Guidelines for Treating Acne

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Abstract: Acne, a chronic inflammatory disease of the pilosebaceous units of the face, neck, chest, and back, is the most common skin disorder occurring universally, with an estimated prevalence of 70–87%.

Mild acne can be purely comedonal or mild papulopustular, with a few papulopustules present as well. Moderate acne is characterized by numerous comedones, few to many pustules, and few small nodules, with no residual scarring. Very severe acne can be recognized by sinus tracts, grouped comedones, many deeply located nodules, and severe inflammation and scarring. Although acne does not affect health overall, its impact on emotional well-being and function can be critical and is often associated with depression, anxiety, and higher-than-average unemployment rates.

To determine the appropriate treatment, a thorough medical and family history should be obtained. Certain medications may aggravate acne and interact with the prescribed drugs, and a family history of severe acne determines a more protracted course. The duration of the disease, past and present response to therapy, and skin type (those with darker skin types are more prone to postinflammatory hyperpigmentation) are factors that will help guide therapeutic decisions. Grading of acne should be attempted, focusing on the most severe lesions present (because adequate treatment covers all less-severe lesions) and on the presence or likelihood of physical or psychological scarring.

Compliance is another important parameter of successful treatment, so every effort should be made to ensure it. Simple regimens with no more than three drugs, along with a fully explanatory consultation dispelling misconceptions that diet or uncleanness are the cause of acne and explaining that the optimal result will be achieved only after months of therapy are mandatory. The patient should be informed about the possible exacerbation of acne at the beginning of treatment and told that picking the lesions will aggravate scarring. The patient should also be advised to apply the topical treatment to the entire affected area and not only on the lesions.

Sebaceous hyperplasia with seborrhea, ductal hypercornification, Propionobacterium acnes colonization of the follicle, and inflammation and immune response are the most notable pathophysiologic factors influencing the development of acne. Treatment should target as many of these factors as possible. A wide range of topical and systemic treatments are available, and new ones are under development.

Mild Acne

Mild Comedonal Acne

Topical retinoid therapy is the treatment of choice for mild comedonal acne. Exerting their action through nuclear receptors, retinoids help eliminate mature comedones and inhibit the formation of new ones. They also have anti-inflammatory actions (particularly third-generation retinoids), making them suitable for inflammatory forms of acne as well. Currently used topical retinoids include tretinoin, isotretinoin, adapalene, tazarotene, retinaldehyde, and 6-retinoylglucoronide.

Tretinoin is available in cream (.025%, .05%, .1%), gel (.025%, .1%), and solution (.05%) forms. Patients should be informed that irritation and a pustular flare at the beginning of therapy may occur. Two newer formulations of tretinoin, polyolprepolymer-2 and a microspponge delivery system, seem to be better tolerated. Tretinoin is photodegradable and may also cause photosensitization, so it should be applied at night beginning with a lower-strength product, particularly in individuals with sensitive skin. In patients with sensitive skin, another retinoid with a lower irritancy potential may be preferable.

Adapalene has a comparable efficacy to tretinoin .025%, with a low irritancy potential due to its intrinsic anti-inflammatory activity. Adapalene is stable with oxygen and light; thus night application is not manda-
EMLA cream have proven useful. Moreover, it has been reported that adapalene gel 1% is equally effective and significantly better tolerated than tretinoin cream and tretinoin microsphere gel 1%. Isotretinoin is available in a gel formulation (0.05%). Its efficacy is similar to tretinoin but with lower local irritancy. The gel form demonstrates no effect on sebum secretion, in contrast to oral isotretinoin, and it produces no systemic toxicity, due to negligible absorption.

Although tazarotene applied once daily is more effective than tretinoin in reducing noninflammatory lesions, its tolerability is no better. Alternatively, tazarotene may be applied in a short contact manner from 30 seconds to 5 minutes once daily with equal results and reduced irritancy; this could be a reasonable approach with other retinoids as well. Although not extensively studied, retinoic acid-glycuronide, retinaldehyde, and motretinide (the latter available only in Switzerland) have shown promising results and with good tolerability profiles. They could be recommended as alternatives to other retinoids.

Azelaic acid, available in a 20% cream formulation with mild comedolytic and antimicrobial effects, may be used as a second-line treatment. It may be especially useful during the summer months, because it does not produce any photosensitization, and in patients who cannot tolerate topical retinoids.

