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Clinical Evidence. Practical Advice

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Therapeutic Update on External Genital Warts

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Introduction

External genital warts (EGW) are a common infection caused primarily by human papillomavirus (HPV) types 6 and 11. EGW negatively impacts upon patient psychosocial function and is a co-factor for infection with other sexually transmitted infections (STI), by allowing an easier portal of entry into the skin. Both patient and provider-applied therapies can be utilized in tandem to effectively treat EGW. More recently, prophylactic strategies using vaccines have been instituted to prevent HPV acquisition and resultant disease. As well, the recent introduction of a new formulation topical immunomodulator has further widened the spectrum of available therapies.

Pathogenesis

- EGW is caused by human papillomavirus (HPV)
- An HPV viron is small and non-enveloped; its protein coat (capsid) is composed of two structural proteins
- The viral genome consists of single, supercoiled double-stranded circular DNA of approximately 8000 base pairs in size[1]
- >200 types of HPV have been identified, approximately 40 infect the anogenital tract[2]
- HPV infections are categorized as low risk or high risk based upon oncogenic potential[3,4]
- High risk-types include HPV 16, 18
  - Responsible for 100% cases of cervical cancer and 80% cases of anogenital cancers
- Low risk types include HPV 6, 11[4]
  - Responsible for 95% EGW cases
  - HPV 6: 74.4%
  - HPV 11: 14.2 %
  - HPV 6 and 11: 3.7%
- Low risk HPV types are also responsible for 10% of cervical intraepithelial neoplasia grade 1, 42% of related low-grade vulvar intraepithelial neoplasia, and 100% of recurrent respiratory papillomatosis

Disease Overview

Epidemiology

- The World Health Organization estimated 300 million cases worldwide of HPV infection without any detectable abnormality; 30 million cases worldwide of active EGW
- Approximately 1 million new cases annually of EGW in the US[5]
- Prevalence in Manitoba (2004): 165.2 per 100,000 for men; 128.4 per 100,000 for women[6]
- Incidence in British Columbia (2004): 1.54 per 1000 males; 1.23 per 1000 females[7]
- In Canada, the incidence of genital warts was estimated to be 107 per 100,000 person-years in 1999, increasing to 126 per 100,000 person-years in 2006.[7]
- Incidence highest in women between the ages of 20-24 years (3.38 per 1000 women)
- Incidence highest in men aged 25-29 years (3.03 per 1000 men)

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Burden of Disease

- Psychosocial impact[8]
  - Feelings of anger, disgust, embarrassment
  - Fear of cervical cancer
  - Concern over recurrence, transmission, and treatment efficacy
  - Change in lifestyle
- Socioeconomic burden
  - 60% increase in office visits (US) in last decade[9]
  - $220 million in health care costs (US 2004, private insurance)[10]
  - A population-based study of EGW treatment in British Columbia confirmed its significant burden on the health care system:[7]
    - Between 1998 to 2006, 39,493 patients were diagnosed with EGW, with 43,586 episodes
    - Overall incidence was 1.26 per 1000 population, at an average cost of $190 per episode for treatment, which translates into about $1 million annually in direct medical costs.
    - The incidence and prevalence of EGW are comparable across Canada.

Natural History

- EGW noted by patient in 65% of cases (52% females; 79% males)[8]
- EGW noted at physician visit in 16% of cases (30% females; 1% males)[8]
- Transmitted most commonly through sexual contact (i.e., genital-genital, oral-genital, genital-anal)
- Infection may also rarely occur due to perinatal transmission (laryngeal papillomatosis) or fomites[11]
- HPV gains access to basal epithelium via abrasions or microabrasions
- Incubation (1-8 months)
- Individual patient immune response results in active growth or host containment (6-9 months)
- Clinical course of EGW include remission or persistent infection with recurrences
- 30% spontaneously resolve within 4 months, 50% at 6 months[12]

Treatment Options (Table 1)

