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EDITORS WELCOME

Dear Canadian Dermatology Community,

Welcome to our first issue of *Canadian Dermatology Today* in 2021! As the country has dealt with a severe resurgence of COVID-19 during the winter months, we can only hope that this note finds all of you in the Canadian dermatology community---along with your loved ones---doing well and staying safe.

In our newest issue, we discuss pediatric alopecia areata and present an article on the management of CSU in pediatric patients. We also have wonderful contributions on hand eczema, melasma, non-invasive cosmetic procedures to increase muscle tone and a practical overview on preventing squamous cell carcinoma in the post-transplant patient. As always, we hope you find these articles informative and helpful.

We are grateful to our sponsors for their ongoing support in 2021, to our authors for their commitment to sharing best practices across the entire Canadian dermatology community and to our readers for their continued readership! Please let us know how we are doing by suggesting topics and feel free to share our registration link at canadiandermatologytoday.com with your peers so that, they too, can subscribe to future issues!

Best wishes,

Kim Papp, MD Jensen Yeung, MD Melinda Gooderham, MD Chih-ho Hong, MD



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PREVENTING SQUAMOUS CELL CARCINOMA IN THE POST-TRANSPLANT PATIENT

Skin cancer is a leading cause of mortality and morbidity in the post-renal transplant patient.[1] Squamous cell carcinoma (SCC) is the most common post-transplant malignancy (up to 250x more common than in the general population).[2] The three main pathogenetic - and synergistic - risk factors are cumulative ultraviolet light exposure, immunosuppression, and oncogenic viruses, especially human papillomavirus (HPV).[3] How else can the dermatologist impact patient care beyond chasing skin cancers at every visit? This article will focus on a few strategies utilized in the Skin Cancer Post-Renal Transplant Clinic (SCREEN Clinic) at St. Paul's Hospital in Vancouver, BC.

Triage patients

Triaging patients into low, medium and high-risk groups is recommended in the dermatologic literature[4,5] and allows the clinician to determine a) appropriate examination intervals and b) how aggressive preventative strategies need to be.

In the SCREEN clinic, anyone with a history of actinic keratoses (AK) or skin cancer is considered high-risk and is followed every two to four months depending on the rapidity of onset of skin cancers. Patients with type V or VI skin phototype are considered low-risk and are followed every two to three years. Everyone else is considered medium risk and is followed one to two times per year. This follow-up is essential. It is common for patients to jump from medium to high-risk as time post-transplant progresses, especially if other predictable risk factors are present (photodamage, low Fitzpatrick skin type, positive family history of skin cancer, tanning bed use, etc.).

Other transplant-specific risk factors for SCC that might prompt more frequent screening include male patient, Caucasian, > 50 years of age at transplant, retransplantation (more potent immunosuppression), time post-transplant (more cumulative immunosuppression), history of lymphoma or leukemia, immunosuppressive regimens containing azathioprine and cyclosporin, and the use of photosensitizing agents such as voriconazole.[1,6]

We find that keeping an easy-to-access tally of skin cancer type, date, and location in the patient's chart is invaluable. This quick reference provides an immediate visual picture of your patients' cumulative skin cancer burden, and all chemopreventative decisions are based on these numbers and timelines.

Patient assessment

At every visit, we focus on the highest risk lesions. Rapidly growing, ulcerated, or tender nodules are prioritized for biopsy. Patients are counselled that a lump that doubles in size in a month or a scab that doesn't heal is a skin cancer until proven otherwise. Some patients have dozens of keratotic lesions of seborrheic keratoses/ HPV/ papillomas/Bowen's disease and their treatment must wait for subsequent visits or these lesions can be treated in the interim with liquid nitrogen, imiquimod, 5-fluorouricil, or electrodesiccation and curettage.

SCC in this population may be large, deep, aggressive, clinically ill-defined, and have unfavourable histologic features such as poor differentiation, lymphovascular invasion, or perineural invasion. These tumors are known to be more aggressive than in the non-transplant population and prompt evaluation, biopsy, and treatment is the norm.

Management of actinic keratoses with field therapy and destructive modalities is a constant revolving cycle in the transplant patient and similar regimens apply as in the non-transplant population. Curettage, topical retinoids, topical 5-fluorouricil, imiquimod, photodynamic therapy, and others are all employed on rotation.

Concerns about the risk of inducing renal dysfunction with the use of cytokine-inducing topical imiquimod (reported in one case[7]) have not been supported in subsequent trials.[8,9] Five percent imiquimod cream used over 100 cm^2 3 times per week for 16 weeks resulted in no detection of graft rejection in 43 patients.[8]

Regular sunscreen use reduces the development of actinic keratoses and invasive SCC in transplant patients.[10] Sun protection counselling begins on the first visit and builds over time. Lymph nodes are checked at each visit in patients with a history of invasive SCC.

Chemoprophylaxis

The clinician may consider acitretin chemoprophylaxis for any patient whose skin cancer burden is unrelenting. There is a large body of evidence supporting its use.[11,12] Some indications for use include > 5-10 skin cancers per year, few but aggressive SCCs, multiple SCCs in high-risk sites, and the impact of cancer burden/ procedures on mental health and quality of life.

There is ample consensus for the use of low starting doses of 10 mg per day or every second day, which is well tolerated.[12,13] The dose may be titrated up, but waiting for at least three to six months before doing so may be prudent, as up-titration may not be necessary. Incremental increases in dose (i.e. 10 mg/day alternating with 20 mg/ day or even 10 mg/10 mg/20 mg per day in a three day cycle) are much better tolerated than large jumps in dose.

Drug interactions are minimal at low doses. Acitretin can be stopped at any time with the expectation that skin cancers will reappear quickly, but rarely explosively.

Laboratory parameters such as aspartate aminotransferase, alanine transaminase, bilirubin and gamma-glutamyl transferase are followed monthly, and cholesterol and triglycerides are followed every three to six months (more frequently in patients on sirolimus or cyclosporin as these medications also increase triglycerides). Common side effects include brittle nails, sticky skin phenomenon, paronychia (advocate good toenail care from the start), blepharitis, and hair thinning – all of which are mild at low doses but pre-emptive counselling is important. Rare side effects of oral retinoids such as benign intracranial hypertension, psychiatric symptoms, and inflammatory back pain must be discussed. Although it theoretically can affect 'wound healing', acitretin therapy is not interrupted for routine skin surgery. Dose reduction will need to occur if the patient goes back on dialysis. Acitretin is contraindicated in women of childbearing potential; isotretinoin is an acceptable alternative in these patients or in patients who need control of acneiform eruptions (common with prednisone or calcineurin inhibitor

[CNI] use) in addition to skin cancer prophylaxis.[11]

The goal of this treatment approach is to reduce clinically significant keratinocyte carcinoma and actinic keratoses thereby reducing skin cancer burden and all of its potential implications and morbidity for the patient. This is a compelling enough goal for most patients. Direct evidence that acitretin reduces the risk of metastatic disease or mortality is lacking.

Alteration of immunosuppression

Reduction in global immunosuppression is a well-accepted skin cancer prevention strategy.[6] In the SCREEN clinic possible scenarios are discussed as soon as a patient develops their first invasive SCC so that an action plan is in place if clinical progression ensues.

Assessing and interpreting a patient's immunosuppression occurs at each visit and is not time-consuming. Older regimens include azathioprine and cyclosporin. New, better-tolerated, modern regimens contain tacrolimus and mycophenolate mofetil (MMF).

The International Immunosuppression & Transplant Skin Cancer Collaborative (ITSCC) and Skin Care for Organ Transplant Patients Europe Reduction of Immunosuppression Task Force have developed criteria for mild, moderate and severe reductions of immunosuppression.[14] No reductions are recommended for actinic keratoses alone. For renal transplant patients with SCC, mild reductions are indicated when patients develop 1-25 skin cancers per year, or fewer higher-risk SCC tumours. Patients who develop greater than 25 skin cancers per year (considered to have a 5% risk of mortality) or aggressive, high-associated-mortality SCC would be candidates for moderate reductions. Severe reductions are reserved for life-threatening skin cancers (i.e. metastatic disease).

When appropriate, a suggested strategy may include asking the transplant team to consider a reduction in overall global immunosuppression if the patient is medically stable and reduction is not contraindicated. The transplant team is likely waiting to hear from the dermatologist in order to initiate these conversations. Modification of immunosuppression may be quite achievable in circumstances where patients are relatively over-immunosuppressed and could benefit from medication review and reconciliation.

Dermatologists may be asked which drug should be decreased. Azathioprine and calcineurin inhibitors are associated with SCC post-transplant; the most robust evidence is for azathioprine.[3,15] Azathioprine doses can be reduced, or the regimen can be switched to incorporate mycophenolate mofetil instead of azathioprine.[1,14] Cyclosporin and tacrolimus doses or formulations can be titrated to lower target levels in patients whose levels may be running high. The role of MMF in skin cancer is controversial and summarized well by Howard et al.[1] Although considered to be less carcinogenic than azathioprine or the CNIs, MMF has been associated with skin cancer development.[1] Doses may be adjusted from full-dose to half-dose, or half-dose to quarter-dose depending on the circumstances and the patient's baseline dosage. The role of prednisone in photocarcinogenesis remains controversial.[16]

Sirolimus is a mammalian Target of Rapamycin (mTOR) inhibitor that is associated with a reduction in AK and keratinocyte carcinoma in transplant patients.[17] However, potential side effects and complications preclude its consistent use and in the SCREEN clinic sirolimus is considered only when other strategies have failed. Common side effects include fatigue, mouth sores, poor wound healing, leg edema, myelosuppression, hypertriglyceridemia and proteinuria. Nonetheless there are clinical scenarios in which the benefits outweigh the risks and replacing a CNI with sirolimus is an effective strategy.

Adjunctive strategies

Niacinamide (vitamin B3) 500 mg b.i.d. was shown to decrease actinic keratoses and keratinocyte carcinoma in immunocompetent (non-transplant) patients with a history of at least two nonmelanoma skin cancers in the past five years.[18] Niacinamide (also called nicotinamide) is well-tolerated, does not cause flushing, is available over-the-counter, and has an excellent safety profile. A case-control trial in transplant patients demonstrated significant reduction of actinic keratoses[19], but other data in the transplant patient population is lacking. Nonetheless, it is being used, as downsides are few. A Canadian pilot study (SPRINTR trial, ClinicalTrials.gov Identifier: NCT03769285) is a feasibility study currently underway as a precursor to a possible larger pivotal trial of niacinamide chemoprophylaxis in post-transplant skin cancer patients.

