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WHAT'S NEW IN PEDIATRIC DERMATOLOGY?

A literature review was performed from January to December 2019 to describe what's new in pediatric dermatology. This article is not a comprehensive review, it is meant to present new developments that may influence daily Canadian dermatology practice.

Newborns

#MeToo – No more Mongolian spots

Do you know where the term "Mongolian spot" comes from? In the 1770s, the concept of race was introduced, and within that framework, Mongolians were considered a degeneration of the original Caucasian race to a new natural environment. Mongolian spots were first described in the Western medical literature in 1885 and quickly became recognized as a sign of racial inferiority. The full background of the term is described in an Art and Practice article in Pediatric Dermatology,[1] but knowing this brief history, the medically accurate term congenital dermal melanocytosis should be preferentially be used. Politely correcting colleagues and explaining the origin of the Mongolian spot are appropriate.[2] Though generally benign, extensive and progressive congenital dermal melanocytosis can be associated with an underlying lysosomal storage disease, and should be considered in patients who also have a developmental delay.

Subcutaneous fat necrosis and hypercalcemia

Though uncommon, subcutaneous fat necrosis of the newborn is often clinically impressive (red-violaceous hot tumors), prompting an urgent dermatology consult. Most textbooks recommend monitoring for hypercalcemia for 6 months. A systematic review of 94 studies found that the majority of reported cases developed hypercalcemia in the first month of life (57%), and in a further 30% of cases it was detected within the first 2 months.[3] In three quarters of patients, hypercalcemia resolved within 28 days of its detection. The authors recommend screening for hypercalcemia with total and ionized calcium at diagnosis then 30, 45, and 60 days following resolution of skin lesions in the asymptomatic child. Families should be counselled about symptoms of hypercalcemia that would prompt early reassessment (irritability, vomiting, polyuria, neurologic symptoms/seizures).

Skin care for preterm infants

Because the stratum corneum does not develop until the late 3rd trimester, the skin barrier is compromised in preterm infants. Evidence-based recommendations for the NICU include tub bathing instead of sponge bathing to reduce temperature instability, air drying the umbilical stump rather than antiseptic cleansing, and avoidance of petrolatum due to an increased risk of candidemia and coagulase-negative Staphylococcus infection in developed countries.[4]

Birthmarks

Infantile hemangiomas

The American Academy of Pediatrics published clinical guidelines on the management infantile hemangiomas in January 2019.[5] Referral of problematic infantile hemangiomas before 1 month of age is ideal *(Table 1)*, with oral propranolol at 2 to 3mg/kg per day for at least 6 months (and usually until 1 year of age) as the treatment of choice. For small, thin, superficial infantile hemangiomas, topical timolol (0.5% gel forming solution or solution, 1 drop massaged into lesion BID) can be effective. Timolol is significantly more potent than propranolol, so caution is advised in large or ulcerated lesions as there is systemic absorption, with recommendation for maximal use of 1 drop per kilogram of patient's weight per day[6] though 1 drop BID is the safest option.[7] Families should be warned to hold timolol application if the child is ill to avoid hypoglycemia.

Nadolol is preferred in some Canadian centres because it does not cross the blood-brain barrier and has less risk of sleep disruption or potential developmental consequences.[8] Nadolol was recently linked to the death of a 17-week old child treated with nadolol at the usual dose of 2mg/kg per day who did not have a bowel movement for 10 days, with speculation that there was increased reabsorption and enterohepatic recirculation because unlike propranolol that is hepatically metabolized and renally excreted, nadolol is excreted via the biliary system or remains in the feces unchanged.[9]

Table 1. Problematic infantile hemangiomas (from Krowchuk et al.) [5]

1. Potential for disfigurement (most common reason for treatment)
   - Segmental on face or scalp
   - Facial >2 cm, or any size on nasal tip or lip
   - Scalp > 2cm
   - Neck, trunk or extremity > 2cm
   - Breast in females
2. Life-threatening complications (beard area, > 5 cutaneous IH)
3. Functional impairment
4. Ulceration
5. Underlying abnormalities

Genetics and targeted therapies

GNAQ mutations were previously identified in blue nevi and uveal melanoma in 2009, and in isolated capillary malformations and Sturge Weber syndrome in 2013. Since that time, GNA11 and GNAQ mutations have also been identified in phakomatosis pigmentovascularis,[10] where the phenotypic outcome of the mutation is seen in both endothelial cells and melanocytes, and now also in cherry angiomas.[11]

The phosphoinositide-3-kinase, catalytic, alpha polypeptide (PIK3CA)-related overgrowth spectrum (PROS) encompasses a broad spectrum of rare mosaic overgrowth disorders, and includes CLOVES – congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis or spinal deformities. Many PROS patients were diagnosed in the past as having Proteus syndrome. Targeted therapy for PROS with a PIK3CA-specific inhibitor taken from the cancer literature, BYL719 (alpelisib), has been reported to improve all the features of PROS including vascular tumors, hypertrophy, congestive heart failure, and scoliosis.[12,13]

