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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 24th 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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A Simple Algorithm for the Treatment of Dermatophyte Toenail Onychomycosis

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Background

Onychomycosis infections of fingernails and toenails may be caused by many types of fungi or yeast species. In practice, almost all infections are produced by the dermatophyte fungi *Trichophyton* sp. (especially *T. rubrum* and *T. mentagrophytes*), *Microsporum* sp., and *Epidermophyton* sp., with toenail infections typically being more severe and more difficult to eradicate than fingernail infections. There has been much discussion about the optimal treatment for onychomycosis, particularly now that topical nail lacquers have become available. This new therapeutic option offers reduced risk of adverse effects compared with standard oral therapies. We propose a simple algorithmic approach to aid in the selection of therapy for dermatophyte toenail onychomycosis (Table 1), and present a balance between efficacy and risk of therapy.

Treatment Options for Onychomycosis

Oral Therapies Approved in Canada

- Terbinafine 250mg/day for 12 weeks
- Itraconazole pulse therapy: for dermatophyte onychomycosis
  - 1 pulse = 200mg twice daily for 1 week on, 3 weeks off
  - 3 pulses are standard for toenail onychomycosis
- Oral therapies provide access to the nail bed and matrix of all toes; both terbinafine and itraconazole may persist in nails for long periods after treatment.
- Oral therapy can also treat concomitant skin infections such as tinea pedis.
- Consult current prescribing information for contraindications and monitoring requirements.
- Liver function testing should be done prior to therapy, and periodically during therapy.

Topical Therapies Approved in Canada

- Ciclopirox nail lacquer 8%, once daily for 48 weeks[1]
- Adverse events are few, with mild localized reactions at the application site.
- May not provide adequate penetration where nails are thick or have severe onycholysis.

Treatment Options for Onychomycosis (continued)

Other Therapies

- Mechanical or chemical debridement: lessens the burden of infection and may benefit any degree of onychomycosis; can be performed in office, or by other healthcare professionals.
- Nail avulsion (chemical or mechanical): typically a last resort, as there is some risk for permanent nail damage.

Combination Therapy

- Dual therapies: oral/topical, oral/debridement, or topical/debridement. In practice, nail avulsion is typically followed by topical or oral therapy to combat the remaining infection.
- Triple therapies: oral/topical/debridement[2]
- Oral therapy combined with topical therapy can provide penetration of the nail plate from inside and out, which may increase the overall amount of antifungal medication reaching the infection, particularly where the nail is thickened, shows extensive onycholysis, has lateral or matrix involvement, or is a dermatophytoma.[3]
- Debridement may increase access to the infection by topical medications.

Nail Presentation	Assumptions	Treatment Option
Distal/Lateral Subungual Onychomycosis (DLSO)		
Mild DLSO (<25% affected area)	Minimal thickening; minimal onycholysis → No matrix or lateral involvement	Topical ciclopirox nail lacquer or oral therapy
	>5 nails	Oral therapy
	Matrix/lateral involvement	Oral therapy
Moderate DLSO (25%–75% affected area)	25%–<50% → 5 nails or fewer; minimal thickening; minimal onycholysis; no matrix or lateral involvement	Topical ciclopirox nail lacquer or oral therapy
	25%–<50% → >5 nails	Oral therapy
	50%–75%	Oral therapy with or without debridement
Severe DLSO (>75% affected area)	>75%	Oral therapy with or without debridement
Any DLSO involving:		
Nail matrix		Oral therapy
Thick nails	>2mm	Oral therapy with debridement with/without topical therapy and/or nail avulsion
Extensive onycholysis		Debridement with oral or topical therapy
Nail spikes (dermatophytoma)		Debridement with oral or topical therapy
Superficial White Onychomycosis (SWO)		Topical ciclopirox nail lacquer or oral therapy depending upon severity and number of nails affected
Proximal Subungual Onychomycosis (PSO)		Oral therapy

Table 1: Simple treatment algorithm for dermatophyte toenail onychomycosis
Onycholysis = separation of the nail plate from the nail bed Matrix = the base or root of the nail, from which the nail grows

Variables to Consider in Treatment Decisions

Nail Disease Variables

- Number of nails affected
- Percentage of affected nail plate area
- Is it DLSO, or another presentation?[4-6]
- Infection confirmed as dermatophyte? (i.e., *Trichophyton* sp., *Microsporum* sp., or *Epidermophyton* sp.)
- Thickness of nails
- Matrix (proximal nail fold) area involved in infection?
- Lateral streaks or central spikes (dermatophytoma) present?