Voriconazole and hydrochlorothiazide are two photosensitizing medications highly associated with development of SCC[6,20] and should be avoided.

Although the evidence is very limited, HPV vaccination may be recommended in challenging skin cancer patients. Conceptually this is an exciting possibility considering the known association between SCC and HPV[21], but evidence is limited to case reports. Two immunocompetent patients given the quadrivalent HPV vaccine had a marked decrease in recorded numbers of SCC and basal cell carcinoma (BCC) in the year post-immunization.[22] In addition to systemic vaccine administration, intralesional diluted HPV vaccine was injected twice into three large squamous cell carcinomas in another patient with multiple leg tumours. Eleven months after the first injection all her leg tumours had regressed, and no recurrence was reported at the 24 month follow-up visit.[23]

Pre-transplant considerations

Dermatologists may be asked to provide a readiness-for-transplantation assessment in patients with a history of SCC. This may be prior to their first transplant or retransplantation after graft failure. It may be helpful for clinicians to refer to this excellent consensus statement by Zwald et al to help guide clinical decision making.[24] Patients with a fully treated high-risk SCC (i.e. > 2 cm, poorly differentiated, recurrent, high-risk site) should ideally wait 2 years; if perineural invasion is present, a wait time of 3 years is preferable.

These are just a few of the many ways in which dermatologists can contribute to the nuanced care of post-transplant recipients.

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Dr. Marissa Joseph graduated medical school at Dalhousie University. She is a board certified pediatrician and dermatologist after completing pediatric training at the Hospital for Sick Children, followed by dermatology residency at the University of Toronto. She completed a MSc in Community Health at the Dalla Lana School of Public Health. Dr. Joseph is full time academic faculty at the University of Toronto. She has received, and been nominated for, teaching awards in both undergraduate and postgraduate medical education. Dr. Joseph is the Medical Director of the Ricky Kanee Schachter Dermatology Centre at Women's College Hospital, with a special interest in inflammatory skin diseases and medical education of dermatology across all skin types. She also works at the Hospital for Sick Children where she manages children with complex dermatologic disease in outpatient and inpatient settings, as well as a pediatric laser treatment program. Dr. Joseph enjoys her diverse practice in general adult, pediatric, medical and surgical dermatology.

AN UPDATE ON PEDIATRIC ALOPECIA AREATA

Introduction

Alopecia Areata (AA) is a common, non-scarring autoimmune alopecia affecting both children and adults. AA is the third most common dermatosis in children[1] and has a significant emotional impact on patients, particularly children. At present, there are no universally effective treatments that guarantee low relapse rates or complete regrowth in severe disease. There is a lack of data for treatment of pediatric alopecia areata. This article provides an overview of pediatric alopecia areata and its management, including relevant peer-reviewed literature in the last 5 years.

Clinical Features

AA is classified into 3 clinical groups: 1) alopecia areata in patches, the most common form; 2) alopecia totalis (AT) complete or almost complete absence of hair on scalp and 3) alopecia universalis (AU) which includes complete loss on the scalp, face, and body.[2] Ophiasis pattern and sisaipho are also uncommon presentations that may confer a worse prognosis. In children, the majority of cases are localized patches and can undergo spontaneous remission. **(Figure 1)**



Figure 1. Patchy distribution of non-scarring alopecia in AA; photo courtesy Marissa Joseph, MD

The association of AA with other conditions such as atopic dermatitis, vitiligo, lupus erythematosus, and thyroid disease (with Hashimoto's thyroiditis being the most common in pediatric AA)[3] has been reported.[2] In data from the National Alopecia Areata Registry, 47.0% (n=1043) of children reported comorbid disease.[1] The most common of which were atopic dermatitis, asthma, hay fever, and allergies. Other diseases present in this population, in order of decreasing prevalence, include Hashimoto's thyroiditis, vitiligo, psoriasis, Type 1 diabetes, inflammatory bowel disease, systemic lupus erythematosus, and rheumatoid arthritis.[1]

Dermoscopy (Tricoscopy) in Alopecia Areata

Dermoscopy is a useful non-invasive tool to evaluate hair disorders. Biopsy can be helpful diagnostically but challenging in young patients. Dermoscopic evaluation may obviate unnecessary biopsies in pediatric patients with alopecia. Although dermoscopic findings of AA are described in the literature, studies are limited.[4] A summary of commonly described dermoscopic features are presented in **Table 1**.

There is little data evaluating dermoscopic findings in pediatric alopecia areata. In one cross-sectional study of 126 pediatric and adult patients, the most common findings were yellow dots (84.1%), vellus hair (62.7%), black dots (48.4%), exclamation mark hairs (30.9%) and broken hairs (9.5 %).[4]

A retrospective comparative analysis of 50 children and 50 adults revealed differences in dermoscopic findings.[6] Yellow dots were less commonly detected in children compared with adults (26/50, 52% vs 48/50, 96%) .

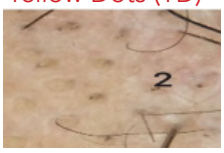
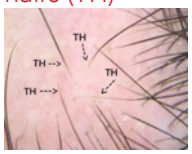
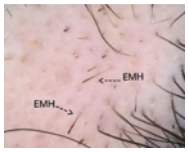
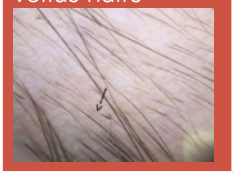
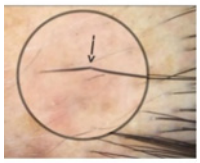
Finding	Description	Adult AA	Pediatric AA
Yellow Dots (YD) 	Round or polycyclic yellow to yellow-pink dots that represent distended follicular infundibula filled with sebum and keratin remnants	↑	↓
Black Dots (BD) 	Remnant of broken hair shafts inside follicular ostia	↑	↓
Exclamation mark hairs/ Tapering hairs (TH)  	Broken hairs that taper toward follicles	↑	↑
Pigtail hairs/Short vellus hairs 	Thin, nonpigmented hairs with length ≤10 mm may demonstrate early disease remission	↓	↑
Broken hairs (BH) 	Due to fracture of dystrophic hair shafts or rapid regrowth of hairs that formerly manifested as black dots.	↑	↓

Table 1.- Dermoscopic findings in variants of alopecia areata[4]

↑ More common ↓ Less common Photos used with permission from Dr. Jeff Donovan[5]

Pigtail hairs and empty follicular openings were more commonly observed in children compared with adults (14/50, 28% vs 2/50, 4% and 40/50, 80% vs 16/50, 32%, respectively).[6]

Differential Diagnosis

It is important to differentiate AA from other forms of non-scarring hair loss in children. The major differential diagnoses of alopecia areata in children are presented in **Table 2.** Less common diagnoses can also be considered, such as androgenetic alopecia, lupus erythematosus, syphilis, and loose anagen syndrome.

Diagnosis	Clinical Features	Diagnostic challenge with AA Differentiating from AA
Tinea Capitis	➢ Scaling, black dot, kerion ➢ Dermoscopy: zigzag hairs, comma hairs and corkscrew hairs.	➢ Black dots on dermoscopy ➢ Absence of scaling due to application of topical products
Temporal Triangular Alopecia (Brauer Nevus)	➢ Temporal region, usually unilateral Triangular, oval or lancet-shaped ➢ Dermoscopy: vellus hairs	➢ Localized area of non scarring hair loss ➢ Dermoscopy -No yellow spots, exclamation mark hairs
Traction Alopecia	➢ Commonly frontotemporal loss ➢ Fringe sign: retention hair along the frontotemporal hairline	➢ May present with patchy hair loss over the scalp in no specific pattern of distribution depending on hair practices
Telogen Effluvium	➢ Associated with hair pull sign ➢ History of shedding, overall loss of density	➢ Diffuse loss, difficult to distinguish from diffuse alopecia areata ➢ Dermoscopy: absence of yellow spots and exclamation point hairs
Trichotillomania	➢ May admit to manipulation ➢ Patchy and non-confluent. ➢ Friar Tuck sign: May spare peripheral hairs	➢ May not admit to manipulation ➢ Dermoscopy: ➢ **V-sign** : two or more hairs emerge from one follicular ostium, simultaneously break at the same length above surface. ➢ **Tulip hairs:** short hairs with darker, tulip flower shaped ends due to diagonal fracture ➢ **Hair powder:** hairshafts damaged by mechanical manipulation.

Table 2. Differential diagnosis of pediatric alopecia areata

Pathogenesis

In AA, $CD8^+$ T cells play a central role in the pathogenesis of disease, with an upregulation of IL-15 and IFNα causing a loss of immune privilege in the hair follicle.[7] Recent advances in the understanding of the regulators in this pathway have led to emerging therapies and new therapeutic targets.[8] For example, Janus Kinase (JAK) 1/2 signalling promotes IL-15 production in hair follicles, and inhibition can dampen the inflammatory response around hair follicles.[9]

Psychological and Psychosocial Support

Management of pediatric AA should include an assessment of the child's emotional well-being and psychosocial stressors.