Porokeratosis has been associated with heterozygous germline mutations in the mevalonate pathway (MVK, PMVK, MVD, FDPS), an end product of which is cholesterol. Porokeratosis lesions develop when a somatic second hit occurs. Loss-of-function mutations lead to cholesterol deficiency and may also result in built up of toxic proximal intermediates in the pathway, both of which may contribute to development of a porokeratosis lesion. A topical 2%lovastatin-2%cholesterol ointment applied BID with occlusion for the first 2 weeks produced significant improvements in familial and linear porokeratosis patients' lesions at 6 months,[14] consistent with previous efficacy of this treatment in CHILD syndrome.[15]

Mek-inhibitors for congenital nevi

Mir and colleagues reported a case of child with a giant congenital melanocytic nevus and neurocutaneous melanosis with a novel AKAP9-BRAF fusion that responded to trametinib.[16] The patient suffered from severe disfigurement and intractable pruritus and surgery was not an option. Biopsies from lesional skin were tested for activating mutations in NRAS, BRAF, and PIK3CA (all negative) then put through an extended sequencing panel for activating mutations where the fusion was uncovered. AKAP9-BRAF fusion produces a kinase that lacks regulatory domains, resulting in constitutive BRAF activation. BRAF-activating alterations have been suggested to confer sensitivity to MEK inhibition, thus trametinib was trialed. Impressive improvements in the patients quality of life and appearance of the nevus are documented *(see Figure 1 in Mir et al).*

Atopic dermatitis

Pharmacists, patients, and being 'natural'.

A Singaporean group trialed a pharmacist-led eczema counselling service and found that parents were highly satisfied with the service and that parents' eczema knowledge improved.[17] The pharmacists involved in the study had been trained by pediatric dermatologists and attended pediatric dermatology clinics for extended periods of time, suggesting an opportunity in Canada for improved pharmacist eczema education and collaboration with broad benefits.

An international social media survey of caregivers by Global Parents for Eczema Research found that only 55% used their eczema medications as prescribed.[18] Trust in the treating physician was highly associated with following prescriptions; concerns about adverse effects, resolution of symptoms, and lack of efficacy were associated with non-compliance. Though the survey captured responses from only a small fraction of the global eczema population (N=86), the results may be helpful to inform the counselling we provide to patients about their treatment plan.

Many patients seek 'natural' alternatives for emollients, perceiving them to be more wholesome and less likely to contain irritants or chemicals.[19] The data in a nicely summarized Pediatric Dermatology review suggests that olive oil may decrease skin barrier function and actually be detrimental to atopic dermatitis, while virgin coconut oil and high-linoleate sunflower oil may have anti-inflammatory and antimicrobial activity. There is insufficient evidence to recommend use of natural oils for moisturization, but in patients/families who insist on a natural alternative, olive oil should be discouraged.

The "Schachner Ladder" for topical treatment

Lawrence Schachner, one of the founders of pediatric dermatology in North America, has published on and advocates strongly for a maximum 3-day duration of treatment with a moderate potency topical steroid to maintain active parental/caregiver engagement.[20] The Shachner Ladder[21] is based on routine use of emollients and topical steroids, starting with the most potent topical steroid and tapering down every 3 to 5 days while maintaining a target of eczema control. For example, a patient with severe eczema would use clobetasol ointment for 3 days, betamethasone valerate 0.1% ointment for 3 days, desonide ointment for 3 days, then transition to a topical calcineurin inhibitor (TCI) or phosphodiesterase-4 inhibitor (PDI) to recurrent areas. Interestingly, the authors suggest introducing the TCI/PDI from the beginning of the ladder to treat the same areas that will receive treatment with the topical corticosteroid ladder to encourage the development of maintenance treatment habits. This combination therapy may also decrease the irritation that can be associated with TCI/PDI use though the authors do not specifically address this issue.

Methotrexate in AD

Children's Hospital of Pennsylvania performed a retrospective chart review of 55 patients with severe AD treated with methotrexate (0.37-0.50mg/kg weekly).[22] About 75% of patients' eczema improved (mean IGA at baseline 4.18, at 6-9 months 2.94) with the majority of improved patients achieving that improvement within 2 months. Half of the patients had minor side effects – the most common being GI upset.

