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# CANADIAN DERMATOLOGY TODAY

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**BIOLOGIC TREATMENT AND PSORIATIC ARTHRITIS: A REVIEW FOR THE DERMATOLOGIST**
Marisa G. Ponzo, MD, PhD, FRCPC

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# EDITORS WELCOME

Dear Canadian Dermatology Community,

It is with great pleasure that we welcome and introduce you to the inaugural issue of *Canadian Dermatology Today*. As disease management becomes more complex and as we have more therapies in our arsenal, it is becoming even more important to communicate best practices and techniques across the clinical community.

This peer-to-peer initiative, written by Canadian dermatologists, is meant to serve as an educational and informational resource for all dermatologists across the country. We do sincerely hope you enjoy this first issue and we look forward to your readership and your ideas for future articles as we grow and expand the reach of this new journal!

Best wishes,

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



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## ABOUT THE AUTHOR



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Aaron Drucker is a dermatologist, clinician scientist and assistant professor at the University of Toronto and Women's College Hospital. He went to medical school at Queen's University (Canada) and did residency at the University of Toronto before completing a Master's and Research Fellowship in Clinical and Translational Research at Brown University. His research focuses on atopic dermatitis epidemiology and evidence-based clinical practice.

# COMORBIDITIES IN ADULT ECZEMA: WHAT'S REAL? WHAT MATTERS?

The observation that psoriasis may be an independent risk factor for myocardial infarction (MI) most famously elucidated in a population-based study from the UK published in JAMA,[1] has been followed by a steady flow of studies on comorbidities of dermatologic diseases.

Psoriasis, atopic dermatitis (eczema), hidradenitis suppurativa, alopecia areata and more have been studied in relation to various extracutaneous comorbidities. Eczema, in particular, has been studied in relation to mental health and sleep disorders, cardiovascular disease and osteoporosis and fracture risk. In this article, I will review the evidence for selected adult eczema comorbidities and provide an opinion on whether each of them might change the way we manage patients. In other words, do they matter?

**Sleep disorders**

Large population-based studies in the US have shown that adults with eczema have three times the rates of insomnia compared with the general population.[2] It makes sense, then, that they also have increased rates of daytime sleepiness and fatigue. Studies have shown that this poor sleep has other consequences; namely that the combination of eczema with sleep disruption has been associated with poor self-ratings of overall health and increased rates of injury.[2,3] These findings make sense clinically. Many of my patients with eczema report that their itch is worse at night, leading to nocturnal scratching and difficulty falling asleep, as well as nighttime wakenings. This leads to fatigue and a general sense of feeling unwell. Additionally, poor sleep and fatigue could lead to decreased concentration and an increased propensity to injury.

In short, sleep disruption in patients with eczema matters. We should ask our patients when we see them in the clinic about their sleep as a secondary measure of disease control. It is part of standardized assessments of eczema symptoms such as the Patient-Oriented Eczema Measure (POEM),[4] but clinicians may opt instead to ask the simple question: "how has your sleep been lately?" In either case, the more formal assessment-method or the routine questioning can both help to illuminate sleep issues that may be impacting our eczema patients. The good news is that for patients whose sleep is adversely impacted by their eczema, we can help. Clinical trials have shown that when eczema is treated effectively, sleep improves as well.[5,6]

**Depression**

The association between eczema and depression is one of the best established and replicated comorbidities. In a meta-analysis, atopic dermatitis was associated with twice the odds of depression compared to controls.[7] We conducted a case-control study of the risk of suicide associated with eczema using population-based data from Ontario and found that having persistent eczema, defined as five or more physician visits for eczema within 5 years, was associated with a 20% increased risk of dying from suicide compared to the general population.[8] Further, we found that, in the month before their death, two-thirds of eczema patients who died from suicide had visited a physician and 13% visited a physician specifically for their skin condition.

Depression, like sleep disruption, can be thought of as a comorbidity and as a symptom of the disease itself. The constant itch and poor sleep experienced by people with severe eczema can lower mood in the absence of a clinical diagnosis of major depressive disorder. Along those lines, in clinical trials, depressive symptoms improve when eczema improves.

We should assess our patients' affect and mood in clinic, and if there is low mood, assess for risk of self-harm. This can be done informally or using validated tools like the 2-question PHQ-2.[9] If, after this assessment, we are concerned, coordinating care with the patient's family doctor and/or directing them to emergency care may be warranted.

