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TABLE OF CONTENTS

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Management and Treatment of Neurofibromatosis Type I

Andrew Ferrier, MD, PhD, FRCPC, FAAD

Overview

Neurofibromatosis type 1 (NF1) is an autosomal dominant tumour suppressor syndrome associated with benign and malignant tumours, predominantly affecting the skin and nervous system.[1] NF1, the most prevalent neurocutaneous syndrome, and the focus of this review, has a frequency of ~ 1/1,900-1/3,500 people worldwide.[2] Disease manifestations can present at birth and emerge with age, negatively impacting multiple clinical domains and imparting a profound impact on a patient's quality of life and life expectancy.[2] Given its progressive nature and marked clinical variability, NF1 warrants a multidisciplinary approach to management and treatment.

Genetics and Pathogenesis

NF1 is the result of germline mutations in the tumour suppressor gene NF1 located at chromosome 17q11.2.[1] Inherited in an autosomal dominant fashion ~ 50% of neurofibromatosis (NF) cases can arise via de novo NF1 gene mutations.[3] Complete penetrance is seen in NF1, although expression is extremely variable, even within members of the same family.[3]

With thousands of identified pathogenic mutations in the NF1 gene, these pathogenic mutations ultimately disrupt the optimal protein production of neurofibromin, a critical regulator of the proto-oncogene, Ras. Ras is involved in multiple signalling pathways, including: stem cell factor (SCF)/c-kit signalling, mammalian (mechanistic) target of rapamycin (mTOR), and mitogen-activated protein kinase (MAPK) pathways. Thus, loss of neurofibromin expression leads to an up-regulation of the aforementioned pathways, facilitating cellular proliferation, differentiation and ultimately tumour development.[4]

Oculocutaneous Manifestations and Management of NF1

Hallmark cutaneous findings in NF1 include café-au-lait macules (CALMs), axillary freckling and cutaneous neurofibromas (cNFs). These cardinal

Timeline of NF1 Clinical Features
Birth - 2 years
CALMs, plexiform neurofibromas, pseudoarthrosis, sphenoid wing dysplasia, optic pathway gliomas
2 years - 6 years
Axillary freckling, Lisch nodules, optic pathway gliomas, CNS tumours, learning disabilities, plexiform neurofibromas
6 years - 10 years
Learning disabilities, attention deficit disorders, scoliosis, plexiform neurofibromas, increased risk of other cancer types (e.g., rhabdomyosarcomas), headaches
Adolescence
Subcutaneous and cutaneous neurofibromas, malignant transformation of preexisting plexiform neurofibromas, isolated MPNST, hypertension
Adulthood
Cutaneous and subcutaneous neurofibromas, MPNST, hypertension

Table 1. Development of clinical features in NF1. Café-au-lait macules (CALMs), central nervous system (CNS), malignant peripheral nerve sheath tumours (MPNSTs); *courtesy of Andrew Ferrier, MD, PhD, FRCPC, FAAD.*

NF1 Clinical Criteria
6 or more CALMs =/> 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in postpubertal patients
Two or more neurofibromas of any type or 1 plexiform neurofibroma
Freckling in the axillary or inguinal regions (Crowe sign)
Optic glioma (OPG)
Two or more iris hamartomas (Lisch nodules) or at least two choroidal anomalies
Osseous lesion (e.g., sphenoid wing dysplasia or long-bone dysplasia [with associated cortical thickening and medullary canal narrowing], with or without pseudoarthrosis)
A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

Table 2. NIH diagnostic criteria for NF1. A: In an individual who does not have a parent with NF1, the diagnosis is established if at least two of the following criteria are met. B: In a child who does have a parent with NF1, the diagnosis is established if at least one of these criteria is met; *courtesy of Andrew Ferrier, MD, PhD, FRCPC, FAAD.*

features, among others, have a central role in NF1 diagnosis and tend to follow a chronologic order of appearance **(Table 1)**. The United States National Institutes of Health (NIH) recently published and updated diagnostic criteria that rely on certain specific clinical features associated with NF1 **(Table 2)**.[5]

CALMs typically manifest as flat, uniformly hyperpigmented macules or patches with regular, well-defined borders, emerging within the first year after birth and often increasing in number during early childhood.[5] The presence of six or more CALMs by one year of age is observed in 99% of NF1 cases,[7] therefore, they are integral to the diagnostic criteria **(Table 2)**. As infants and young children predominantly present with CALMs alone, the diagnosis of NF1 necessitates the emergence of a second feature. Consequently, it is not uncommon for children with multiple CALMs and no family history of NF1 to undergo several years of follow-up before a definitive diagnosis is made or ruled out. While NF1 accounts for the majority of cases associated with multiple CALMs, such pigmented lesions can also occur in various other conditions.[6] Given that approximately 15% of the general population exhibits one to three CALMs,[6] the presence of three or more CALMs should prompt specialist referral.

Freckling in the axillary or inguinal regions (Crowe sign) occurs in 90% of patients by age 7 **(Table 1)**.[8] Freckling presents as clusters of hyper-pigmented macules and is part of the diagnostic criteria **(Table 2)**. While the axillary and inguinal areas are most often involved, freckling can also present in other intertriginous sites (e.g., neckline or inframammary areas) or can appear diffusely.[9]

Presenting as soft, fleshy, pedunculated, or sessile tumours, cNFs constitute the most prevalent tumour type in NF1.[10] These benign growths affect both the epidermis and dermis, typically emerging just before or during adolescence and demonstrating a tendency to augment in size and quantity with advancing age.[10] While cNFs do not harbor malignant potential, they can provoke irritation, pruritus or cosmetic concerns, thereby warranting surgical intervention if necessary **(Table 3)**.

Plexiform neurofibromas (PNFs) represent a distinct subtype of neurofibroma originating in the subcutaneous tissues, with growth observed throughout childhood, adolescence and adulthood.[11] These tumours, histologically benign in nature, often arise congenitally from one or multiple nerve fascicles. PNFs may manifest as tender, firm nodules with a palpable “bag of worms” consistency or remain non-palpable, featuring deep subcutaneous components potentially leading to soft tissue distortion, bony overgrowth or nerve deficits. Disfigurement and pain

can manifest in various anatomical locations, including the head and neck; orbit; extremities; thorax; paraspinal nerve roots; abdomen; and pelvis, significantly impacting quality of life and increasing mortality risk.[11]

Approximately 50% of NF1 patients have clinically apparent PNFs.[12] Evaluation of such lesions is best achieved with MRI, coupled with annual physical examination to detect symptomatic tumours **(Table 3)**. Multidisciplinary surgical interventions can be employed to debulk symptomatic or progressive PNFs. As well, oral selective mitogen-activated protein kinase (MEK) inhibitors such as selumetinib have

Feature	Diagnostic evaluation	Management
CALMs, axillary freckling	• Cutaneous exam • Refer to genetics, NF specialist, or dermatologists for more > six CALMs	• None required • Camouflage treatment if cosmetically distressing
Cutaneous neurofibromas	• Cutaneous exam • Referral to genetics or dermatology	• Symptomatic or disfiguringlesions: surgery, laser removal, or electrodessication
Plexiform Neurofibromas	•Annual physical + neurologic examination • MRI (w/ contrast) of symptomatic body part	• MRI surveillance if progression or malignancy risk • Surgical consultation for symptomatic lesions • +/- MEK inhibitors (selumetinib • Pain & symptom management
MPNST	• Regional MRI of symptomatic body part • Refer to surgeon for biopsy/resection/ histologic confirmation & oncologist	• Surgical resection and adjunctive radiation or chemotherapy therapy • Educate MPNST signs and symptoms (e.g., pain, unexpected growth of a tumour, or change in texture from soft to firm)
OPGs	• Ophthalmologic exam < 10 years old • Brain/orbit MRI if abnormal eye exam or signs or symptoms of OPG • Annual height and weight measurement to screen for precocious puberty (+/- endocrinology referral	• Annual ophthalmologic screening through adulthood or for 10–25 y after initial diagnosis of OPG
Behavioural/ learning difficulties	• Referral to psychologist or psychiatrist for neurocognitive testing	• Academic support such as individualized educational plans, along with physical, occupational, and speech therapy.
Bone abnormalities	• Orthopedic evaluation • Plain radiographs	• Orthopedic referral for bracing +/- surgery
Osteopenia/ osteoporosis	• DEXA scan • Vitamin D level	• Calcium and Vitamin D supplementation • Regular DEXA scan
Hypertension	• Annual blood pressure assessment • Doppler ultrasonography • Refer to cardiology if murmur	• Routine BP assessment commencing in childhood • Persistent hypertension rule out secondary causes (e.g., renovascular disease or pheochromocytoma)
Breast cancer	• Mammogram +/- MRI • Physical exam	• Annual mammogram at age 30

Table 3. Diagnostic evaluation and management for common clinical features of NF1. Adapted from Miller, DT, et al., 2019 and Stewart, DR, et al., 2018; *courtesy of Andrew Ferrier, MD, PhD, FRCPC, FAAD.*

been approved for symptomatic or inoperable NFs in pediatric patients three years of age and older.

