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Clinical Evidence. Practical Advice.

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Acne: Maximizing Effectiveness With Combination Therapy

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Acne Management

Effective management of acne is contingent upon understanding the pathophysiologic features of this condition. At the level of the target organ, the pilosebaceous glands, the primary factors involved are:

1. androgenic stimulation or hypersensitivity
2. enlargement and increased function of sebaceous (oil) glands
3. altered follicular epithelial growth and shedding
4. proliferation of *Propionibacterium acnes* (*P. acnes*) within the follicle
5. inflammation.

Types of Acne Lesions

Non-inflammatory lesions: Comedones		Inflammatory Lesions – all of these can scar	
Basic acne lesion is a comedone		Papules	• Tender to the touch • Small, red bumps.
<ul style="list-style-type: none"> • Enlarged, plugged pilosebaceous follicle - Whiteheads (plugged follicle) - Blackheads (plugged follicle with partially oxidized fatty acids). 		Pustules (pimples)	• Papules topped by pus-filled lesions • May be red at base.
		Nodules	• Large, painful, solid • Deep within skin.
		Cysts	• Deep, painful, pus-filled.

Educating the Patient

- Dispel myths regarding inadequate facial cleansing, the use of steam or abrasives, and the effect of diet on acne (although dairy products may aggravate acne in a small group of patients).
- Manage expectations: cure vs. control, most treatments take 8-12 weeks for noticeable improvement.
- While medicines are effective at reducing the number of new lesions, treatment of stains and scars may require fading gels, facials, and surgical correction.
- Cautions: avoid picking, vigorous scrubbing, and drying.
- Routine skin care should be gentle.

Goals of Treatment

1. Heal existing lesions and prevent scarring.
2. Prevent new lesions from forming.
3. Minimize psychological stress and embarrassment.

Aggravating Factors

- Certain drugs (e.g., androgens, lithium)
- Occlusive cosmetics may enhance comedogenesis
- Premenstrual flares due to changes in hormone levels
- Friction of rubbing or scrubbing skin
- Occlusion from helmets, backpacks, or tight collars
- Squeezing or picking at blemishes
- Stress.

Mild Acne – Topical Therapy

- Comedonal +/- a few inflammatory lesions

Topical Retinoids

- 1st line therapy – most effective in preventing and treating microcomedones and comedones.
- Use early for best results.
- Add antimicrobial therapy when inflammatory lesions are present.
- Should be applied to entire affected area.

Retinoid Mechanism of action

- Inhibits the microcomedo formation.
- Clears mature comedones and inflammatory lesions.
- Maintains remission of acne.
- Treating the microcomedo prevents disease progression.
- Enhances collagen production and can be used to reduce acne scars.
- Topical retinoids include: Tretinoin, Stieva A[®], Retin A[®] (plus others); Tazarotene (Tazorac[®]); Adapalene (Differin[®]).

Topical Antibiotics: Erythromycin and Clindamycin

- Inexpensive
- Useful for inflammatory, but not comedonal acne.
- Mechanism of action: antimicrobial and anti-inflammatory.
- Evidence of increasing antibiotic resistance due to over-use of antibiotics.

Benzoyl Peroxide (BPO)

- Major action is antibacterial (has little comedolytic effect).
- There is early evidence that BPO will inhibit antimicrobial resistance, thus it is frequently combined with antibiotics.
- Because of its effectiveness in antimicrobial activity, it can be useful for the treatment of inflammatory acne.
- Inexpensive.
- Concentrations <10% are effective and less irritating.
- Remind patients of bleaching effects on clothing, bedding, towels.

Combination Therapy for Mild-to-Moderate Acne

- Topical retinoids, BPO and antibiotics can be used. They are now marketed in various combinations, i.e., Benzaclin[®], Benzamycin[®], Clindoxyl[®], and Stievamycin[®].
- Should be used when inflammatory lesions are present (to help speed action of antibiotics).
- Antibiotic should be discontinued when inflammatory lesions resolve (2-4 months).
- Continue to use topical retinoids for maintenance when remission has been obtained.
- Time for Results: 8-12 wks.

Antibiotic + Topical Retinoid is Better than Antibiotic Alone in Preventing Microcomedone Formation

- Treats most mild-to-moderate acne with combination therapy (antibiotic + topical retinoid).
- Targets more pathophysiologic factors.
- Clearing is faster and greater than antibiotic therapy alone.