**Cardiovascular disease**

Cardiovascular disease and its risk factors are considered to be more controversial comorbidities associated with eczema. A systematic review of the association between eczema and cardiovascular disease found significant heterogeneity between studies, including cross-sectional, case-control and cohort studies, with some studies showing an increased risk and others showing a decreased risk for cardiovascular outcomes like myocardial infarction and stroke.[10] A more recent meta-analysis found that when limiting to cohort studies (the best study design for this research topic), there was an increased risk of cardiovascular outcomes associated with eczema such as an increased risk of myocardial infarction (n = 4; relative risk [RR], 1.12; 95% CI, 1.00-1.25), stroke (n = 4; RR, 1.10; 95% CI, 1.03-1.17), ischemic stroke n = 4; RR, 1.17; 95% CI, 1.14-1.20), angina (n = 2; RR, 1.18; 95% CI, 1.13-1.24), and heart failure (n = 2; RR, 1.26; 95% CI, 1.05-1.51. This same meta-analysis found that increasing atopic eczema severity was associated with increased risk of cardiovascular outcomes.[11] However, these observational studies all suffer from confounding and other biases, which may temper our interpretation of the results. Additionally, even in well-done cohort studies that have found an association between severe eczema and cardiovascular disease, the absolute risk has been low, on the order of 25 extra strokes per 100,000 person-years with eczema.[12]

Explanations for a potential association between eczema and cardiovascular disease include a systemic inflammatory state, decreased exercise due to the risk of eczema flares with sweating and heat and other lifestyle factors such as obesity and smoking. Eczema has been associated with increased rates of obesity and smoking, with positive associations seen in multiple meta-analyses.[13,14] However, those associations do not correlate with my own clinical experience.

In my opinion, either eczema is not a true cardiovascular risk factor, or it is a very minor and not clinically actionable one.[15] As such, I believe eczema patients should receive age-appropriate cardiovascular risk screening and treatment without any modification related to their skin disease. In patients who are overweight or who smoke, a healthy lifestyle should be encouraged independent of their eczema.

**Osteoporosis and fractures**

Associations between eczema and bone health are less well-studied. We conducted a systematic review (in press) and found 15 studies on the topic; unfortunately, most were cross-sectional and of poor-quality. Recently, though, a large cohort study using data from the UK was published which found eczema to be associated with an increased risk for various types of fractures commonly associated with osteoporosis, including an increased risk of hip (HR, 1.10; 99% CI, 1.06-1.14), pelvic (HR, 1.10; 99% CI, 1.02-1.19), spinal (HR, 1.18; 99% CI, 1.10-1.27), and wrist (HR, 1.07; 99% CI, 1.03,-1.11) fractures.[16] As with cardiovascular disease, the risk was accentuated in people with more severe eczema. Severe eczema was associated with double the risk for spinal fractures and 1.5 times the risk for hip fractures compared with the general population.

There are many potential reasons for an association between eczema and poor bone health and fractures. Poor sleep leading to fatigue could increase the risk for injury overall. Systemic inflammation associated with severe eczema could lead to aberrant bone turnover. My suspicion is that the relationship seen with severe eczema may relate to intermittent treatment with systemic corticosteroids such as prednisone. Systemic corticosteroids, which are known to increase fracture risk, are often prescribed for eczema despite recommendations to limit their use.[17]

While the association between eczema and fractures is poorly understood, taking a general medical history including, history of fractures is worthwhile, as is assessing previous and current use of systemic corticosteroids. If there is a significant history of systemic steroid use, a referral for bone mineral density testing or fracture preventive treatment may be indicated.

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| Comorbidity | Clinical takeaways |
|---|---|
| Sleep disorders | • Ask patients about the effect of eczema on their sleep<br>• Effective treatment can improve sleep |
| Depression | • Assess patient's mood in clinic<br>• Assess for self-harm in clinic |
| Cardiovascular disease | • No specific action required<br>• Patients should have age-appropriate screening as in the general population |
| Osteoporosis and fractures | • Ask about history of systemic corticosteroid exposure<br>• Refer for bone testing or fracture prevention if indicated |

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Dr. Ramien is a hospital-based academic dermatologist at the University of Calgary. Since completing a fellowship in Pediatric Dermatology in 2014, Dr. Ramien has maintained both pediatric and general dermatology practices. She is active in teaching for residents, in particular in the DRIVE program, and in research, where she leads projects on severe cutaneous reactions and eczema education in children. She volunteers as a co-chair on the board of directors for Camp Liberté and an associate editor for the Journal of Cutaneous Medicine and Surgery.

# 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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# THE BELTLINE AND BEYOND: A REVIEW OF MINIMALLY INVASIVE BODY CONTOURING MODALITIES

Body contouring refers to the use of surgical or non-surgical interventions to modify the shape of the body, most commonly targeting adipose tissue. While tumescent liposuction is the most popular means of body sculpting, there is rapidly growing interest in minimally invasive body contouring technologies[1,2]. These include cryolipolysis, laser therapy, radiofrequency, ultrasound, and High Intensity Focused Electro-Magnetic Technology (HIFEM).

The following report will review treatment classes, their mechanism of action, treatment protocols and potential adverse events.