In one recent study, 78.1% of AA patients aged 4 to 16 years reported impairment in health related quality of life scores (CDLQI, 6.3 +/- 5.9) with feelings of self-consciousness and skin symptoms being most frequently reported.[10]

Christensen et al,[11] also demonstrated the psychological impact of alopecia areata on children and their caregivers. Sixty-nine pediatric patients with alopecia areata, as well as sixty-four parents completed an online survey to elucidate the prevalence of bullying and emotional burden associated with AA. Respondents revealed that 18% of elementary school children (6/34) had been bullied, while 13% of middle school-aged children (2/15), and 40% of high school/college-aged adolescents (8/20) were bullied.[11] The types of bullying included online, physical, verbal, exclusion, rumors, and threats. Forty-eight percent of these children were embarrassed by their AA, and another thirty-three percent had stayed home at least once from school because of their AA. A multidisciplinary approach including the involvement of a pediatrician, psychologist or psychiatrist should be considered in cases of significant emotional distress. Families can be directed to patient support organizations such as the Canadian Alopecia Areata Foundation.[12]

Screening for Comorbidities

A recent retrospective chart review of 298 patients aged 0-21 years with AA who underwent thyroid testing revealed abnormalities in 20% of patients (n=59) with hypothyroidism being the most frequent abnormality detected in almost half of these patients (49%, n=29). There was no demonstrated association between age, duration of disease or pattern of alopecia and abnormal thyroid findings. Routine thyroid testing for all pediatric patients with AA is not recommended, suggesting it should be reserved for patients with risk factors such as Down syndrome, atopy, and family history of thyroid disease or clinical findings suggestive of potential thyroid dysfunction.[3]

Treatment Options for Pediatric Alopecia Areata

Counselling about AA should include a discussion about the natural history of the disease, available treatment options, and management of patient expectations.[13] Therapeutic options are limited by age, temperament and lack of evidence or safety data. The quality of evidence in the peer-reviewed literature is not robust and consists mainly of case reports and case series. Recommendations for treatment and management are extrapolated from adult studies. However, clinicians should expect that children will have less tolerance for discomfort, that there may be long-term adverse effects associated with certain therapeutic agents and that the lack of approved therapies may pose treatment challenges. There are no specific guidelines for the management of pediatric alopecia areata. The British Association of Dermatologists' guidelines for the management of AA states that "*children may be treated in a similar fashion to adults*".[13]

No treatment

Spontaneous remission occurs in >50% of patients with limited patchy hair loss for less than one year.[2,12,14] This may be an option for patients with recent, localized disease, especially very young children where there are concerns about adverse effects of treatment. Families should be warned that complete regrowth is unlikely within 3 months of the development of any individual patch.[13]

Topical Treatments

Topical corticosteroids are a mainstay of treatment as they are well-tolerated, and easy to apply. Class I or II steroids are typically used with clobetasol propionate 0.05% having been shown to be superior to hydrocortisone acetate 1% (17/20 patients vs 7/21 patients showing ≥ 50% improvement).[14]

Topical calcineurin inhibitors have been used in AA. One case series involving eleven patients in which tacrolimus 0.1% was used b.i.d. for 24 weeks, demonstrated no clinical response. Despite the lack of evidence, both tacrolimus and pimecrolimus are used in AA.[13,14]

Topical minoxidil has been used, typically in conjunction with topical corticosteroids. The use of minoxidil is considered off-label, and there are no guidelines regarding the ideal dose, the minimum age in which to initiate treatment, or the duration of treatment in children. One small case series reported that 2% minoxidil t.i.d. helped limit post steroid hair loss in pediatric AA. Clinicians should be aware that hypertrichosis may be more common in children, especially at higher concentrations.[15]

Topical contact sensitizers have been used with varying success in adult patients, but there is a paucity of data demonstrating their efficacy in pediatric AA. In one study, three out of thirty-three children with AT/AU achieved a sustained response to treatment with squaric acid dibutylester (SADBE).[14] Diphenylcyclopropenone (DPCP) 2% in acetone sensitization, followed by DPCP 0.0001% two weeks later can also be used. A retrospective study of DPCP-treated pediatric patients reported that after six months of treatment 14/108 (13%) subjects showed complete regrowth, and 27/108 (25%) showed partial regrowth. The majority of patients reported adverse effects including edema, urticaria, vesicles, erosions, dermatitis and lymphadenopathy.[14] Anthralin 0.5-1% has also been used as short contact therapy. It can cause stinging, burning, and brown staining of the scalp, clothing and bathtub.[13]

Topical retinoids have been used to treat adult AA, but no studies have been conducted in children.[2,13]

Topical Janus Kinase inhibitors are novel therapeutic options for the treatment of AA. There is considerable interest in the use of topical JAK inhibitors to avoid the potential for immunosuppression with systemic use. JAK inhibitors might be most effective when delivered in a liposomal base, since small molecules are poorly soluble in water. Case reports of topical use in pediatric AA have been published. One case series of eleven patients, aged 4-16, used non-patented formulations of topical tofacitinib 2% in a liposomal base. All of the children had failed both systemic and topical steroids prior to participating in the study. Three of

eleven patients had cosmetically acceptable hair growth and eight of eleven had improvements in their Severity of Alopecia Tool (SALT) score; two patients subsequently lost response, and the patient who did not respond subsequently responded to oral tofacitinib. There were no significant side effects, with only one of eleven experiencing skin irritation.[16]

Topical bimatoprost use in AA is not well-established. The existing and very limited data has not shown benefit in most cases.[18] The use of topical bimatoprost has typically been reserved for the eyebrows and eyelashes; areas where topical steroids should be avoided. One case report presents a 9-year-old girl who received intralesional triamcinolone, clobetasol proprionate 0.05% and 5% minoxidil topically. After two months, bimatoprost 0.03% b.i.d. was started as monotherapy to the scalp, resulting in complete regrowth by two months; the treatment was discontinued at seven months with no relapse. Given the heterogeneity of the condition, the patient's previous treatment, and the possibility of spontaneous remission it is not possible to definitively attribute her response to the bimatoprost. It has a favorable safety profile, but further studies are needed.[14]

Intralesional Corticosteroids

Although intralesional corticosteroid injections are commonly used in adult patients with AA, their use in children is limited by tolerability and is impractical for extensive disease. It is typically used in children age 10 or older, and with limited involvement.[14]

Systemic Corticosteroids

Systemic corticosteroids have long been used, but concerns remain about adverse effects of long-term use, as well relapse post-steroid withdrawal. In children with extensive patchy AA or AT/AU, high dose pulse methylprednisolone was shown to have a poor long-term outcome, with 66% of patients having less than 30% regrowth after a median of twelve months.[13,19] Drawing conclusions using the data from trials involving systemic corticosteroids is difficult, as the studies have differing methodologies, and AA, by its very nature, has a heterogeneous and unpredictable clinical course.

Other Systemic treatments

In a retrospective study of hydroxychloroquine, nine patients with AA aged 6-16 were treated with 200 mg p.o. b.i.d. over a period of four to twenty-four months. A baseline ophthalmologic exam was done in six of nine patients, as well as baseline laboratory testing. Fifty-five percent of patients (5/9) experienced hair regrowth while on therapy. The most common adverse effects were headache and gastrointestinal intolerance, which led to treatment discontinuation in some cases.[20]

Cyclosporine has been used as monotherapy or in combination with systemic corticosteroids in the treatment of AA.[21] There are no specific pediatric studies evaluating the use of cyclosporine.

Methotrexate has also been used in pediatric and adult AA, with data largely coming from case reports and small case series. One retrospective chart review evaluated the efficacy of methotrexate with or without oral corticosteroids in children with AA.[22] Fourteen patients aged three to sixteen years, started at 2.5 or 5 mg weekly titrating up to between 7.5mg-15 mg weekly. Eight patients (57%) experienced good regrowth with methotrexate, including a 3-year-old child who was maintained on 2.5 mg weekly throughout the treatment course. Three children (21%) were partial responders. Twelve of the children had been treated with systemic corticosteroids and transitioned to treatment with methotrexate. Seven of the eight responders also completed a prednisone taper either before, concurrent with or overlapping with the initiation of methotrexate, suggesting that this combination approach may be more efficacious.[22]

Oral *minoxidil* has been suggested as a potential treatment in pediatric AA. Originally a strong vasodilator first introduced as an antihypertensive, it has been dosed in children at 0.2 mg/kg/day. Since low-dose oral minoxidil has been used off-label for hair loss in adults, it is hypothesized that it may be a treatment option for children and adolescents. There have been no studies to date establishing dosing or safety in pediatric AA.[15]

Oral *Janus kinase inhibitors*, such as tofacitinib citrate have been used in AA.[8,9,23,24] The data in pediatric AA is limited to small case series. In a retrospective cohort study of thirteen adolescents (seven of whom had AT), subjects were treated with oral tofacitinib citrate at 5 mg b.i.d. for two to sixteen months (median five months). Nine of the thirteen patients experienced clinically significant hair regrowth and achieved an overall 93% median improvement in their SALT score from baseline at an average of 6.5 months of treatment. Despite the risks associated with immunosuppression, adverse events were reported as mild.[25]

Another study of four pediatric patients aged eight to ten years

with AT and AU who were treated with oral tofacitinib reported promising results Three of the four initiated tofacitinib at 5 mg b.i.d. and one patient initiated tofacitinib at 5 mg o.d. and ultimately titrated to 5 mg b.i.d. at the three month mark. Three patients had significant regrowth, two with complete regrowth. One patient had scant regrowth. There were no laboratory abnormalities or adverse effects reported.[17]

Conclusion

Pediatric alopecia areata is a common dermatosis, with a variable and unpredictable course, that can have a significant emotional toll on patients and their families. There is variable evidence supporting even our most commonly used treatments. There is a need for future high quality studies in evaluating existing and emerging treatments for efficacy, safety and clinical outcomes.

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MELASMA MANAGEMENT: HOW I DO IT

Melasma is a common acquired disorder of hyperpigmentation which has a strong predilection for females and is more common in individuals with Fitzpatrick skin phototypes III-VI.[1] It is most common on the face but can occur on the neck, upper chest, extensor forearms and upper back.[2]

The pathogenesis of melasma is both multifactorial and incompletely understood.[2] There is an increase in epidermal and dermal melanin without a similar increase in the number of melanocytes. Melanocytes are enlarged with elongated dendrites and increased numbers of melanosomes. An increase in mast cells, dermal blood vessels, abnormalities of the basement membrane and solar elastosis can also be seen.[2] The number of blood vessels, vessel size and density are all increased in lesional melasma skin.[2,3] Increasing evidence is emerging that points to melasma as a disorder of photoaging in genetically predisposed individuals.[3,4]

Melasma can cause significant psychological distress and negatively affect quality of life.[1,2] Medical management of melasma has been shown to produce feelings of confidence and influence self-esteem in a positive way making this a very important condition to treat.[2]

Management of melasma is challenging. It is often recalcitrant to treatment and frequently recurs following successful treatment. It can be frustrating to patients and physicians alike when expectations are not met or if/when the condition recurs. Additionally, there is a paucity of strong evidence surrounding treatment as many products are best described as cosmeceuticals or are compounded.

My practice contains a large population of melasma patients, and their treatment is both challenging and rewarding. Several key aspects of management are crucial for a successful therapeutic relationship and the focus of this article will be on topical and oral agents which are the mainstay of my practice.