Omalizumab for severe AD in children

This UK-based randomized clinical trial enrolled 62 patients 4-19 years of age with severe eczema (SCORAD >40) into either treatment with omalizumab (total IgE and weight-based, like asthma dosing) or placebo for 6 months.[23] The median baseline IgE level in this study was 120 times the upper limit of normal. Roughly three-quarters of patients had coexisting food allergies and rhinoconjunctivitis, and one third had asthma. At week 24, there was a significantly greater reduction in SCORAD (primary endpoint) and EASI for the omalizumab group. In contrast to 2 previous RCTs that did not show treatment response to omalizumab,[24,25] this larger study population was homogeneously severely atopic children. The small difference in SCORAD between the placebo and omalizumab treatment groups coupled with the negative results from previous studies suggest omalizumab is not effective in treating AD. Patients with lower baseline IgE responded better to omalizumab suggesting that neutralization of IgE plays a role in response to treatment. These results are interesting for the pediatric eczema patient with severe eczema, allergies, and asthma. In the future, possibly higher doses of omalizumab or the higher-affinity anti-IgE ligelizumab might be even better options for this specific subset of highly atopic pediatric patients.

Off- and On-Label Dupilumab

Elaine Siegfried and colleagues published a practical guide to off-label access and dosing of dupilumab in pediatric atopic dermatitis patients.[26] For patients < 12 years old, who remain off-label for dupilumab's current Canadian indication at the end of 2019, they provide dosing suggestions based on collective experience and expertise. In brief, patients 6-11 years old >30kg would be loaded with 400mg and maintained at 200mg q2weeks; if < 30kg, 200mg loading and 100mg maintenance is recommended. For patients less than 6 years old, they did not give dosing recommendations. This built on a previous case series that recommended adult doses for patients > 40kg and half doses for patients < 40kg, in patients 7 years or older.[27] A very recently published multicenter retrospective review of 111 dupilumab-treated children showed experienced pediatric dermatologists use loading doses of 5-8mg/kg and maintenance doses of 2-7.2mg/kg in the youngest age group 0-5 years old.[28]

Other useful tips from Siegfried et al's publication include a proviso to include on insurance forms that require use of other

medications before dupilumab approval: "Your denial to support this treatment and thereby expose this patient to other less well-studied, and potentially higher-risk second line agents offers no added potential benefit, and is not supported by any current evidence-based guidelines. Your attempt to enforce general, age-based criteria without regard to the extenuating factors in this case is essentially the practice of medicine by an organization." and a model informed consent statement for caregivers/ patients to sign acknowledging that they are aware they are on off-label treatment.

Dupilumab was granted Health Canada approval for adolescents in September 2019, based on the results of the pivotal trial that was published in JAMA Dermatology in November 2019.[29] Approved dosing for 12-18 year old patients is the same as adult dosing for patients > 60kg (ie. 600mg loading dose then 300mg q2weeks) and for patients <60kg, 400mg loading dose followed by 200mg q2weeks.

Psoriasis

An interesting cross-sectional analysis from the Danish National Birth Cohort found recurrent tonsillitis to be associated with pediatric psoriasis, though the temporality of the association could not be confirmed.[30]

The AAD and National Psoriasis Foundation published guidelines for the management and treatment of pediatric psoriasis.[31] Dermatologists are key players in the management of pediatric psoriasis as quarterbacks for primary and specialist care of associated comorbidities. Unique to children is the opportunity to intervene early to minimize the impact on the child's emotional-psychological development in the context of their visible skin difference and the limited number of therapeutic options that often result in off-label use of medications for severe pediatric psoriasis.

Accompanying the above guidelines published in the JAAD was a practical Canadian expert guide to managing pediatric psoriasis with biologics.[32] Particularly useful content in this manuscript included Table 3. Baseline screening and monitoring for systemic biologics and Figure 1. Treatment algorithm for moderate to severe plaque psoriasis.

Infections and infestations

Lice treatment

A systematic review and meta-analysis of 16 studies (N=1779) found occlusive agents (dimeticone, isopropyl myristate, petroleum products, natural oils) to have a higher cure rate for lice than neurotoxic agents (permethrin, pyrethin).[33] The Canadian Pediatric society recommends permethrin and pyrethins as first-line treatments, despite increasing permethrin resistance, but occlusive agents can be considered a viable alternative. Commonly available occlusive products in Canada include Resultz (isopropyl myristate/ ST-cyclomethicone solution) and Nyda (dimeticone solution).

Hyperpigmentation in children with fever and rash returning from travel

Generalized hyperpigmentation after a febrile maculopapular eruption 3-8 days prior has been reported in infants with Chikungunya fever.[34] The chik sign, brown-black pigmentation involving the nasal tip, was present in all 12 reported patients. A recent case report raised the possibility that the chik sign might also be seen in Dengue fever.[35] In Canadian families returning from topical countries, particularly during monsoon season when mosquito breeding increases, sudden-onset generalized pigmentation in a child should raise the possibility of this diagnosis. In contrast, adults do not develop centrofacial/ neck pigmentation until weeks after Chikungunya fever. Chikungunya IgM and IgG antibodies can be tested to confirm the diagnosis and are usually present within a week.