## Cryolipolysis

Cryolipolysis borrows the concept of cold-induced panniculitis, delivering targeted, controlled cooling to the subcutaneous layer to induce selective adipocyte apoptosis[3,4]. Histological assessment shows cool-induced adipocyte damage peaks at 14 days and is subsequently cleared by macrophages through an inflammatory process which lasts up to 3 months[2,3,5]
The most commonly used technology in North America is CoolSculpting® (ZELTIQ Aesthetics, Inc., Pleasanton, CA, USA), approved for treatment of the flanks, abdomen, submentum, upper arms, bra fat, and medial thighs[2,5]. Subcutaneous fat is cooled to -10°C for 35 to 60 minutes based on the anatomic area. Fat reduction ranges from 14-25.5% per treatment[6-8]. Localized areas of fat accumulation tend to respond better given the nature of the applicator[2].Treatment response is typically seen at 3 weeks post-procedure but may continue for up to 6 months[3]. Cryolipolysis is overall well tolerated. Initial cold-associated discomfort subsides after 5-10 minutes of treatment[9]. Erythema, edema, ecchymosis and delayed onset pain may occur post-treatment lasting from a few days to weeks[9]. Rare side effects such as paradoxical adipose hyperplasia (PAH) occur in 0.0051-0.021% of cases but may be underreported[10,11]. There is a disproportionate number of cases among Hispanic males seeking abdominal and chest treatment, potentially related to anatomic sexual dimorphism[11].

Cryolipolysis provides an effective treatment option for fat reduction with high levels of patient satisfaction[12]. Skin laxity may improve through normal elastic recoil properties but more commonly a secondary intervention is required to address skin laxity[13].

## Laser-assisted Lipolysis

Laser-assisted lipolysis uses a 1060-nm diode laser that triggers heat-mediated inflammation to induce adipocyte apoptosis (SculpSure® Cynosure, Westford, MA, USA). Treatment temperatures selectively target adipocytes at 42-47°C which disrupts cell membrane integrity and fat is eventually cleared from the interstitial space[14,15]. The device's contact cooling system is necessary to preserve the integrity of the skin and adnexae, preventing potential thermal complications[2].

Laser lipolysis is indicated for fat reduction of the abdomen, flanks and submentum – it does not address skin laxity. The ideal treatment duration for 1060-nm is targeted to 20 and 25 minutes to avoid undertreating, or subcutaneous nodules if heated too long[2]. Slimmer abdomens and pinchable fat respond best to treatment with reduction of 11.5% reported with a single treatment[2]. Anecdotally, patients require 1-3 sessions with improvement seen 3 months post-procedure[2]. Tolerability is favourable - mild to moderate tenderness lasting up to 2 weeks is common[16].

## Magnetic Resonance Contouring

High intensity focused electromagnetic technology (HIFEM) is the newest technology for body contouring, inducing fat reduction and potentially improving muscle thickness, strength and tone[17].

HIFEM technology was initially approved for contouring of the abdomen and buttocks (EMSculpt®, BTL Industries, Inc., New York, NY, USA). Electromagentic energy is used to stimulate 20 000 supramaximal muscle contractions during a 30-minute treatment session[18,19]. The high level of contractions may stimulate lipolysis which releases a large amount of tissue-damaging free fatty acids into the surrounding fat to induce adipocyte apoptosis[20] demonstrated by a 91.7% increase in the adipocyte apoptotic index in 120 histologic samples[18].
The major differentiator with HIFEM technology is the resultant effect on muscle tissue. A recent study showed an 18.6% reduction of adipose tissue thickness, 15.4% increase in rectus abdominis muscle thickness, and 10.4% reduction in diastasis recti[18]. Positive results have also been reported for gluteal toning and lifting as well as with a secondary device (Emsella®, BTL Industries, Inc., New York, NY, USA) for urinary incontinence[19,21].

Treatment protocols include a minimum of four 30-minute sessions over 2 weeks and a single maintenance treatment session performed every 3 to 6 months[18]. Treatment is well tolerated with rare reports of painful, gripping muscle contractions or brief electric shocks[18]. Contraindications to treatment include pregnancy, metal or electronic implants.

The ideal HIFEM patient has not been established. Patients who respond best to treatment typically have a low to medium BMI and less than 2.5cm of pinchable fat[18,19]. This is likely due to the distance between the EM coil and target tissue[18,19]. It is unclear if HIFEM is suitable to treat visceral fat. Lastly, skin laxity is not targeted with HIFEM technology.

**Radiofrequency**

Radiofrequency treatment is most commonly associated with skin tightening, and more recently, fat reduction[22]. Volumetric heating and tissue impedance selectively target collagen-rich tissue to induce tissue remodeling and tightening over 60-90 days[23]. Adipocyte apoptosis and fat reduction occur through this bulk heating process[17]. Radiofrequency heats tissue to 43-45°C for up to 45 minutes, followed by epidermal cooling to reverse the thermal gradient[17]. Tissue cooling is an essential component in order to avoid complications such as burns, infection, scarring and dyspigmentation[17]. Treatment is generally well tolerated with heat-related discomfort noted at the time of the procedure. Topical anesthetic is not recommended and may enhance dermal sensitivity and interfere with penetration of RF waves[13]. Transient erythema and edema lasting 24 hours may occur[24]. Rare side effects such as dysesthesia, fat atrophy, subcutaneous nodule formation are reported[24].