The most important aspect of management is setting realistic patient expectations. I spend considerable time reviewing the overall natural history of this condition with patients in order to align our goals. I emphasize the fact that there is no cure to this condition. I review the two phases of treatment that they will undergo; an active treatment phase which most often includes topical hydroquinone. During this stage patients will see dramatic improvement in their melasma and overall skin tone and health. Once we are both pleased

with the results, we enter into a maintenance treatment phase which includes a skin care regimen that is entirely safe to continue over the long term and takes advantage of botanical brightening agents without the use of hydroquinone. Often, after the summer season or a significant amount of time in the sun, the hyperpigmentation will return, and the patient returns to the active treatment phase again. Once patients understand the overall treatment approach, they are less surprised if the pigment returns and are able to understand that they are still on track for the successful management of their disease and cope with the fact that their treatment wasn't a failure.

A thorough patient history is key especially with regard to exogeneous hormone use. The use of oral contraceptive pills or hormone replacement therapy can induce or worsen melasma and make it more difficult to treat. A 63-year-old female patient I recently saw with severe melasma had been prescribed an oral contraceptive pill for no clear indication. The discontinuation of the offending medication in this circumstance was enormously helpful.

Photography is another key component to successful treatment. Standardized photographs in the same room, with the same lighting, comparing 'before' and 'after' photographs is essential. Patients are often thrilled to see their progress, and this will help clinicians make objective management decisions.

When treating a patient, I take a full-face approach for almost all patients (except those with only a small patch of melasma limited to the upper lip). When speaking to patients about their treatment goals, it is common to hear the wish for the whole skin to be improved, not just the brown patches. Therefore, all steps in my regimen are applied to the entire face with few exceptions.

In my experience, the results of melasma treatment are much improved with the use of as many brightening and photodamage-repairing ingredients as possible. Of course, hydroquinone plays an essential role in this regard as the gold standard for skin brightening. However, in my clinical experience, the use of glycolic acid, salicylic acid, niacinamide, retinoids, antioxidants and botanical brighteners may help to create even better results. This is certainly supported in the peer-reviewed literature on melasma management by numerous studies demonstrating improved results with hydroquinone if other ingredients are added (such as a retinoid and corticosteroid).[5,6]

Botanical brighteners refer to non-hydroquinone brightening agents including: ascorbic acid, arbutin, green tea, emblica, licorice, mulberry, niacinamide, silymarin and others.[2,5,6,8]

My treatment regimens include a multi-step, multi-layered approach of products applied to the entire face. The overall regimen remains the same throughout the entire treatment period and only the true brightening products are changed over time between hydroquinone and botanical brighteners. I have consistently been impressed with the results my patients achieve with a complete, thorough, multi-step approach to the treatment of their melasma **(Figure 1)**. I have not seen equivalent results with the use of a traditional Kligman's formula to individual melasma patches. It is important to harness the power of each of the individual ingredients and use them all synergistically to help treat this difficult-to-manage skin condition.



Figure 1. Patient results from 'before' and 'after' multi-step treatment approach; photo courtesy of Allison Sutton, MD

There is a paucity of evidence to support the use of most of these agents. For a comprehensive review of the data for each non-hydroquinone brightening ingredient, please review Dr. Miller-Monthrope's excellent summary in Volume 1, Issue 4 of this publication from 2020.[5]

The key ingredients and the steps taken to incorporate these ingredients into the patient's treatment will now be described. Thorough washing and exfoliating will help to shed stratum corneum and prepare the skin for enhanced penetration of leave-on products. In my experience, choosing products with salicylic acid and glycolic acid may help with gentle epidermolysis.

The application of hydroquinone is next, and it is recommended to be used twice daily. I usually begin hydroquinone at 4% but have titrated to a concentration of 10% when needed and have achieved excellent results with the above combinations, without the need to go above a 10% concentration.

Four percent kojic acid is a helpful addition to the compounded hydroquinone formula. Kojic acid has poor efficacy when used as monotherapy, however, can be very effective in combination with hydroquinone.[1] Kojic acid can lead to a significant irritant contact dermatitis. Therefore, if a patient presents with dermatitis, I suggest first removing kojic acid from the modified Kligman's formula to see whether the patient responds. I exclude topical corticosteroids in my modified Kligman's formulas. In my experience, they do not provide significant benefit and may cause corticosteroid-induced acne, telangiectasias and even hypopigmentation as a side effect. I work with a local pharmacist to create a compound that is cosmetically elegant, moisturizing, and as stable as possible.

The next element of my treatment approach involves a layer of 10% glycolic acid lotion, which is used for the above-mentioned reasons.

An antioxidant, particularly one with ascorbic acid, and a sunscreen are the last two layers in the morning routine. Consistent, rigorous, daily photoprotection is a critical aspect of long-term management of this condition. At every appointment it is important to remind the patient of its importance. The goal is to prevent UV light exposure. There is new evidence that visible light can also aggravate melasma, especially short wavelength visible light (415nm).[2] Short wavelength visible light has been shown to induce prolonged hyperpigmentation in healthy volunteers compared to longer wavelength (630 nm) visible light exposure.[7]

A sunscreen must be used every single morning and re-applied at least once a day if not more frequently, depending on exposure. A minimum SPF of 30 is suggested. Physical blockers such as titanium dioxide and zinc oxide protect against UVB, UVA and modestly against visible light.[8] I routinely recommend these; however, they can be difficult to use in skin of color patients due to a white-to-gray sheen they may produce.[2] Iron oxides are also able to block both UV and short wavelength visible light and may be more cosmetically acceptable to skin of color patients as they provide a better color match. In addition to UV and visible light, heat is also thought to be a trigger for melasma, and avoidance should be attempted.[1]

In the evening after washing and exfoliating, hydroquinone is applied a second time followed by a topical retinoid. The choice of topical vitamin A is based on several factors including skin sensitivity, comorbidities, as well as cost.

Given that most of the active ingredients in this approach can be irritating to the skin, it is critical to include some products meant to hydrate and soothe the skin. Implementing this without the use of topical corticosteroids is preferable, and clinicians may consider including a bland emollient in the patient's regimen that contains ingredients such as aloe which can calm the skin.

The newest and most exciting addition to our therapeutic armamentarium has been oral tranexamic acid (TA). Its use in melasma is off-label but there are several studies consistently showing significant improvement in melasma scores with its use. TA's mechanism of action is uncertain but is thought to be based on 1) competitive inhibition of plasminogen activator – this inhibits conversion of plasminogen to plasmin in keratinocytes which in turn reduces arachidonic acid and prostaglandins leading to a decrease in tyrosinase activity 2) a decrease in angiogenesis and mast cells thereby possibly counteracting the vascular component of melasma and 3) competitively antagonizing tyrosinase which further impairs melanogenesis due to its structural similarities to tyrosinase.[2]

I use TA at a dose of 250 mg p.o. b.i.d. and have found this to be generally well-tolerated and extremely helpful in managing melasma. The main clinical issue is to identify the

appropriate treatment duration. Most studies use oral TA for a 3-6 month duration. In practice, most of my patients do not want to discontinue its use, as it is incredibly helpful in improving melasma. Interestingly, I have not found TA to be efficacious in managing other conditions of hyperpigmentation such as post-inflammatory hyperpigmentation.

Patients are provided with written instructions reviewing the steps in which to apply the products and they are also counselled extensively on the anticipated and normal adverse reactions of erythema, scaling and mild pruritus that often accompany the use of this regimen of products.

Patients are seen in follow up at months two, four and six. I will continue use of hydroquinone for a maximum of 6 months, however most patients require a shorter treatment course. As soon as patients demonstrate excellent improvement, the active treatment phase concludes, and a slow taper of hydroquinone begins until it is no longer required. This hydroquinone taper takes place over a period of one month and the introduction of non-hydroquinone brighteners occurs concurrently, which may result in less rebound hyperpigmentation.

I attempt to maintain the patient's improvement on the full regimen of topical agents with botanical brighteners, retinoids, alpha and beta hydroxy acids, antioxidants and photoprotection for as long as possible.

In terms of choosing non-hydroquinone options for the brightening agent, this depends on the clinician's familiarity with cosmeceutical products in your armamentarium. Additionally, comorbidities such as acne are important to consider. Several of the botanical brighteners, including vitamin C-based products, tend to aggravate acne. Therefore, one option to consider when acne is a comorbidity includes the use of topical azelaic acid 15% gel. The majority of evidence for azelaic acid's efficacy in treating melasma is with the 20% cream formulation which is not available in Canada.[1,6] The remaining brightener options are cosmeceuticals and therefore, gaining familiarity with the individual products is the best method to determine their suitability for use in the clinician's practice. Vitamin C, arbutin, green tea, emblica, licorice, mulberry, niacinamide, silymarin and others[2,5,6] are options that have demonstrated improvement in hyperpigmentation in smaller studies. In my experience, they are not as effective as hydroquinone and I therefore use them predominantly in the maintenance phase of management. In certain situations these agents could be first-line treatment options such as in use with a pregnant or lactating patient, one with exogenous ochronosis or with a patient who wishes to avoid hydroquinone use.

Melasma can certainly be challenging to treat, however it can also be extremely rewarding to improve. Melasma patients are generally motivated patients who are pleased with improvement in their skin. It is important to take the extra time to set realistic expectations and to review normal reactions. Finally, the combination of many brightening and anti-photoaging ingredients can lead to better outcomes.

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MANAGEMENT OF PEDIATRIC CHRONIC SPONTANEOUS URTICARIA

Chronic urticaria (CU) occurs when pruritic wheals and/or angioedema manifests on most days of the week and persists for at least 6 weeks.[1] Recent evidence suggests that the point prevalence of pediatric CU is similar to adults, affecting ~ 0.5%-1.5% of children, with no sex predilection.[2-6] While ~ 20% of CU cases have an underlying physical/inducible trigger (chronic inducible urticaria, CIndU),[6] in most cases the hives occur spontaneously (chronic spontaneous urticaria, CSU).[7]

Update on pathogenesis

The exact etiopathogenesis of CSU remains unknown, however recent advances highlight mast cell activation through immune mechanisms. Half of adults with CSU are believed to have an autoimmune basis for their disease, where mast cell activating immunoglobulin IgG antibodies against the IgE molecule or its high affinity receptor FcεRI are implicated. Autoimmune CSU is suspected on the basis of either a positive *in vivo* autologous serum skin test (ASST) and/or a positive *in vitro* assay (*e.g.* basophil activation test).[1,8,9] Neither ASST nor *in vitro* tests, are currently recommended for routine use as their clinical utility remains unclear.[1,8,9] Furthermore, in the majority of adult CSU cases, IgE-type autoantibodies (*e.g.* IgE anti-interleukin(IL)-24 or anti-thyroid peroxidase) are capable of directly crosslinking and activating the FcεRI, a mechanism referred to as auto-allergy **(Figure 1)**.[10-13] These patients often have elevated serum IgE levels and may be better/faster responders to the anti-IgE monoclonal antibody, omalizumab.[14] Pathogenic IgM and IgA-type autoantibodies are also being discovered, but their role in CSU induction remains unclear and warrants further investigation.[15] While it is suspected that the immune pathogenesis of pediatric CSU is similar to that of adults, it has not yet be demonstrated.

