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Clinical Evidence. Practical Advice.

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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 Department of Dermatology and Skin Science, 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). He is the founder of the Dermatology Update symposia, now in its 25th year. As well, 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.

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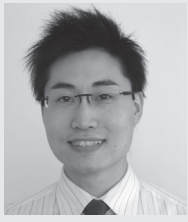

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Update on Topical Approaches for Managing Scalp Psoriasis

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Introduction

Patients suffering from scalp psoriasis frequently seek medical care because of the persistent discomfort due to itching and social embarrassment caused by the visible flakes that are shed onto clothing. However, the presence of hair makes it challenging to apply medication to the scalp. In addition, available therapies often do not facilitate ease of use and may produce irritation and cosmetically unpleasant effects that can discourage patient adherence. Such therapeutic challenges often impede patients from deriving the full benefits from prescribed treatments. This article explores some of the current options and new advances in the topical management of this common skin disorder and offers strategies that may improve treatment outcomes.

Clinical Features

- Psoriasis can be limited to the scalp, but it frequently involves more than one area of the body.
  - Common concurrently affected sites include elbows, knees, buttocks, fingers, and nails.
- Between 50%-80% of all psoriasis patients have scalp involvement at some stage of their condition.[1]
- The scalp may be the first site to show psoriasis; these lesions usually persist longer than those appearing elsewhere on the body.
- Psoriasis presents as well demarcated plaques that are characterized by scaling and erythema. Patients can experience varying degrees of itching and flaking.
  - Patches are commonly located on the occipital scalp, over the ears, and along the frontal hairline.
- The most common differential diagnosis is seborrheic dermatitis. Although it can mimic psoriasis, seborrheic dermatitis tends to be more diffuse, waxier in texture, and less scaly. It can also spread down the forehead and involve the nasolabial folds and eyebrows.
  - Psoriatic scales are generally thicker and drier in appearance; the skin may crack and bleed.
  - Scalp psoriasis can coexist with seborrheic dermatitis, and the persistence of yeast organisms in both conditions may share similar etiologies.
- Tinea or fungal infections frequently involve the hair shaft, leading to hair breakage, scaling, and swollen lymph nodes in the posterior cervical chain. It is more prevalent in children.

Therapeutic Considerations

- The presence of hair and scale build-up can interfere with medications reaching the scalp.
- Certain vehicles, such as ointments and creams, can be messy to apply and adhere to the hair shaft, resulting in a greasy appearance and prompting more frequent hair-washing. In addition, it is possible that not enough of the drug will actually reach the scalp, rendering the treatment ineffective.
- Medications should be applied to dry hair. Before application, comb hair to remove any loose scales. At affected areas, separate hair and gently rub the medication directly onto lesions.
- Issues surrounding cosmetic acceptability can lead to poor adherence, loss of effect, and patient dissatisfaction with the treatment.
- Convenient and/or simplified dosing can improve medication adherence.
  - A study involving psoriasis patients demonstrated substantially higher rates of adherence with once-daily dosing (83%) vs. a twice-daily regimen (44%).[2]
- The vehicle can be as important as the active agent in achieving efficacy, tolerability, and treatment adherence.
  - Vehicles significantly impact the penetration and potency of active ingredients, i.e., lotions, gels and foams are superior to creams and ointments.
  - Alcohol-based solutions can sting and irritate.
  - Future management may include optimized vehicles (e.g., quick-break gel or foam, or lotions).

Topical Treatment Options for Scalp Psoriasis

When compared with phototherapy and medicated shampoos, topical agents are most commonly prescribed for scalp psoriasis. Although there is a broad range of topical therapies, factors that can limit treatment options include irritation, convenience, ease of application, cosmetic acceptability, effectiveness for reducing itch and scale, and safety for prolonged use without loss of benefit. A therapeutic approach that addresses as many of these variables as possible will improve treatment outcomes.

OTC Treatments

- Many OTC combination preparations for scalp psoriasis utilize tar, salicylic acid, or zinc pyrithione; familiarity with these agents by pharmacists is useful for explaining their benefits and potential side-effects to patients.
- Salicylic acid is a keratolytic agent that promotes the release of scales and facilitates drug penetration. Salicylic acid is often used in combination with tars and corticosteroids. Skin irritation is a common side-effect.
- Zinc pyrithione may be helpful in reducing itching and flaking due to its antimicrobial properties.