There are now a number of radiofrequency devices indicated for body contouring. Vanquish® (BTL Industries, Boston, MA, USA) is a monopolar radiofrequency device used for fat reduction of the mid-section. Its novel panels placed 1 cm above the skin allow contactless treatment of a large surface area, decreasing the overall treatment time and potentially the number of treatment sessions, making it a suitable option for patients with elevated BMI (i.e. >25)[2, 25, 26] truSculpt® (Cutera, Brisbane, CA, USA) is another monopolar RF device with various size hand pieces that allow flexible treatment of both small and large areas. The Venus Legacy® (Venus Concept, Toronto, ON, Canada) combines multipolar RF and-or pulsed electromagnetic fields to promote either skin tightening or fat reduction depending on the applicator used, allowing increased versatility. Pulsed EM stimulates angiogenesis and growth factor release to induce collagen formation through a non-thermal mechanism. Patients with low to moderate BMI and presence of skin laxity tend to be ideal candidates for this class of technology[17].

**Ultrasound**

Ultrasound technology has been used in medicine for many years for ablation of renal calculi, cardiac ablation and ablation of various benign and malignant tumors[13]. Two classes of ultrasound are used for body contouring.

The first class (Ultrashape, Syneron Candela) uses low-intensity/low frequency nonthermal pulsed ultrasonic waves to induce cavitation at specific depth resulting in fat cell lysis[27]. The absence of thermal effect limits its effect on collagen and skin tightening. Studies have shown its efficacy in treating focal adiposity of the abdomen, hips and thighs in nonobese patients (BMI < 30)[27,28]. The recommended protocol involves 3 treatments at 2-week intervals. A single treatment yields a mean reduction in waist circumference by 1.3–2.5 cm[27-29]. Three treatments reduced waist circumference by 2.3–3.5 cm[27,29].

The second class (Liposonix, Solta Hayward, CA, USA) uses highly convergent energy to deliver heat at 56°C to a focal zone known as High-Intensity Focused Ultrasound (HIFU), inducing coagulative necrosis, adipocyte apoptosis and neocollagenesis[13]. HIFU may also induce ultrasonic cavitation of adipocytes. HIFU has been evaluated for treatment of focal adiposity of the abdomen, waist, hips, outer and inner thighs, and buttocks, and in male breast hypertrophy[30,31]. A single treatment is typically sufficient[13]. Total treatment time is 45-60 minutes involving two to 3 passes over the target

area[31]. Mean reductions in waist circumference range from of 4.2 to 4.7 cm 12 weeks post-procedure[30,31].
Clinical improvement with ultrasound contouring is typically noted by 2 weeks and continues up to 12 weeks for both classes of treatment[30-32].
Treatment-associated symptoms include pain during and post-treatment, ecchymoses, erythema and dysesthesia[28-32].
Severe adverse events such as burns, blisters or scars were not reported.

## Discussion

Minimally invasive body contouring procedures continue to gain traction in aesthetic dermatology as patients seek effective treatments with limited recovery and low risk of adverse events. These treatment modalities offer options for non-obese patients seeking modest to moderate improvement. None of the named technologies induce changes in lipid profile or liver enzymes. The success of these treatments is largely based on a comprehensive clinical assessment, understanding of the various modalities, and where combination therapy may be necessary. Identification of the contributory changes in the treatment area – increased fat, skin laxity, cellulite or volume loss – should ultimately guide therapeutic decision-making. Discussion around treatment expectations is key, including anticipated clinical outcomes, time to improvement and need for maintenance therapy.

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# SYPHILIS: CASE REPORT AND UPDATE FOR DERMATOLOGISTS

Case Report:  An otherwise healthy 26-year-old woman presented with a one-month history of oval ulcers on the tongue and red-brown scaly papules on the palms, soles, trunk and arms ***(Figure 1).*** She did not recall a history of genital ulceration and did not have systemic symptoms. She had initially been diagnosed with hand, foot and mouth disease by her primary care physician but the eruption persisted prompting a referral to dermatology. She reported one regular male sexual partner for the past several years.

Based on clinical suspicion, syphilis serology was ordered and skin biopsy was performed on a palmar lesion. The *Treponema pallidum* enzyme immunoassay (EIA) was reactive, and the rapid plasma reagin (RPR) was positive at 1:128. HIV testing was negative. Skin biopsy revealed a lichenoid and perivascular dermatitis, with positive immunohistochemical stain for spirochetes, consistent with the clinical and serologic diagnosis of secondary syphilis. She was treated with 2.4 million units of intramuscular benzathine penicillin G at the British Columbia Centre for Disease control. Sexual partners were traced and notified.

**Epidemiology**

The incidence of syphilis has increased over the past two decades. In Canada, the rate of infectious syphilis (primary, secondary and early latent stages) increased 85% between 2010 and 2015, with the highest rates occurring in British Columbia, Nunavut, and Manitoba[1]. Similar rates of increase are reported in other developed countries such as the United States, Australia, and the United Kingdom[1].

The highest rates of syphilis are observed in men. HIV-positive men who have sex with men (MSM) are disproportionately affected. In Canada, the overall incidence of syphilis is > 300 times greater in HIV-infected MSM compared to the general male population[2]. This is particularly concerning because infection with syphilis increases the likelihood of both transmitting and acquiring HIV, and is associated with increased HIV viral loads[3].