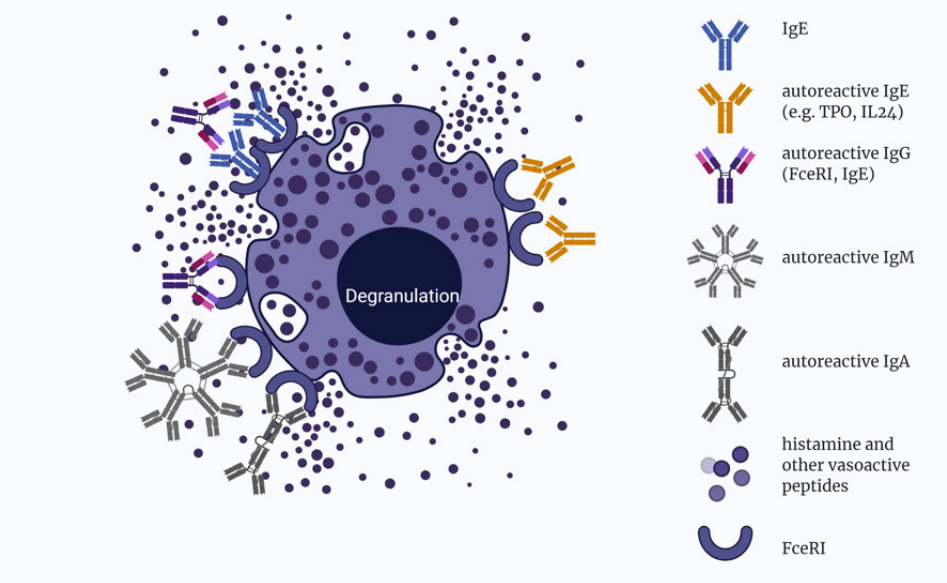


Figure 1. Pathogenesis of chronic spontaneous urticaria (CSU)

Legend. *It is believed that mast cell activation and degranulation is triggered by functionally active autoantibodies either of IgE-type (e.g. anti-IL-24 IgE, anti-TPO IgE, Autoreactive CSU) or IgG antibodies against the IgE molecule or its high affinity receptor, FcεRI (Autoimmune CSU). Self-reactive IgM and IgA antibodies are being described as well, but the role remains unclear. FcεRI, high affinity IgE receptor; IgE, Immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A; IL-24, interleukin-24; TPO, thyroid peroxidase. Created with Biorender®.*

Burden of disease

Due to intractable itch, secondary loss of sleep and impact on school/work productivity, CSU is associated with severe impairment in quality of life, often rated similar to other chronic diseases such as type I diabetes mellitus and epilepsy.[16,17] School performance is consequently affected and the prevalence of mood/anxiety disorders is increased in children with CSU.[17] Similar to adults, pediatric CSU is a chronic condition with an annual resolution rate of only 10 per 100-patient-years.[6] Hence, a safe and effective treatment is imperative for many years.

Treatment objectives

The goal of treatment is to control CSU completely with as much or as little medication needed until spontaneous resolution occurs. Disease severity and control can be quickly assessed in clinic using the Urticaria Activity Score (UAS-7) and the Urticaria Control Test (UCT).[18,19] In general, good disease control/mild disease is defined by a UCT score ≥ 12 and an UAS-7 score ≤ 6. On the other hand, UAS-7 ≥ 28 and UCT ≤ 11 correspond to severe and poorly controlled disease.[19,20]

Treatment guidelines in children

So far, treatment guidelines dedicated to children with CSU are largely lacking and treatment decisions are either based on personal experience or extrapolated from general (adult) CSU guidelines. The EAACI/GA²LEN/EDF/WAO guidelines are the most widely-accepted CU/CSU guidelines worldwide and endorsed by many dermatologic societies including the Canadian Dermatology Association.[1] While they focus primarily on adult CU/CSU, children are included as a special population. The same management of pediatric CSU is recommended starting with second-generation (non-sedating) antihistamines (sgAHs) at the licensed dose for the patient's age. In the case of uncontrolled disease, clinicians should proceed with caution regarding further management, given the relative lack of studies in pediatric CSU **(Figure 2)**.[21] The SIP/SIAIP/SIDerP Italian guidelines are the only guidelines focusing on the pediatric population. Unlike other guidelines, the Italian guidelines divide the pediatric group into ≥12 and <12-years-old and recommend omalizumab prior to the titration of sg-AHs in teenagers (≥12 years-old) given omalizumab's indication for CSU in this age group **(Figure 2)**.[22,23] Of note, systemic glucocorticoids are only recommended for the short-term treatment of acute exacerbations of CSU, due to their poor safety profile[1,8,9], whereas the use of first-generation antihistamines (fgAHs) is strongly discouraged due to their anticholinergic side effects and hence, neither of these modalities is included in the step-wise treatment algorithm.[24-28] Other potential treatments that may be considered on a case-by-case basis in resistant cases include: leukotriene receptor antagonists (LTRA), phototherapy, hydroxychloroquine and more.[1]

What is the evidence behind treatment recommendations for pediatric CSU?

H1-antihistamines (H1-AH)

H1-AHs prevent H1 receptor activation by histamine.[26] They are the first and usually the second line treatment of CSU regardless of the patient's age. AHs are classified as older fgAHs (e.g. hydroxyzine, diphenhydramine) and newer sgAHs. First-generation antihistamines cross the blood-brain barrier and have potent dose-dependant anti-cholinergic adverse effects (e.g. sedation, reduced cognitive activities).[24-31]

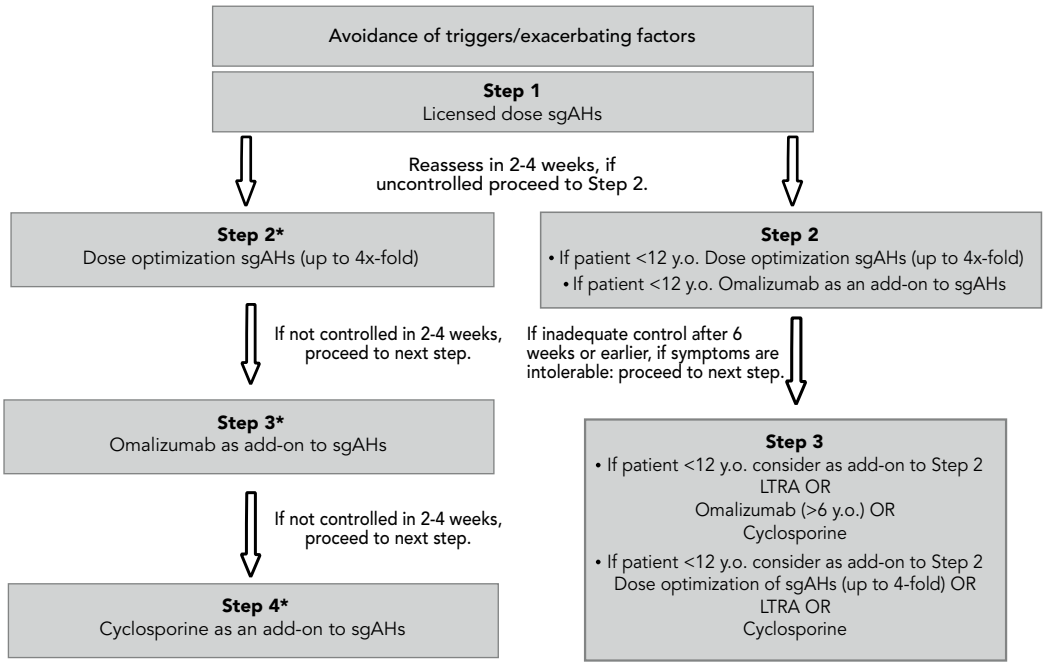


Figure 2. CSU treatment guidelines for children.

Well-designed published studies assessing the safety and efficacy of commonly used fgAHs for CSU in children are largely lacking and yet, these medications remain commonly used first-line, particularly in the primary care setting.[1,21] Second-generation antihistamines have a better safety profile and efficacy due to their H1 receptor selectivity and are more convenient to use due to their longer half-life.[31-35] The sgAHs licensed for pediatric use are summarized in **Table 1**. The only study that compared sgAH (cetirizine 5 mg daily) to a fgAH (oxatomide 25 mg daily) in children (2-6 years-old)[36] confirmed superiority of cetirizine in terms of itch, erythema and rapidity of clinical improvement ($p<0.05$). Complete CSU control was seen in 46% of children treated with cetirizine as opposed to 28% with oxatomide at 28 days.[36]

H1-antihistamines at licensed dosage

Six randomized controlled trials (RCTs) assessed the safety and efficacy of various sgAHs at their licensed dosage in children with CSU. Desloratadine and rupatadine in children aged 2-11, led to a 54% and 61% CSU improvement (defined as ≥ 50% decrease from baseline in a modified 7-day cumulative UAS-7 score), respectively.[37] Similar results were reproduced in two additional desloratadine double-blind RCTs in patients over 12 years of age (21 patients of pediatric age group).[38,39] Fexofenadine was also studied in adults and adolescents in a double-blind RCT, demonstrating satisfactory CSU control and a favorable safety profile.[40] Finally, levocetirizine hydrochloride was assessed in two RCTs for infants/children 6-11 months (study 1, n = 69) and children aged 1-5 years (study 2, n = 173) with allergic rhinitis and CSU showing a safety profile comparable to placebo.[41] Data from an allergic rhinoconjunctivitis study in children, further supports the safety of bilastine in this age group (**Table 1**).[42]

