

Skin Therapy Letter[®]

Volume 1 • Number 2 • October 2005

Clinical Evidence. Practical Advice.

EDITOR: DR. STUART MADDIN

Dr. Stuart Maddin, MD, FRCPC

EDITOR-IN-CHIEF

Dr. Stuart Maddin, Chairman of SkinCareGuide, is one of North America's leading dermatologists, and is the author



of numerous dermatologic journal articles, monographs and textbooks. In addition to providing consultative input to a number of pharmaceutical and biotech companies, he is the director of the clinical trials unit at the Division of Dermatology, University of British Columbia. Dr. Maddin has also acted in an advisory capacity to a number of drug regulatory agencies, such as the Health Protection Branch (Ottawa), the AAD-FDA Liaison Committee and WHO (Geneva). As well as being the founder of the Dermatology Update symposia, now in its 21st year, he is past President of the Canadian Dermatology Association and served as Secretary-General of the International Committee of Dermatology — International League of Dermatological Societies.

Dr. Deborah Koudys, MD, CCFP, FCFP

FAMILY PHYSICIAN ADVISOR

Dr. Deborah Koudys graduated from medical school at the University of Western Ontario in 1979, and following a residency in Family Medicine in London,



Ontario, she entered into private practice with 8 other Family Physicians, where she continues to practice today. She is an Adjunct Professor of Family Medicine at the University of Western Ontario, and a Fellow of the College of Family Physicians of Canada.

Psoriasis Vulgaris

L. Guenther, MD, FRCPC*Professor of Dermatology, University of Western Ontario, London, Canada*

Psoriasis Vulgaris

Psoriasis vulgaris is an autoimmune disease in which activated T-cells express TH1 cytokines. It is manifested by cellular hyperproliferation, lack of differentiation and inflammation. Approximately 1/3 of patients have a relative with psoriasis, and 85% have a link with the HLA-Cw6 gene.

Impact on the Sufferer

Psoriasis has a greater mental and physical impact than myocardial infarction, hypertension, diabetes mellitus, arthritis, and cancer; only depression had a greater mental impact, and congestive heart failure a greater physical impact.[Rapp SR, et al. J Am Acad Dermatol 41:401-7 (1999).] A 1998 US National Psoriasis Foundation survey showed that 40% of individuals with psoriasis had trouble receiving service in establishments such as hair salons, pools and health clubs. In the 18-34 year age group:

- 81% felt embarrassed
- 75% felt unattractive
- 54% suffered from depression
- 10% had contemplated suicide.

Diagnostic Features of Psoriasis Vulgaris

- Red, scaly plaques that are often itchy and are commonly located on the elbows, knees, lumbo-sacral area, and scalp, although any part of the skin may be affected
- Chronic, but may have periods of remission
- May have concomitant nail changes (pitting, onycholysis, oil drop changes, subungual hyperkeratosis, nail plate thickening)
- May have psoriatic arthritis (in ~30% of population).

Treatment: Self-help and Medical Treatments

Treatment depends on:

- the sites of involvement
- severity
- response to previous treatment
- other medical conditions
- concomitant medications
- proximity to medical resources (e.g., phototherapy units)
- patient preference.

1. Patient Self-help

- Avoid trauma (e.g., a scrape). In ~1/3 of patients injury to the skin can induce psoriasis in the area of injury (called the “Koebner phenomenon”).
- Clean with mild cleansers and tepid water.
- Moisturizers minimize scaling, painful fissuring and itching. They should be applied immediately after bathing.
- Salicylic acid is a keratolytic and increases the penetration of topical corticosteroids. It is helpful for thick scaling and on the palms, soles and scalp.
- Apply tar bath oils, creams, lotions and ointments once or twice daily. Use is limited by the smell, potential to stain, irritation, and folliculitis.
- Shampoos containing tar, salicylic acid, zinc pyrithione, ketoconazole and many “dandruff” shampoos can help with scalp scaliness.
- Hydrocortisone cream may be helpful for facial and fold psoriasis; however, a stronger topical corticosteroid is usually required elsewhere.
- Oral antihistamines help with itching. Non-sedating ones should be used during the day and sedating ones at bedtime.