There are several reasons for the rise in syphilis in MSM. Advances in HIV treatment as well as the more recent widespread uptake of pre-exposure prophylaxis for HIV have resulted in a more optimistic risk perception about HIV among MSM. This so-called "HIV optimism" has lead to an increase in risky sexual behaviours, decreased condom use, and a rise in sexually transmitted infections (STIs)[4] . Other behaviours implicated in the rise in STIs among MSM include serosorting (unprotected sex in partners with the same HIV status), and meeting sexual partners via online dating applications[5,6].

Interestingly, there has been a disproportionate increase in the incidence of syphilis compared to other STIs, which cannot be explained by changes to norms and behaviours. Between 2005 and 2014, cases of infectious syphilis in British Columbia rose 90%, compared to a 40% rise in chlamydia and 64% rise in gonorrhea over the same time period. The majority of these cases occurred in HIV-positive MSM, which has led to the hypothesis that antiretroviral therapy may impair anti-treponemal immunity by downregulating both the innate and acquired immune responses to *T. pallidum*, but this hypothesis remains untested[7].

Despite the marked male predominance, the incidence of syphilis is also steadily increasing among women. Along with this, there has been a rise in the incidence of congenital syphilis[7]. Heterosexual transmission of syphilis in both men and women is associated with use of illicit drugs, particularly methamphetamines and injection drugs[8]. The patient in this case did not have any of the above risk factors, reinforcing the importance of considering syphilis in the differential diagnosis in all patients, regardless of demographics.

**Clinical Presentation**

The primary, secondary and early latent phases of syphilis are highly infectious and timely intervention is important in limiting the spread of infection. The signs and symptoms of untreated primary and secondary syphilis will resolve spontaneously as the infection progresses to the latent phase. If these stages go unrecognized this puts the patient at risk for development of tertiary syphilis, which can affect the cardiovascular system, bone, skin (noduloulcerative or gummatous lesions) and other organs. There is risk of developing neurologic, ocular or otic involvement at any stage of infection[9].

Although most dermatologists would include syphilitic chancre in the differential diagnosis for a solitary, painless genital ulcer, less common presentations may pose a diagnostic challenge. Chancres may be multiple, may present at less common sites (fingers, nipples, and both keratinized and mucosal surfaces of the oral and anogenital areas), and early chancres may present as papules prior to ulcerating[10].

Up to to 97% of cases of secondary syphilis involve skin or mucosa, and the clinical presentation is highly variable. The skin findings may occur with or without lymphadenopathy and systemic symptoms[11]. This case serves as a reminder of some of the classic morphologic features of secondary syphilis. The erythematous papules on the palms and torso demonstrate a typical collarette of scale (Biett's collarette). The oral lesions have the characteristic morphology of mucous patches, which present as well-demarcated oval shaped plaques, erosions or shallow ulcers, with a raised border and white–grey membranous surface. Mucous patches may also involve the buccal mucosa, lips and oral commisures ("split papules"). However, nearly any morphology may occur including psoriasiform, annular, lichenoid, nodular eruptions, leukoderma and patchy nonscarring alopecia among

a long list of less common presentations[9].

New clinical variants of syphilis continue to be described. An urticarial vasculitis- like variant was recently reported, in an HIV-negative individual. This patient had urticarial plaques persisting beyond 24 hours and complement and fibrinogen deposition around the blood vessels and at the dermo-epidermal junction. Immunohistochemical stain for spirochetes showed marked invasion of treponemes into the epidermis[12]. Secondary syphilis can mimic pemphigus vulgaris, both clinically and histologically[13]. Another report describes hemorrhagic crusting of the lips and a diffuse pustular eruption on the trunk, in an HIV-positive individual with secondary syphilis[14]. These presentations place syphilis on the differential diagnosis for bullous or pustular drug eruptions, immunobullous disorders, and other bacterial and viral infections such as impetigo and varicella. Importantly, syphilis can present with atypical cutaneous findings in HIV-positive individuals, which should raise the clinical index of suspicion for syphilis and decrease threshold for syphilis testing in this population.

**Diagnostic Testing**

Although the specifics of syphilis testing differ between provinces, most laboratories in Canada have adopted a reverse-sequence testing algorithm[15]. This algorithm involves using an automated initial screening test (eg. EIA or chemiluminescence immunoassay; CIA) to detect the presence of anti-treponemal IgM and IgG antibodies. Once reactive, treponemal tests generally remain reactive for the lifetime of the patient, although there is a low rate of sero-reversion if the infection is treated early in the primary stage[16].

All specimens with positive screening treponemal tests then undergo a non-treponemal test (most commonly the RPR). The non-treponemal test is used for staging, monitoring response to treatment, and determining reinfection. The RPR measures antibodies against cardiolipin, which are formed by the host in response to lipoidal material released from damaged host cells, providing a rough indicator of disease activity[16]. This is why the RPR may also be positive in many other conditions, including chronic inflammatory diseases, other infections, pregnancy and injection drug use. False negative non-treponemal tests can also occur, early or late in infection, and rarely in cases where very high antibody concentration interferes with the mechanism of the test (the prozone phenomenon)[9].