H1-antihistamines updosing

Only three studies have focused on the safety and efficacy of updosing sgAHs in children. Rupatadine 10 mg vs. 20 mg daily was found to be equally safe and effective for adults and adolescents with CSU.[43,44] Another RCT that included children ≥ 12 years old, demonstrated a dose-dependant urticaria control with an increasing fexofenadine dose up to 60 mg b.i.d. compared to the 20 mg fexofenadine group after which, the response plateaued for the 120 mg and 240 mg doses of fexofenadine.[45] Side-effects were similar to placebo regardless of the dose (maximal dose of fexofenadine used was 240 mg twice a day).[45] Unfortunately, robust studies in young children are limited. However, given the favorable safety profile of these drugs, many clinicians feel comfortable with sgAHs up-dosing (up to fourfold) in children.[46,47]

Omalizumab

Omalizumab, a monoclonal anti-IgE antibody, is approved by Health Canada for sgAH-resistant

sgAH	Licensed dose	Contraindications	Side Effects	Other
Loratadine	• 2-6 yo: 5 mg o.d. • ≥6 yo: 10 mg o.d.	Hypersensitivity	Headache	• Not metabolized by the CYP3A4.
Desloratadine	• 6-11 months: 1 mg o.d. • 1-5 yo: 1.25 mg o.d. • 6-11 yo: 2.5 mg o.d. • ≥12 yo: 5 mg o.d.	Hypersensitivity	Headache, diarrhea	• Active metabolite of loratadine. • Safest in patient with renal failure.
Cetirizine	• 6-12 months: 2.5 mg o.d. • 1-2 yo: 2.5 mg o.d. • 2-5 yo: 2.5-5 mg o.d. • 6-11 yo: 5-10 mg o.d. • ≥12 yo: 10 mg o.d.	Hypersensitivity	Drowsiness, headache	
Levocetirizine	• 6 months to 5 yo: 1.25 mg o.d. • 6-11 yo: 2.5 mg o.d. • ≥12 yo: 5 mg o.d.	Hypersensitivity, end-stage renal disease, hemodialysis, patients ≤11 yo with renal impairment	Diarrhea, drowsiness	
Fexofenadine	• 6 months to 2 yo: 15 mg b.i.d. • 2-12 yo: 30 mg b.i.d. • ≥12 yo: 60 mg b.i.d.	Hypersensitivity	Headache, vomiting	• Safest in patient with renal failure. • Not metabolized by liver/the CYP3A4.
Rupatadine	• 2-12 yo: If 10-25 kg: 2.5 mg o.d. If >25 kg: 5 mg o.d. • ≥12 yo: 10 mg o.d.	Hypersensitivity, history of QTc prolongation and/or torsades de pointes, concurrent use of CYP3A4 inhibitors or other QTc-prolonging drugs	Drowsiness, headache	
Bilastine	• ≥12 yo: 20 mg o.d.	Hypersensitivity, history of QT prolongation and/or torsades de pointes	Drowsiness, headache	• No impact of CYP P450 metabolism.

Table 1: Second-generation antihistamines approved in pediatric patients

Legend. *CYP, cytochrome-P450 ; yo, years-old; o.d., daily; b.i.d., twice daily.*

CSU in patients ≥12 years-old and severe asthma in patients ≥6 years-old. Omalizumab's efficacy in CSU is thought to result from the inhibition of IgE-mediated FcεRI activation of mast cells and basophils[48], free serum IgE depletion and decreased FcεRI expression.[49] Additional mechanisms are being explored including normalization of basopenia.[50] While omalizumab's clinical program in CSU included 39 patients younger than 18 years of age[51-53], data regarding the potential use of omalizumab in younger children is only emerging. So far, case reports and case series include a total of 76 AH-resistant pediatric CU patients aged 4 to 17 years.[46,49,54-65] The most commonly used dosages were 150-300 mg subcutaneously every 4 weeks. Most patients (66 of 76) had a satisfactory response, whereas complete CSU control was seen in 44/76 patients. Importantly, no new safety signals were identified.

Cyclosporine

Cyclosporine inhibits T-cell activation and downstream production of IL-2, IL-3, IL-4, TNF-α and other inflammatory cytokines[66,67] as well as the suppression of histamine release.[68,69] Its use in CSU is off-label and studies assessing cyclosporine in pediatric CSU consist of one retrospective chart review, one case series and one case report including only 24 AH-resistant CSU patients in

total, aged from 9 to 18 years.[70-72] The starting dose of 3 mg/kg/day was usually used with slow adjustments depending on response. CSU was controlled completely in all 24 patients, although a publication bias (i.e. cases who failed treatment were not published) may have been present and cannot be excluded as potentially confounding these reported results. Patient response to treatment was fast—usually within 2 weeks.[70,72] In 23/24 patients, cyclosporine serum levels were monitored and kept below 200 ng/mL. No serious adverse events were reported, however total treatment duration varied from 10 weeks to 17 months.[70-72]

Oral glucocorticoids

The efficacy of systemic corticosteroids in improving disease severity of acute urticaria and CSU has been shown.[73] However, the inevitable serious side effects associated with their prolonged use and/or repeated short courses of treatment are the reason why clinical guidelines for the treatment and management of CSU strongly discourage the use of this class of medication in CSU, with the exception of short-term use (~10 days) for acute CSU exacerbations only.[1] Despite this, systemic corticosteroids remain commonly prescribed for both adults and children with CSU, especially in the primary care setting.[21,74]

Other treatments studied in childhood CSU

In rare cases, CSU remains uncontrolled despite dose optimization of sgAHs and/or adjunctive use of omalizumab/cyclosporine. In these cases, a case-by-case decision for the next adjunctive therapy may include LTRAs. LTRAs (montelukast and zafirlukast) inhibit leukotriene signaling providing an anti-inflammatory effect.[75-77] They have an excellent safety profile and the only contraindications to their use are hypersensitivity to the formulation (montelukast and zafirlukast) and hepatic failure (zafirlukast).[78-81]The rationale for LTRAs in CSU is demonstrated by their efficacy in other Th2-mediated diseases such as asthma and hay fever. *In vitro* studies validated their role in wheal suppression.[75-77] However, LTRAs did not live up to their promise in the clinic,[82-84] hence their use remains off-label in CSU. The only RCT including a pediatric cohort (95 patients > 12 years of age) showed a modest advantage of the combination of cetirizine 10 mg and zafirlukast 40 mg o.d. vs. cetirizine 10 mg as monotherapy.[77] The estimated efficacy benefit of adding zafirlukast 40 mg to cetirizine 10 mg was approximately 10%.

Hydroxychloroquine, an antimalarial agent, has demonstrated anti-inflammatory properties through the modulation of antigen presentation, inhibition of DNA synthesis and pro-inflammatory cytokines.[85] The recommended maximal daily dose of 5mg/kg of real weight is recommended to minimize the risk of retinopathy, associated with long-term therapy.[86,87] While, the overall safety profile is reassuring, regular ophthalmologic follow-up after five years of use (or based on individual risk factors) and episodic monitoring of biochemical/hematologic parameters is warranted.[88] Promising efficacy of hydroxychloroquine (400 mg daily) in sgAH-resistant adult CSU was demonstrated in a small RCT (vs. placebo) of 48 patients,[89] data in children however, is limited to only 1 successful case report (9-month-old infant).[90]

A prospective case-control study involving 58 patients (≥ 14 years-old) treated with high-dose vitamin D supplementation (at 300 000 IU/month)[91] and a case report of a 14-year-old patient treated with vitamin D (50,000 IU weekly for 5 doses then 2000 IU daily)[92] demonstrated that high-dose vitamin D supplementation in patients with proven vitamin D deficiency may lead to better control of CSU. However, given the observational nature of the study, the potential for confounding is present. Additionally, the safety of using such high doses of vitamin D in children is not well established.[93]

Phototherapy is sometimes used off-label in CSU patients given the long-term experience in using this treatment modality for a wide variety of pruritic dermatoses. Two phototherapy regimens (psoralen and ultraviolet A [PUVA] vs. narrowband ultraviolet B [NB UVB]) were compared in an observational study involving adolescents (aged >14). Similar reductions in CSU symptoms was demonstrated in both treatment groups.[94]

Allergen-specific immunotherapy in children with CSU and a proven IgE-mediated allergy was evaluated in two studies supporting a potential benefit in these patients.[95] Further, while children were excluded from the recently published RCT employing ligelizumab (a newer generation anti-IgE monoclonal antibody) in moderate-to-severe sgAH-resistant CSU, one active RCT that includes adolescents is ongoing.[96] Finally, data in pediatric CSU on ketotifen, cromolyn sodium, doxepin, sulfones, H2-AHs, a pseudo allergen free-diet and conventional immunosuppressants (e.g. methotrexate) is even more limited.

Conclusion

While more research in pediatric CSU is ongoing, important questions remain, including whether 1) the pathogenesis of pediatric CSU is similar to adult CSU, 2) treatment options currently approved for use in adults and adolescents can be extrapolated for use in younger patients, 3) all sg-AHs are as effective as each other, and 4) up-dosing of sgAHs can be recommended in children. Unfortunately, there is a paucity of literature regarding the efficacy and safety of many drugs used in CSU in pediatric patients of all ages.

For now, the use of sgAHs as a first-line treatment for pediatric CSU is widely-accepted and supported by the international guidelines and several well-designed RCTs.[36-45] While, no specific sgAH is recommended over another, age-specific recommendations should be taken into consideration **(Table 1)**.[1,8,9] We and others, have safely up-dosed sgAHs in children. In fact, our recent data suggest that approximately 90% of children with CSU can be well- and safely- controlled with sgAHs at the licensed and/or increased dosage (up to fourfold).[46] In cases of disease refractory to AHs, omalizumab is approved for children >12 years for CSU and >6 years for asthma.[51-53] However, there is also likely to be a benefit in younger age groups.[49,54,57-65] LTRAs and cyclosporine may be considered on a case-by-case basis. However, given the superiority and better safety profile of sgAHs over the sedative fgAHs in pediatric (and adult) CSU, clinicians should refrain from using fgAHs on a regular basis.

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IS THE CLINIC THE NEW GYM? NON-INVASIVE PROCEDURES TO INCREASE MUSCLE TONE

Non-invasive cosmetic procedures have increased 217.3% between 2012 and 2017[1], allowing for less risk and downtime than traditional aesthetic surgery. Initially with a focus on the face, these procedures have expanded to body contouring, which is defined as modification of the body's appearance through changes in size or shape. Options for body contouring have expanded beyond liposuction and surgical correction to include many non-invasive energy-based devices, which has resulted in increased patient interest. Statistics from the American Society of Dermatologic Surgery show that the number of treatments for non-invasive body contouring went up by 43% in 2018 in comparison to 2017 and grew four-fold since 2012[2].