2. Medical Treatment

Avoid Aggravating Medications

In some patients beta-blockers, ACE inhibitors, antimalarials and lithium may aggravate the disease or make it more resistant to treatment.

Topical Agents

These are the most commonly used treatments, either as monotherapy for localized disease, or as adjunctive treatment for moderate-to-severe disease.

Topical Corticosteroids

- Available in low, medium, high and ultra high potency
- Use lotions for the scalp, creams and ointments elsewhere, and gels anywhere
- Use the steroid with the lowest effective potency, particularly on the face and folds
- Safe for short-term or intermittent long-term treatment
- Once daily is often as efficacious as twice daily
- May be able to maintain remission with intermittent use 2-3 times/wk
- Adverse effects include:
 - atrophy
 - striae
 - telangiectasia
 - contact sensitization
 - tachyphylaxis (lack of effect with continued use)
 - flare upon discontinuation
 - adrenal suppression.

Topical Calcipotriol (Dovonex®)

- Cream and ointment for trunk and limbs; also a solution for the scalp
- Use twice daily to obtain control, then once or twice daily to maintain remission
- May also maintain remission with weekday calcipotriol and weekend superpotent topical corticosteroid (e.g., Ultravate®)
- Synergistic with potent or superpotent topical corticosteroids, ultraviolet B (UVB) phototherapy, psoralen + ultraviolet A (PUVA) phototherapy, methotrexate, cyclosporine, and acitretin
- Safe long-term, 100g/wk maximum
- Adverse effects:
 - irritation (usually mild; rarely results in discontinuation)
 - facial dermatitis.

2. Medical Treatment (continued)

Topical Dovobet®

- Contains calcipotriol and betamethasone dipropionate in the same concentrations as Dovonex®, and Diprosone®, respectively
- Once daily application
- ~50% of patients are clear or almost clear after 4 weeks of treatment
- Faster and more efficacious than its individual components
- Similar cutaneous adverse events to betamethasone dipropionate; ~ half that of calcipotriol
- Consider maintaining remission after Dovobet® treatment with either calcipotriol monotherapy or calcipotriol during weekdays and Dovobet® on the weekends.

Topical Tazarotene (Tazorac®)

- Selective retinoid
- Commonly used once daily with a mid- or high-potency steroid once daily
- Improvement may be maintained with Mon/Wed/Fri tazarotene and Tues/Thurs clobetasol ointment
- Synergistic with topical corticosteroids, calcipotriol, phototherapy (UVB, PUVA)
- Contraindicated in pregnancy
- Irritation limits use.

Topical Calcineurin Inhibitors

- Topical pimecrolimus (Elidel®, 1% cream) and tacrolimus (Protopic®, 0.03% and 0.1% ointment) twice daily for facial and intertriginous psoriasis
- Do not cause atrophy
- May cause burning or stinging, particularly initially.

Intralesional Corticosteroids

- Small plaques may be injected with triamcinolone 10mg/cc diluted with saline or water to 5mg/cc.

Moderate-to-Severe Disease

Psoriasis is considered to be moderate-to-severe if it affects 10% or more of the body surface area, OR less than 10% if:

- a) plaques are very red, thick, and scaly, or
- b) there is a significant impact on quality of life (e.g., functional impairment, marked discomfort) or
- c) disease is resistant to topical agents. Phototherapy, traditional systemic agents and biologic agents are used with adjunctive topical agents.

Phototherapy

- Broad band UVB (290-320nm), Narrow band (311nm) to be given 2-5 times/week or
- PUVA (UVA: 320-400) to be given 2-3 times/week.