Hypopigmentation resulting from topical retinoids and azelaic acid is desirable for dark-skinned patients with postinflammatory hyperpigmentation. Salicylic acid (1–5%) a b-hydroxyacid with mild keratolytic and anti-inflammatory properties, can be used complementary to topical retinoids to treat mild comedonal acne. A-hydroxyacids (6–15%) reduce follicular corneocyte adhesions, enabling desquamation and preventing formation of new comedones. In higher concentrations (30–70%) for brief exposures, they will unroof pustules. They may be recommended as second-line treatment and complementary to retinoids.

Physical treatments aiming to eliminate larger comedones through extraction or electrocauterization under EMLA cream have proven useful.

Mild Papulopustular Acne

Mild papulopustular acne is usually responsive to twice-daily topical treatment involving a topical retinoid and an antibacterial. Along with their comedolytic and anti-inflammatory properties, topical retinoids also enhance the penetration of other topical agents. The most commonly used antibacterial agents are benzoyl peroxide, azelaic acid, and topical antibiotics, including clindamycin and erythromycin. Benzoyl peroxide is available as a solution washing gel or cream (1–10%). Its major disadvantage is irritation, which can be minimized by using lower concentrations, which seem equally efficacious. It bleaches hair and clothes and may cause contact allergy. Very rarely it produces photosensitivity. Its effectiveness against P. acnes is well recognized, with evidence of acquired bacterial resistance; in fact, it helps control antibiotic-resistant propionobacteria. It does not have any significant comedolytic or anti-inflammatory properties, however. Combined treatment with adapalene is possible, because benzoyl peroxide is stable to oxygen exposure (in contrast with tretinoin). Topical antibiotics (eg, clindamycin, erythromycin) reduce the population of P. acnes and demonstrate a mild anti-inflammatory effect, but the emergence of bacterial resistance limits their use. Therefore, as a monotherapy they have little to offer, and their use should be limited to 3–4 weeks. A combination with zinc or benzoyl peroxide could be more useful, because bacterial resistance could be avoided. When used in combination with a topical retinoid, topical antibiotics should be withdrawn as soon as inflammatory lesions subside. If this is not possible, then they should be replaced by benzoyl peroxide or a combination of an antibiotic with benzoyl peroxide.

Azelaic acid is a second-line option for treating mild papulopustular acne.

Moderate Acne

Systemic drug therapy is an integral aspect of treatment for moderate acne. Systemic therapy should always be considered in disease with a tendency for physical or psychological scarring or postinflammatory hyperpigmentation; in widespread disease involving the shoulders, back, and chest; and in patients resistant to topical treatment. Options include oral antibiotics, hormonal therapy, and oral retinoids.

Oral antibiotics prescribed for acne include erythromycin, the tetracyclines (tetracycline, doxycycline, lymecycline, and minocycline), and trimethoprim sulphonmethoxazole. They all target P. acnes and inhibit its growth, but erythromycin and the tetracyclines have additional anti-inflammatory properties. Erythromycin at a dose of 1 g/day with meals may cause gastrointestinal upset, in which case intestine-soluble preparations are preferable. Tetracycline is administered at a dose of 1 g/day; once marked clinical improvement is noted, the dose can be reduced to 500 mg/day. The patient should be instructed to take the medication 1 hour before meals and without milk; otherwise, absorption will be reduced. Lymecycline at a dose of 150–300 mg/day should be taken before meals as well. Doxycycline and minocycline started at a dose of 100–200 mg/day and tapered to 50 mg/day once improvement is achieved are taken with food, which slightly decreases absorption but maximizes compliance. Trimethoprim/sulphonmethoxazole (TMP/SMX), at 800 mg
SMX and 160 mg TMP, or trimethoprim, at 300 mg twice daily, are third-line agents. High sebum secretion rates result in decreased concentration of the systemic antibiotic in hair follicles, necessitating increased doses.

Once inflammatory lesions subside, instead of decreasing the dose, it may be preferable to discontinue the antibiotic completely. This will decrease the patient’s exposure to the antibiotic and thus decrease bacterial resistance. The dermatologist should be aware of possible interactions of antibiotics with other prescribed drugs, particularly with oral contraceptives. Although no firm evidence exists, a slight increase in contraceptive failure rate has been reported during antibiotic therapy. All antibiotics may cause vaginal candidiasis and pseudomembranous colitis. Doxycycline may cause photosensitivity and photo-onycholysis. Minocycline has been linked to vestibular disturbances, pigment deposition, and, rarely, drug-induced lupus erythematosus, which usually occurs early in treatment.