Finally, a highly specific treponemal test (such as the Treponema pallidum particle agglutination test; TPPA or the fluorescent treponemal antibody absorption test; FTA-Abs) may be done as a confirmatory test[16]. In some provinces this is done routinely on all samples, and in others it is done only if there is discordance between the treponemal and non-treponemal test results[15].

There is a risk of false negative serology in early syphilis, prior to development of antibodies. Therefore, if clinical suspicion for early syphilis is high but serology is negative, the test should be repeated in 2- 4 weeks[15]. Skin biopsy with immunohistochemical staining using antibodies against treponemal antigens can be a useful diagnostic tool in this situation. These stains are much more sensitive and specific than previously used silver stains such as Warthin-Starry[11]. Additionally, *T. pallidum* can be directly detected by PCR on swabs of lesional exudate from chancres or by darkfield microscopy. However, practical considerations (ie. availability of the test or swabs) may limit the usefulness of these tests in the dermatology clinic setting.

Successful response to treatment is measured by both clinical improvement and a reduction in non-treponemal test titres. The RPR is repeated at specified intervals following treatment, which vary based on the stage of syphilis and comorbidities. In patients successfully treated for syphilis, the non-treponemal tests will usually eventually become nonreactive[16]. Interpretation of syphilis testing can be complex. Diagnosis and management cannot be based solely on current serologic testing. Results need to be

interpreted in the context of both clinical and serologic history to determine whether the case is new or previously treated, and if new, what stage. Because of this complexity and the need for partner tracking and notification, management of syphilis is best done in coordination with infectious disease specialists and public health services.

**Conclusion**

The resurgence of syphilis is concerning from both an individual patient and public health perspective. By developing an awareness of the protean mucocutaneous manifestations, and a maintaining degree of clinical suspicion, dermatologists have an opportunity to contribute to the control and elimination of infectious syphilis.

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## FIGURES




*Figure 1: Clinical images of secondary syphilis. A) Mucous patches on the tongue.*

*B, C &D) Erythematous papules with characteristic collarette of scale on the palms and trunk.*

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Dr. O'Toole is a dermatologist with the SKiN Centre for Dermatology in Peterborough, Ontario where she also serves as a sub-investigator for multiple clinical trials. She is an adjunctive professor at Queens University and involved in teaching medical students and residents. After receiving a Master's of Health Science in Health and Behavioural Communication at Ryerson University in Toronto, Ontario, Dr. O'Toole received her medical degree from McMaster University in Hamilton, Ontario, and completed her residency in dermatology at the University of Ottawa in Ottawa, Ontario. Dr. O'Toole is the author or co-author of 15 publications and is involved in approximately 30 clinical trials on atopic dermatitis, psoriasis, alopecia, acne and vitiligo.

# USHERING IN A NEW ERA OF PSORIASIS TREATMENTS

I often find myself counseling my patients about this being an "exciting time" to be a psoriasis patient. This is due to the fact that our knowledge of the disease has evolved at such a rapid pace, and, with it, our ability to clear the skin in both a safe and efficacious manner has become more advanced than ever before.

In my dermatology training, a dermatologist teacher of mine often used the metaphor of a tree when discussing treatment options for managing psoriasis with his patients. His rationale was quite simple: this metaphor was understandable to all patients of all backgrounds including those with lower health literacy. I have found this simplistic treatment discussion so useful in my own discussions with patients now that I am in independent practice that I often find myself "borrowing" it as an educational tool on a near-daily basis.

In this patient counseling discussion, I refer to some of the more traditional agents for psoriasis, including methotrexate or cyclosporine as cutting the trunk of the immune-system tree. As such, these medications are associated with a higher risk of side effects, including infections and immunosuppression[1]. These older treatments can also require extensive workup and monitoring

during treatment. They also often take between six to twelve weeks for optimal onset of action[2]. Unfortunately, by that time, we may often observe a loss of motivation on the part of the patient as they struggle with active disease that does not seem to be effectively managed according to their expectations of the therapy. Additionally, the patient may be lost to follow up before the medication has started to work and this can pose another challenge in the utilization of these older treatments. Patients (and physicians) are often nervous to try these agents which underscores the need for safer and more effective treatment options.

Around 15 years ago, therapies with monoclonal antibodies were introduced for the treatment of psoriasis and psoriatic arthritis. When describing these agents, often called "biologics", I liken them to cutting a large branch of the immune system tree. The early biologics include tumor necrosis factor alpha agents (i.e. adalimumab, etanercept and infliximab) and IL 12/23 inhibitors (i.e. ustekinumab). These drugs were welcomed by providers and patients alike with benefits including less frequent and cumbersome dosing, fewer adverse events, and a more potent and enduring efficacy profile[2].

Within the last 2-3 years, our understanding of psoriasis and psoriatic arthritis has grown by leaps and bounds. The therapeutic landscape has evolved with newer, more targeted and safer agents. With more specific drug targets, I equate their mechanism to simply cutting the twigs in the immune system tree that specifically drives psoriasis and/or psoriatic arthritis. The IL-23 inhibitors (i.e. risankizumab, tildrakizumab and guselkumab) and IL-17 inhibitors (i.e. ixekizumab, broadalumab and secukinumab) are examples of these modern targeted agents. Patients understand that with the more targeted nature of these medications, they can benefit from a more precise and cleaner safety profile.