Traditional Systemic Medication

- Methotrexate 5-25mg once weekly: helps skin and arthritis; may cause bone marrow suppression and hepatotoxicity (a liver biopsy should be done after a cumulative dose of 1.5gm)
- Cyclosporine 2.5-5mg/kg/day: treatment should be limited to 1 year due to risk of nephrotoxicity
- Acitretin 25mg-50mg/day: often combined with phototherapy; teratogenic, so rarely used in women with childbearing potential (must avoid pregnancy for at least 2-3 years after discontinuation). Adverse effects also include mucocutaneous dryness, lipid elevation, hepatotoxicity, and bony abnormalities.

Biologic Agents

- Treatments that target specific cells, molecules and receptors
- Alefacept (Amevive®) is currently the only approved biologic agent in Canada for the treatment of psoriasis
- Etanercept (Enbrel®) may halt radiographic progression of psoriatic arthritis
- Studies have also shown efalizumab, infliximab and adalimumab to be efficacious in the treatment of psoriasis.

Optimal Management of Acne to Prevent *P. acnes* Resistance

M. T. Haroun, MD, FRCPC

Assistant Professor of Medicine, Division of Dermatology, University of Toronto,
Sunnybrook and Women's College Health Sciences Centre, Toronto, Canada

Acne Vulgaris

Acne vulgaris is a disease of the pilosebaceous follicle characterized by noninflammatory (open and closed comedones) and inflammatory lesions (papules, pustules, and nodules). Its pathogenesis is multifactorial, i.e., hormonal, bacterial and immunological (inflammatory) factors are involved, and their interaction results in the production of acne lesions. Although it is not a life-threatening condition, it can have a detrimental effect on a patient's quality of life. It is readily responsive to treatment with the goals being to clear the lesions, prevent scarring, and reduce the psychological distress.

Possible Causes of Acne

Hormones are known to affect sebum production, but may well play a role in follicular hyperkeratinization independent of the effect on the sebaceous gland. During adrenarche, an increase in adrenal androgens leads to:

- an increase in the size of sebaceous glands and a resulting increase in sebum production
- abnormal desquamation and greater adhesion of the shed keratinocytes in the sebaceous follicle, leading to obstruction in the follicle, and resulting in production of the microcomedo: the precursor of all acne lesions.

Colonization of the pilosebaceous apparatus by the anaerobic diphtheroid *Propionibacterium acnes* (*P. acnes*) occurs in this anaerobic environment where sebum provides the nutrition for its survival. This gram-positive bacterium contributes to the inflammation by

- releasing enzymes
- inducing cytokine release from other cells
- inducing immune response (e.g., antibody production).

Topical Treatments

Topical antibiotics have been used to treat acne for more than 40 years and are still widely used. Their efficacy is partly due to their reduction of the *P. acnes* population and partly due to the reduction of inflammatory mediators. The emergence of resistant strains has in some cases been associated with a failure to respond to antibiotic therapy. This resistance was first reported with the topical antibiotics clindamycin and erythromycin.[Crawford WW, et al. *J Invest Dermatol* 72:187-90 (1979).] The use of benzoyl peroxide (BP) helps to reduce the occurrence of resistance and can be effective in the treatment of both nonresistant and resistant *P. acnes* strains. BP does not promote antimicrobial resistance and has been shown to prevent such resistance when used concomitantly with topical erythromycin.

| Clinical Study | Treatment | Results |
|---|---|---|
| Double-blind study of patients with mild-to-moderate acne [Eady EA, et al. <i>Br J Dermatol</i> 134:107-13 (1996).] | 5% BP/3% erythromycin (BP/E) gel vs. erythromycin alone applied for 6 weeks | The number of erythromycin-resistant strains was significantly reduced in the BP/E group compared with the group who received erythromycin alone. |
| Open study of patients with erythromycin-resistant strains of <i>P. acnes</i> . [Eady EA, et al. <i>Br J Dermatol</i> 134:107-13 (1996).] | 5% BP/3% erythromycin (BP/E) gel vs. erythromycin alone applied for 6 weeks | Highly significant reductions were also seen in acne grade and lesion counts with the BP/E combination. |
| Two double-blind randomized, parallel, vehicle-controlled trials of acne patients [Lookingbill DP, et al. <i>J Am Acad Dermatol</i> 37:590-5 (1997).] | BP/clindamycin combination, BP, clindamycin or vehicle gels applied once nightly for 11 weeks | The combination gel was significantly superior to the two individual agents in global improvement and reduction of inflammatory lesions. |
| Randomized, multicenter, single-blind trial of moderate-to-severe acne patients [Leyden JJ, et al. <i>J Cutan Med Surg</i> 5:37-42. (2001).] | 5% BP/1% clindamycin, 5% BP or 5% BP/3% erythromycin applied twice daily for 10 weeks | Compared with BP, BP/clindamycin demonstrated significantly greater reductions in inflammatory lesions. BP/clindamycin was comparable to BP/E. |