Tars

- Tar compounds slow the proliferation of skin cells and reduce inflammation, itching, and scaling.
- Following treatment, the agent should be removed using any mild, unmedicated shampoo.
- Acceptance by patients is limited due to irritation, staining, and the odiferous quality of tars.
  - They can stain light-coloured hair and clothing.
- Tars can cause folliculitis and may be carcinogenic.

Corticosteroids

- Potent and ultrapotent corticosteroids, such as betamethasone dipropionate and clobetasol propionate, are widely used for their anti-inflammatory, immuno-suppressive, and antiproliferative properties.
- They are commonly available as solutions, lotions, gels, and shampoos in a range of potencies.
- Prolonged use can result in tachyphylaxis.

Vitamin D3 Analogues (Calcipotriol/Calcipotriene)

- Calcipotriol promotes normal keratinization, suppresses inflammatory responses, and modulates both epidermal proliferation and differentiation.
- They are available in solution or gel formulations.
- There is no loss of effect with prolonged use.
- They are helpful for reducing scaling, but their usefulness for controlling erythema and itch is limited.
- To avoid the potential effects on calcium metabolism, limit use to 15g daily, or 100g weekly.[3]
- Due to the degradation of corticosteroids by vitamin D3 analogues, concurrent application should be avoided.

Calcipotriol + Corticosteroid Combination Therapy

- Stable commercial preparations of calcipotriol + betamethasone dipropionate have the dual benefit of controlling scalp psoriasis symptoms with a low risk of skin atrophy and without tachyphylaxis.[1,4]
- Randomized double-blind, controlled studies showed that the two agents in combination have a more rapid onset of action and greater efficacy than monotherapy with either agent.[5,6]
- A two-compound formulation of betamethasone dipropionate 0.5mg/g + calcipotriol 50µg/g in a novel gel vehicle received Health Canada approval in November 2008 for the treatment of scalp psoriasis.
  - This new gel formulation achieved marked improvement to clearance in 92% of scalp psoriasis patients following once-daily use for up to 8 weeks.[7]
  - The gel vehicle enhances drug permeation, improves cosmetic acceptability, minimizes irritation, facilitates ease of use, is odourless, and offers once-daily dosing.
  - Investigations reporting benefits of the new formulation did not use pretreatment or concomitant therapy with a keratolytic agent.[4-7] As such, adjunctive care for descaling is not required while patients are undergoing treatment.

Topical Treatment Options for Scalp Psoriasis (continued)

- To encourage adherence and allow for adequate absorption, the agent should be applied during the evening and remain on the scalp overnight.
- For cosmetic reasons, patients can remove the gel in the morning by applying any mild, unmedicated shampoo to dry hair. Gently rub the shampoo into hair (in the treated area) to emulsify the gel medication, then wet hair, lather, and rinse. Hair washing is recommended for cosmetic and hygienic purposes, and is not required as part of therapy.
- Recently published findings support the new agent's safety, tolerability, and efficacy when used once-daily, as needed, for up to 52 weeks.[4]
- Studies report very similar rates of side-effects for all treatment groups, including placebo; the most common adverse event was pruritus.[3,5]
- To avoid the potential effects on calcium metabolism, limit use to 15g daily, or 100g weekly.[3]

- Safety for use in pregnant and nursing women, as well as in patients aged ≤18 years, has not been established. It is not recommended for these patient populations.

Considerations for Management

- Patients consider scalp psoriasis to be the most difficult aspect of their disease, which can lead to loss of self-esteem, social stigmatization, and even depression.
  - About 1 in 3 patients are self-conscious of their scalp psoriasis, and 1 in 5 report depressive symptoms.[8]
- Scratching and picking at scales can aggravate lesions and lead to spreading of the psoriatic plaques over a larger surface area (Koebner phenomenon).
- Management strategies (e.g., proper instructions for use, side-effects, and concomitant and OTC medications that can exacerbate psoriasis) should be reinforced.
  - Explain to patients that the major goals of treatment are to relieve the itching and reduce the scaling. Antihistamines are ineffective at controlling itch.
  - Wearing light-coloured clothing can minimize the visibility of flakes.
  - If necessary, patients may be advised to use OTC shampoos containing salicylic acid or tar to help soften and release the scales.
- Suggest patient participation in national organizations or web-based social networks. Psoriasis virtual communities can provide education and practical advice, as well as psychological and social support.