Non-responders

- Add systemic antibiotics or hormones.
- Treat non-responders as patients with moderate acne.

Tips for Topical Treatment

- Apply to entire area, not just affected spots.
- Use regularly; consistency is important.
- Expect improvement after 8-12 wks.
- If irritation occurs, reduce duration +/- frequency of application.
- When possible use aqueous rather than alcohol-based products (less irritating).
- Consider a gentle start-up schedule:
 - alternate night treatments with topicals
 - apply between dinner and bedtime
 - wash off prior to bedtime, do not sleep with products on skin

- combine with mild, gentle cleansers
- avoid the nose, eyes, and corners of the mouth.
- Cosmetic Options:
 - includes cleansers and moisturizers
 - camouflage make-up: encourage cover-up and camouflage cosmetics to reduce embarrassment
 - products should be oil free and tested to be non-comedogenic
 - reduce use of hair products (conditioners, gels, hair spray, mousse) – may extend onto forehead, neck, back causing comedones

Moderate Acne – Topical/ Systemic Therapy

- Means an increase in the number and extent of inflammatory lesions.
- Greater involvement of the face and trunk.

Using topical preparations is preferable if moderate acne responds. However, systemic therapy, i.e., oral antibiotics or hormonal therapy, may be needed to clear moderate acne.

Rational Use of Oral Antibiotics

To minimize the development of resistant *P. acnes*:

- Limit use to maximum 6 months to reduce risk of resistant bacteria
- Restrict to tetracycline family if possible (i.e., tetracycline 1g/d, minocycline 100mg/d)
- Use in combination with benzoyl peroxide.

Hormonal Therapy

- An adjunctive therapy to topicals in mild acne in women desiring contraception.
- Primary therapy in moderate nonscarring acne.
- One of 2 preferred forms of contraception in severe acne treated with Accutane®.
- For women desiring contraception: Diane 35®, Yasmin®, Tricyclen®, Alesse®.
- When contraception is not required consider spironolactone.
- Maximum effectiveness seen at 4-6 months.
- Add topicals to increase speed of improvement.

Mechanism of Action for Hormonal Therapy

Estrogen effects:

- decreases adrenal and ovarian androgens
- reduces 5- α reductase levels
- increases sex hormone-binding globulin leading to lower testosterone levels.

Progestins vary in androgenic potential:

- antiandrogenic: cyproterone acetate
- low in androgenic potential: desogestrel, norgestimate.

Severe Acne – Systemic Therapy

- Inflammatory nodules
- Extensive papulopustules
- Ongoing scarring
- Purulent and/ or serosanguinous drainage

- Sinus tracts
- Psychosocial/ occupational impact
- Inadequate therapeutic response.

Oral isotretinoin (Accutane®)

- Treatment of choice for severe acne
- Reduces sebaceous gland function and sebum excretion
- Secondarily reduces proliferation of *P. acnes*
- Reduces follicular plugging.

Isotretinoin Adverse Events

- Can cause dryness of facial skin
- Isotretinoin is teratogenic
- Women must be abstinent, permanently sterilized or use two separate effective forms of birth control
- Monitor for depression and other mood changes
- Other mucocutaneous side effects
- Rarely: hepatitis, hypertriglyceridemia.

Agent	<i>P. acnes</i>	Sebum	Inflammation	Comedones
Benzoyl peroxide*	++	-	+	+
Topical antibiotics	++	-	+	+
Azeleic Acid	+	-	+	+/-
Topical retinoids	-	-	+	+++
Estrogenic OCs	-	+	-	-
Antiandrogens	-	++	-	-
Oral antibiotics	+++	-	++	-
Oral isotretinoin	++	++++	++	++

Table 1: Acne medications and mechanism of effect. *use with antibiotics to reduce risk of selecting for resistant *P. acnes*

Conclusion

Educate and counsel. Most patients with acne are teenagers who are very self-conscious about their looks and expect immediate treatment results. However, adult acne is becoming more common, and can be very distressing as well. It is critical that all patients be counseled about compliance with the treatment and to expect results no sooner than 8 weeks after beginning therapy.