Table 1: Clinical trials demonstrating efficacy for combination treatments with BP and clindamycin or erythromycin

Topical Treatments (continued)

Advantages of BP/Antibiotic Combination

1. less irritation than BP alone
2. increase tolerability to topical retinoid
3. better efficacy than BP alone.

There are many acne grading systems, but it may be easier to use a descriptive grading system using the terms mild, moderate, and severe with descriptors of comedonal, inflammatory, nodular, and scarring acne.

Comedonal Acne

Non-inflammatory (comedonal) acne is best treated with a topical retinoid. Options include tretinoin, adapalene, and tazarotene. Not only do retinoids inhibit comedo formation, they can usually clear all degrees of comedonal acne, but this may take a few months. BP has mild comedonal activity.

Oral Treatments

Acne that does not respond to topical therapy, causes scarring, or presents with nodular lesions should be treated orally. Options for oral therapies include antibiotics, hormonal therapy and isotretinoin. Isotretinoin is usually used as monotherapy. Both oral antibiotics and hormonal therapies should be used in combination with topical retinoids and BP.

Prescribing habits to minimize resistant strains of *P. acnes*

1. Antibiotics should not be used as monotherapy, nor should they be used to treat mild acne.
2. Avoid topical antibiotics if non-antibiotic topical preparations will suffice.
3. Use alternatives to antibiotics for maintenance.
4. Stop antibiotic treatment when the skin clears or if no further improvement is noted.
5. If there is a failure to respond to oral antibiotics or a rapid relapse after discontinuation consider other therapy (e.g., systemic retinoid, anti-androgens [in women]).
6. If the antibiotic is needed again, use the same antibiotic.
7. Use full doses of antibiotics and do not taper.
8. Avoid concomitant topical and systemic use of different antibiotics to reduce the risk of developing resistance to both.
9. Do not switch or rotate antibiotics in non-responders.
10. Use BP during antibiotic therapy.

| Feature | Systemic Drugs | Topical Drugs |
|-------------------------------|--|--|
| Sebum overproduction | Estrogen, spironolactone, other anti-androgens, isotretinoin | None. |
| Follicular keratinization | Isotretinoin, antibiotics (indirect effect), anti-androgens | Tretinoin, adapalene, tazarotene, salicylic acid Antibiotics and BP (indirect effects). |
| <i>P. acnes</i> proliferation | Tetracycline, minocycline, doxycycline, erythromycin, trimethoprim, isotretinoin | Clindamycin, erythromycin, BP, BP/antibiotics combos. |
| Inflammation | Corticosteroids, isotretinoin, dapsone, antibiotics, NSAIDS | Intralesional corticosteroids, topical antibiotics, BP/antibiotic combos, some retinoids. |

Table 2: Major pathophysiologic features of acne and drugs that affect them

Side-Effects

Mild-to-moderate inflammatory acne can usually be managed with two topical drugs. Typically one is applied in the morning and the other at bedtime. A retinoid is used to deal with the precursor of all acne lesions, i.e., the microcomedo, and an antibacterial agent for its effects on *P. acnes*. Topical antibacterial options include BP or a BP/antibiotic combination. BP is extremely effective against *P. acnes*, but can be irritating. The irritation can be minimized by using the lowest concentration of BP in a water-based vehicle that does not reduce its efficacy. Another way to reduce the irritation induced by BP is to combine it with an antibiotic. BP/antibiotic combinations also reduce the irritation that can be induced by a topical retinoid. Only if a patient is allergic to BP (estimates range from 1%-2% of the population) should a topical retinoid be used with a topical antibiotic alone.