The transformation of PNFs into malignant peripheral nerve sheath tumours (MPNSTs) occurs in ~3-15% of patients, representing the leading cause of death in NF1 patients.[12] Rapid growth, pain, change in lesion texture from soft to firm, or a family history of MPNSTs are some clues of malignant degeneration.[12] Both MRI and PET scans are highly sensitive imaging modalities for malignant transformation **(Table 3)**. For management, a multimodality approach is used including complete tumour resection with negative margins and adjuvant radiotherapy.[13] Chemotherapy is used only for palliation in unresectable and metastatic tumours.[14]

Additional cutaneous manifestations of NF1 include juvenile xanthogranulomas (JXGs) and nevus anemicus. JXGs manifest as small, waxy, yellowish nodules on the skin in some children with NF1, typically resolving spontaneously. Despite speculation about a link between JXGs and leukemia in NF1 children, clinical studies suggest they are not a significant risk factor.[10] Nevus anemicus, a flat skin macule paler than surrounding skin, occurs in approximately half of individuals with NF1.

In approximately 70% of NF1 patients the iris may show tan-coloured hamartomas known as Lisch nodules.[7] Lisch nodules can appear between ages 5 and 10 years and are useful in establishing a diagnosis of NF1 in a child **(Table 1)**. While visible with the naked eye these lesions are best visualized with an ophthalmoscope or slit lamp.[10] These lesions are not malignant, nor do they impact vision. All patients with suspected NF1 should be referred to an ophthalmologist for slit-lamp examination for potential Lisch nodules **(Table 3)**.

Optic pathway gliomas (OPGs) occur in approximately 15% of children younger than six years of age with NF1.[15] As the most common central nervous system-associated tumour seen in children with NF1, the majority of OPGs are asymptomatic and intervention is rare.[16] OPG symptoms can include headache, nausea, vomiting, visual defects, and precocious puberty.[16] While no formal guidelines exist annual eye examinations under the age of 10 is warranted, and every two years up to 18 years **(Table 3)**.

Extracutaneous Manifestations and Management of NF1

The extracutaneous manifestations of NF1 encompass a wide array of cognitive and behavioural challenges, and skeletal, neurologic and cardiovascular abnormalities, along with the development of benign and malignant tumours. Approximately half of individuals with NF1 encounter various forms of learning difficulties, with attention-deficit/hyperactivity disorder observed in 50% of this demographic.[17] It is imperative to conduct routine screening for developmental delays and behavioural issues. Early initiation of psychoeducational, neuropsychological and academic testing should be pursued upon the earliest signs of academic or social concerns **(Table 3)**.

Skeletal abnormalities in NF1 exhibit variability and usually manifest during childhood **(Table 1)**. The diagnostic criteria encompass distinct features such as sphenoid wing dysplasia, dystrophic scoliosis, and long-bone dysplasia **(Table 2)**. Noteworthy focal skeletal manifestations include macrocephaly; hypertelorism; short stature; pectus deformity; and osteopenia. It is imperative to conduct annual surveillance, involving collaboration with relevant specialists (i.e., orthopedist, endocrinologist) for comprehensive monitoring and management.

Cardiovascular system abnormalities are well documented in NF1. Pulmonic stenosis, mitral valve anomalies, septal defects, and tetralogy of Fallot are some of the more often documented heart defects.[18] As these defects increase the risk of fatal cardiovascular events it is critical that physicians screen and make the appropriate referrals or workup.

Primary (essential) hypertension is commonly found in adults, and less commonly in children, with NF1.[10,12] While primary hypertension is most common, secondary hypertension (e.g., moyamoya disease, renal artery stenosis, and pheochromocytoma) is known to occur. Annual blood pressure assessments should be initiated in all NF1 patients and, if clinically suspected, workup for any secondary causes of hypertension including MRI and magnetic resonance angiogram of the abdomen **(Table 3)**.

Tumours associated with NF1 encompass a diverse spectrum including, but not limited to, gastrointestinal stromal tumours; early-onset breast cancer; leukemia; neuroendocrine tumours, and rhabdomyosarcoma.[19] Females with NF1, particularly those under 50 years of age, face an increased risk of breast cancer and exhibit significantly poorer five-year survival rates and excess mortality.[20] According to the National Comprehensive Cancer Network guidelines, women clinically diagnosed with NF1 should undergo annual mammograms starting at age 30 and consider contrast-enhanced breast MRI between ages 30 and 50.[20]

Genetic Counselling and Conception

Patients and their families should receive comprehensive genetic counselling, covering aspects

such as the disorder's inheritance pattern (including potential recurrence risk in other offspring), prognosis and psychosocial adjustment. Addressing the progressive nature of the disease and its variable clinical presentation is essential. Those with NF1 who desire children should undergo preconception genetic counselling to understand inheritance risks and the condition's manifestation variability. While many NF1 patients opt for natural conception, prospective parents should be educated about the array of reproductive options available to them.

Conclusion

NF1 manifests with a wide range of clinical features impacting various organ systems. Recognizing characteristic cutaneous signs and specific tumour types should prompt clinicians to refer patients to specialists well-versed in NF1 and its related conditions. Given the considerable variability in NF1 manifestations both within and among patients, it is crucial to tailor management strategies to each individual's needs at various stages of life.

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Financial Disclosures

None declared.

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Major adverse cardiovascular events (MACE): including non-fatal myocardial infarction, were observed more frequently in patients ≥50 years of age with RA during a clinical trial comparing another JAK inhibitor versus TNF inhibitors.

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Updates and Pearls from the Society of Pediatric Dermatology Meeting

Cathryn Sibbald, MD, MSc, FRCPC

The 49th annual Society of Pediatric Dermatology (SPD) meeting was a tremendous success, attracting over 650 attendees, the highest number ever recorded. The 3-day conference featured a wide range of new developments and tips and tricks from experts in the field.

Artificial Intelligence (AI)

Dr. Albert Yan delivered an enlightening talk about AI in dermatology. He highlighted an example of ChatGPT writing a letter of medical necessity for ustekinumab, complete with citations from large trials demonstrating its benefit. On further interrogation, it was revealed that these references were fabricated "to illustrate what an ideal reference should be".

Dr. Yan also compared 5 different generative AI systems. He highlighted those with excellent performance in advanced search capabilities (ChatGPT-4o and Gemini Pro), evaluating published references and summarizing articles (Perplexity), generating images (Gemini Pro) and voice interactions (ChatGPT-4o). While Copilot works well for advanced search capabilities, both Copilot and Claude were outperformed by other systems in all other domains. He recommended a New England Journal of Medicine (NEJM) podcast on AI for those interested in learning more.

Skin Findings of Systemic Disease and Neonatal Presentations

Dr. Lisa Weibel described many cases where skin findings were crucial for diagnosis. In one instance, dystrophic nails in a 3-year-old led to radiographs of the knees, which confirmed absent patellas and resulted in a diagnosis of Nail Patella Syndrome, an autosomal dominant condition associated with potential glaucoma and impaired renal function. Another patient presented at the age of 5 years with missing lunulas on the fingers and pachydermia. Further examination revealed atrophic pitted scars, radial furrowing of the lips, and pain on sun exposure. Subsequent tests confirmed erythropoietic protoporphyria, a condition typically presenting in childhood.

Other cases included dermatitis herpetiformis that presented with acral petechiae, Langerhans cell histiocytosis with purpuric nail streaks, along with pigmented facial skin tags indicating basal cell carcinomas in a child with Gorlin's syndrome, and superficial erosions in a neonate with congenital syphilis.

In her neonatal talk, Dr. Wiebel discussed a patient with large congenital mastocytomas refractory to conventional treatments that included antihistamines and topical steroids, who was then treated with omalizumab. Janis Chang also reported success with this off-label treatment in one of the Cases of the Year.

Quick Hits

This year, we introduced daily Quick Tips to feature practical medical, surgical, and professional advice.