- Patients may prefer self-applied therapies for initial treatment
- Combination therapy may be more effective than monotherapy
- Inadequate responders may improve with transition to or addition of other therapies or modification of the existing approach
- According to Canadian STI Guidelines[13] therapies are broadly grouped as patient-applied or office-based treatments:
  - Office-based treatments
    - Podophyllin resin (when no other treatment is available)
    - Surgical excision
    - Cryotherapy
    - Bichloracetic acid or trichloroacetic acid
  - Patient-applied treatments
    - Podophyllotoxin
    - Imiquimod
- Cytodestructive therapies involve the physical removal or chemical destruction of EGW:
  - Cryotherapy (liquid nitrogen)
  - Surgical/ablative techniques (surgical excision, carbon dioxide laser, electocautery)
  - Trichloroacetic or bichloroacetic acid
  - Podophyllin resin
  - Podophyllotoxin (0.5%) - standardized concentration of purified podophyllin
- Immunomodulatory therapy with topical imiquimod
  - Immune response modifier
  - Antiviral and antitumor effects
  - TLR-7 agonist
  - Induces Th1-type immune response and the generation of cytokines such as IFN-alpha
  - Pregnancy Category C
  - Due to its favourable efficacy, safety, and tolerability profiles, as well as lowest recurrence rate, Canadian Consensus Guidelines on HPV[14] recommends the use of imiquimod prior to initiating more invasive strategies, such as destructive/excision or laser therapies.
  - Imiquimod 5% cream (Aldara™)
    - Approved by Health Canada in 1999
    - Officially indicated for the treatment of external genital and perianal warts in immunocompetent adults
    - Applied 3 times weekly for up to 16 weeks to a specific treatment area
    - In a Phase 3 clinical trial, 72% of women and 33% of men had complete clearance of baseline target warts (analyses did not include non-target or new warts)[15]
    - Side-effects include erythema (67%), erosion (32%), excoriation/flaking (25%), edema (16%)[15]
  - Imiquimod 3.75% cream (Vyloma™)
    - Approved by Health Canada in March 2011 for the topical treatment of external genital warts and perianal warts (whether present at the start of therapy or emerging during therapy) in immunocompetent adults.
    - Developed with the goal to shorten treatment duration, simplify dosing regimen, and improve tolerability, thereby encouraging adherence.
    - Two recent identical, gender stratified, randomized, placebo-controlled clinical studies involving 981 patients >12 years of age with 2-30 lesions in the inguinal area, perineal region, perianal area, penile shaft/glans/foreskin, scrotum, or vulva demonstrated imiquimod 3.75% applied once-daily for up to 8 weeks was well tolerated and efficacious in the treatment of EGW (Table 2 and Figure 1).[16,17]
    - Efficacy was measured in terms of number of EGW (baseline and new).
    - In patients achieving complete clearance, almost 70% maintained clearance at 12 weeks post-treatment.[17]
    - Common side-effects included pain, irritation, and pruritus at the treatment site.

Method	Treatment	Comments
Antiproliferative Therapies	Podophyllum resin 10%-25%	• Physician-administered • Removal of warts by destruction of infected tissue • Potential for systemic toxicity, especially if applied to large areas or in patients with renal insufficiency • Teratogenic (fetal death reported) • Antimitotic (causing tissue necrosis) • Local side-effects include erythema, edema, pain, burning, itching, severe necrosis, and scarring • Modest efficacy and potency; shelf-life unpredictable
	Podophyllotoxin 0.5% solution or gel	• Can be applied by the patient (twice-daily for 3 days, then off for 4 days; may repeat treatment cycle for up to 4 weeks); skin protectant, e.g., petroleum jelly, should be used on normal adjacent skin • Low cost, low toxicity • It does not contain any mutagenic substances, unlike those found in podophyllum resin • Potential systemic toxicity if applied to large area, limit use on EGW 3 times weekly for up to 4 consecutive weeks
Immunomodulatory Therapies	Imiquimod cream	• Self-administration may improve patient adherence • Enhances the cytotoxic immune reaction, usually seen as an inflammatory response • Low rate of recurrence due to reduction of the viral load and/or induction of HPV-specific cellular immune memory • Side-effects are mild to moderate and include local erythema and erosion at the site of application
	Imiquimod 5%	• For 5% imiquimod apply directly to the affected skin 3 times/week for up to 16 weeks; use on alternating days - leave on affected skin for 6-8 hours before washing off with soap and water • Reduce frequency of application or temporarily interrupt therapy if there is concern over the degree of inflammation
	Imiquimod 3.75%	• For 3.75% imiquimod apply daily at bedtime for up to 8 weeks • Reduces treatment duration; simplified once-daily dosing improves tolerability
Destruction/Excision Therapies • For more extensive disease • May require local or general anesthesia • Scaring and pigmentary changes common	Topical trichloroacetic acid 85% (TCA) or bichloroacetic acid	• 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 • Inexpensive; safe in pregnancy
	Local cryotherapy	• Most common destructive mode; inexpensive • Involves freezing with liquid nitrogen • Offers ease of use with no systemic effects • Can cause pain, ulceration, and pigmentary changes • 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	• CO2 laser therapy is usually reserved for extensive and/or treatment-resistant warts • May require a long time for recovery and is expensive
Combination Therapy • Can provide a better result over monotherapy	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
	Excision/destruction + cidofovir	• Due to cidofovir's broad antiviral activity, it has been used successfully as a topical gel for refractory patients