Encouraging Treatment Adherence

- Nonadherence to treatment occurs in up to 40% of patients with psoriasis.[9] Fears about treatment side-effects and the nuisance of using prescribed therapies can discourage adherence.
- Pharmacists can alleviate patient concerns regarding the side-effects from topical corticosteroid use (e.g., thinning of the skin) by explaining the benefits over risks when used properly.
- Pharmacists perform a vital educational role by imparting details on proper administration and therapeutic objectives. Nonadherence can be reduced when patients have an accurate understanding of their psoriasis and the selected treatment.
- Clinical strategies that can promote adherence include selecting fast-acting topical agents, treatments that facilitate ease of use (i.e., simple and convenient dosing), or combination agents that can enhance the rate and degree of improvement.

Conclusion

With the potential for escalating morbidity, diminished quality of life, and significant financial burden, it is essential to stem disease progression by managing both the physical and emotional aspects of psoriasis. Continuing efforts aimed at addressing unmet therapeutic needs have led to the development of new topical antipsoriatic therapies that are safer and more effective. The advent of two-compound agents that can target multiple pathogenic factors are proving to be particularly useful. The investigation of novel treatment combinations and new compounds for scalp psoriasis are ongoing in the quest to provide further enhancements in efficacy that will lead to improved patient adherence and treatment outcomes.

References

1. Papp K, et al. *J Eur Acad Dermatol Venereol* 21(9):1151-60 (2007 Oct).
2. Zaghloul SS, et al. *Arch Dermatol* 140(4):408-14 (2004 Apr).
3. Xamiol® [calcipotriol and betamethasone dipropionate] product monograph. Thornhill, ON: LEO Pharma Inc. (2008 Nov).
4. Luger TA, et al. *Dermatology* 217(4):321-8 (2008).
5. Jemec GB, et al. *J Am Acad Dermatol* 59(3):455-63 (2008 Sep).
6. van de Kerkhof PC, et al. *Br J Dermatol* 160(1):170-6 (2009 Jan).
7. Buckley C, et al. *Dermatology* 217(2):107-13 (2008).
8. Chen SC, et al. *Arch Dermatol* 138(6):803-7 (2002 Jun).
9. Richards HL, et al. *J Eur Acad Dermatol Venereol* 20(4):370-9 (2006 Apr).

A Review of Therapeutic Options for Genital Warts

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Introduction

Condylomata acuminata (genital or venereal warts) pose a significant health concern, especially amongst young adults. Considered to be one of the most common forms of sexually transmitted infections (STIs), external genital warts (EGWs) are caused by infection with the human papillomavirus (HPV), the same virus that causes the majority of cervical cancers. Relatively recent therapeutic advances include a topical immunomodulatory agent and a prophylactic vaccine, which have significantly broadened the options for management. Herein, a review of conventional and newer therapies will be discussed.

HPV Facts

Over 100 HPV types have been described, 40 of which infect the anogenital tract; the most common of these are HPV types 6, 11, 16, and 18.[1]

- HPV 6 and 11 are low risk for causing cancer, but they cause 90% of genital warts.
- HPV 16 and 18 are considered to be high risk types and contribute to 70% of cervical cancers.

HPV Pathogenesis

The principal route of genital infection is through sexual contact. The virus is believed to enter through micro-abrasions in the epithelium. Transmission to newborns by way of passage through the infected birth canal can also occur.[2] The infection rate between sexual partners is approximately 60%.[3]

Risk Factors

It is estimated that 550,000 Canadians are infected with HPV annually.[4] The rate of infection appears to accelerate following the onset of sexual activity and decrease with increasing age. Prevalence is highest amongst individuals under 25 years of age. The risk level is based on a combination of factors including age, lifestyle, immunocompetency, and other variables.