Dr. Denise Metry provided an overview of the new criteria for LUMBAR syndrome (Lower body hemangioma-urogenital anomalies-myelopathy-bony deformities-anorectal and arterial malformations-renal anomalies), and also discussed her general approach. Diagnosis requires a segmental hemangioma of any size in the lumbosacral, sacrococcygeal or pelvic region along with an abnormality of another organ system e.g., (urogenital, spinal cord, bony, anorectal, arterial, or renal).[1] If the hemangioma is located midline in the posterior aspect, she recommends imaging the spine and ordering an ultrasound of the kidneys and pelvis. For anterior hemangiomas, she advises only a renal and pelvic ultrasound. Finally, if the hemangioma affects the leg, she suggests an ultrasound with Doppler.

Dr Tony Mancini discussed a case involving nasal cartilage ulceration in an infant, which was ultimately diagnosed as a sign of child abuse. A new "red flag" for us to keep in mind, given similar cases reported in the literature.[2]

Involving Child Protective Services

Dr. Romy Cho from the Hospital for Sick Children (SickKids) bravely tackled the question of when to involve child protective services in pediatric dermatology. She referenced a recent review that provides approaches for managing children with suspected abuse.[3] For anogenital warts, there are ongoing challenges in differentiating sexual from non-sexual transmission, given that the virus can lay dormant for many years. The current review advises against the subtyping of human papillomavirus (HPV) or the old age cut-off of 5 years as determinants of abuse likelihood.

She discussed important considerations when evaluating dermatological photos, emphasizing the importance of timely and thorough documentation. She recommended describing any limitations of the photographs, assuming they depict the patient in question, providing a clear differential of the possible diagnoses, and stipulating when or if an in-person assessment is necessary.

Hormonal Treatments

Dr. Andrea Zaenglin reviewed systemic hormonal treatments in adolescents. To screen for polycystic ovarian syndrome (PCOS), the ideal time is 2-3 years post menarche. Screening includes total and free testosterone and dehydroepiandrosterone sulfate (DHEAS) levels. Notably, diagnosis in adolescents is based on the concomitant presence of clinical and/or biochemical hyperandrogenism with persistent oligomenorrhea. An ultrasound of the ovaries is not included in the diagnostic criteria, as multi-cystic ovaries are common in adolescents.[4] In likely cases of PCOS, subsequent investigations include fasting glucose and lipid profiles.

Two main hormonal treatments for adolescents are spironolactone and oral contraceptives. Spironolactone has demonstrated safety and efficacy for adolescent acne, usually at doses from 25 mg to 200 mg. Many clinicians will prefer to wait until after menses are established to start this treatment to avoid interference with the detection of menstrual abnormalities; however, Dr. Zaenglin referenced a systemic review that found no hormonal disruption from spironolactone use.[5]

For those prescribing combined oral contraceptives, estrogen doses of 20 µg or lower could have negative effects on bone health. Compromised bone density is most likely to occur within the first 3 years post menarche. Combinations of 30 ug of ethinyl estradiol are available with drospirenone, norethindrone, and norgestrel e.g., (Yasmin). These combinations are associated with a 45-60% decrease in inflammatory and comedonal acne at approximately 6 months, similar to systemic antibiotics. As a reminder, a quick screen for contraindications can be accomplished with 5 questions:[6]

1. Do you or your family members have a history of blood clots?
2. Do you have high blood pressure?
3. Do you have migraines with aura?
4. Do you have lupus, liver or heart disease?
5. Do you take medications for seizures or HIV?

The Debates: Beta-blockers, Food-triggered Eczema, and Vitiligo

Dr. Elena Pope and Dr Sarah Chamlin debated the superiority of nadolol versus propranolol for the treatment of infantile hemangiomas. Both medications have demonstrated significant benefits in treating infantile hemangiomas and are well tolerated. Some key differences include the CNS distribution coefficient (0.066 for nadolol, 20.2 for propranolol) and the half-life [longer for nadolol]). She discussed a randomized controlled trial that demonstrated the non-inferiority of nadolol compared to propranolol.[7] Sleep disturbances are more commonly reported with propranolol, with some cases resolving after a switch to nadolol. Although long-term psychological or learning deficits have been discussed, no publications to date have confirmed these risks with propranolol. Both medications have been associated with reports of infant death, 1 with nadolol and 6 with propranolol.

Dr. Jim Treat and Dr. Kashi Oza debated whether food can trigger eczema. Dr Treat proposed that "foods don't cause flares…scratching causes flares" and suggested that foods may lead to more scratching which could cause flares. Dr. Oza referred to a large double blind randomized controlled study that investigated the impact of food or placebo challenges in patients with atopic dermatitis. The study found that the severity of atopic dermatitis correlated with the positivity rate of food challenges.[8] Notably however, patients with dermatitis as their only symptom were just as likely to react to the placebo as to the challenged food. This suggests that the classic type 1 hypersensitivity symptoms remain the best predictor of a food allergy, although dermatitis may concurrently flare with exposure.

Finally, Dr. Nanette Silverberg and Dr. Leslie Castelo-Soccio discussed aggressive versus conservative approaches to treating pediatric vitiligo. Recent expert recommendations included topical steroids and calcineurin inhibitors as first-line treatment options.[9] Other "less aggressive" options discussed were vitamin D analogues, coal tar, and camouflage. For natural sunlight exposure, Dr. Castelo recommends starting slowly with 5-15 minutes at non-peak hours and building up until the skin colour turns pink (not red), to achieve the desired effect. The proposed reasons for a more aggressive approach include preventing the psychological disability associated with active disease and maintaining the melanocyte reservoir. Other topical treatments discussed include ruxolitinib cream. Systemic off-label options used in pediatrics include minocycline at a dose of 100 mg daily, dexamethasone at a dose of 2-2.5 mg on 2 consecutive days weekly, low-dose methotrexate, and Janus kinase (JAK) inhibitors including tofacitinib.

Topical Absorption in Pediatrics

Dr. Larry Schachner reviewed concerns with topical absorption of medications in the pediatric patient population. Among these, he outlined case reports of toxicity attributed to lidocaine, diphenhydramine, henna and *N,N*-diethyl-*m*-toluamide (DEET) **(Table 1)**. When prescribing a eutectic mixture of local anesthetics (EMLA), he suggested using only the 5 g and not the 30 g tubes.

Scarring Alopecia

An approach to managing scarring alopecia in pediatric patients was discussed by Dr. Marissa Joseph. She highlighted several conditions, including central centrifugal cicatricial alopecia (CCCA), discoid lupus, lichen planopilaris and late presentations of traction, trichotillomania, and tinea. Scarring alopecia in

Medication	Potential adverse effect	Suggested limits
EMLA	• Lidocaine toxicity • Methemoglobinemia • Seizures	• 0-3 months: 1 g maximum total dose • 3-12 months: >5 kg: 2 g maximum total dose • >1-6 years: 10 g total> 100 cm^2/>4 hours • 7-12 years: 20 g/ 200 cm^2/>4 hours
DEET	• Encephalopathy	• 6 months -<2 years: 10% once daily • 2-12 years: maximum total dose 10%, up to TID • >12 years: 30%
Diphenhydramine	• Hemorrhage (thymus, heart, lungs), cerebral edema	• >2 years: 1-2% topically TID-QID
Henna tattoo	• Hemolysis in patients with G6PD deficiency	• Avoid in patients with G6PD deficiency

Table 1. Select Topical Medications with Potential Toxicity in Pediatric Populations; *adapted from presentation by Dr. Larry Schachner at SPD, 2024*
Abbreviations: EMLA: eutectic mixture of local anesthetics, 2.5% lidocaine and prilocaine; **DEET:** *N,N*-diethyl-*m*-toluamide; **G6PD:** glucose-6-phosphate dehydrogenase; **QID:** 4 times a day; **TID:** 3 times a day