Table 1: Overview of therapeutic options for external genital warts[14-20]

Location	Complete Clearance (Per-protocol)	Complete Clearance (ITT)	Partial (≥75%) Clearance (Per-protocol)
Overall	33.8	28.3	45.9
Women overall	43.1	36.6	56.2
Vulva	51.0		
Perineum	64.9		
Perianal	78.5		
Inguinal	45.0		
Men overall*	22.7	18.6	33.6

Table 2: Overall and anatomic site-specific clearance rates, by gender, following treatment with imiquimod 3.75% cream[16,17]
* Anatomic site-specific clearance rates in men have not yet been published.
ITT = intent-to-treat; primary analysis includes all randomized subjects
Per-protocol = only data from adherent subjects are analyzed

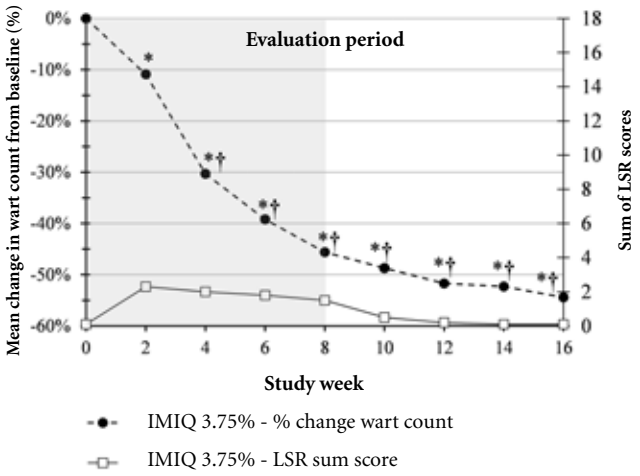

Figure 1: Change in wart count compared with baseline (left axis, circle) compared with local skin reaction (LSR) sum score (right axis, square) for imiquimod 3.75% in women. Modified from Baker et al.[16]

Prevention

Two vaccines available for the prevention of HPV acquisition:

- Quadrivalent (HPV types 6, 11, 16, 18) vaccine (Gardasil®)[21]
  - Prevention of EGW caused by HPV 6, 11 and cervical cancer and other cancers caused by HPV 16, 18 including vulva and vaginal cancers, cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia, and vaginal intraepithelial neoplasia
  - Indicated in females aged 9-45 years
  - Indicated in males aged 9-26 years
- Bivalent (HPV types 16, 18) vaccine (Cervarix®)[22,23]
  - Adjuvant results in very high serum antibody levels against HPV, excellent subtype cross-protection
  - Excellent for prevention of cervical cancer and other cancers caused by HPV 16, 18
  - Does not protect against EGW acquisition
  - Indicated in females aged 10-25 years

Conclusion

EGW is a worldwide problem. The scope of diseases, both oncogenic and nononcogenic, caused by HPV is broad. EGW is a manifestation of nononcogenic HPV subtypes 6 and 11. Therapeutic strategies to eradicate EGW have been developed and preventative vaccines are now widely available. Hopefully, the development of novel therapeutic molecules targeting EGW will supplement current tools in the treatment armamentarium against HPV and facilitate the eradication of this prevalent disease.