Patient Variables

- Presence of peripheral vascular disease
- Diabetes
- Age of patient
- Obesity
- Other co-morbid conditions, e.g., liver disease
- Oral drugs patient is using
- Compliance
- Drug insurance status
- Patient preference

Physician Variables

- Physician preference and experience

Other Treatment Considerations

Efficacy of Therapy

- Efficacy should consist of both mycological eradication and outgrowth of the infected nail.
- Mycological cure is suggested by negative microscopy exam and negative culture in successive samples.
- For clinical success, the infected toenail must be grown out and replaced by a healthy nail (average time: 9-16 months); success of treatment is typically assessed around month 12; for some patients, trauma or medical conditions may prevent the nail from returning to a 'normal' appearance, and thus, success will only be a nail appearance as normal as possible for the individual patient condition.
- 'Booster' therapy may be provided to the patient: extra courses of oral therapy may be given following completion of the standard oral regimen (4 wks terbinafine; 1 pulse itraconazole).[7]

Special Patient Populations

- Elderly: slower nail growth, reduced immune response.[8]
- Diabetics/peripheral vascular disease: higher rates of onychomycosis, requires adequate antifungal therapy to prevent spread of infection, concomitant foot trauma, ulceration, amputation.[9] Use caution when performing debridement, sampling, to avoid injury to skin.
- Children: no treatments have been specifically approved for use in children.
- Fingernail infections: fingernails grow at a faster rate than toenails and typically show higher cure rates.

Non-DLSO Presentations

- Superficial white onychomycosis infections may be treated adequately using topical therapy and debridement of infected areas with a curette or scalpel.
- Proximal subungual onychomycosis, due to the deep-seated nature of infection, is most adequately treated with oral therapy; may be associated with immunocompromised status.

Nondermatophyte Infections

- Nondermatophyte infections are difficult to identify, but need to be recognized accurately, as standard antifungal therapies may not be as effective in nondermatophyte moulds as for dermatophytes.[10]
- Recommended treatment may be specific to the organism causing infection.[11,12]

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Therapeutic Advances in Topical Acne Agents

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Background

Acne vulgaris is a multifactorial disease characterized by different types of lesions at various stages of development. Several obstacles encountered in the treatment of acne include irritation resulting from topical medications and the emergence of bacterial resistance to both topical and oral antibiotics. Over the last 20 years, the number of topical agents for the treatment of acne has been enriched. Advances in vehicle technology have produced improvements in efficacy and local tolerance. Our increased knowledge of acne pathogenesis has also led to therapeutic advances, such as the combined use of benzoyl peroxide (BPO) with topical or oral antibiotics, in order to reduce the potential for bacterial resistance.

Topical Acne Agents

- BPO
- Retinoid
  - Tretinoin
  - Adapalene
  - Tazarotene
  - Isotretinoin
- Topical antibiotics
  - Clindamycin
  - Erythromycin
  - Sulfacetamide
- Combination products
  - Retinoid with erythromycin
  - BPO with erythromycin
  - BPO with clindamycin

Retinoids for Initial/ Maintenance Therapy

Retinoids are pivotal for treatment in the early stages of acne, as well as for maintenance therapy, with both anti-comedonal and anti-inflammatory activity.

- Topical retinoids can be used for all types and grades of acne, either initially or early in the therapy.
- Topical retinoids are effective as monotherapy in pure comedonal acne.
- Topical retinoids act by down-regulating TLR2 and CD14 messenger RNA, which reduces their cell surface expression, and results in anti-inflammatory activity.[1]
- Several studies have shown that retinoids can enhance the effects of topical antibiotic-BPO combination creams.[2] This may be because retinoids can improve the penetration of other topical agents.
- Maintenance therapy or long-term use of retinoids may help to prevent the re-emergence of micro-comedones.
- Maintenance therapy with retinoids may diminish the need for chronic antibiotic use, especially oral antibiotics. This, in turn, may lead to decreased bacterial resistance associated with both oral and topical long-term antibiotic use.

Topical Acne Agents and Bacterial Resistance

- Topical antibiotic agents should not be used as monotherapy.
- The combination of BPO with a topical antibiotic can result in a greater improvement in efficacy than monotherapy with either agent alone.
- The addition of BPO to all long-term oral or topical antibiotic treatment has been shown to help suppress the emergence of antibiotic-resistant bacteria.
- BPO may also reduce the further development of resistant strains that are already present.
  - For this reason, most new topical antibiotic acne agents include BPO.
- Retinoids, although recommended in all forms of acne, have no apparent activity in preventing antibiotic resistance when used in combination with an antibiotic.