Medication	Indication	Precautions/ Comments
Clascoterone 1% cream (Androgen receptor inhibitor)	FDA/HC: 12 years +, BID: acne vulgaris (IGA success of 19-21% vs 7-9% placebo at week 12)	• Headache (1.3%) *Reversible biochemical HPA suppression in 9% with 4-6x dose x 2 weeks
Ruxolitinib 1.5% cream (JAK1/2 inhibitor, downregulates IL-4/13/31)	FDA: 12 years +, BID for atopic dermatitis (IGA success of 51-54% at week 8 vs 8-15% placebo)	• Nasopharyngitis (3%) • Bronchitis, Ear infection, Urticaria, Folliculitis, Diarrhea, All in 1%)
Ruxolitinib 1.5% cream (JAK1/2 inhibitor, downregulates IL-4/13/31)	FDA: 12 years +, BID for non-segmental vitiligo (facial VASI75 30% at 24 weeks vs 8-13% placebo)	• Application site acne (6%) • Pruritus (5%)
Roflumilast 0.3% cream (PDE4 inhibitor)	FDA/HC: 12 years +, once daily for plaque psoriasis including intertriginous areas (IGA success in 37-42% at week 8 vs 6-7% vehicle)	• Diarrhea (3.1%) • Headache (2.4%) • Insomnia (1.4%) • Nausea (1.2%)
Roflumilast 0.3% foam (PDE4 inhibitor)	FDA: 9 years + once daily for seborrheic dermatitis (IGA success in 73-80% at week 8 vs 41-58% vehicle)	• Nasopharyngitis (1.5%) • Nausea (1.3%), and Headache (1.1%)
Roflumilast 0.15% cream (PDE4 inhibitor)	FDA: 6 years +, once daily for atopic dermatitis (IGA success in 29-32% at week 4 vs 12-15% placebo)	• Headache (2.9%) • Nausea (1.9%) • Application site pain (1.5%), • Diarrhea (1.5%) • Vomiting (1.5%)
Berdazimer 10.3% gel (Nitric oxide releaser)	FDA: 1 year +, once daily x 12 weeks for molluscum (complete clearance 37% vs placebo 20% at 12 weeks)	Local irritation, itch, pain, dermatitis
Birch Triterpenes 10% gel (Filsuvez)	FDA: 6 months +: q 1-4 days, Junctional or dystrophic EB	Localized reaction, SCC reported in 4 adults
Beremagene geperpavec (HSV1 vector based Collagen 7)	FDA: 6months + weekly, for EB with collagen 7 mutation	Needs application by qualified health care personnel
Ritlecitinib (JAK3/TEC inhibitor)	FDA/HC: 12 years + Severe alopecia areata, 50 mg daily (SALT ≤20 in 23% at week 24 vs 2% placebo)	• Nasopharyngitis (10%) • Headache (9%) • Acne (9%) • Nausea (9%) • Upper respiratory infection (6%)
Lebrikizumab (IL-13 inhibitor)	HC: 12years +40kg: 500mg weeks 0,2 then 250mg q2weeks until week16 then 250mg q4weeks (roughly 33% with IGA of 0 or 1 at 16 weeks)	• Nasopharyngitis (7.9%), • Conjunctivitis (5.8%) • Injection site reactions (4.5%)
Spesolimab (IL-36 receptor inhibitor)	FDA: 12 years + pustular psoriasis 1 dose IV +/- repeat 1 week later then q 4weeks subcutaneous (pustulation score 0 at week 1 in 54% vs 6% placebo)	• Fast onset Pyrexia (6%) • Urinary tract infection (3%), • Arthritis (3%), • Drug-induced liver injury (3%)

Table 2. Select New Medications in Pediatric Dermatology[20]
Abbreviations: BID: twice a day; **EB:** epidermolysis bullosa; **Facial VASI75:** Facial Vitiligo Area Scoring Index 75% Improvement; **FDA:** US Food and Drug Administration; **HC:** Health Canada; **IGA:** Investigator Global Assessment; **IL:** interleukin; **IV:** intravenous; **JAK:** Janus kinase; **PDE4: phosphodiesterase 4**; **SCC,** SALT, Severity of Alopecia Tool; **TEC:** tyrosine kinase expressed hepatocellular carcinoma

the vertex in adolescents with a family history of CCCA should prompt consideration of this diagnosis. Using a dermatoscope to identify a peripilar white/grey halo (representing characteristic fibrosis) in these patients can help increase the diagnostic yield of a biopsy.[10] The progressive nature of CCCA underscores the benefit of early recognition and treatment, involving high potency corticosteroids, a 3-month course of doxycycline (in the inflammatory phase), and anti-seborrheic shampoos.

New and Repurposed Medications

The expansion of pharmacologic options was highlighted in several talks. Medications recently approved in the United States are listed in **Table 2**. Although only a subset is currently approved by Health Canada, others have been submitted for approval.

Dr. Julie Schaffer provided an excellent overview of molecular pathways and targeted therapies. She highlighted selumetinib, a mitogen-activated protein kinase/extracellular signal-related kinase (MEK) inhibitor approved for plexiform neurofibromas in children 2 years and older. A study has shown that selumetinib use was associated with significant fading of café au lait macules in 3 out of 4 patients with concurrent plexiform neurofibromas.[11] Along with its benefits, prevalent dermatologic toxicities were reviewed including xerosis (more common in pre-pubertal children), paronychia, and acneiform rashes (older patients with skin phototypes 2 and 3).[12] Trametinib, another MEK inhibitor, was successfully used topically twice daily in an infant with Schimmelpenning-Feuerstein-Mims syndrome, with a reduction in the thickness and pruritis of epidermal and sebaceous nevi.[13]

Challenges with Biologics

In a panel session, Dr. Steven Humphreys presented a new consensus guideline outlining the safety of live vaccine administration to patients receiving dupilumab. The consensus concludes that it is appropriate to consider administering live vaccines without dupilumab interruption with shared decision making, given the lack of evidence for adverse effects.[14]

For patients with a suboptimal response to dupilumab, we were encouraged to consider poor adherence, interval weight gain, and complicating factors (secondary allergic contact dermatitis, psoriasis skewing, and the formation of anti-drug antibodies). Increasing the dose of dupilumab (from 200 mg to 300 mg) may be preferable to decreasing the interval for patients who are apprehensive of needles.

With respect to discontinuing therapy, Dr Siegfried presented data on pediatric patients who have achieved clinical remission (Investigator Global Assessment [IGA] 0/1 for 12 weeks) and thereafter discontinued dupilumab. In the 6–11-year group, 60.3% of 73 patients maintained an IGA 0/1 12 weeks after discontinuation. In the 12–18-year group, 43.3% of 30 patients maintained an IGA 0/1 12 weeks after discontinuation.

Other speakers highlighted coincidental benefits of dupilumab, such as the elimination of diffuse filiform warts in a young girl, and the clearance of actinic prurigo in a 7-year-old girl.[15,16] Conversely, case reports of demodex folliculitis and crusted scabies developing after starting dupilumab were also presented.[17,18] Comments from the audience highlighted that the community is observing more cases of demodex and scabies in children, and these skin conditions should be considered when starting and monitoring patients receiving dupilumab.

Pediatric Dermatology Research Alliance (PeDRA)

Reviewing PeDRA activities, Dr. Lara-Corrales discussed new consensus recommendations for the use of methotrexate in pediatric patients.[19] Some key points include the lack of necessity for test doses, a maximum dose of 1 mg/kg/week (or 25 mg), the lack of contraindication for live vaccines, the safety of inactivated vaccines, and recommendations to hold methotrexate if liver enzymes are ≥ 3 times the upper limit of normal for 2 consecutive months and during systemic infections. In pediatric populations, the onset of effect for atopic dermatitis, psoriasis, and lichen planus is 8-12 weeks, versus 12-16 weeks for alopecia areata and morphea. Finally, folic acid supplementation is recommended at a dose of 1 mg/day on non-methotrexate days, unlike the conventional 5 mg dose for adults.

Other presentations included medical errors by Donald Redelmeier, misinformation by Timothy Caulfield, and the traditional Cases of the Year. For those interested, recordings will be available for purchase in August 2024. Also, the 15th World Congress in Pediatric Dermatology will take place in Buenos Aires from April 11-15, 2025, and the 50th annual SPD conference will be held in Seattle from July 23-26, 2025.

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* Clinical significance is unknown.

References: 1. DUPIXENT® Product Monograph, sanofi-aventis Canada Inc., July 12, 2023. **2.** Data on file, sanofi-aventis Canada Inc., September 1, 2023.

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Keratinocyte Carcinoma: Canadian Landscape and an Evidence-based Approach to Follow-up

Jorge R. Georgakopoulos, MD, FRCPC

Introduction

Dermatologists play a vital role in the early detection, prevention and effective management of skin cancer in patients with a prior history of the disease. Regular monitoring and timely interventions greatly enhance the overall prognosis and quality of life for patients with skin cancer. Dermatologists possess the requisite expertise to accurately diagnose and oversee the management of cutaneous skin cancers.

Skin cancer screening via total body skin exam (TBSE) is often considered one of the safest, easiest, and most cost-effective tests in medicine.[1] Despite dermatologists' ability to offer such invaluable care for this patient population, offering routine skin checks for all patients with a prior history of skin cancer becomes exceptionally challenging given the high demand for dermatology care across Canada. It is important for dermatologists to maximize the efficiency of care during TBSEs by adhering to evidence-based guidelines when determining the frequency and duration of follow-up. These guidelines also provide a solid foundation for discussions with patients regarding the rationale for discharge back to their primary care provider.