Body contouring treatments have conventionally addressed skin, fat and muscle, but there has been a greater focus towards fat reduction. In 2017, liposuction was the second most common surgical cosmetic procedure[1] and subsequent non-invasive modalities for fat reduction include cryolipolysis, laser, radiofrequency, and high-intensity focused ultrasound (HIFU), which all employ heating or cooling as a means to minimize fat. While these devices lead to destruction of adipose cells and overall fat reduction[3], there are limitations to their use. The lipolytic responsiveness of adipose tissue is inversely proportional to an individual's BMI and thus the ideal patient for these devices has a low BMI with isolated discrete bulges of fat[3], leaving a large

proportion of patients who are not suitable candidates for these devices. Muscle tissue comprises a larger proportion of human body composition as compared to fat[4] and can play a large role in body contours and appearance. Classically the only way to build muscle mass has been through physical exercise. Recent advances have led to non-invasive body-contouring devices that stimulate muscle contractions using either electromagnetic muscle stimulation (EMMS) (High-Intensity Focused Electromagnetic Technology (HIFEM) and Magnetic Muscle Stimulation (MMS)), or Bio-Electric Current Stimulation. Both electric and electromagnetic stimulation have been used in the past as an adjunct to muscle training, with a focus on functional effect rather than appearance[5,6,7]. The following devices are the first of their kind to utilize these technologies as a means to impact body shape.

High Intensity Focused Electromagnetic Therapy (HIFEM):

High intensity focused electromagnetic therapy is based on the concept of electromagnetic induction first described by Faraday in 1831. The technology uses rapidly changing alternating magnetic fields to induce electric currents in the underlying tissue, which stimulate motor neurons in the area and provoke muscle contraction (Emsculpt, BTL Industries, Marlborough, MA). Motor neurons are selectively activated due to their large diameter and lower resistance. The device operates with intensities up to 1.8 T and frequencies up to 3kHz, and by optimizing the parameters of frequency, pulse width and intensity, is able to produce supramaximal involuntary muscle contractions. Supramaximal contractions occur when the muscle does not have the opportunity to relax fully between contractions, which is not reproducible with voluntary muscle contractions in exercise.[3,8,9,10]

HIFEM is delivered as a series of four 30-minute treatments spaced two to five days apart. The applicator is placed on the skin of the treatment area and the treatment is delivered with increasing intensity until the patient's tolerability threshold is reached **(Figure 1)**. No anesthesia is required.



Figure 1. Patient receiving abdominal HIFEM treatment

Studies have demonstrated the effects of HIFEM technology on the abdomen[8,9,10] and gluteal muscles[11,12], as well as strengthening the muscles of the pelvic floor[13] to treat urinary incontinence. Currently, studies are underway to examine strength and tone in the biceps, triceps and gastrocnemius muscles, with initial results showing improvement in muscle thickness in these areas[14]

Many studies have demonstrated improvement following a series of HIFEM treatments. An examination of 22 patients (avg. BMI 23.8 kg m^{-2}) at baseline and 3 months following a series of four HIFEM sessions of 30 minutes each and spaced apart by 2-3 days, showed an average waist reduction of 4.37 ± 2.63 cm ($P < 0.01$) three months after the last treatment, with 91% of patients stating that their abdominal appearance had improved.[9] In another study, results from MRIs taken at baseline and at the two-month follow up mark demonstrated statistically significant reductions in adipose tissue thickness (-18.6%), increase in rectus abdominus thickness (+15.4%) and a reduction in abdominal separation, or diastasis (-10.4%). The patients' weight did not change significantly through the study period, and the results continued to improve in the four patients randomly selected for six-month follow up.[10] In yet a third study, when the gluteal muscle was treated, seven patients demonstrated a significant increase ($p = .001$) in the size of the examined muscles at 1-month (+10.81 ± 1.6%) and 3-month (+13.23 ± 0.91%) follow-up.[12] Results of these studies further support the role of electromagnetic energy in building muscle tone.

In an effort to validate that the results demonstrating muscle growth were related to muscle hypertrophy and not simply swelling or increased water content in the muscle, Duncan and Dinev performed histologic examination of muscle from Yorkshire pigs following four 30-minute HIFEM treatments[15] and showed both hypertrophic and hyperplastic changes to the muscle along with an increase in muscle mass density of 20% compared with baseline, further providing evidence that HIFEM builds muscle tone.

While the initial treatment objective of HIFEM was to induce muscle thickening, studies have shown a secondary increase in apoptosis of fat cells, demonstrating that fat reduction is possible using non-thermal

means. Weiss and Bernardy examined the apoptotic index of fat in pigs receiving one treatment with a HIFEM device and showed evidence of adipocyte apoptosis.[16] It is believed that the induction of supramaximal contractions leads to increased metabolic activity in the treatment area, leading to subsequent lipid breakdown. A study involving 33 patients measuring subcutaneous fat thickness with ultrasound of the abdomen following four sessions of HIFEM demonstrated a statistically significant reduction in subcutaneous fat on ultrasound averaging
19.0% / 4.47 +/- 3.23 mm
($p < .01$) at 1 month after treatment and
23.3% / 5.78 +/- 4.07 mm
3 months after treatment.[17]
Interestingly, there was no effect demonstrated on gluteal fat after MRI following four treatments with HIFEM in seven subjects[12], which differs from the results shown in the studies of abdominal fat. It is unclear why this difference exists, and further study is warranted.

The longest follow up of the HIFEM procedure is currently one year[8], in which twenty-one subjects from the original cohort of forty-four were recalled for a follow up CT or MRI at one year. Repeat imaging of nineteen of these twenty-one subjects demonstrated that subcutaneous fat thickness remained reduced, rectus abdominus muscle thickening was maintained at one year in all subjects, and the overall difference in muscle thickness between 6-weeks and 1-year following treatment was not significant. No treatment related adverse events were reported at either the six week or one year follow up mark.

High Intensity Focused Electromagnetic Therapy with Radiofrequency:

The second generation of HIFEM device includes the addition of radiofrequency (Emtone, BTL Industries, Marlborough, MA) which is a combined device emitting synchronized RF and HIFEM energies at the same time, allowing for muscle heating prior to contraction. The addition of radiofrequency also allows for the heating of subcutaneous fat in the area of treatment, leading to fat cell apoptosis. Studies are underway to examine the effects of combined HIFEM and RF[18,19], and determine if the combination of these two modalities will allow for greater improvement to muscle tone and fat apoptosis than either modality alone.

Magnetic Muscle Stimulation (MMS):

Similar to HIFEM, magnetic muscle stimulation utilizes a magnetic field to generate a current to induce involuntary muscle contractions (CoolTone, ZELTIQ Aesthetics, Pleasanton, CA) and is indicated for use on the abdomen, thighs and buttocks. Treatment consists of four 30-minute sessions in a two-week period, with each treatment spaced at least 48 hours apart.

Interim results of a study examining the use of MMS in 110 patients found that after four treatments to the abdomen, buttocks or a combination of both areas, improved scores on the body satisfaction questionnaire and subject-rated Global Aesthetic Improvement Scale at the 4-week follow up visit were noted.[20] Improvements were greater for patients receiving treatment to the buttocks, which may reflect differences as a result of the amount of fatty tissue overlaying the treated muscle group. Primary endpoint results from this study at 12 weeks are pending.

Bio-electrical Muscle Stimulation:

Direct electrical muscle stimulation utilizes electrical impulses delivered through electrodes placed on the skin to mimic an action potential and thus stimulate muscles to contract. The waveform targets skeletal muscle with a frequency that creates an action potential to the entire muscle group being treated. These devices deliver 10 to 30 mA of energy to motor neurons, creating different types of torsional contractions by changing the polarity of the electrodes (truSculpt flex, Cutera, Inc. Brisbane, CA). The variety of contraction sequences throughout the treatment is meant to simulate a traditional workout. Muscles are initially stimulated in a twisting motion to warm up, then contracted sequentially to the point of exhaustion, and then finally stimulated with faster, deeper contractions to increase the basal metabolic rate.[21]

Treatment with bio-electrical muscle stimulation consists of a series of up to six 45-minute sessions, each spaced 2-4 days apart. Areas for treatment include the abdomen, buttocks, and thighs with the capacity to treat up to eight areas at once. No anesthesia is required.

Studies on the effects of bio-electrical muscle stimulation are currently underway and will inform the degree of impact to muscle tone in the treated areas.

Safety:

The safety of muscle stimulation procedures has been demonstrated through the

existing peer-reviewed literature, all of which shows no significant adverse events, with some patients experiencing mild redness immediately following treatment, as well as muscle fatigue to the treated area in the days following. The World Health Organization has examined the relationship between electromagnetic exposure and adverse events such as childhood cancers, adult cancers, depression, cardiovascular disorders, reproductive dysfunction, immunological modifications and neurodegenerative disease and found no association. A possible link between childhood leukemia and long-term exposure to residential power-frequency magnetic fields has been found. However, since animal studies have been largely negative and there were methodological problems with the studies linking the two, the evidence for electromagnetic exposure and childhood leukemia was deemed not strong enough to be causal.[22] However, published data highlights the importance of monitoring the total dosage of electromagnetic energy being generated per treatment as a precaution.[23]

Discussion:

Devices to stimulate muscle tone expand our current modalities for body contouring beyond fat reduction, and for the first time, allow for stimulation of muscle growth outside of traditional exercise. With increased options for non-invasive body contouring, patient selection is key in optimizing treatment outcomes. Currently, it seems that patients with lower BMIs at baseline and less than 2.5cm of pinchable fat have the best outcomes[9,10], with further studies soon to provide greater clarity on the ideal candidates for these treatments. For many patients, the best outcome will be achieved from a combination of different body contouring procedures versus treatment with one modality alone. A study comparing patients treated with EMMS alone, cryolipolysis alone, and EMMS and cryolipolysis in combination found that the multimodal approach of cryolipolysis and EMMS was safe and more effective than either modality alone.[24] Further studies are needed to delineate the safest and most effective method of combining these procedures. While initial data support muscle stimulation treatments as safe and effective, long-term data will continue to guide our treatments with these novel devices.