- Becoming sexually active at an early age
- Previous infection with another form of STI
- The lifetime number of sexual partners
- Engaging in unprotected sex with multiple partners, especially those with known histories
- The sexual promiscuity of partners
- Immune status
- Proper condom use may reduce the risk of transmission, but because HPV can be present anywhere along the anogenital tract only partial protection is provided.
- Male circumcision may reduce the incidence of HPV infection according to a recent study by Tobian, et al.[5]

Diagnostic Features

Prior to making a confirmed diagnosis, it is necessary for clinicians to obtain a medical and sexual history from patients, if not already known. Examination of the pelvic region, entire genital tract, and the thighs, as well as mouth and throat, may reveal nodules indicative of, but not limited to, infection with HPV. Screening for other STIs may also be considered, especially in high-risk individuals.

- In most cases, direct visual inspection can identify the growths on the genital mucosa.
- Anogenital warts are generally asymptomatic, but they can cause pruritus, bleeding, or mild burning. They present as:
  - lesions that appear primarily on surface areas of the vulva, penis, and perianal skin.
  - small, discrete, sessile, flat or raised papules or nodules.
  - large exophytic masses.
  - a singular papule or multiple verrucous clusters.
  - lesions that range in colour from whitish, pink, flesh-coloured to reddish brown.
  - having a multifocal distribution that generally correlates with regions sustaining the greatest degree of friction during sexual activity.

Diagnostic Features (continued)

- For hard-to-see warts, a 3%-5% acetic acid solution (i.e., white vinegar) can be applied to the suspect lesion (Figure 1). After a few minutes, the condylomata should appear as whitened patches on the mucosa. Positive changes are not diagnostic for HPV, as these results can also be produced by lichen planus, yeast infections, and other skin disorders.
- A biopsy may be considered if:[6]
  - diagnostic uncertainty exists.
  - lesions are unresponsive to convention treatments.
  - lesions worsen during therapy.
  - the patient is immunodeficient.
  - the warts are pigmented, indurated, fixed, bleeding, or ulcerated.
- The lesion prevalence in women may be attributable to larger surface areas of mucosal skin.
- A Pap test can help to establish the presence of a cervical lesion.[7]

