamycin gel 	<ul style="list-style-type: none"> ● Sodium sulfacetamide

TABLE IV. ORAL ACNE THERAPY		
<i>Antibiotics</i>	<i>Antiandrogen</i>	<i>Antisebaceous, Anticomedonal, Anti-inflammatory</i>
<ul style="list-style-type: none"> ● Tetracycline (250–1000 mg qd in divided dose) ● Doxycycline (50–200 mg qd in divided dose) ● Minocycline (50–200 mg qd in divided dose) ● Erythromycin (250–1000 mg qd in divided dose) 	<ul style="list-style-type: none"> ● Oral contraceptives ● Spironolactone 	<ul style="list-style-type: none"> ● Isotretinoin (0.5–2 mg/kg per day)

is to be certain that the patient (and the parents if the patient is an adolescent) have not fallen prey to the numerous myths about the disease. Acne is not caused by dirt, diet, or impure thoughts. Patients commonly believe that one particular food, usually a greasy or sweet one, worsens their acne. Hair falling on the forehead does not cause pimples, and the disease cannot effectively be treated with soap and water. Popping pimples is bad—it promotes scarring and prolongs the life of many lesions. Stress may play a role but tranquilizers have no positive effect on acne.

Physicians and patients must communicate particularly well during the treatment of acne. The first visit is very important in that patients can be given realistic expectations and be disabused of incorrect ideas. Teens in particular expect quick results; however, they need to understand that 3 to 6 weeks is the quickest that acne can be expected to improve. Bigger lesions may take longer as do open comedones. For many patients any mark on the face after a pimple heals is considered a scar and they need to understand the distinction between true scars and transient postinflammatory pigment changes.

There is wide variation in acne regimens. Some physicians use 1 or 2 drugs in each patient while others use 5 or 6. In general 1 or 2 properly chosen drugs do better and are easier for the patient to comply with than a more complex regimen. Treatment may be topical (Table III) or oral (Table IV). Typical acne regimens are outlined in Table V.

KEY POINT

Teenagers need to understand that 3 to 6 weeks is the quickest that acne can be expected to improve.

The central lesion in both comedonal and inflammatory acne is the microcomedo; therefore, most effective regimens include a retinoid such as tretinoin or tazarotene. Indeed, if one is sufficiently patient, topical retinoids are excellent monotherapy for all but the most severe acne. Because topical retinoid monotherapy takes several months to clear inflammatory acne, it is prudent to add a drug that

TABLE V.

TYPICAL ACNE REGIMENS

- Benzoyl peroxide/erythromycin gel
- Topical retinoid + benzoyl peroxide
- Azelaic acid + benzoyl peroxide
- Topical retinoid + oral tetracycline/doxycycline/minocycline
- Isotretinoin

reduces inflammation by reducing *P acnes* populations. Purely noninflammatory (comedonal) acne is the mildest form of the disease but can be the hardest to treat. Comedones are usually firmly ensconced in the follicle and left untreated cannot be easily expressed. Tretinoin (vitamin A acid) cream is the standard against which all other anti-comedonal agents are compared. It inhibits comedo formation and eliminates comedonal acne in a few months. The only significant side effect is irritation, which is greatest after a few weeks and usually does not require intervention. A moisturizing lotion may be prescribed. Because their skin is inherently irritable, patients with atopic diseases may not tolerate topical retinoids even with moisturization. Other drugs are also useful for inflammatory acne. Adapalene is a naphthoic acid derivative that binds to nuclear retinoid receptors and has retinoid effects. It is effective for comedonal acne and has a measure of anti-inflammatory activity. It is roughly

In the past 10 or so years most dermatologists have observed a decrease in the efficacy of topical erythromycin and clindamycin. This decrease is due to a dramatic increase in *P acnes* resistance to the drugs. Fortunately, the resistance does not translate into hard-to-treat infections, just hard-to-treat acne. The solution is to use the drugs only in conjunction with benzoyl peroxide, which effectively prevents the acquisition of resistance.

Oral antibiotics that are effective in the treatment of acne include erythromycin, tetracyclines, trimethoprim-sulfamethoxazole, and ciprofloxacin. Because of concerns about the generation of a resistant gastrointestinal flora, the latter 2 drugs are reserved for problematic cases. Tetracycline antibiotics have the advantage of additional anti-inflammatory activity in acne and are the most widely prescribed agents. Of the tetracycline antibiotics, doxycycline and minocycline have the most beneficial effects on acne and are well tolerated and safe.

Because of the clear link to androgens, acne is often thought of as a hormonal disease, but it is unusual for a hormonal drug to be effective as monotherapy. Occasionally it is useful to add hormonal therapy to an acne regimen for women. Two types of drugs may be used, oral contraceptives and spironolactone. Although only 2 oral contraceptives are currently approved for marketing as an acne treatment, it is likely that most are helpful in acne to a degree.