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HAND ECZEMA IN THE YEAR 2021

The ongoing COVID-19 pandemic has changed our hand hygiene awareness and practices. Frequent handwashing or use of hand disinfectant have become far more common in our daily life and, though necessary to curb the spread of the virus, add further stress on our skin and skin barrier function. As a consequence, more people have started suffering from dry skin or developing hand eczema.

Introduction

Hand eczema (HE) was already a common skin disease even pre-COVID-19, with a prevalence of about 10% in the general population.[1,2] It has an important socioeconomic impact due to its high indirect health care costs and association with prolonged sick leave.[3,4] Hand eczema is a clinically heterogeneous entity whose classification has historically been controversial.[1] Recent publications, though varying slightly in the details, share similarities in their approach to classifying HE. Approaches to classifying hand eczema into certain subtypes according to underlying pathogenesis are more common and often discriminate between irritant or allergic contact dermatitis, atopic hand eczema and protein contact dermatitis.[5-7] The clinical picture is used as an additional feature when etiological factors remain unclear. Recently, the question of whether hyperkeratotic hand eczema might have to be considered as an entirely different and separate disease entity from "hand eczema" in general has been postulated. Additional research has addressed the diagnostic challenges associated with hyperkeratotic hand eczema.[8,9] Dyshidrotic endogenous eczema has been described as a separate entity in a similar way[5,6,10] and poses challenges with regards to diagnosis and treatment. It has been observed in association with allergic contact dermatitis.[10]

A comprehensive understanding of the molecular pathogenesis of hand eczema is still lacking, though more details emerge.[11,12] Future classification systems will likely include molecular subtyping.

The pathogenesis of hand eczema is multifactorial.[13] Endogenous and exogenous factors contribute to its development, including atopic predisposition, skin irritation by repeated contact with water or irritants or wearing of occlusive gloves.[2-4] The strongest independent risk factor for the development of hand eczema is a history of atopic dermatitis in childhood.[14]

To date, there has been no peer-reviewed data demonstrating an association between the increased prevalence of hand eczema in adults with the onset of the COVID-19 pandemic. Two recent publications from Denmark have thoroughly investigated this topic in young children at daycare centres and in school-aged children. Both studies demonstrated that 28.6% of daycare and 40.9% of school children, with no previous history of hand eczema developed hand eczema upon their return to daycare or school after lockdown.[15,16]

Skin barrier function

The common denominator in the pathogenesis of different hand eczema sub-types is skin barrier dysfunction.[13] An intact skin barrier protects individuals from environmental stressors, from the loss of water or heat[2], and also prevents the penetration of irritating substances and microorganisms.[17-20] Epidermal barrier dysfunction enables increased penetration of allergens and development of contact allergy which affects approximately 20% of the adult population.[2,18,21,26,27] Both endogenous and exogenous factors can contribute to epidermal barrier dysfunction such as genetic predisposition and exposure to irritants or allergens.[2]

The epidermal barrier function is largely based on an intact stratum corneum (SC), which is formed by the corneocytes and lipids and often described as a "brick and mortar" model.[2] Its protein mass consists mostly of keratin intermediate filaments and filaggrin (FLG), but it also contains proline-rich-proteins, hornerin, involucrin, loricrin and antimicrobial peptides.[2]

In a recent study on the hand eczema proteome, our research group identified specific patterns of barrier protein expression in hand eczema using mass spectrometry. The results of our research indicate that FLG, filaggrin 2 and hornerin all were downregulated compared to healthy skin, whereas desquamation-related enzymes, such as cystatin E/M, and kallikrenin-related peptidase 5 and 7 all were upregulated along with the antimicrobial peptides S100A7 and S100A8/A9.[12] Genetic abnormalities in genes coding for epidermal barrier proteins and a dysfunctional immune response both play an important role in the dysfunction of the epidermal skin barrier.[2]

Several studies have described an increased risk for hand eczema among FLG mutation carriers[22] or patients with contact sensitization.[23] FLG is essential for the structural integrity of the epidermal barrier and its degradation products are largely involved in the process of moisturization and maintenance of the skin's acidic milieu. This is essential for lipid synthesis, desquamation and skin inflammation.[2] The concept of the "acid mantle of the skin" was established by Alfred Marchionini in 1928 and refers to the acidic nature of the stratum corneum, which is essential for the homeostasis of the barrier, proper functioning of the epidermal barrier and for the skin's antimicrobial defence mechanisms. Normal skin flora grows optimally at acidic pH levels, whereas pathogenic bacteria grow well in a neutral pH milieu.[24] Various factors like age, skin texture, anatomic site, sweat, skin care, cleansing products and irritants can influence the skin's pH.[24]

Environmental factors like skin contact to irritants or water can play an important role in developing an impaired epidermal skin barrier. Irritant contact dermatitis is the most frequent subtype of hand eczema.[6] Wet-work occupations are considered high-risk factors for the development of hand eczema. A recent study looked at transepidermal water loss (TEWL) after skin occlusion of the hands for either 72 consecutive hours or 8 hours per day for seven days. In healthy skin, occlusion did not affect the TEWL, whereas in skin that was irritated by sodium lauryl sulfate beforehand, it was increased ($P = 0.049$).[25] This study demonstrates that in already-irritated skin, occlusion should be avoided or reduced to a minimum.

How to care for your hands during COVID-19

During the COVID-19 pandemic, irritant exposure has substantially increased and, subsequently, the overall risk of developing irritant contact dermatitis and hand eczema has also increased. It is important to match good hand hygiene with diligent hand care to reduce the effect of damaging influences. Skin care recommendations can be found online from different dermatological societies, including the American Contact Dermatitis

Society.[28] Moisturizing is the most important element of good hand care. Preferably, products free of fragrances, preservatives and dyes should be used on a regular basis, ideally after every hand-washing. Moisturizers come in various galenic bases. Ointments are preferred for use on very dry skin.[28] Emollients are important components of moisturizing products. Emollients work by providing a seal and helping to restore the epidermal barrier function through hydration and retention of moisture.[2] Newer products focus on active ingredients that stimulate production of intercellular lipids and contribute to the restoration of lipid bilayers. Emollients containing ceramides improve the skin barrier function through skin hydration and reduce the transepidermal water loss.[2,29] Through occlusive substances like beeswax or petrolatum, a physical barrier function can be added to a moisturizer.[28] Barrier creams provide a protective layer on the skin and are often recommended for prophylaxis. However, it has still not been fully elucidated whether their effect is superior to that of a regular moisturizer.[2,30] Jordan et al. studied the effect of a combined regimen involving the use of hand protection cream, cleanser and a repair cream in 42 healthy male and female adult volunteers prone to occupational irritant contact dermatitis due to frequent wet work or contact with detergents and found this three-step approach to be successful in skin hydration and improvement of epidermal barrier function.[31]

Skin cleansing products can cause irritation and dryness of the skin. Adding moisturizing components can alleviate their negative influences on the skin barrier. Soaps wash away intercellular lipids and damage barrier proteins, though they are effective in removing dirt and inactivating viruses. Synthetic detergents have a pH of 5.5-7 which is thought to be beneficial for the skin's acid mantel and natural microflora. They have less than 10% soap content and are generally less irritating than soap.[28] Alcohol-based hand sanitizers have become an integral part of our daily lives and are omnipresent. To protect the hands as much as possible from their irritating potential it is recommended to choose products containing moisturizers and to apply a moisturizer immediately after use. Washing hands with soap and water directly before or after using a hand sanitizer should be avoided (see **Figure 1**).[28]

Wearing protective gloves poses the risk for development of irritant as well as allergic contact dermatitis to the glove itself. The culprit allergens are often rubber accelerators, and the sweating and the occlusive milieu under the gloves further promote skin barrier impairment and break down. Choosing accelerator-free gloves and applying a moisturizer beforehand will help to protect the skin.[28] Ideally, wearing cotton gloves underneath is recommended if protective gloves are required for a duration of more than 10 minutes.[1]

Perspective

Hand eczema is a common skin disease with a high socioeconomic impact. As a result of the COVID-19 pandemic, the prevalence of hand eczema is on the rise. The treatment landscape for hand eczema has suffered from a lack of innovation with no new novel therapeutic options having been made available in over a decade.

Fortunately, this situation may change in the near future as several new therapeutic approaches like topical delgocitinib or gusacitinib are currently under investigation and may alter our approach to the management of this disease profoundly.[32] With continued good skin care practices and an enhanced therapeutic armamentarium it may be possible to get hand eczema under control.

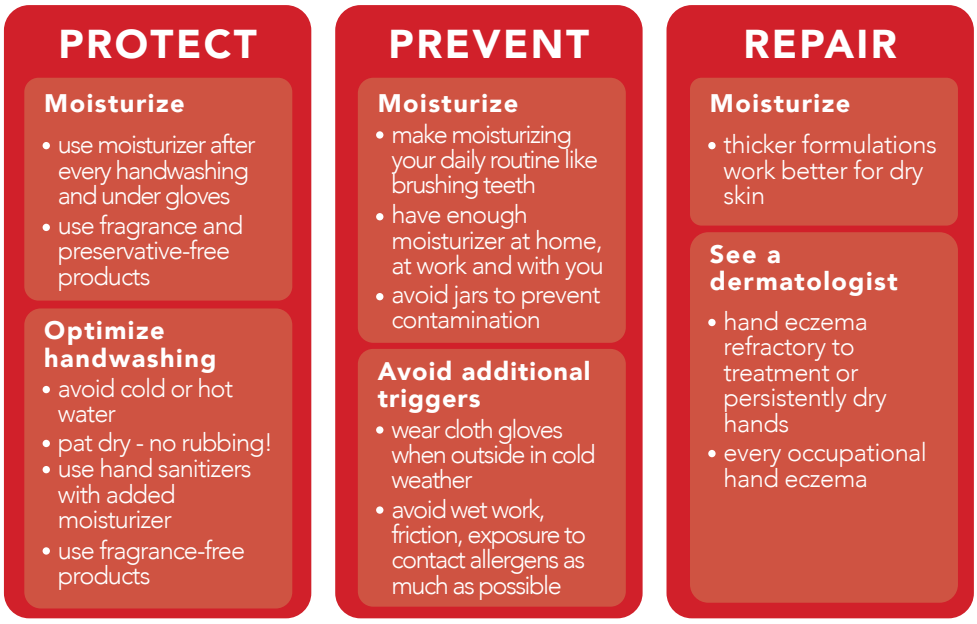


Figure 1. Hand skin care recommendations for patients courtesy of Sonja Molin, MD

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