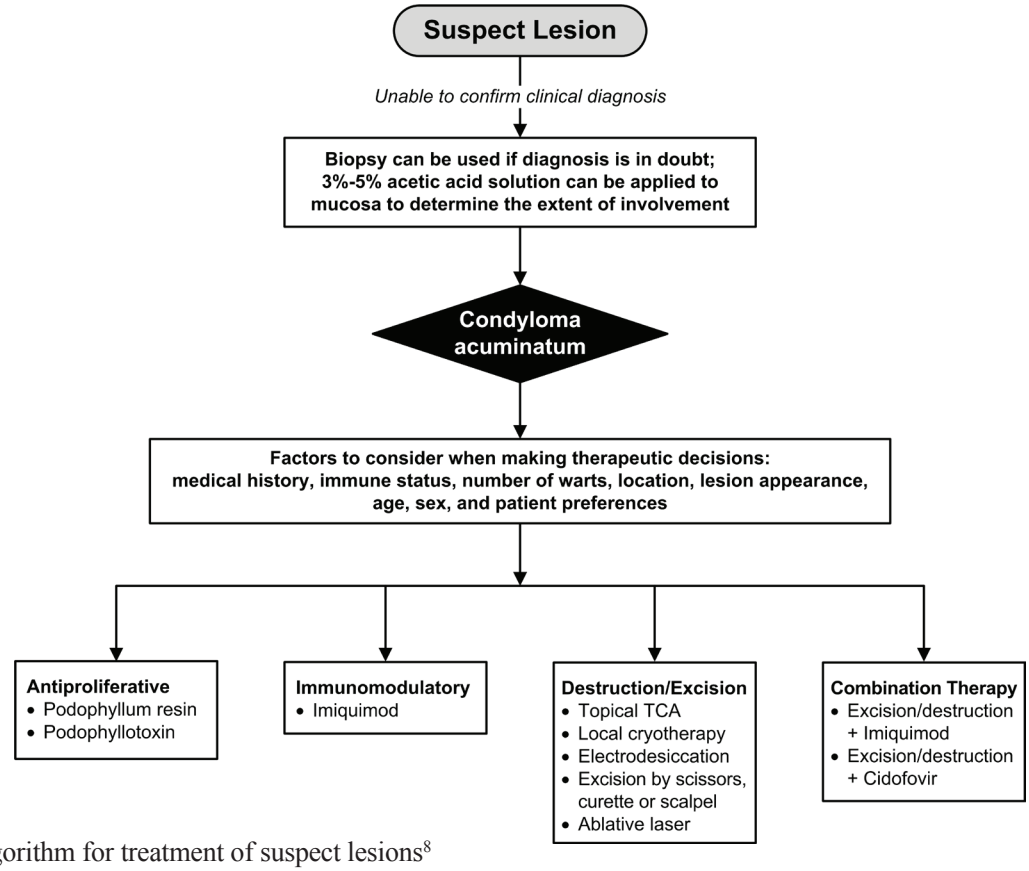

Figure 1: Algorithm for treatment of suspect lesions[8]

Treatment

The primary treatment objectives are to eliminate visible warts and limit the psychological distress caused by EGWs. In about 10%-30% of patients, EGWs are usually self-limited in immunocompetent individuals and typically resolve within 12-24 months if left untreated; however, lesions may also remain unchanged, or proliferate in size and number.[6,7]

- The spectrum of available treatments includes self-applied and provider-administered therapies.
- The most widely used treatment modalities can be broadly categorized as antiproliferative, destruction/excision, immunodulatory, and combination therapies (Table 1).
- The majority of therapeutic options provide symptomatic relief rather than treat the disease itself. The one exception is a topical immune response modifier (i.e., imiquimod), which exerts a field effect that can target both clinical and subclinical manifestations of HPV.
- Therapeutic decisions should be guided by wart type, location, number, sex, patient preferences, physician experience, and unique circumstances (e.g., young age, immunosuppression, pregnancy).
- Given the wide range of patient and treatment variables, there is a lack of conclusive evidence confirming the superiority of any one modality, or combination thereof, over another.
- The majority of patients require a course of therapy rather than a single treatment.[6]
- It is important to iterate to patients that available treatments can induce wart-free periods, but none provide complete clearance of HPV infections.

Treatment (continued)

Method	Treatment	Comments
Antiproliferative Therapies	Podophyllum resin 10%-25%	• Physician-administered • Removal of warts by destruction of infected tissue • Potential for systemic toxicity
	Podophyllotoxin 0.5% solution or gel	• Can be applied by the patient • Low cost, low toxicity • Contains no mutagenic substances, unlike those found in podophyllum resin
Immunomodulatory Therapy	Imiquimod 5% cream	• Self-administration may improve patient compliance • Enhances the cytotoxic immune reaction, which is usually seen as an inflammatory response • Applied directly to the affected skin 3 times/week for up to 16 weeks - frequency of applications can be reduced if there is concern over the degree of inflammation • Low rate of recurrence due to reduction of the viral load • Effective for treating multiple warts covering larger areas, as well as subclinical lesions • Side-effects are mild to moderate and include local erythema and erosion at the site of application • Higher drug cost than podophyllotoxin
Destruction/Excision Therapies All options have the potential to cause scarring	Topical trichloracetic acid 85% (TCA)	• Causes cellular destruction by chemical cautery • Most effective when treating small, moist lesions • Damage to surrounding tissue can be minimized by protection with petroleum jelly • If TCA is applied to nonaffected tissue, instruct patients to wash the area with liquid soap or baking soda • Can cause pain and ulceration
	Local cryotherapy	• Most common destructive mode • Involves freezing with liquid nitrogen • Offers ease of use with no systemic effects • Can cause pain and ulceration • Safe for use during pregnancy
	Electrodesiccation	• Warts are burned off with a low-voltage electrical current
	Excision by scissors, curette, or scalpel	• Provides definitive clearance of abnormal tissue • Particularly suitable for larger exophytic warts • Local anesthesia is required
	Ablative laser	• Use of CO_2 laser therapy is usually reserved for extensive and/or treatment resistant warts • May require a long time for recovery and is expensive
Combination Therapy Combination therapy can provide a better result over mono-therapy	Excision/destruction + imiquimod	• Cryotherapy combined with imiquimod appears to be very commonly used • Initial therapy with imiquimod may reduce wart size and improve surgical outcomes • Initial treatment with imiquimod followed by excision of residual lesions may provide long-term clearance of EGWs, especially if prior monotherapy was insufficient[9]
	Excision/destruction + cidofovir	• Due to cidofovir's broad antiviral activity, it has been used successfully as a topical gel for refractory patients[8]