How does one treat acne during pregnancy? Tetracyclines may cause staining of teeth and bones and is contraindicated. Although commonly perceived as a teratogen, topical tretinoin does not raise circulating vitamin A levels and does not result in fetal deformity. Nevertheless, many patients and physicians want to avoid worries and the drug is usually not prescribed during pregnancy. Benzoyl peroxide, azelaic acid, and oral ery-

KEY POINT

Mild acne can be treated with topical benzoyl peroxide or antibiotics; severe acne requires oral therapy.

equivalent to topical tretinoin, but is somewhat less irritating. Tazarotene is a potent anticomedonal retinoid cream that is only slightly more irritating than tretinoin. Azelaic acid is a dicarboxylic acid that has both antibacterial and comedolytic effects. Topical application of this drug is fairly effective in reducing comedones, and it is the least irritating of the preparations. The side effect of hypopigmentation may be desirable in some patients.

thromycin are considered to be safe for use during pregnancy; however, since nausea and heartburn are common during pregnancy, erythromycin should probably not be administered and the acne should be treated topically.

KEY POINT

Isotretinoin is a potent therapy for severe acne. After 4 to 6 months, most patients have little or no disease, and 80% have complete long-term remission and possibly cure of the disease.

A word must be said about topical steroids in the treatment of acne—*don't*. Topical steroids will actually cause acne and invariably atrophy of facial skin if used for any length of time. Intralesional triamcinolone acetonide is useful to calm large nodules but can cause pitting and hypopigmentation, both of which will eventually resolve. Commonly used is 0.05 mL of a 2-mg/mL dosage.

Nodular, scarring acne that resists oral antibiotics and topical retinoids is usually treated with oral isotretinoin. Isotretinoin is a potent therapy for severe acne. If treated with 1 mg/kg per day for 4 to 6 months, most patients have little or no disease, and 80% have complete long-term remission and possibly cure of the disease. Unfortunately, isotretinoin has significant side effects. There is an initial flare of acne in many patients that can be blunted by beginning at a low dose (eg, 20 mg) and then increasing to ~1 mg/kg after 1 month. Patients with truncal acne may have a particularly severe flare of disease. These patients are usually started on 20 mg of isotretinoin along with 20 mg of prednisone for the first month. The drug also produces dry skin and mucosae, elevated triglycerides in about 30% of patients, and occasional muscle or joint aches. Transaminase levels are occasionally elevated, but investigation usually determines that this elevation is muscle-derived rather than of hepatic origin.

Recently there has been much public concern expressed about depression caused by isotretinoin.

Large studies have failed to show a correlation between isotretinoin and mental illness. Discuss the use of isotretinoin with patients and parents if appropriate and agree to discuss any problems that may arise during usage. The more important issue is teratogenicity. This drug when taken orally produces a high rate of miscarriage and babies born with deformity; therefore pregnancy must be rigorously avoided. Fortunately isotretinoin is rapidly eliminated, and female patients may conceive safely 1 full menstrual period after stopping the drug.

ROSACEA

Rosacea is a chronic adult skin disorder affecting both the skin and the eye. Rosacea usually starts in the late 20s. It is most common in fair-skinned persons, especially those with a history of facial rubor. Some patients express only persistent redness and telangiectases; others develop sebaceous overgrowth (rhinophyma), inflammatory papules, or nodules. Lesions are most numerous on the central face. Approximately 50% of rosacea patients have ocular involvement, which may manifest as irritation, styes, chalazia, and corneal damage. Ocular disease severity bears no relation to skin disease severity.

The cause of rosacea is uncertain. Vascular reactivity is certainly a predisposing factor, but it is not known why some patients develop sebaceous hyperplasia and others develop pimples. The normal flora mite *Demodex folliculorum* has been implicated, but no studies exist to confirm the suspicion. Gastric disease caused by *Helicobacter* species was once implicated but now has been disproved as a cause of rosacea.

Topical drugs that are helpful in treating rosacea include metronidazole, azelaic acid, and sodium sulfacetamide; however, response may take weeks to be apparent. Ocular rosacea and more severe inflammatory rosacea respond well to oral doxycycline or minocycline, and in rare cases isotretinoin may be useful.

SUMMARY

The goal of acne treatment is to stop the formation of new comedos, or pimples, and to reduce the severity of skin lesions. Several topical medications are available that will control or reduce, if not

eliminate, all but the most severe acne. Oral therapy should be prescribed for the most hard-to-treat acne and topical steroids should not be used. Rosacea also responds well to topical therapy. The primary care physician should communicate clearly with the patient stressing that there are no “quick fixes” and acne and rosacea take time to respond to treatment.

SUGGESTED READING

Plewig G, Kligman AM. *Acne and Rosacea*. 2nd ed. Berlin, Germany: Springer-Verlag; 1993.

Webster GF. Inflammation in acne vulgaris. *J Am Acad Dermatol*. 1995;33:247–253.



Dialogue Box

ADVISORY BOARD

How do you initiate treatment with isotretinoin?

WEBSTER

Although the recommended dose is 0.5 to 2.0 mg/kg per day, that is not a prudent initial dose. I typically start isotretinoin at 20 mg a day since there's always a risk of a flare when you start with a higher dose. By starting at a low dose, you minimize the flare. After the first month if the medication has been well tolerated, I generally increase the dose to a milligram per kilogram.