Skin Cancer as a Chronic Disease

By its definition, a condition qualifies as a chronic disease if it lasts for more than one year, necessitates continuous medical attention, and/or restricts activities of daily living.[2] Skin cancer as a chronic disease is a novel concept that aims to provide a more comprehensive understanding of skin cancer patients experiencing considerable morbidity due to their condition, requiring heightened healthcare resources.[3]

A population-based study conducted in Canada revealed that the incidence of keratinocyte carcinoma (KC), encompassing both squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), increased by

30% between 2003 and 2017.[4] Furthermore, about 60% of patients with a history of KC will develop another carcinoma within 10 years.[5] After a primary BCC, 50% of patients will have at least one more BCC within 5 years.[6,7] Similarly, there is a 42% risk of a second SCC within 5 years, increasing to 72% for those with two or more SCCs.[5]

Epidemiology of Keratinocyte Carcinoma in Canada

The epidemiology of SCC and BCC in Canada reveals a significant burden of KC, although reported data is limited. A retrospective analysis by Jung et al. on 98,645 patients in Alberta from 1988 to 2007 reported 66,192 cases of BCC (34,825 males and 31,367 females), 12,494 cases of SCC *in situ* (6,106 males and 6,388 females), and 19,959 cases of invasive SCC (12,315 males and 7,644 females).[8] Another study by Tang et al. from the Ontario health administrative database (ICES) highlighted an increase in the incidence and mortality of KC from 1998 to 2017, with the incidence rising from 328.6 to 356.7 per 100,000 adults and the annual mortality rate increasing 4.8-fold from 6.39 to 30.53 deaths per 1,000,000 adults.[9]

Adding to this data, Hayes et al. examined KC cases in New Brunswick between 1992 and 2001, identifying 8,550 new cases of BCC (4,513 males and 4,037 females) and 3,036 new cases of invasive SCC (1,851 males and 1,185 females).[10] When age-standardized to the 2000 world population, the incidence rates per 100,000 population were 86.9 for males and 67.7 for females for BCC, and 34.0 for males and 16.1 for females for invasive SCC. The study also

Source	Location	Recommendations
Peris et al, 2023[12] *European Association of Dermato-Oncology*	Europe	**Low-risk:** No follow-up **High-risk:** Every 12 months for at least 3-5 years
National Comprehensive Cancer Network, 2024[13]	United States	**All risks:** Every 6 months year 1-5, every 12 months thereafter for life
Nasr et al, 2021[14] *British Association of Dermatologists*	United Kingdom	**Low-risk:** No follow-up **High-risk:** Every 6 months year 1, every 12 months starting year 2 for 5-10 years
Zloty et al, 2015[15] *Canadian Non-melanoma Skin Cancer Guidelines Committee*	Canada	**Low-risk:** Yearly (duration not reported) **High-risk:** Every 6 months year 1-3, every 12 months starting year 4 (duration not reported)

Table 1. Follow-up recommendations for basal cell carcinoma from major dermatologic associations; *courtesy of Jorge R. Georgakopoulos, MD, FRCPC*

Source	Location	Recommendations
National Comprehensive Cancer Network, 2024[16]	Unites States	**Low-risk:** Every 3-12 months for year 1-2, every 6-12 months year 3-5, every 12 months thereafter for life **High-risk:** Every 3-6 months for year 1-2, every 6-12 months year 3-5, every 12 months thereafter for life
Alam et al, 2018[17] Invited working group	United States	**All risks:** At least yearly (duration not reported)
Keohane et al, 2021[18] British Association of Dermatologists	United Kingdom	**Low-risk:** 1 post-treatment visit only **High-risk:** Every 4 months year 1, every 6 months year 2 then stop
Stratigos et al., 2020[19] European Association of Dermato-Oncology	Europe	**Low-risk:** Every 6-12 months for 5 years **High-risk:** Every 3 months year 1-2, every 6 months 1-5, every 12 months thereafter for life

Table 2. Follow-up recommendations for squamous cell carcinoma from major dermatologic associations; *courtesy of Jorge R. Georgakopoulos, MD, FRCPC*

revealed that the lifetime probability of developing BCC in New Brunswick was approximately 13%, with a 5% probability of developing invasive SCC. BCC accounted for approximately 74% of KC in this population, with a BCC to invasive SCC ratio of 2.8 to 1. These findings collectively underscore the growing public health challenge posed by SCC and BCC across Canada.

Follow-up Guidelines from Major Dermatologic Organizations

There are numerous guidelines from dermatologic associations worldwide for the follow-up of patients with a history of KC.[11] Post-treatment follow-up is designed to detect recurrence and metastasis, monitor for new primary tumors, and reinforce ongoing preventive behaviours. There remains uncertainty about the optimal frequency for follow-up skin examinations after KC treatment, which has significant implications for both patient outcomes and healthcare resources. Herein, we summarize the available practice guidelines from major dermatologic associations to provide dermatologists with an evidence-based framework for follow-up care, helping them reflect on whether their current follow-up practices are sufficient or excessive.

Basal cell carcinoma **(Table 1)**: Follow-up guidelines for BCC vary across various regions and organizations. According to the European Association of Dermato-Oncology, low-risk BCC requires no follow-up, while high-risk cases should be monitored every 12 months for at least 3-5 years. The National Comprehensive Cancer Network in the United States recommends follow-up every 6 months during the first 5 years for all risk levels, then annually for life. The British Association of Dermatologists suggests no follow-up for low-risk BCC, with high-risk patients being seen every 6 months in the first year, then annually for 5-10 years. In Canada, the Non-Melanoma Skin Cancer Guidelines Committee advises yearly follow-up for low-risk BCC and more frequent follow-up for high-risk cases, with every 6 months for the first 3 years, and then annually starting in year 4, although the duration is not specified.

Squamous cell carcinoma **(Table 2)**: Follow-up guidelines for SCC differ based on risk levels and regional practices. The National Comprehensive Cancer Network (NCCN) in the United States advises more

Tumour specific factors	Aggressive subtype, large tumours, recurrence, and location (head and neck; eye, ear, nose or mouth)
Non-modifiable individual factors	Skin pigmentation/type, hair colour, eye colour.
Environmental	Lifetime sun exposure, sunbathing frequency before age 30, tanning bed usage, living at low latitudes and high elevation during both childhood and adult life, recreational activities and environmental pollutants.
Iatrogenic	Long-term immunosuppressive therapy (i.e., organ transplantation, autoimmune conditions, autoinflammatory conditions, HIV/AIDs), radiation therapy, psoralen and ultraviolet A (PUVA) therapy, biologic therapy, and chronic wound healing.
Occupation	Individuals engaged in occupations for a prolonged period of time with extended exposure to radiation (ultraviolet or man-made) and chemicals; including but not limited to outdoor jobs, airline pilots and crew, farmers and agricultural workers, fisherman, construction workers, and military personnel.
Genodermatosis	Xeroderma pigmentosum, basal cell nevus syndrome (Gorlin syndrome), oculocutaneous albinism (OCA), epidermodysplasia verruciformis, dyskeratosis congenita, Bazex-Dupré-Christol syndrome, epidermolysis bullosa, Bloom syndrome, Rombo syndrome, Fanconi anemia, Ferguson-Smith syndrome.
Field cancerization	Phenomenon in which a large area of tissue is affected by genetic and epigenetic alterations, making it more susceptible to the development of multiple skin cancers. This concept suggests that the entire field of tissue surrounding a primary tumor may be at risk for the development of additional tumors, even if they are not clinically visible.[20,21]

Table 3. Complex skin cancer in context of keratinocyte carcinomas; *courtesy of Jorge R. Georgakopoulos, MD, FRCPC*

frequent follow-ups for high-risk patients, ranging from every 3-6 months in the first 2 years to annually for life, while low-risk patients are monitored less frequently. In contrast, the British Association of Dermatologists recommends just one post-treatment visit for low-risk SCC, with high-risk patients receiving more regular check-ups in the first 2 years before follow-up stops. The European Association of Dermato-Oncology suggests frequent follow-ups for high-risk cases, especially in the first 2 years, tapering to annual visits after 5 years.

Table 3 summarizes the key patient factors dermatologists should consider when identifying individuals with complex skin cancer. The term 'complex skin cancer' refers to a multifaceted spectrum of conditions, encompassing patients with skin cancer who are at a heightened risk for future cutaneous malignancy. This complexity underscores the need for specialized and comprehensive approaches in both diagnosis and management by dermatologists and allied health professionals. These factors should be carefully considered when determining follow-up intervals.

Conclusion

The management of KC in Canada demands a nuanced approach, especially in light of the rising incidence of the disease. Data shows a significant increase in KC cases, with incidence rates climbing over the past decades. As dermatologists play a crucial role in providing continuous care for these patients, the growing demand for dermatology services across Canada poses a challenge. The lack of consensus on follow-up guidelines further complicates this issue, requiring dermatologist to utilize guidelines based on their unique clinical practice and regional healthcare landscape. In the future, establishing standardized follow-up protocols is essential to optimize patient outcomes while managing the increasing strain on dermatology care.