Advances in Topical Acne Formulations

Advances in topical agents have:

- reduced the potential for irritation from tretinoin, due to the microsphere technology and novel pump dispenser.
- permitted the use of microsphere tretinoin and adapalene in the morning, or directly before or after BPO application.
- enabled the quick application of microsphere retinoids after facial washing.
- reduced the irritation from clindamycin 1% plus BPO 5% alone, or in combination with a retinoid, because of the increase in humectants and emollients in the clindamycin/ BPO formulation.

Advances in Topical Acne Formulations (continued)

- decreased the emergence of bacterial resistance due to the addition of BPO to topical antibiotic agents, and the use of BPO with long-term oral antibiotics.

Vehicle Technology in Topical Acne Agents

- Many new topical acne formulations have aqueous-based gel vehicle delivery systems that do not contain alcohol; they are suitable for use in all skin types.
- It is known that topical acne agents cause cutaneous irritation related in part to impaired epidermal barrier function.[3]
- The use of gentle cleansers and moisturizers has been shown to reduce this cutaneous irritation.[4]
- The addition of vehicle components, such as humectants and emollients, to topical acne agents serves as a more natural approach to reducing epidermal barrier impairment and increasing skin moisturization.
- The clindamycin 1%/ BPO 5% and the tretinoin microsphere gel formulations include both glycerin (a humectant) and dimethicone (an occlusive emollient).
  - Dimethicone's occlusive properties result in less greasiness for enhanced cosmetic acceptability.

Tretinoin Microsphere Technology and Pump Delivery Systems

Tretinoin has been formulated with a patented microsphere delivery system and a novel pump bottle design, which, according to the manufacturer, allows for proper dosage and clean dispensing of the active agent. Clinical trials have shown:

- lower levels of irritation due to the slow release of tretinoin from the microspheres into the epidermis.[1,5]
  - Reduced irritation may increase tolerability and patient adherence.
  - This is a less irritating water-based gel formulation that contains no alcohol and may be applied to the face immediately after washing with no waiting period.
- the microsphere technology leads to greater photostability of the tretinoin and allows for morning use, if necessary.[6]
  - Retinoids formulated in a conventional gel or cream vehicle are unstable in the presence of ultraviolet light or BPO.[1]
  - Adapalene is also photostable and may be applied immediately before or after a BPO containing product.[7]
- that controlled dispensing with this delivery system can avoid the overuse of tretinoin, thus reducing irritation and increasing treatment adherence.[1]
  - The dual chambered pump dispenser releases the correct pea-sized amount for full face application and may help to maintain the optimal dosing level.

Combination Therapy

- Because the typical clinical presentation of acne vulgaris exhibits lesions at different stages, employing a combination approach that utilizes multiple agents to produce additive or synergistic benefits is logical.
- Studies have shown that the topical combination of retinoids and antimicrobial agents expedites clinical response.[2] This may be due to enhanced penetration of agents by the retinoids.
- Retinoids, as discussed, can be prescribed as initial therapy. If inflammatory lesions are present, the addition of a BPO alone, or in combination with a topical or oral antibiotic, should be the next step.
- A study showed that the combined use of a clindamycin 1%/ BPO 5% formulation with a 0.04% tretinoin microsphere gel, can result in good resolution of post-inflammatory hyperpigmentation in ethnic skin, i.e., individuals of colour.[8]

Conclusion

The multifactorial nature of acne vulgaris often requires a combination of topical and/or oral agents for successful management. Common challenges of this multipronged approach include the potential development of skin irritation, which results in nonadherence, as well as concern over bacterial resistance. Recent advances in topical acne agents offer simpler dosing regimes that can promote patient adherence. Furthermore, the cumulative benefits of these advances may lead to improved therapeutic outcomes and overall increase in quality of life.

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HPV Vaccines

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Background

In 2006, a quadrivalent HPV vaccine was approved for use in Canada, the first of two vaccines for human papillomavirus (HPV) prevention. The second is a bivalent vaccine that is currently undergoing regulatory review by Health Canada. The efficacy of both vaccines heralds a new era in the prophylactic treatment of cervical cancer. Consequently, provincial ministries of health are beginning to formulate immunization programs for pre-adolescent girls.