ADVISORY BOARD

Do you split the dose into 2 equal doses?

WEBSTER

No, I don't split it. It's hard enough to get patients, especially adolescents, to take a medication once a day. I tell them to take it once with food. This gives them high blood levels, and it's actually better than twice a day without food so far as the half-life is concerned. The only reason why splitting the dose is listed as an option is because that's how it was used in the original studies.

ADVISORY BOARD

What is the impact of isotretinoin on the reproductive potential of male patients treated with this agent?

WEBSTER

Although isotretinoin is teratogenic in women, this is not the case in males. In fact, the only thing isotretinoin does to sperm is correct aberrant motility. Thus, it can potentially make men who are relatively infertile more fertile.

ADVISORY BOARD

Isn't isotretinoin a prokeloidal agent? Isn't it more of a problem in black patients?

WEBSTER

We still don't know whether that's true. The current dogma is that isotretinoin is a prokeloidal agent in everybody, not just blacks. Thus, you don't want to perform a surgical procedure, particularly a dermabrasion or a laser abrasion, while a patient is taking isotretinoin and maybe not for a while after the patient stops taking it. However, studies are lacking to say whether that's even true. We do know that isotretinoin and all the oral retinoids predispose you to the development of pyogenic granulomas, and that is the main reason not to do surgery while a patient is taking isotretinoin. In addition, no one knows what the waiting time is before it's safe to perform a dermabrasion. Some dermatologists say a year because it takes that long for the sebaceous glands to come back, but no one really knows.

ADVISORY BOARD

How do the 3 main anticomedonal agents compare?



Dialogue Box

WEBSTER

When you average them out and survey dermatologists, most would say that adapalene is the weakest comedolytic but the least irritating, tretinoin is in the middle, and tazarotene, although slightly more irritating, is probably most effective. Over a very narrow range, the degree of skin irritation induced is proportionate to their efficacy, but the resulting irritation is not necessarily treatment limiting. They are all good drugs.

ADVISORY BOARD

Why do benzoyl peroxides prevent drug resistance?

WEBSTER

Because they are antiseptics not antibiotics. Benzoyl peroxide is an oxidizing agent that generates a lot of peroxide most bacteria are simply not capable of standing up to. By effectively reducing the total number of bacteria, you naturally have a lower probability of fostering a mutation that is resistant. In addition, even if you have resistance present, you're not dealing with the selective force of 1 antibiotic that they can grow through.

ADVISORY BOARD

Does the old adage that you have to make the skin "red and dry" with benzoyl peroxide for it to be effective have any merit?

WEBSTER

That rationale harkens back to the days when acne was treated with peels and benzoyl peroxide was used as a peeling agent. Studies have since demonstrated that the main mechanism of action is the killing of *P. acnes* and the weakest available benzoyl peroxide formulation is as effective as the strongest. As a result, concentration of the benzoyl peroxide should no longer be regarded as the

limiting factor. And it is no longer necessary to titrate the concentration from 2.5% to 5% to as high as 10% to 20%. The important thing is to make sure that patients apply it everywhere they get a pimple and not just spot-treat.

ADVISORY BOARD

How do you use azelaic acid?

WEBSTER

Azelaic acid is a weird drug. Although it's weak on its own, if you add it to benzoyl peroxide it works as well as a drug such as Benzamycin®. Studies are going on now to determine whether azelaic acid is doing anything or if the benzoyl peroxide alone is as effective as Benzamycin® and the azelaic acid is just riding along. I use it particularly in black patients and medium-pigmented patients because it's also a "melanocyte discourager" and makes the postinflammatory hyperpigmentation go away. If you talk to black patients and tease out what they hate most about acne, it's the fact that they get postinflammatory pigmentation that outlives the original acne lesion by many weeks.

ADVISORY BOARD

In patients with acne rosacea, how do you treat those patients with solely telangiectatic lesions? How do you treat patients with primarily pustular lesions arising from sebaceous hyperplasia?

WEBSTER

Telangiectatic lesions are fairly resistant to anything other than laser treatment. Since no medications will shrink telangiectases, I turn the pulse dye laser on them to make them go away. For sebaceous hyperplasia, a variety of topical and systemic agents are available. I typically initiate treatment with a topical metronidazole agent such as Noritate™ or MetroGel®.



Dialogue Box

ADVISORY BOARD

Does Noritate have FDA approval for the treatment of the erythema associated with acne rosacea?

WEBSTER

Yes, but when you look at how the studies were done, erythema alone was not differentiated from peri-lesional erythema. When the FDA was judging the efficacy of Noritate against erythema, it was not against just blush and telangiectases but the redness that surrounded pustules.

ADVISORY BOARD

How does tetracycline work in acne rosacea?

WEBSTER

Tetracycline is a great drug for rosacea. Since *P. acnes* plays no role in acne rosacea, tetracycline's efficacy stems more from its antineutrophil chemotactic and anti-inflammatory effects than its antibacterial action. This is why erythromycin is not as good as tetracycline—it's not as anti-inflammatory as the tetracycline family.