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A New Paradigm Shift in the Management of Atopic Dermatitis

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Introduction

Atopic eczema (or atopic dermatitis) is a common inflammatory skin condition that dermatologists, pediatricians, family physicians, and primary-care providers see on a daily basis. It generally presents as a chronically relapsing, highly pruritic, inflammatory skin disease that is associated with significantly reduced quality of life for patients and their families. Irritability, fatigue, sleep disturbances, treatment dependence, mood changes, and other psychological sequelae are frequently reported. Also, the social stigma associated with this visible skin condition should not be neglected.[1-3]

Overview of Atopic Dermatitis

- Eczema is characterized by a chronic course of recurring flares, as it often presents with periods of remission and flare-ups; continuous treatment and skin care are necessary.[1-3]
- Eczema can occur at any age, but it typically appears in early childhood (although late-onset disease is possible), with disease flares occurring periodically throughout the patient's life.[1]
- It is estimated that up to 17% of Canadians will develop atopic eczema at some point during their lifetime.[4]
- Atopic eczema has become more prevalent over the past few decades. Approximately half of eczema patients will develop the disease before 1 year of age.[2] Of these, approximately one-third will continue to suffer from eczema in adulthood.
- Most patients (approximately 85%) have mild to moderate disease.[1]

Pathogenic and Other Contributing Factors

- The exact cause of atopic eczema is unknown, however, it is believed to have a multifactorial pathogenesis, with genetics, impaired immune responses, the environment, and skin barrier defects being the most predominant contributing factors.[3]
- The epidermis is the body's first line of defense against environmental insults, as it forms a protective layer between the body and exogenous factors.[5]
  - An intact epidermal layer is essential for the skin to function as a physical and chemical barrier against environmental agents.[5]
  - Any breakdown in the epidermis increases skin moisture loss and the penetration of infectious and noxious external agents.[5]
- Several genetic factors are known to contribute to the dysfunction of the epidermal barrier in atopic eczema.
  - In particular, genetic defects associated with increased IgE (antibody) production and protease expression, and decreased levels of structural proteins in the epidermis have been linked to atopic eczema.
  - Gene mutations are believed to engender some of the aforementioned structural abnormalities in the epidermis and induce immune dysregulation.[4]
- The scratching that can result from symptomatic pruritus may additionally cause skin trauma and excoriation, potentially leading to further inflammation, disease exacerbation, and secondary infections.
- Environmental factors may also contribute to skin barrier dysfunction, including washing with harsh soaps and detergents, and exposure to various infectious and noxious agents.
  - Soap or detergent use is one of the most common triggers of atopic eczema flares by adversely affecting the skin barrier. The use of inappropriate cleansing agents increases transepidermal water loss (TEWL), induces the release of pro-inflammatory cytokines, and elevates skin pH - provoking scaling, dryness, tightness and roughness, erythema, and swelling.

Treatment Rationale

Management of atopic dermatitis is frequently multimodal, incorporating several non-pharmacologic and pharmacologic approaches.

- Basic skin care practices, such as quick daily bathing and gentle cleansing of skin with mild, unscented soaps/cleansers, followed by moisturization (hydration) with emollients can minimize the skin impairment and treat the symptoms of dry skin and itching.[6]
- Additionally, the avoidance of irritants and other triggers known to exacerbate atopic eczema may prove useful in preventing flares.[6]
- However, despite vigilant skin care practices, most patients will continue to experience atopic eczema symptoms and recurrent flares that will require pharmacologic treatment.[6]

Treatment Options

Topical Corticosteroids

- Topical corticosteroids have been the predominant atopic eczema therapy for more than four decades - they provide flare control through their anti-inflammatory, anti-proliferative, immunosuppressive, and vasoconstrictive actions.
- Common adverse effects of topical corticosteriods include striation, skin thinning and atrophy, and potential systemic effects.[3]

Topical Calcineurin Inhibitors

- The topical calcineurin inhibitors (TCIs), tacrolimus and pimecrolimus, are alternative topical anti-inflammatory agents in the clinician's armamentarium.
- These agents may be used on all body parts, including sensitive areas, such as the face, neck, and groin.
- They can also be used in patients who have experienced steroid related side-effects or in those suffering from a chronic disease that is unresponsive to topical steroids, as well as in patients for whom therapy with steroids is inadvisable or has been unsuccessful.[2]
- The calcineurin inhibitors do not cause the adverse effects on collagen synthesis or skin thickness as compared with topical corticosteroids.[7]
- Long-term treatment with tacrolimus has also been associated with improvements in collagen synthesis and skin thickness.[7]