Treatment choice should be based on pathophysiology, severity and the psychosocial impact of the disease:

1. Mild: topical retinoids +/- topical antibiotics +/- topical BPO.
2. Moderate: add oral antibiotics or hormones if the patient is unresponsive to topical treatments alone.
3. Severe or unresponsive disease: oral isotretinoin.

Herpes Labialis (Cold Sores)

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Background

Cold sores are caused by the herpes simplex virus (HSV). There are two subtypes of HSV (HSV-1 and -2). Although HSV-1 is the most common cause of cold sores, there is a significant overlap in the epidemiology of the two subtypes and approximately 10% of cold sores in adults are caused by HSV-2. Socioeconomic status and age influence the frequency of HSV-1 infection. Seroconversion occurs during childhood in developing countries and in lower socioeconomic populations. Approximately 1/3 of children have been infected by 5 years of age; this frequency increases to 70%-80% by early adolescence. In developed countries approximately 20% of children are infected prior to the age of 5 and the antibody prevalence increases to 40%-60% in the second and third decades of life. Once an individual has been infected with HSV-1, the virus lies dormant in nerve cells and reactivation may recur, particularly around times of stress. The recurrent infection can manifest as classical cold sores but may also result in asymptomatic shedding. Reactivation is estimated in approximately 30% of HSV infected individuals.

Symptoms

- Recurrent clusters of small blisters localizing along the vermilion border of the lips can also occur near the nose, chin and in the mouth especially in the immunosuppressed.
 - outbreaks may occur in the eye or be widespread in eczema herpeticum
 - most common initiating factor in recurring erythema multiforme.
- Prodromal symptoms in the form of pain or tingling often occur 1-2 days before blisters appear.
- The blisters often break or ooze, weeping a clear fluid, containing infectious virus.
- Crusting can be prolonged if secondary bacterial infection occurs.
- The blisters generally heal within 7-10 days.

Diagnosis

The diagnosis is usually made clinically. Same day laboratory confirmation is provided by direct immunofluorescence, which distinguishes between HSV-1 and -2. The ideal sample for this test is obtained by collecting scalpel scrapings from the blister base, which is then smeared onto a glassslide and air dried before submitted to the laboratory. The virus can also be cultured, but results will take 3-7 days.

Causes of Herpes Labialis

- Most frequently caused by HSV-1 (genital herpes are more often caused by HSV-2).
- Recurrences are often triggered by stress, exposure to the sun, or fever.
- Some patients report that eating foods with high concentrations of arginine (such as nuts, sunflower seeds and chocolate) increases the likelihood of an outbreak.
- HSV-1 is spread through kissing or by using utensils, toothbrushes or towels that have been in contact with open sores.

Prevention

Prevention of future outbreaks is an important concern. Patients should:

- Wash hands carefully and frequently when they have a cold sore
- Limit sun exposure and apply sun block frequently to lips and surrounding skin before exposure
- Avoid triggering situations
- Exercise caution when touching other parts of the body, particularly genitals and eyes.

Treatment

- Most cold sores will clear up on their own after 7-10 days. The following actions sometimes help to minimize the pain and discomfort associated with cold sores:
 - applying an over-the-counter cream to the affected area
 - using rubbing alcohol to dry the lesions
 - taking ibuprofen or acetaminophen for the pain
 - applying ice or heat to the blisters
 - avoiding picking or squeezing the blisters.
- Treatment options are focused on reducing the discomfort associated with cold sores and lessening the duration of the outbreak. Newer approaches aim to prevent the outbreak from progressing from the prodrome stage.
- Take into consideration the difference in cost, viral resistance and convenience to the patient.
- In Canada, prescription drugs include acyclovir cream or capsules (Zovirax[®]), famciclovir (Famvir[®]), penciclovir cream (Denavir[®]), valacyclovir caplets (Valtrex[®]).

Topical

- Acyclovir cream (Zovirax[®])
 - apply 4-6 times per day
 - shown to be effective in reducing the severity of cold sores in the immunocompromised.
- Docosanol cream (Abreva[®])
 - apply 5 times per day at prodrome
 - OTC
 - shown to have a positive effect in one trial.