Conclusion

Since multiple factors are involved in the pathophysiology of acne, treatment that counteracts the majority of them can be expected to achieve the best results. When considering the options for reducing the *P. acnes* population, it is best to choose those that do not encourage resistance patterns.

Excessive Facial Hair

J. Shapiro, MD, FRCPC and H. Lui, MD, FRCPC

Hair Research and Treatment Centre, and Division of Dermatology, University of British Columbia,
Vancouver, British Columbia, Canada

Hirsutism

Excessive facial hair in women, or hirsutism, is a common problem that may be caused by androgen overproduction, increased sensitivity to circulating androgens, or other metabolic and endocrine disorders. Approximately 80% of women are affected by the presence of excessive hair growth in areas usually recognized as places where male secondary sexual characteristics occur. This can be a source of distress, leading to anxiety, depression and a reduced quality of life.

Differential Diagnosis

It is very important to determine the etiology of this condition. Diagnostic evaluation of the potentially hirsute patient first involves confirmation of the presence of hirsutism and then exclusion of associated or etiological abnormalities and disorders. Investigate or rule out underlying conditions that produce excess androgens using tests such as:

- Serum testosterone
- Serum DHEA (Dehydroepiandrosterone)
- Rule out testosterone secreting tumors.

Hair Removal Techniques

| Technique | Body Area | Advantages | Disadvantages |
|---------------------------------------|--|--|--|
| Plucking | • Face • Eyebrows | • Inexpensive • Regrowth can take weeks | • Painful • Slow |
| Waxing | • Face • Eyebrows • Groin • Trunk | • Regrowth can take weeks | • Painful • Slow • Risk of folliculitis |
| Depilatories | • Extremities • Groin • Face | • Quick | • Can be irritating • Regrowth in days |
| Shaving | • All areas | • Easy • Inexpensive | • Quick regrowth • Risk of folliculitis • Time consuming |
| Electrolysis | • All areas, but usually the face | • May give permanent removal | • Painful • Very time consuming • Expensive • Risk of scarring and skin pigment changes |
| Laser and Intense Pulsed Light (IPL) | • All areas | • May give permanent hair reduction • Efficient | • Painful • Repeat treatments needed • Dark hair required • Expensive • Risk of scarring and skin pigment changes • Rare reports of paradoxical hypertrichosis [Alajlan A, et al. <i>J Am Acad Dermatol</i> 53(1):85-8 (2005 Jul).] |
| Eflornithine 13.9% cream | • Face • Neck | • Regrowth can take weeks • Minimal adverse effects • Can be used in conjunction with other treatments | • Must be continued indefinitely to prevent regrowth |
| Antiandrogens and oral contraceptives | • Inhibits androgen | | • Takes months to show benefit • Some adverse effects |

Table 1: Methods for removing unwanted hair

Treatment Options

Current methods for removing unwanted hair include plucking, waxing (including the sugar forms), depilatories, shaving, electrolysis, laser, intense pulsed light (IPL), and eflornithine 13.9% cream. All these methods are temporary with the time of regrowth ranging from a few days to a few months. Short of surgical removal of the hair follicle, the only permanent treatment is electrolysis. However, the practice of electrolysis lacks standardization. For hirsutism associated with Polycystic Ovary Syndrome (PCOS), treatments include oral contraceptive pills or antiandrogens, such as spironolactone, flutamide and finasteride.

Patients should be adequately advised of the available treatment modalities for hair removal. No single method of hair removal is appropriate for all body locations or patients, and the one adopted will depend on the character, area and amount of hair growth as well as on the age of the patient and their personal preference.

Women and Hirsutism

Women who have hirsutism will need to be evaluated to rule out causes of elevated androgens. PCOS needs to be excluded if there are suspicious clinical features. Medications such as spironolactone and oral contraceptives, e.g., cyproterone acetate + ethinyl estradiol, can be of value.