TEN, SJS, and MIRM

TNF inhibitors were rapidly effective in 2 case reports of pediatric TEN – the first triggered by carbamazepine and treated with etanercept 50mg sc after dexamethasone 1mg/kg and cyclosporine 3mg/ kg failed to arrest progression,[36] the second triggered by Mycoplasma pneumoniae and treated with a single dose of infliximab 5mg/kg.[37]

Efficacy of TNF inhibitors for Mycoplasma pneumoniae-related reactive disease is particularly interesting in light of the emergence of an increasing number of cases of MIRM (Mycoplasma pneumoniae-induced rash and mucositis). MIRM can also be triggered by other respiratory infections including influenza B reported in a case series this year,[38] so the concept is evolving towards reactive infectious mucositis and rash. Initiation of cyclosporine 3-5mg/kg/d early in the course of severe MIRM may reduce severity and decrease length of hospital stay,[39] but etanercept or other TNF inhibitors could be an equally effective option.

Skin tumors

Spitzoid proliferations.

A retrospective cohort study of pediatric patients at Boston Children's Hospital over an 18 year period found that the majority of the 622 lesions biopsied were typical Spitz nevi (82.3%).[40] Atypical Spitzoid proliferations accounted for 17.2% of lesions biopsied and there were 3 melanomas (0.5%). Typical and atypical Spitzoid proliferations were biopsied around 7 years of age, while the average age of the Spitzoid melanoma patients was 17.2 years. The authors recommend not excising typical-appearing, dermoscopically bland Spitz tumors in the absence of other worrisome features. They recommend that patients be referred to a dermatologist for appropriate assessment, rather than non-expert providers sampling or directly referring for excision. Previous studies have recommended q6monthly follow-up for 2-3 years or until the lesion stabilizes. For patients with atypical Spitz tumors, recommendations include expert dermatopathology consultation and regular clinical monitoring with clinical lymph node examination.

Multiple pilomatricomas

Multiple pilomatricomas can be associated with underlying syndromes including myotonic dystrophy, familial adenomatous polyposis-related syndromes (i.e. Gardner syndrome), Turner syndrome, Kabuki syndrome, or Rubinstein-Taybi syndrome. A comprehensive literature review identified 66 cases and concluded that in the presence of 6 or more pilomatricomas, an associated syndrome should be sought (>95% specificity).[41]

Say 'no' to slime

Slime, also known as 'flubber' or 'gak', is a new fad in 'tweens' worldwide and has resulted in a flurry of publications on slime-induced pediatric hand dermatitis. Homemade slide can be made from white craft glue and borax or another activator substance that crosslinks glue polymers. Children customize their slime recipe with glitter, shaving cream, shampoo, cornstarch and food colouring to name only the most common additives (and potential sources of allergens). Borax and other irritants disrupt the skin barrier and predispose to sensitization. Implicated allergens on patch testing have included MCI/MI, fragrance, parabens, sodium lauryl sulfate.[42-49]

Tips – a rapid summary of pearls for pediatric dermatology practice

Vibration anesthesia using an electric toothbrush in the finger of a disposable glove (bristle side of the brush against the skin) is an economical alternative to the Buzzy-Bee or other purpose-made devices to reduce the pain of injections or cryotherapy.[50]

Nail braces consisting of an adhesive or a wire and adhesive apply upward tension on the nail plate. In a case series of 38 pediatric patients, nail brace application led to good responses in ingrown nails by 16 weeks in most patients, with rapid relief of pain.[51]

Umbilical granulomas treated with in-office application of table salt followed by surgical adhesive tape for 24 hours resulted in complete resolution and no complications in a series of 17 infants.[52]

A teenaged female developed severe methemoglobinemia after applying topical 7.5% dapsone gel daily to her face, chest, and back for 2 weeks.[53] Her serum dapsone level was nearly twice the upper limit of normal steady-state concentrations for patients taking 200mg of oral dapsone daily.

Distraction kits are common in pediatric hospitals but might be underutilized in the dermatology community. A publication in Pediatric Dermatology describes how to compile a distraction kit

and highlights its value.[54] Specific distraction tools to consider include bubbles, fidget spinners, Find-it books, glitter wands and light spinners, vibration therapy, music and electronic tablets.

Topical sirolimus 1% ointment was used to treat a 5-year-old boy with benign cephalic histiocytosis involving the face, trunk, and extremities. To test its efficacy, a split-face model was used for the first 6 weeks until it was determined to be effective.[55]

Both the JAAD and Pediatric Dermatology published comprehensive reviews on dermatologic care of sexual minority patients this year. Their content is somewhat overlapping but very relevant and necessary to provide appropriate and respectful care to the broad patient population.[56-59]

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