In the psoriasis clinical trials of the 2000s, a realistic treatment goal was a PASI 75 by 12 weeks[3]. Today's newer agents aim for a PASI 90 or even PASI 100 – which is often obtainable both in trials and real-world studies[4,5,6]. We, as dermatologists, are in a unique position to offer clear or nearly clear skin to our patients where this was only a dream in the past.

With these more ambitious treatment goals, we are seeing success even in the harder to treat areas such as the scalp, genitals, nails and palmoplantar psoriasis. The psoriasis therapeutic landscape is competitive and with that comes the desire by many pharmaceutical companies to create therapies that not only clear the skin quickly, but also that may stand out as the "agent of choice" for these difficult cases. For example, secukinumab has marketed its efficacy in ankylosing spondylitis and nail psoriasis[7,8] and ixekizumab as the agent of choice for managing genital psoriasis[9].

The past twenty years have seen a true evolution within the psoriasis therapeutic landscape. The paradigm has shifted from a mentality of immunosuppression to that of more immunomodulation. Dermatologists that had previously been limited to a few rudimentary immunosuppressive agents now have a full armamentarium of tailored and precise treatment options. With this movement towards immunomodulation, comes a need to update our guidelines. Specifically, the diagnostic tests often ordered by specialists for patients prior to starting these agents. The previous recommendations were designed in an era of patients being initiated on methotrexate, cyclosporine or early biologics where infection and immunosuppression risk was very real. Today, the risk of these adverse effects is much lower with these targeted agents.

For example, past treatment options for a patient who had a history of tuberculosis or a solid organ malignancy may have been limited to oral retinoids and topicals. Now, due to more targeted immunomodulatory therapies where the mechanism of action is truly "anti-inflammatory" as opposed to "immunosuppressive" (i.e. PDE4 inhibitors and targeted

biologic agents), there are many safe and effective options available for treatment.

Another push towards updating our older recommendations for initiating biologic treatment in patients is the move toward examining healthcare needs through the lens of societal cost and burden, where the allocation of scarce health care resource and an eye on cost-effectiveness is becoming more important. In my experience, I have sometimes found TB skin testing, extensive laboratory investigations and radiologic imaging for every patient to be time consuming for the patient and inefficient for the healthcare system and often leads to false negatives. Thus, work-up should be patient-specific – low-risk patients may not need these tests which ultimately lead to attrition rates and loss to follow up. Certainly, higher-risk patient populations, such as immigrants, healthcare workers, homeless, indigenous populations, sex workers etc., should be investigated prior to starting biologics with tuberculosis testing, (TBST or Quantiferon assay), chest x-ray, stool cultures, hepatitis and HIV serologies and/or other viral titres.

There have been studies both in risankizumab and guselkumab in patients with proven latent tuberculosis (positive TBST or quantiferon gold assay[4,5]). In these trials, none of the 31 patients with latent TB went on to develop active tuberculosis despite the use of risankizumab,[5]. In the guselkumab clinical trials, some of the latent TB patients patients started the biologic agent prior to anti-TB treatment and still did not develop active disease[4]. In response to these studies, newly approved risankizumab is the first biologic agent where the label does not require tuberculosis testing (instead, leaving it up to the discretion of the provider)[10]. In the real world, it would certainly be clinically appropriate to have patients in higher risk groups undergo TB screening prior to initiation of treatment (i.e. indigenous populations or those living on reserves, homeless persons, and immigrants or high-risk travellers).

One final reason I tell my patients it is an exciting time to be a psoriasis patient is the growing level of support patients have access to outside their immediate care circle, such as: improved patient access to drugs through the industry-sponsored patient support programs, bridging and compassionate programs and even increased access to these newer therapies via the public reimbursement mechanisms, all of which have contributed to this exciting era of psoriasis therapies. The government's recognition of the impact of skin disease on quality of life and workplace performance is increasing, as is research in this field.

Ultimately, it is an exciting horizon for psoriasis treatment and management. We have more efficacious medications, with improved safety profiles and longer duration of effect. With these tailored and personalized treatment options we, as dermatologists, are in a position to really make an incredible difference in the lives of our patients.