Antimicrobials

- Antimicrobials are commonly prescribed for clinically infected eczematous lesions where *Staphylococcus aureus* colonization is suspected as a contributing factor.
- Short-term combination topical therapy with an antibiotic and corticosteroid is widely used. However, overuse and prolonged treatment increases the risk for developing antibiotic resistance.
- A recent report in *Cochrane Database Systematic Review* did not find clear evidence of benefit for antimicrobial interventions in atopic dermatitis patients.[8]

Lifestyle/Non-pharmacologic Strategies

- Identify and eliminate triggering factors
- Avoid allergens
  - Environmental (e.g., house dust, dust mites, pollens, animal dander, moulds, smoke)
  - Food (e.g., milk, egg whites, peanuts, soybeans, tree nuts, fish, shellfish, wheat)
- Minimize exposure to irritants (e.g., wool, perfumes, soap, hot baths or showers)
- Use emollients to hydrate and rehydrate
- Ensure that sports equipment is dried completely - sweat is a common irritant
- Encourage patient self-education, suggest visiting reputable websites (e.g., Canadian Skin Patient Alliance, Eczema Society of Canada, and the Canadian Dermatology Association)

A Paradigm Shift in the Management of Eczema

- Conventional therapeutic approaches have been recently challenged by a newer strategy that takes a preventative long-term approach to treating atopic eczema.[7,9]
- The clinical justification for preventative maintenance therapy is that it can improve atopic eczema related skin barrier dysfunction and diminish the immunological inflammatory abnormalities often associated with chronic eczematous flares and disease exacerbation.[9]
- The preventative maintenance approach uses intensive topical anti-inflammatory therapy until visible lesions have nearly cleared.[7,9] This is followed by low dose intermittent application, usually twice-weekly, of anti-inflammatory agents to previously affected skin areas to prevent flares and disease exacerbation.[7,9]
- Several clinical trials comparing the preventative to the traditional "reactive" approach using topical corticosteroids have shown that preventative therapy is an effective strategy.[10]
- In 2002, Hanifin et al. published a randomized, double-blinded, 20-week clinical trial comparing the preventative application of 0.05% fluticasone cream with vehicle cream.[11]
  - Patients preventatively receiving 0.05% fluticasone cream were 7.7 times less likely to experience a flare relapse than those receiving vehicle.
- Alternatively, preventative use of 0.1% and 0.03% tacrolimus ointment was recently studied in two large, multicentre, randomized, double-blind, 12-month clinical trials involving adult (n=257) and pediatric (n=125) atopic eczema patients.[9]
  - Patients were randomized to twice-weekly preventative tacrolimus therapy or twice-weekly vehicle after an initial flare treatment with twice-daily tacrolimus ointment.
  - Preventative application of tacrolimus significantly reduced the number of disease exacerbations requiring substantial therapeutic intervention in both treatment populations.
  - Preventative therapy also resulted in significantly fewer treatment days (12.4 vs. 31.5), and increased flare-free time until first relapse (142 days vs. 15 days) in adult patients.[9-14] In addition, preventative therapy in children significantly reduced the

number of treatment days (34.0 vs. 59.9), and prolonged the time to first relapse compared with reactive treatment (295 days vs. 56 days).[12-15]
  - Similar results have also been shown in trials reporting the use of pimecrolimus cream for flare prevention in children.[13]
- TCIs may offer benefits over corticosteroids in the long-term treatment of atopic eczema given their lack of association with skin atrophy and decrease in collagen synthesis.[3-7,9]
- Based on the above studies, in September 2010, Health Canada approved a new indication for the use of tacrolimus ointment as maintenance therapy in moderate to severe atopic dermatitis.[16]

Conclusion

As there is no cure for atopic eczema, a long-term strategy for disease control and management is of significant importance for this chronically relapsing condition. Recent insights into the mechanisms that drive cutaneous inflammation have led to a better understanding of atopic eczema and highlighted the role of the epidermal barrier in its pathogenesis. Targeting the skin barrier and restoring its function may prove an effective treatment strategy for atopic eczema. Preventative treatment with topical steroids or topical calcineurin inhibitors offer a novel therapeutic approach with clinical implications for physicians and their patients. Furthermore, studies have shown that topical tacrolimus may confer additional benefits, as it improves the functionality of the skin barrier and does not cause skin atrophy. As demonstrated in clinical investigations, the substantial reduction in flare-ups among preventatively treated patients may result in fewer atopic eczema-related physician visits and quality of life improvements (e.g., work/school performance).