Patients taking minocycline should have their liver function and antinuclear factor checked every 3–4 months. Tetracyclines may also cause tooth discoloration and are contraindicated in pregnant women and children.

Oral antibiotics should be used for a minimum of 6–8 weeks and a maximum of 4 months or longer in a responsive patient if other treatments cannot be tolerated. They should always be combined with a topical agent, such as a topical retinoid, and, when given longer than 2 months, with benzoyl peroxide as well, to reduce bacterial resistance. Dissimilar oral and topical antibiotics should be avoided; in case of relapse after successful treatment, the same antibiotic should be prescribed. Resistance to erythromycin is still the most common type of antibiotic resistance encountered, followed by resistance to tetracyclines. Resistant P. acnes appear 12–24 weeks after the start of therapy.

If the patient, while on antibiotics, demonstrates a flare of acne, this can be caused by either of two reasons: bacterial resistance or gram-negative folliculitis. Gram-negative folliculitis necessitates the short-term use of amoxicillin or preferably, isotretinoin.

Oral antibiotics may be combined with hormonal therapy to treat acne in women. Hormonal therapy, combined with topical retinoids with or without topical antimicrobials, is an excellent option in women with moderate papulopustular acne. Women with moderate acne with small nodules can benefit from the combination of oral antibiotics with hormonal treatment plus topical retinoids (with or without topical antimicrobials).

Hormonal therapy is indicated in women with proven ovarian or adrenal hyperadrogenism, hirsutism, androgenetic alopecia, severe sebum secretion, and acne beginning or worsening in adulthood, flaring premenstrually, and located on the beard area. Women who are nonresponsive to other therapies and those who desire contraception and control of their menstrual period are also good candidates for hormonal treatment. Hormonal therapy for acne consists of antiandrogens and agents that inhibit androgen production from the ovary or the adrenal glands. Antiandrogens include cyproterone acetate, spironolactone, and flutamide. Cyproterone acetate inhibits ovulation and blocks the androgen receptor. At a low dose, it is combined with estradiol (35–50 μg) in an oral contraceptive (Dianette). To increase effectiveness, particularly in women with abnormal androgen metabolism, 10–100 mg of cyproterone acetate is added to Dianette during days 5–14 of the menstrual cycle.

Spironolactone blocks the androgen receptor and inhibits 5-a reductase. Usually, therapy begins at a dose of 50 mg/day, with the dosage increased until improvement occurs. It may also be given on days 4–22 of the menstrual cycle. Spironolactone may induce high potassium levels.

Flutamide, an antiandrogen, is administered at a dose of 250–500 mg/day, but lower doses (62.5–125 mg/day) may be effective. Hepatotoxicity, which is age- and dose-dependent, is a concern.

Oral contraceptives block ovarian androgens. Estrogens are combined with progestins, preferably of the second generation (ethynodiol diacetate, norethindrone, levonorgestel) or the third generation (desogestrel, norgestimate, gestodene). Third-generation progestins have the lowest androgenic activity. The lower doses of estrogen used in modern oral contraceptives reduce the risk of thromboembolism, but headaches, breast tenderness, leg edema, and weight gain remain of concern.

Glycocorticosteroids at low doses block adrenal androgen production and are indicated in late-onset congenital adrenal hyperplasia. Prednisolone (2.5–5 mg) and dexamethasone (.25–.75 mg) are administered at bedtime. Dexamethasone has the potential for greater adrenal suppression.

For moderate acne nonresponsive to the aforementioned measures or acne rapidly relapsing on two or three occasions after a temporary good result, necessitating long-term oral therapy, isotretinoin should be considered.

Severe Acne

Isotretinoin is the treatment of choice in cases of severe or very severe nodular acne. Patients with severe psychological disturbance, excessive seborrhea, visible scarring, and gram-negative folliculitis are also good candidates.

Isotretinoin is the most effective anti-acne treatment to date that targets all pathogenetic mechanisms. The optimal dosage is .5–1 mg/kg/day until a total cumu-
lative dose of 120–150 mg/kg is reached. This will usually take 4–6 months. Lower doses may be administered in the event of intolerable side effects, but the relapse rate is high. Doses >1 mg/kg/day are rarely needed and are prescribed mostly for patients with severe chest and back involvement. Longer treatment schedules are needed when low-dose regimens (1–5 mg/kg/day) are prescribed to treat severe acne with deep nodules, particularly in extracutaneous involvement and long-standing disease. Treatment should be discontinued once cure is achieved.