Oral

- Acyclovir (Zovirax[®])
 - 400mg 5 times a day shown to reduce the duration of infection by 27%.
- Famciclovir (Famvir[®])
 - indicated for the treatment of recurrent episodes of mucocutaneous herpes simplex virus infections in HIV-infected patients (500mg b.i.d. x 7 days).
 - expanded indications are currently being explored in clinical trials.
 - famciclovir 500mg t.i.d. has been shown to reduce the time of active lesions by 48%. [Spruance, et al. *J Infect Dis* 179:303-10 (1999).]
 - combination with topical steroids to the lesion may enhance benefit but the best topical is not yet established.
- Valacyclovir (Valtrex[®])
 - 2g every 12 hours for two doses will prevent outbreak of cold sores if taken early in the prodrome. [Spruance, et al. *Antiviral Res* 53:a53 (2002).]
- Both valacyclovir and famciclovir have been shown to reduce orofacial herpes outbreaks after laser resurfacing. [*Plastic Reconstr Surg* 104:1103-80 (1999).] Both of these drugs have been used world wide for the prophylaxis and treatment of cold sores.
- Oral antivirals can be taken daily to prevent recurring blisters for those patients who experience frequent episodes.

The Oral Antiviral Family

Acyclovir is a “nucleoside analogue” (it can insert itself into virus DNA during viral replication) and specifically targets virus infected cells. It prevents the production of new virus by stopping viral DNA from properly forming. Famciclovir and valacyclovir work in a similar manner to acyclovir. Because of the way they act, these three drugs require the virus to reactivate in order to be effective. Therefore, they are only effective against virus that has escaped from the nerve-cell and is replicating in other parts of the body. Thus, they do not cure a ‘dormant’ (latent) HSV infection, since the latent virus is not replicating. There is no antiviral treatment available that can eradicate latent HSV infection.

Conclusion

Cold sores can be an embarrassment. They can provide a source of herpes that can autoinoculate into the eye as well as infect others. In atopic dermatitis it can become very widespread and can also produce erythema multiforme. Treatment both topically and systemically can modestly reduce the duration and intensity of the outbreak. The use of topical antivirals as prophylaxis is ineffective. Significant advances in recent studies have shown that high dose therapy in the early prodrome can prevent the eruption.

Management of Onychomycosis

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What is Onychomycosis?

- The colonisation/ infection of the nails by fungi
- Most often seen on toenails, mainly the big toenail
- Infection of fingernails is almost never seen without associated toenail involvement.

Why is It Important?

- Nail dystrophy can be uncomfortable or painful.
- It can be unsightly causing embarrassment.
- Nail fungus can be a reservoir for infection of feet, groin, trunk and other areas.
- Can be a source for chronic tinea pedis and other types of tinea (e.g., cruris, corporis).
 - increases risk of complications such as foot cellulitis
 - increases risk of idiopathic reaction with eczema on the feet and hands.

Risk Factors for Onychomycosis

- 6.9% of Canadians have onychomycosis.[Gupta AK, et al. *J Am Acad Dermatol* 43(2 pt1):244-8 (2000)]
- It is uncommon in children.
- Most prevalent in patients with
 - advanced age
 - diabetes
 - peripheral vascular disease
 - immunosuppression
 - trauma to nails (e.g., runners often experience nail trauma)
 - not to be confused with nail dystrophy of runners
 - occupations requiring occlusive foot wear.

How to Recognize Onychomycosis

Nail changes include:

- Nail discoloration
 - on the surface of nail
 - white superficial onycholysis
 - on the nail itself or subungual changes.
- Onycholysis
 - separation of nail from nail pad.
- Subungual hyperkeratosis
 - distal nail
 - lateral nail
 - proximal nail.
- Nail thickening and crumbling.

Although nail dystrophy may be due to various causes, fungal invasion is found in more than 50% of cases. Other causes of nail dystrophy include mechanical trauma (the fifth toenail is very frequently distorted by chronic trauma) and psoriasis although the differential diagnosis is extensive. Onycholysis may be due to various factors, as is thickening of nails (see below). Nail pitting and the oil-drop sign (spotty yellow-brown discoloration of the nail) are specific to psoriasis. Of note, psoriatic nails and distorted nails from trauma may become infected by fungi.