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A Practical Approach to Classification and Treatment of Scars

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Introduction

Scarring, whether from planned surgical procedures or a sequela of inflammatory conditions such as acne, striae, burns or trauma, is often associated with considerable emotional impact. As a result, patients often seek the advice of physicians regarding scar revision. This paper focuses on a comprehensive and practical approach to classifying and managing scars in terms of colour and texture, and discusses topical treatments accessible to family physicians in more detail.

Scar Formation

- Scars are part of the normal healing process after cutaneous injury. The process is part of the remodeling phase of wound repair, following the phases of hemostasis and inflammation.
  - The wound repair phase involves re-epithelialization, neocollagenesis, neovascularization, and pigment deposition.
- Scar formation can take up to months to fully realize the severity and extent. Once the skin re-epithelializes (i.e., wound closure is established and intact), the structural integrity of the injured site should be amenable to most scar treatment protocols, which may then be initiated.
- Patients undergoing scar treatment should be cautioned to avoid direct sun exposure whenever possible to prevent excess vascular or pigment deposition in the repaired tissue.

Classification of Scars

- All scars can be categorized according to both colour and texture (Tables 1 and 2). Both of these components must be considered and addressed independently to attain improvement of the visible quality of the scar.[1]
- Active inflammation must first be resolved before determining the correct classification of a scar. Inflammation is characterized by a purple discoloration, tenderness, and focal elevation of the skin.

Scar Colour	Features
Red	• Red scars are due to either persistent inflammation (which should be eliminated before initiation of scar treatment) or dilated capillaries in the dermis. • In response to dermal injury, blood vessels dilate in order to provide oxygen, chemical factors, and nutrients necessary for the skin to adequately recover from the injury.
Brown	• Scars may appear brown due to either melanin or hemosiderin deposition. • More melanin is released into the dermis after skin injury in dark-skinned individuals; they are thus more prone to developing post-inflammatory hyperpigmentation. • Hemosiderin is deposited due to extravasation of red blood cells where the skin is injured.
White	• White colour in scars is due to the absence of melanin or dermal fibrosis. • Inflammation may partially destroy melanocytes that produce melanin, decreasing pigmentation in a scar.

Table 1: Classification of scars by colour

Scar Texture	Features
Elevated	• Elevated scars are the result of excessive collagen deposition and fibrosis at the site of skin injury.[2] • Elevated scars can be classified as either hypertrophic or a keloid. • Hypertrophic scars show vertical growth only and do not extend beyond the confines of the defect initiating the scar. • Keloid scars display both vertical and lateral growth, extending beyond the confines of the defect initiating the scar. • Darker skin types are generally more susceptible to the formation of hypertrophic and keloid scars. These skin types may be genetically more prone to collagen deposition post-skin injury.
Depressed	• Depressed scars may be classified as icepick, boxcar, or rolled in nature.[3] • Icepick scars are usually small (< 2mm width), superficial (< 1mm depth), and have an acute angle at the base. They typically occur in multiples due to focal collagen injury from prior inflammatory acne. • Boxcar scars may appear crateriform as they have right angles. They may be several millimeters in diameter and can be as deep as 2 mm. • Rolled scars are larger in diameter with shallow, rolled, nonangled borders. They are often the result of a deep cyst or nodule that has involuted or retracted.

Table 2: Classification of scars by texture

Treatment Options

- Every scar can be broken down and categorized according to colour and texture, both of which must be addressed independently to improve the scar's appearance.
- This paper will focus mainly on topical therapies used to improve the appearance of scars, although tables with comprehensive options for scar revision are presented.