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None declared.

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Low-tech Treatments for Acne Scarring: CROSS, Subcision, and Injectables

Vincent Richer, MD, FRCPC

Introduction

Dermatologists routinely treat acne with the objective of preventing acne scarring. Once control of acne has been achieved, our patients are often keen to improve textural skin changes such as atrophic acne scars. We often equate the management of atrophic acne scars with the need to reach for high-tech devices such as resurfacing lasers or radiofrequency-microneedling. While these modalities can play a pivotal role in resurfacing the skin, low-tech treatments can also be used in monotherapy or combination treatment to improve specific types of acne scars. In this article, we discuss the CROSS technique, subcision, and the use of injectables for acne scars.

CROSS Technique

CROSS is an acronym that stands for Chemical Reorganization of Skin Scars.[1] It is a technique whereby a chemical peeling agent is carefully placed at the bottom surface of an acne scar to increase collagen deposition and decrease scar depth. The putative mechanism of action is focal precipitation of proteins and coagulative necrosis leading to neocollagenesis.[1]

This technique is well-suited for ice-pick scars, which are notoriously difficult to treat with resurfacing

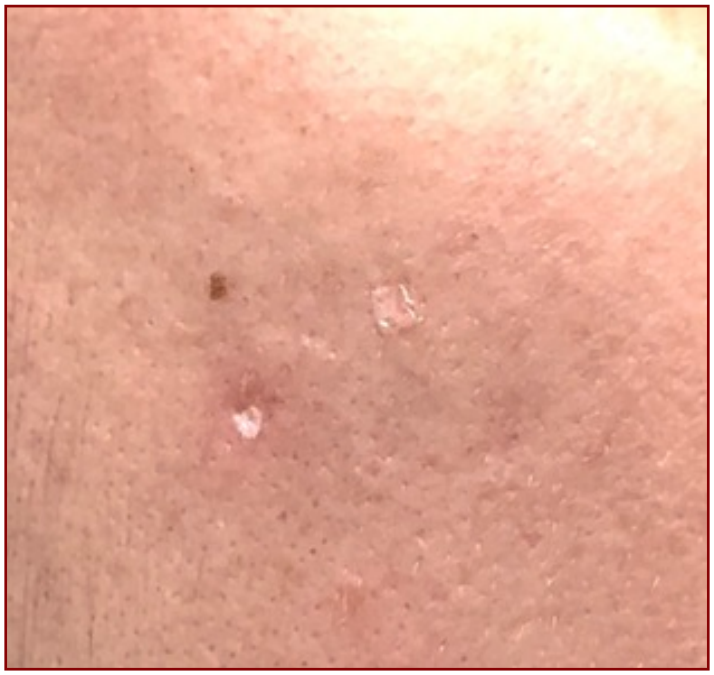

Figure 1. Frosting occurring seconds after application of 88% carbolic acid to ice-pick scars; *courtesy of Vincent Richer, MD, FRCPC*

modalities. Care must be exercised to avoid treating beyond the limits of the scar to avoid scar spread, the most concerning complication associated with this treatment. This can be done using a toothpick, split wooden cotton applicator or even the needle of an insulin syringe.[2]

The CROSS technique has been performed primarily using trichloroacetic (TCA) acid at concentrations of 50-100%.[3] Several concentrations and treatment protocols have been reported. Higher TCA concentration (100% vs 65%) and a greater number of treatment sessions (6 rather than 3) are associated with improved outcomes. Peel depth directly correlates with the concentration and amount applied. Patience must be exercised when using TCA, as the frosting reaction of the skin can take minutes to establish itself, and physicians must overcome the urge to reapply a thin coat quickly which may result in overtreatment. Local crusting occurs over 5-10 days.

Post-procedure hyperpigmentation is the most commonly reported side effect, especially in Fitzpatrick phototypes IV and V patients. Post-procedure erythema has also been very commonly reported, especially in fair-skinned patients. Post-procedure hypopigmentation was less commonly reported but is a significant concern in Fitzpatrick phototype VI patients for whom this procedure may not be well suited. The most dreaded complication of TCA CROSS is widening of the treated scar. Widening of scars is believed to occur when excess acid from the applicator spills over to surrounding tissue.

More recently, 88% carbolic acid has been used to perform CROSS technique. Carbolic acid is also known as phenol, a component of deep phenol-croton oil peels. By itself, phenol is a weaker peeling agent categorized as a medium-depth peeling agent. The literature suggests it may be a more forgiving agent when performing CROSS technique, with fewer instances of scar spread.[4] Carbolic acid/phenol is not recommended for large area/field treatment as it may be associated with hypopigmentation and cardiotoxicity.

In the author's practice, all CROSS technique treatments are now performed with carbolic acid 88%. After cleansing the skin, the treatment is administered using a very fine paintbrush, which enables even coating of the scar walls. Care is taken to ensure the brush is just barely imbibed with peeling agent. Frosting is quickly evident **(Figure 1)**, and within minutes dissipates to erythema that will evolve to crusting. Like TCA CROSS, carbolic CROSS can be used in monotherapy or in combination with other treatments

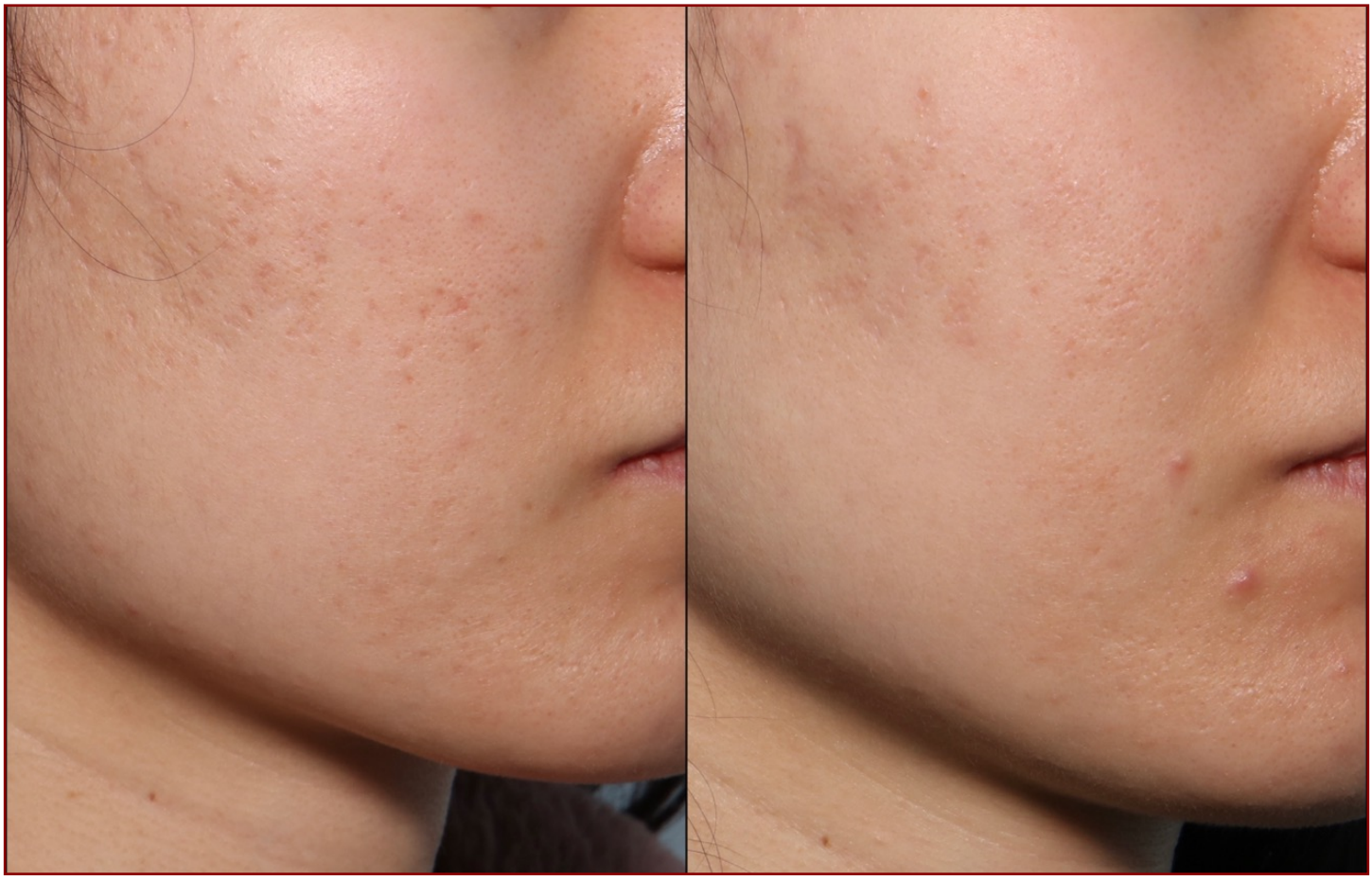

Figure 2. Ice-pick scars of the cheek improved after 4 treatments of carbolic CROSS; *courtesy of Vincent Richer, MD, FRCPC*

such as laser resurfacing. Several treatments are usually necessary, with 5-6 often needed to see significant change **(Figure 2)**.