Facts About HPV

- Over 100 human papillomavirus (HPV) types have been described, 40 of which infect the genital tract.[1]
  - They infect differentiating epithelial cells of skin or mucosae.
- Almost all cervical cancers can be traced to infection with at least 13 oncogenic HPV types.
  - HPV 16 and 18 (high risk types) contribute to 70% of cervical cancers.[1,2]
  - These vaccines provide an opportunity to prevent this cancer by immunization against the high risk (HR) HPV types.
- For oncogenic potential, the viral genome integrates itself into the host cell genome and then develops a persistent infection. This infection, which must persist for years, in combination with co-existing factors, permits the progression to cancer.[3]
- In Canada, there are approximately 1,300 cases and 400 deaths from cervical cancer annually.[1] Lifetime risk of cervical cancer for Canadian females is 0.7% or 1 in 138 women.[1] This is in spite of over 50 years of screening through Pap testing.[1]

In addition to the high risk types, there are other HPV types:

- HPV 6 and 11 are low risk (LR) for causing cancer, but they cause 90% of genital warts[1,4]
  - Warty projections can occur anywhere on the genital skin surface, but they appear primarily on the vulva, penis and perianal skin.
  - Usually self-limited lesions in immunocompetent individuals that resolve within 12–24 months.
- Although squamous cell cancers of the mouth and oropharynx are rare, they have been associated with HPV.[1,5,6]

Patient Questions

As a frontline physician, it would be sensible to consider the kinds of questions patients are likely to ask about these vaccines and to whom would recommendations be appropriate.

When is HPV acquired?

HPV is one of the most common sexually transmitted infections, with the highest prevalence in adolescents and young adults under the age of 25 years. The acquisition rate of HPV infection is high following the sexual debut of girls, with almost 40% being infected by some type of HPV within 2 years.[1] It is estimated that up to 80% of women will develop an HPV infection at some time in their lives.[1]

What are the vaccines?

- The quadrivalent HPV vaccine that acts against types 6, 11, 16 and 18 is given as a 0.5ml injection intramuscularly in 3 doses at 0, 2, and 6 months.
- A soon-to-be licensed bivalent vaccine that acts against types 16 and 18 is also administered in a 3-dose schedule at 0, 1, and 6 months.

What will the vaccines do?

- Clinical trials in women aged 16–26 years have found that both vaccines are at least 95% effective in preventing persistent HPV 16 and 18 infection.[7]
- They are almost 100% effective in preventing vaccine-type specific cervical cancer precursors in girls and young women not previously infected with these types.[2,7]
- The quadrivalent vaccine is 97% effective in preventing vaginal and vulval intraepithelial neoplasia, and is 99% effective in preventing genital warts caused by HPV 6 and 11.[1]
- Given to females prior to sexual debut, it is anticipated that up to 70% of cervical cancers could be prevented.[3,7]

Patient Questions (continued)

What might the vaccines do?

- Both vaccines appear to offer some cross protection against other closely related HPV types, such as 31, 45 and 52
  - Together these 3 types are estimated to cause another 12% of cervical cancers.[8]
  - It is not known how complete and durable this protection is.
- Evidence for efficacy in older women up to 45 years shows promise, providing these women have not already been infected by the HPV types in the vaccine.
- They may provide protection against infection for males. These trials are ongoing.

What won't the vaccines do?

- They will not provide any therapeutic benefit if a patient has a pre-existing infection with the specific HPV types contained in the vaccines.
- Change cervical cancer screening recommendations.

Are these vaccines safe?

- Safety was established through placebo controlled trials.[2,7]
  - For both vaccines, local injection site reactions, e.g., pain, were common (~ 93%); placebo was only 6%-8% lower.
  - There was no difference between vaccine and placebo groups in the frequency of systemic adverse events.
  - Serious adverse events were no more common in the vaccine group vs. the placebo group and none were considered vaccine related.
  - Use during pregnancy or in those who are immunocompromised has not been evaluated.

What are the Unanswered Questions?

How long will protection last?

- Studies support the efficacy of these vaccines lasting >5 years, with no sign of waning immunity. Research extending beyond this time has not yet been reported.

Can protection be achieved using less than 3 doses?

- In the original trials, children aged 9-13 years showed a much higher antibody response than those aged 16-26 years. This offers an opportunity to look at a 2-dose schedule in this younger age group, and such a study is underway.

When will the length of protection be established?

- At present, there are insufficient vaccine failures to answer this question. Longitudinal follow-up of the early trial participants is ongoing and the answer regarding length of protection should be available before pre-adolescent recipients need to know if they require a further booster dose.
- It is common to use new vaccines in immunization programs without knowing the answers to these long-term protection questions. Findings from careful prospective surveillance will provide the impetus to implement the necessary modifications to the programs, such as the need for a booster dose.

Conclusion

The National Advisory Committee on Immunization (NACI) recently released its recommendations for the use of the quadrivalent vaccine, which include:

- For use in females 9-26 years of age.
- Due to limited data, the quadrivalent vaccine is not recommended for females <9 years of age, males (all ages), or pregnant women.
- Although not recommended for women >26 years, these patients can be vaccinated following individual consultation.
  - Full recommendations can be viewed at: www.naci.gc.ca.

The recommendations for the use of the bivalent vaccine will be available following its approval in Canada.

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