Causes of Onycholysis

- Psoriasis
- Trauma
- Hyperhidrosis
- Eczema
- Chemical (e.g., solvents, nail hardeners)
- Drug-induced:
 - photo-onycholysis (with doxycycline and other photosensitizers)
 - chemotherapy.
- Impaired peripheral circulation
- Systemic disorders
 - hypo- and hyperthyroidism
 - porphyrias.
- Idiopathic
- Onychomycosis

Causes of Nail Thickening

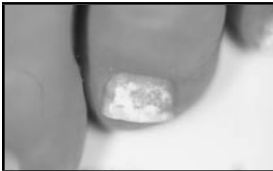
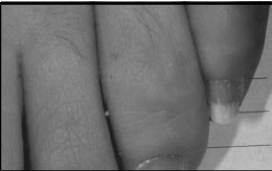
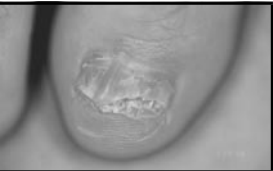
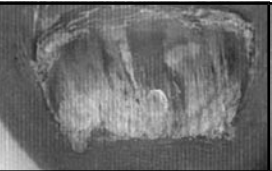

- Onychomycosis
- Psoriasis
- Eczema
- Trauma
- Yellow nail syndrome
- Other rare causes

Diagnosis of Onychomycosis

- Diagnosis should be confirmed by
 - direct microscopic examination of nail clippings
 - culture.
- Procedures are simple.
- Results will guide the treatment.
- Some fungal strains are especially hard to treat.
- Nail clippings should include the full thickness of the nail plate.
- One positive culture/identification of fungus out of three consecutive samples is necessary for diagnosis.

Treatment of Onychomycosis

Patients with onychomycosis should be treated unless they are of advanced age or there are contraindications to available therapies.

				
White superficial onychomycosis	Mild distal subungual hyperkeratosis	Moderate distal hyperkeratosis	Lateral subungual hyperkeratosis	Proximal subungual hyperkeratosis
Topical treatment	Topical or systemic treatment	Systemic +/- topical		

Topical treatment can be used to control the spread of the infection and as an adjunct to systemic treatment. Removal of dermatophytomas (densely packed hyphae forming subungual masses) is advised. Nail removal is not recommended unless there are unusual circumstances.

Systemic Treatments

The most often prescribed systemic treatments are terbinafine and itraconazole, the former being because it generally has a higher cure rate. Fluconazole is seldom used.

Terbinafine

Terbinafine 250mg is given daily for 12 weeks. Pretreatment serum transaminase (ALT, AST) tests are advised as a baseline for all patients before taking terbinafine tablets. These tests should be repeated after 3 weeks of treatment to check for hepatic toxicity.

Itraconazole

Itraconazole is mainly given in pulses of 7 days, e.g., 200mg b.i.d. x 7 days at week 1, week 5 and week 9 for a total of 3 pulses over 3 months. Itraconazole must be taken immediately after a full meal. Azole compounds have multiple drug interactions that must be addressed before starting the treatment.

Topical Treatment

Ciclopirox Nail Lacquer

Topical ciclopirox 8% nail lacquer is to be applied once daily for 48 weeks and nail debridement should be performed by a health professional. The active ingredient penetrates as deep as 0.4mm into the nail after one application.[Bohn M, et al. *J Am Podiatr Med Assoc* 90:491-4 (2000)] A meta-analysis of 10 trials disclosed a mean mycological cure rate of 52.6% with this topical treatment.[Gupta AK, et al. *J Am Acad Dermatol* 43(4 Suppl):S70-80 (2000)] Ciclopirox nail lacquer is the only Health Canada approved topical treatment with proven efficacy.

Systemic	Topical
Terbinafine – 250mg/day x 12 weeks	Ciclopirox nail lacquer – daily x 48 weeks
Itraconazole – 200mg/day x 12 weeks or 200mg b.i.d. x 1 week/month for 3 months	
Fluconazole – 150mg/week x 9 months	

Table 1: Treatment of onychomycosis

Systemic and Topical Combination

Oral terbinafine may be advantageously combined with topical ciclopirox nail lacquer. In a recently published trial, the mycological cure rate was 56% for patients receiving 12 weeks of oral terbinafine alone and 70.4% for patients treated with a combination of oral terbinafine for 12 weeks plus daily ciclopirox nail lacquer for 48 weeks.[Gupta AK. *J Drugs Dermatol* 4:481-5 (2005).]

Conclusion

Diagnosis of onychomycosis can only be established with a positive culture or observation of fungus in the nail clippings. Consideration should be given to cost and possible complications before starting treatment. Recurrent disease is a problem even after a complete cure.

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