Subcision

Subcision is a procedure whereby fibrotic strands beneath a scar are released mechanically with a needle, a cannula or another device. It is most relevant for treating rolling scars where tethering can be observed when the skin is pinched on clinical exam. Although it does not rely on sophisticated equipment, it is an uncomfortable procedure that does require a degree of anesthesia, usually local. One of the interesting advantages of subcision is the avoidance of post-inflammatory pigment alteration that may be seen with device-based resurfacing.

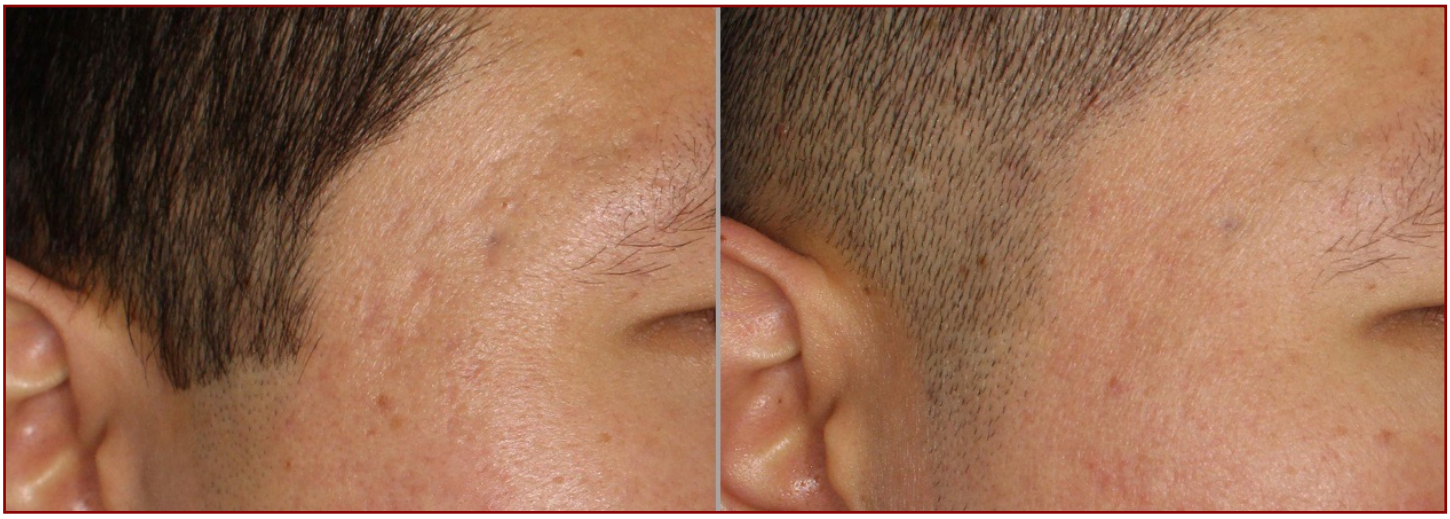

Figure 3. Improvement of rolling acne scars of the temple after 5 sessions of cannula subcision and 1550 nm fractional nonablative resurfacing; *courtesy of Vincent Richer, MD, FRCPC*

Figure 4. Rolling scars of the left cheek and left forehead treated with 2 sessions of injections with a low viscosity, low elasticity HA. Of note, this patient was very experienced with resurfacing laser treatments over the previous years and was very appreciative of the cosmetic correction with low downtime, despite its expected 6+ month outcome. Injecting the forehead with HA fillers is a procedure at risk of a vascular occlusion; *courtesy of Vincent Richer, MD, FRCPC*

Needle subcision is traditionally performed with a Nokor needle, which has a characteristically triangular tip. The needle is moved back and forth parallel to the skin surface once introduced under the scar to release underlying tethers. Cannula subcision is an interesting alternative to perform subcision over large areas.[5] After performing a small perforation in the skin with a larger gauge needle, a 22 or 19 gauge cannula is placed under the skin and pressed back/forth under the treatment area, parallel to the skin surface. Infiltration with local anesthesia can be performed to minimize pain. Often, clicking sounds are audible to the operator and to the patient as tethers are released. Practically, the procedure requires fewer punctures of the skin since the cannulas can reach larger areas. As with needle subcision, cannula subcision requires repeat treatment. Although cannula subcision punctures fibrotic tethers, rather than completely severing them, physician and patient satisfaction scores are similar for both procedures. Communication with the patient during the procedure is helpful in order to monitor pain as well as rare vasovagal symptoms. The "pushing and pulling" sensation of the procedure is one that the majority of our patients have never previously felt, and it may be very unusual to them. Other subcision tools have been used, such as surgical wires or blunt-blade instrument ("liberators").[5] Edema and erythema are common and expected side effects, while ecchymosis or hematoma are unusual following subcision.

In the author's practice, subcision is used in combination prior to laser resurfacing **(Figure 3)**. It enables enhanced scar improvement per treatment session without increasing the risk of hyperpigmentation that a more aggressive laser treatment may produce, especially for our patients with skin of colour.

Injectables

Rolling scars or lipoatrophy from acne scarring may be treated by injectables that aim at re-volumizing the skin. Traditionally called "dermal fillers," these treatments can include hyaluronic acid (HA) gels, polymethylmethacrylate (PMMA), poly-L-lactic acid (PLLA), and calcium hydroxyapatite (CaHa).

PMMA is the main injectable with an on-label indication for acne scarring. It consists of beads of PMMA within a carrier of bovine collagen. Consequently, it requires skin testing prior to treatment to test for sensitization to bovine collagen. Bovine collagen provides immediate and short-term revolumization, while PMMA beads subsequently trigger local synthesis of collagen from fibroblasts, leading to a long-lasting correction. Because these beads remain within the skin essentially permanently and PMMA does not have a reversal agent, development of delayed-onset nodules/granulomas or the occurrence of a vascular occlusion would be especially challenging to manage.

HA dermal fillers, with their rheological versatility and reversibility, are an attractive off-label alternative to treat rolling scars.[6] Although it may be tempting to use an HA with high viscosity/elasticity to maximize lift of the base of the scar, excess palpability of the filler can feel unnatural to patients. The "tower technique" has been described when treating rolling acne scars with fillers. It involves injecting a deeper depot of HA that is tapered off as the injection becomes more superficial. If significant fibrotic stranding/tethering is present within the acne scars, subcision prior to HA injection will be necessary. Dermatologists who inject HA fillers should be well aware of the expected recovery e.g., (pain, swelling, risk of bruising), as well as rare (delayed-onset nodules) and catastrophic (vascular occlusion) potential side effects.

In the author's practice, a very small amount of a low viscosity/elasticity HA filler is injected with a needle very superficially in rolling scars. Tangential lighting is used to highlight the treatment area and avoid missing subtle scars. Cannula subcision is performed prior if there is evident tethering when the scar is distended/manipulated. Follow-up 2-4 weeks later usually reveals significant correction of rolling scars **(Figure 4)**.

Biostimulatory fillers like PLLA and dilute CaHa[7] can readily revolumize areas and improve rolling scars, but may be more challenging to use focally. Silicone microdroplets have been reported to treat acne scarring, however this is off label and like PMMA may be associated with late complications that may be difficult to manage due to the permanency of the product. Novel injectable treatments for acne scars, such as tropoelastin, are actively being researched.

Conclusion

Treating acne scars can be as challenging as it is rewarding. Low-tech treatments such as the CROSS technique, cannula subcision and/or injectables can be effectively and safely used in monotherapy or in combination with resurfacing treatment modalities.

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Dermatology Treatments and their Effects on Patch Testing

Sophia Colantonio, MD, FRCPC

Introduction

Patients are often sent for patch testing to rule out allergic contact dermatitis, but it is a clinical conundrum of what to do when they are on systemic agents. The clinical question is, should the systemic agents be held for 4-5 half-lives and then patch tested to ensure there is no blunting of the immune system? The reality is that in this population without systemic treatments, patients are seldom clear enough to patch test. Their backs are covered in dermatitis and testing runs the risk of eliciting an uninterpretable "angry back". The other consideration is patients' strong preference to remain on systemic medications that control their significant itch, rash and associated sequelae. In an ideal world, it would best to patch test patients prior to the initiation of a systemic agent but clinically this is not always feasible.