Ornithine Decarboxylase (ODC)

ODC is an enzyme that has been associated with the prolongation of the anagen or growth phase of the hair. Thus, when ODC is decreased, the length of time the hair is in the growth phase is also reduced.

Eflornithine HCl 13.9%, rather than removing the hair, is an irreversible inhibitor of ODC, thus it reduces the rate of hair growth. It appears to be effective regardless of whether the unwanted facial hair is hereditary or whether it is due to medical conditions such as an androgen excess disorder, e.g., PCOS.

Combination Therapy

Eflornithine 13.9% cream can slow hair growth and thus reduce the frequency of the need for hair removal by other means, such as lasers and IPL treatments. Studies have shown that the two processes can be started simultaneously, and eflornithine treatment can continue right through laser treatments. [Dawber RP. *Curr Med Res Opin* 21(8):1227-34 (2005 Aug).] Treatment should be undertaken using combination therapy to possibly include:

1. hormonal suppression, e.g., oral contraceptives, long-acting gonadotropin-releasing hormonal analogues and insulin sensitizers
2. peripheral androgen blockade, e.g., spironolactone, flutamide, cyproterone acetate or finasteride
3. mechanical/cosmetic amelioration and destruction of the unwanted hairs, e.g., electrolysis, lasers, IPL, depilatories, shaving, waxing, etc.
4. application of eflornithine 13.9% topical cream.[Azziz R. *Obstet Gynecol* 101 (5 Pat 1):995-1007 (2003 May).]

Paradoxical hypertrichosis has, however, been reported in a small number of patients receiving laser or IPL treatment for excess hair removal. [Alajlan A, et al. *J Am Acad Dermatol* 53(1):85-8 (2005 Jul).]

Conclusion

Hirsutism can cause embarrassment and lead to anxiety and depression. There are a limited number of treatments available that vary in efficacy, degree of discomfort and cost. It is very important to make sure that the patient is aware of all the available treatment modalities, since no one method is effective for all patients or body locations, and results from therapy may not always be satisfactory.

This article has been adapted from an article by Drs. Shapiro and Lui to be published in the November 2005 issue of Skin Therapy Letter®.

Get more clinical information at

www.SkinTherapyLetter.ca

A Physician's site for:

- **A-Details™: Online drug presentations**
- **Skin Therapy Letter® articles**
- **Meeting Abstracts and Proceedings**
- **Refer your patients for self-help to www.SkinCareGuide.ca**

or any of the following sites:

| | | | |
|--|--|--|--|
| AcneGuide.ca | EczemaGuide.ca | FungalGuide.ca | HerpesGuide.ca |
| RosaceaGuide.ca | SkinCancerGuide.ca | PsoriasisGuide.ca | PsoriaticArthritisGuide.ca |
| BotoxFacts.ca | Lice.ca | MildCleanser.ca | |

**Please provide us with your feedback and topic suggestions
by e-mailing us at physicians@skincareguide.com**

*The following companies have provided an unrestricted educational
grant for the 2005 distribution of this publication:*

Allergan Inc.
Barrier Therapeutics
Dermik Laboratories
Galderma Canada
LEO Pharma Inc.
Novartis
Ombrelle
Stiefel Canada

Copyright 2005 by SkinCareGuide.com Ltd. Skin Therapy Letter® – Family Practice Edition is published quarterly by SkinCareGuide.com Ltd, 1107-750 West Pender, Vancouver, British Columbia, Canada, V6C 2T8. All rights reserved. Reproduction in whole or in part by any process is strictly forbidden without prior consent of the publisher in writing. While every effort is made to see that no inaccurate or misleading data, opinion or statement appear in the Skin Therapy Letter® – Family Practice Edition, the Publishers and Editorial Board wish to make it clear that the data and opinions appearing in the articles herein are the responsibility of the contributor. Accordingly, the Publishers, the Editorial Committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion, or statement. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described herein, should only be followed in conjunction with the drug manufacturer's own published literature.