Treatment Options Targeting Scar Colour

Table 3 lists comprehensive options targeting scars with abnormal colour. Topical therapies within each category will be discussed in more detail.

- Cosmetic camouflage using makeup creams and powders in a patient's normal skin tone will help conceal the abnormal scar colour.
- Topical vasoconstrictors such as oxymetazoline, epinephrine or cocaine may be used to constrict blood vessels, decreasing a scar's redness.
- Lightening creams containing hydroquinone, azelaic acid or kojic acid may be helpful to decrease brown hyperpigmentation.
- Hydroquinone 2%-5% alters conversion of dopa to melanin by inhibiting the activity of tyrosinase. Side-effects include allergic and irritant contact dermatitis, post-inflammatory hyperpigmentation, and cutaneous ochronosis. Animal studies have shown teratogenicity and induction of renal adenoma, but these findings have not been seen in humans.[4]
- Kojic acid 2% is a tyrosinase inhibitor produced by fungi such as *Aspergillus oryzae*. Side-effects may include irritation.
- Azelaic acid 15% (Finacea®) is a tyrosinase inhibitor and may be antiproliferative and cytotoxic towards melanocytes. Side-effects include erythema, scale, burning, and pruritus.
- Topical retinoids such as tretinoin 0.01%-0.1% (Retin-A Micro®, Stieva-A®), adapalene 0.1%-0.3% (Differin®, Differin® XP™), and tazarotene 0.1% (Tazorac®) may reduce brown pigmentation by inhibiting tyrosinase transcription, interrupting synthesis of melanin. Side-effects include xerosis, erythema, skin peeling, and sun sensitivity.
- Chemical peels involve the application of a chemical agent on the skin, causing controlled destruction of parts of the epidermis and dermis, potentially decreasing hyperpigmentation. This leads to exfoliation and later epidermal and dermal regeneration. Common chemical peel agents include alpha hydroxy acids (glycolic acid, lactic acid), beta hydroxy acids (salicylic acid) and trichloroacetic acid. Depth of the chemical peel varies depending on the chemical agent chosen. This should be done in consultation with a dermatologist. Side-effects may include pigmentary changes, infection, erythema, and scarring.[5]
- Topical calcineurin inhibitors such as tacrolimus 0.03%-0.1% (Protopic™) and pimecrolimus 1% (Elidel®) have immunomodulatory effects that may help with repigmentation of white scars. Side-effects include burning and pruritus. Although the US FDA has a black box warning on these therapies regarding risk of lymphoma and skin cancer development, clinical evidence in humans has not suggested causality.[6]
- Silicone gels have been shown to reduce the redness of scars.[7]

Scar Colour	Treatment Options
Skin coloured	No treatment necessary

Red	• Topical treatment
	  • Vasoconstrictors
	  • Camouflage
	• Laser (vascular-targeting)

Brown	• Topical treatment
	  • Lightening creams
	  • Topical retinoids
	  • Chemical peels
	  • Camouflage
	• Physical treatment
	  • Microdermabrasion
	  • Micropuncturing
	• Laser (pigment-targeting, ablative)

White (hypopigmented or depigmented)	• Topical treatment
	  • Topical calcineurin inhibitors
	  • Camouflage
	• Phototherapy
	  • UV light therapy (PUVA, UVA1, NB-UVB, BB-UVB)
	• Physical treatment
	  • Surgical excision
	• Laser (pigment-stimulating, ablative)

Table 3: Treatment options targeting scar colour[1]

Treatment Options Targeting Scar Texture

Table 4 lists comprehensive options targeting scars with abnormal texture. Topical therapies within each category will be discussed in more detail.