We will explore various clinical scenarios involving patch testing and discuss the advice the dermatologist should provide patients regarding holding their medications.

Patch Testing on Topical Agents

Patients undergoing patch testing should avoid application of both topical corticosteroids and calcineurin inhibitors on their backs 1 week before patch testing.[1] There is a dearth of information on best practices for topical phosphodiesterase 4 inhibitors such as topical crisaborole and topical roflumilast, and recommendations for avoiding application to the patch testing site. All topicals can be used on areas that are not going to be patch tested before and during patch testing. For example, if a patient is due to be patch tested, they should be advised to stop using their topical steroid and/or topical calcineurin inhibitor on their backs. However, they can apply their topical medicaments to their hands, arms, face, chest, abdomen, legs, popliteal fossa, and feet.

Patch Testing on Phototherapy or a Tan

Tanning the skin from either phototherapy or sunlight suppresses the Langerhans cells responsible for antigen presentation. This can lead to false negatives for patch testing. It is recommended to avoid phototherapy or tanning the patch test site for 1-2 weeks prior to patch testing.[2] If patients have patch testing scheduled during the summer months it is important to remind them to avoid getting a tan on their backs. If they come for their patch testing session with

a tanned back, they will need to be reschedule to a later date in the Fall.

Patch Testing on Conventional Systemic Oral Agents

The conventional wisdom regarding patch testing on older systemic agents such as prednisone, methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine is to patch ideally during a drug holiday or at the lowest possible dose given that these agents have dose-dependent inhibition.[3] Patch testing done on doses of prednisone of 20 mg or greater will decrease the accuracy results. A randomized, double-blind, clinical cross-over trial (n=24) of patients with known allergic contact dermatitis to nickel showed significantly decreased reactions if patch tested while on prednisone.[4] A total of 25% of patching positive reactions to 5% nickel in petrolatum were lost while on 20 mg of prednisone.[4] However, a case study by Olupona and Scheinman[5] in 2008 found that patch testing at a dose of prednisone of 10 mg did not interfere with patch testing results.

Patch Testing on TNF-alpha Inhibitors, IL-12/23 Antagonists, Il-17 Antagonists, Il-23 Antagonists

When discussing novel systemic treatments, the greatest amount of evidence exists for both TNF-alpha inhibitors and IL-12/23, inhibitors given that these medications have been on the market the longest. Neither of them appears to affect patch test results.[3] There is only one case report of a patient patch tested on secukinumab 300 q monthly and low-dose methotrexate 10 mg q weekly who reacted to fragrances and sorbitan sesquioleate.[6] Allergic contact dermatitis can elicit T_H1, T_H2, T_H9, T_H17, and T_H22 responses. Various allergens such as nickel induce primarily a T_H1/T_H17 response.[7] Nickel allergy patients produce Il-23 in response to nickel stimulation.[6] Fragrance and rubber induce primarily a T_H2 response.[7] The case report of the patient reacting to fragrances given Il-17 inhibition is not surprising given the mechanism of action. The key question is whether or not Il-17 and Il-23s are blunting some reactions to select allergens such as nickel. Further studies on this matter are required.

Patch Testing on Il-4/13 Antagonists and Il-13 Antagonists

Dupilumab is being used as an off-label treatment for allergic contact dermatitis with good effect. Its onset of action is 1-4 weeks. A phase 4 clinical trial on 30 participants is underway to explore dupilumab's ability to treat patients with allergic contact dermatitis who have failed allergen avoidance.[7] The ability of dupilumab to effectively treat allergic contact dermatitis raises questions regarding its impact on patch testing results. There is debate in the literature regarding the accuracy of patch testing while on dupilumab.

A systematic review of 5 studies with 28 patients by Mufti et al.[3] found that 67.9% (n=19) of who had undergone patch testing before and after starting dupilumab 67.9% (n=19 patients) maintained positive reactions. The largest study in this systematic review was a retrospective chart review (n=23 patients) by Raffi et al.[8] conducted in 2020, with 125 patch test pairs done before and after initiating dupilumab therapy. Only 10.4% of reactions were lost after initiating dupilumab therapy. Of note, all 5 studies in the systematic review by Mufti et al.[3] were case reports/series or retrospective chart reviews that have a higher rate of bias.

To date, the best data on patch testing while on dupilumab therapy comes from Bocquel et al.[9] who conducted a prospective multicentre study in France between November 2020 and January 2022. It enrolled 76 dupilumab-treated patients who had undergone patch testing at least 4 months after initiating dupilumab. Data was collected at three visits: before, during and after patch testing. All patients were patch tested to the European Baseline Series (n=36) and some were also patched to an additional French series of allergens REVIDAL-GERDA (n=15). There was a total of 1230 paired allergens. A total of 83% of patch tests results were the same (either +/+ or -/-); 2.8% were positive on dupilumab therapy (-/+); 3.6% of reactions were lost on dupilumab therapy (+/-); and 10.6% of results were uninterpretable due to either angry backs or indeterminate reaction. This study did demonstrate good reproducibility of patch test results while on dupilumab therapy. This study provides the only high-quality prospective data on the impact of dupilumab on patch testing results.

The median time to no detectable concentration is 10-11 weeks for dupilumab 300 mg q2weeks[10] Withholding dupilumab for patients requiring the medication for a variety of indications such as concomitant atopic dermatitis, asthma, nasal polyps, and eosinophilic esophagitis requires entering into a risk-benefit discussion. Pausing dupilumab for 2.5 to almost 3 months for many patients is not feasible as their underlying diseases will likely flare and cause additional harm. Given the recent study by Bocquel et al.[9] discussed above, the benefit of holding therapy is minimal, leading to capturing only 3.6% reactions that would have otherwise been blunted due to dupilumab.

It is important for patients to understand the benefit of withholding dupilumab therapy given that the best data available appears to be minimal. It is my practice to patch test patients while on dupilumab as well as Il-13 antagonists. There is a lack of information on the impact of Il-13 antagonists given that they are relatively new to the market.

Patch Testing on JAK Inhibitors

There is only one case study to date that has been published on JAK inhibitor use during patch testing by Mainville et al.[11] The patient had previously undergone patch testing while on dupilumab and was positive to fusidic acid +2, amerchol L 101 +3, thiuram +1, 4-tert butylphenol formaldehyde resin +1, corticosteroid mix +1, budesonide +1, betamethasone-17-valerate +1, clobetasol-17-propionate +1, dexamethasone-21-phosphate disodium, desoximethasone +1, betamethasone dipropionate +2 and methylprednisolone aceponate +1. When the patch testing was repeated when the patient was being treated with upadacitinib, only fusidic acid +2 and amerchol L 101 +3 remained positive (both at the same reaction levels as during testing while being treated with dupilumab).

Upadacitinib has a short half-life of 8-14 hours.[12] Considering the higher range of the half-life to be 14 hours it would take 70 hours, almost 3 days, to reach a clearance of 5 half-lives. My current practice in the patch testing clinic is, if possible, to discontinue JAK inhibitors 3 days before patch testing and to resume treatment immediately after the final patch testing readout. In many cases, patients either forget to stop taking their JAK inhibitor, or are not counselled to discontinue the medication 3 days before patch testing. In these instances, I discontinue the JAK inhibitor the day of patch testing and resume it immediately after the final readout. I have had a few instances where the patient referred for patch testing does not want to discontinue their JAK inhibitor due to the risk of eliciting a severe flare of atopic dermatitis. In these cases, I try to reduce the dose of their JAK inhibitor to the lowest dose possible (e.g., upadacitinib 15 mg po daily or abrocitinib 50 or 100 mg po daily). I still proceed with patch testing in these individuals. The patient and I have a detailed discussion that their JAK inhibitors may reduce the accuracy of the testing. They will likely experience a downgrading of reactions such as +3 to +2, a +2 to +1, or +1 to an equivocal or negative reaction. However, does it truly matter in a clinical setting if we are losing these weaker reactions? Presumably, the JAK inhibitor is doing its job and these weak allergens are not contributing to the patient's ongoing flares. The allergen is still able to elicit a positive reaction, albeit an attenuated one, while on JAK inhibitors; it is likely still relevant to the patient's ongoing flares. Additional studies are needed in this area to further elucidate this matter.

Conclusion

This paper provided real-world insights on how a dermatologist should counsel a patient who is about to undergo patch testing with respect to their topical and systemic treatments.

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