Starting with a lower dose (.5 mg/kg/day) for the first month to avoid a flare of the disease and increasing the dose to 1 mg/kg/day during the second month might be a wiser course of treatment. Intermittent administration of isotretinoin at a dose of .5 mg/kg/day for 1 week every 4 weeks for a total of 6 months has proven effective in patients with mild acne and low sebum excretion. It cannot be recommended for average cases, however, because of a high relapse rate. Pustules respond most readily to isotretinoin, followed by papules. Whereas a flare might be observed at the end of the first month of treatment, the response is clinically evident at the end of the second month; patients should be informed of this. Clearing the macules before isotretinoin administration is mandatory, because this will prevent a severe flare of the disease.

But if, despite precautions, a flare supervenes (which occasionally resembles acne fulminans), then prednisolone at a dose of .5–1 mg/kg/day for 4–6 weeks is necessary, with reduction of the isotretinoin dose or discontinuation and gradual reinitiation. In very severe disease, pyoderma faciale, or acne fulminans, oral prednisolone for 2–6 weeks may precede the initiation of isotretinoin therapy. Patients should be informed about isotretinoin’s effect on blood lipid levels, as well as its possible mucocutaneous, ophthalmologic, neurologic, musculoskeletal, and gastrointestinal side effects. Depression and suicidal behavior is another issue, and although the link to isotretinoin is a matter of debate, it is best to assume that a link exists, albeit in a very small number of patients, and thus all patients should be informed in detail of this potential risk. The most important issue is that of teratogenicity; the dermatologist should make every effort to ensure that female patients are maintaining effective contraception 1 month before initiation of, throughout the course of, and up to 6 weeks after discontinuation of isotretinoin therapy. Treatment is initiated on the second or third day of the menstrual period once pregnancy is excluded by two negative pregnancy tests. Pregnancy tests should be obtained before initiation of isotretinoin therapy as a baseline and again after 1 month and 2 months of therapy. If no abnormalities are detected, then no further testing is needed. If significant alterations are noted, then discontinuation of isotretinoin should be considered. For milder alterations, a dosage reduction may restore any laboratory abnormalities. If therapy exceeds 1 year, any skeletal effects should be recorded and evaluated accordingly. Should serum lipids levels increase, a lipid-lowering agent (gemfibrozil or atorvastatin) may be added.

Isotretinoin is absolutely contraindicated in pregnancy, lactation, and severe hepatic and renal dysfunction. Concomitant use of tetracyclines increases the risk of pseudotumor cerebri and should be avoided. If pseudotumor cerebri occurs as result of isotretinoin alone, then the drug should be discontinued immediately. Vitamin A and high doses of aspirin should also be avoided.

One-third of patients relapse after successful isotretinoin treatment. Usually this is noted in the first year after discontinuation of therapy. In this case, another course of isotretinoin may be administered, or another modality may be tried according to the severity of the acne. Women with endocrine abnormalities must maintain the successful result with appropriate hormonal treatments.

Maintenance Therapy

Maintenance therapy is mandatory after every successful acne treatment. Topical retinoids are generally recommended; benzoyl peroxide may be added in some cases.

Cosmetic Use

Cosmetics play an important role in treating all forms of acne. They should be noncomedogenic and should improve the skin’s appearance by minimizing erythema and providing adequate camouflage. In particular, patients receiving isotretinoin therapy need moisturizing agents for the skin and lips to overcome the drying effects of the drug.

Treatment During Pregnancy

For pregnant patients, oral or topical erythromycin and benzoyl peroxide are the safest choices. Should severe inflammatory lesions occur, short courses of oral steroids may be instituted.

Conclusion

With all of the available treatments for acne, we should no longer encounter patients who are severely scarred emotionally or physically. The dermatologist should remember that combination therapies work better and
should not reserve drastic therapies only for patients with severe acne.

The roles of lasers and phototherapy or photodynamic therapy in treating acne need to be further elucidated before any recommendations can be made. In the future, treatment likely will include new agents such as leukotriene inhibitors, as the pathogenetic mechanisms are further explored and appropriate targeting of therapy is achieved. Figure 1

References