Table 1: Treatment options for genital warts[7,10]

The therapeutic horizon may include a topical formulation whose active constituent is a defined mixture of catechins extracted from green tea with demonstrated efficacy and safety for EGWs.[11] This herbal prescription drug gained US FDA approval in 2006 for the treatment of external genital and perianal warts caused by certain strains of HPV.

A Prophylactic Approach

In 2006, Health Canada approved a quadrivalent HPV vaccine that acts against HPV types 6, 11, 16 and 18.

- It is indicated for use in females 9-26 years of age and is given as a 0.5ml injection intramuscularly in 3 doses at 0, 2, and 6 months.
- The quadrivalent vaccine is 97% effective in preventing vaginal and vulval intraepithelial neoplasia, and is 99% effective in preventing genital warts caused by HPV types 6 and 11.[1]
- There is no evidence suggesting that therapeutic benefits may be derived from the immunization vaccine if patients are already infected with vaccine HPV types.
- Recent studies suggest that the quadrivalent vaccine may also provide cross-protection against HPV strains that are not contained in the vaccine, but are closely related. However, durability of immunity and the significance of these findings remain to be established.[12,13]
- Studies investigating this vaccine in males are underway.

Conclusion

The increasing incidence of HPV infections is of mounting concern and the most prevalent clinical manifestation of this communicable disease is genital warts. Although disease morbidity can be mild, the emotional distress of having genital warts can result in severe psychological impacts, hence, successful management is essential.

- For the initial treatment of genital warts, many patients prefer self-applied therapies.
- Because monotherapy is often insufficient, combination therapy may be more advantageous.
- Throughout the course of treatment, patients must be monitored for response rate and side-effects.
- Patients exhibiting an inadequate response will necessitate a transition to other therapies or modification of the existing approach.
- According to the Canadian Consensus Guidelines on HPV,[7] due to its favourable efficacy, safety, and tolerability profiles, as well as lowest recurrence rate, imiquimod represents an effective strategy for the management of genital warts, and should be considered prior to initiating more invasive strategies, such as destructive/excision or laser therapies.

Instruction and education provided by pharmacists, especially for patient-applied therapies, can assist in maximizing treatment efficacy and safety. When appropriate, pharmacists may also recommend strategies that can limit the spread of HPV and encourage regular screening.

References

1. Dobson S, et al. *Canada Communicable Disease Report* 33(ACS-2):1-31 (2007 Feb 15).
2. Kaye JN, et al. *J Gen Virol* 77 (Pt 6):1139-43 (1996 Jun).
3. Palefsky JM. *Clin Dermatol* 15(3):439-47 (1997 May-Jun).
4. Money DM, et al. *J Obstet Gynaecol* Can 29(8 Suppl 3):S3-6 (2007 Aug).
5. Aaron AR, et al. *N Engl J Med* 360(13):1298-309 (2009 Mar 26).
6. Centers for Disease Control and Prevention. Genital warts treatment guidelines 2006. Available at: http://www.cdc.gov/std/treatment/2006/genital-warts.htm. Accessed March 17, 2009.
7. Roy M, et al. *J Obstet Gynaecol Can* 29(8 Suppl 3):S37-41 (2007 Aug).
8. Varela A, et al. *Skin Therapy Lett-FP US Ed* 1(2): 1-3 (2006).
9. Carrasco D, et al. *J Am Acad Dermatol* 47(4 Suppl):S212-6 (2002 Oct).
10. Bourcier M, et al. *Skin Therapy Lett-FP Ed* 3(2): 1-3 (2007 Jun).
11. Stockfleth E, et al. *Br J Dermatol* 158(6):1329-38 (2008 Jun).
12. Brown DR, et al. *J Infect Dis* 199(7):926-35 (2009 Apr 1).
13. Wheeler CM, et al. *J Infect Dis* 199(7):936-44 (2009 Apr 1).

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