- Elevated scars
  - Strategies for prevention of hypertrophic and keloid scars during surgical procedures include minimizing tension and everting wound edges during closure, avoiding anatomic locations more prone to hypertrophic or keloid scars such as across joints, angle of the jaw, shoulders, mid-chest, and upper back, placing incisions in areas that follow skin creases, and achieving efficient hemostasis.[2]
  - Very high potency topical corticosteroids such as clobetasol propionate 0.05% (Dermovate®) or halobetasol propionate 0.05% (Ultravate®) ointments or creams may be used for minimally hypertrophic scars. They are usually ineffective with more hypertrophic or keloid scars.
  - Intralesional corticosteroids such as triamcinolone 10-40 mg/mL (Kenalog®) may help decrease the elevation seen in hypertrophic and keloid scars.
  - Corticosteroids act to suppress the immune responses as well as diminish collagen synthesis, inhibit fibroblast growth, and enhance collagen degeneration. Adverse effects of topical and intralesional corticosteroids include hypopigmentation around the injection site, dermal atrophy, telangiectasia, widening of the scar, and delayed wound healing.
  - Topical imiquimod (Aldara™) is an immunomodulator that stimulates interferon-α, inducing collagen

breakdown. In off-label use, studies have shown that nightly application of imiquimod to keloidal scars improves cosmetic appearance over an 8-week period. Adverse effects of imiquimod include erythema and irritation.[8,9]

- Over-the-counter (OTC) topical silicone gel products (e.g., Kelo-cote® and Dermatix™ Ultra) applied twice-daily for 4 months have also shown beneficial effects on both treatment and prevention of hypertrophic and keloid scars.
  - The postulated mechanism of action involves reducing transepidermal water loss (TEWL), enhancing hydration, and decreasing activation of dermal fibroblasts through inhibition of cytokine production. These combined processes normalize collagen deposition and diminish scar hypertrophy.[10]
  - Silicone gel may be used for existing and new hypertrophic and keloid scars resulting from burns, surgical procedures, trauma, and wounds. Treatment has been shown to reduce redness, hardness, elevation, itching, and pain.[7,10]
  - For post-surgical or -trauma treatment, it may be considered a first-line prophylactic strategy in the prevention and development of hypertrophic or keloidal scars.[11]
  - Both gel and sheet products have comparable efficacy, but for greater practical contouring of flexural areas gels may be preferred, as optimal occlusion is achieved by close apposition of the product with the scar.[10]
  - The gel is well-tolerated with no common adverse effects.[9]
  - Spray formulations are especially useful on sensitive or larger skin areas.
  - Preparations containing silicon dioxide dry rapidly, allowing for cosmetics or sunscreen application over the silicone treatment.
- Occlusive dressings such as pressure dressings and silicone gel sheeting (Cica-Care™) are commonly used to treat burn scars. The mechanism of action is through mechanical compression and reduction in oxygen tension, along with silicone's effects discussed above. Pressure dressings must maintain a pressure of 25-40 mmHg, up to 24 hours a day, for 9-10 months for best results. Silicone gel sheets must be used 24 hours a day for 3-4 months.[8,9]
- Topical onion extract (Mederma®) and vitamin E are widely used OTC products for scar revision, but clinical effects were not found to be significant over placebo.[9]

- Depressed scars
  - Cosmetic camouflage using makeup creams and powders in a patient's normal skin tone will help fill in and conceal dark shadows created by the scar's depressions.
  - Chemical peels (see treatments for scar colour) serve to exfoliate and resurface the skin's surface, decreasing the relative depth of depressed scars.

Scar Texture	Treatment Options
Normal texture	No treatment necessary

Elevated (hypertrophic or keloid)	• Topical treatment
	  • Topical corticosteroids
	  • Topical imiquimod
	  • Topical silicone gel
	• Physical treatment
	  • Intralesional corticosteroids
	  • Intralesional 5-FU
	  • Intralesional verapamil
	  • Intralesional bleomycin
	  • Intralesional interferon-α-2b
	  • Occlusive dressings
	• Surgical excision
	• Laser (ablative)

Depressed (icepick, boxcar or rolled)	• Topical treatment
	  • Chemical peels
	  • Camouflage
	• Physical treatment
	  • Microdermabrasion
	  • Dermabrasion
	  • Soft tissue fillers
	  • Profibrotic agents
	  • Volumizing agents
	• Punch and surgical excision
	• Subcision
	• Laser (ablative, non-ablative)

Table 4: Treatment options targeting scar texture[1]

Conclusion

- All scars can be classified by their colour and texture. A multimodal approach targeting both aspects is essential to optimal scar management.
- Many topical therapies are available to family physicians to improve scar appearance. Failing this, referral to a dermatologist for further topical, physical, light, laser, or surgical interventions for scar revision should be considered.

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