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# BIOLOGIC TREATMENT AND PSORIATIC ARTHRITIS: A REVIEW FOR THE DERMATOLOGIST

In busy dermatology practices, assessing for psoriatic arthritis (PsA) on top of discussing the diagnosis and management options for psoriasis (PsO) can be a challenge. Interestingly, data suggests that dermatologists are poor in evaluating for PsA in their PsO patients. In a study evaluating the prevalence of PsA in dermatology clinics, nearly one third of patients with plaque-type psoriasis were found to have PsA.[1] Moreover, about 40% of those were newly diagnosed with PsA and had not been given a diagnosis of PsA before. This suggests that dermatologists are possibly missing cases of PsA. Dermatologists are uniquely positioned to diagnose PsA early and prevent worsening of the patient's rheumatologic disease. PsO typically appears 7-12 years before PsA[2] and 64.5% of patients had PsO diagnosed prior to a diagnosis of PsA.[3,4] By comparison only 19.4% of patients were diagnosed with PsA before a PsO diagnosis. Even a 6-month delay in symptom onset to the first visit with a rheumatologist was associated with worsening peripheral joint erosion and worse long-term physical function.[5]

**Clinical clues for early detection of PsA in PsO patients**

Clinical clues in PsO patients that suggest a higher risk of PsA include presence of scalp lesions (3.9x), nail dystrophy (2.9x), intertriginous psoriasis (2.4x), severe disease (2.2x), and ≥3 body sites of involvement (2.2x).[6] First degree relatives with PsA incur an increased relative risk of 39-fold for

the PsO patient to develop PsA ($p<0.01$). Basic screening questions for PsA have been described and include inquiring about joint pain, morning stiffness (>30 min upon waking), and back pain (axial involvement; pain/stiffness that improves with movement). A positive response to 2 or more screening questions should trigger a more complete PsA assessment. Assessment of dactylitis, enthesitis (specifically pain at the Achilles tendon and lateral epicondyle insertion points), and synovitis is relatively fast and may help to identify patients that may have PsA that may benefit from a rheumatology referral. Investigations that may be considered prior to rheumatologic referral are C-reactive protein (CRP)[7] and X-ray of the affected joints.

**Biologics in PsA**

The therapeutic armamentarium for PsO has exploded within the last 15 years. We now have multiple agents that can be used to treat PsO and achieve clear or near clear results. But what about our patients with concurrent PsA? The American College of Rheumatology (ACR) criteria 20/50/70 is a composite measure of PsA efficacy that can be used to roughly gauge treatment efficacy. It can be considered in some respects to the Psoriasis Area and Severity Index (PASI) 50/75/90. Beyond the ACR, perhaps the best outcome measure for efficacy of biologics in PsA is assessment of the drug's ability to halt radiographic progression. Currently available agents (anti-TNFą agents, anti-IL12/23 agents, anti-IL17a agents, and anti-IL23 agents) have shown great efficacy for PsO but differential efficacy for the treatment of PsA, including prevention of radiographic progression and treatment of axial disease. Multiple anti-TNFα's and IL-17a's have demonstrated halting of radiographic bone progression. Figure 1 represents a summary of efficacy of various biologics for PsO and PsA.

**Anti-TNFs and PsA**

Anti-TNFα agents were the first biologic agents on the market for treatment of PsO and PsA. Five TNFα inhibitors (**etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab**) are currently approved in Canada and other countries for use in PsA. The efficacy of the drugs for PsA is comparable, and given the breadth of agents available, the choice of agent can be tailored to patient preferences for route (subcutaneous versus intravenous), frequency of administration, and potential cost to the patient. Meta-analyses and clinical trials have extensively documented the efficacy of anti-TNFα agents in patients with PsA.[8] Studies have shown efficacy of etanercept,[9-11] infliximab,[12-15] adalimumab,[16-21] golimumab,[22,23] and certolizumab pegol[24,25] compared to placebo. Monotherapy with a TNFα inhibitor was superior to methotrexate monotherapy after controlling for multiple variables in a retrospective trial.[26] In summary, the various trial efficacy data included reduced arthritis activity (ACR20 responses in 50 to 65% of patients within three months), delayed radiographic progression; improved physical function and quality of life measures. Other features of PsA, such as enthesitis and dactylitis are also improved in patients treated with TNFα inhibitors.

**IL-12/IL-23p40 Inhibitors and PsA**

Ustekinumab is a monoclonal antibody that targets the shared p40 subunit of IL-12 and IL-23 with high affinity. In the PSUMMIT-1 trial, the week 24 data showed significantly more ustekinumab patients achieved ACR20 than placebo at a dose of 90mg and 45 mg (ACR20 50% and 42% respectively versus placebo 23%).[27] In another phase III randomized controlled trial, the PSUMMIT-2, efficacy of ustekinumab in PsA patients was seen in patient who were primary failures to TNFα inhibitor therapy.[28] Despite having been exposed to anti-TNFα therapy, 44% of the ustekinumab treated patients achieved ACR20 (vs. 20% for the placebo arm), a statistically significant difference. Furthermore, dactylitis, enthesitis, and spondylitis were also ameliorated with ustekinumab and delay in radiographic joint damage was seen.[29] Inhibition of radiographic progression was sustained to week 52. Ustekinumab has not been shown to inhibit PsA axial disease progression when a

marker of PsA axial disease was used a surrogate (ankylosing spondylitis data).

**IL-17a inhibitors and PsA**

IL-17a inhibitors include secukinumab, and ixekizumab which are indicated for PsO and PsA. Randomized control trials have shown efficacy in PsA including prevention of radiographic progression and treatment of axial disease. FUTURE2 trial data showed that significantly greater secukinumab-treated patients (300 and 150 mg), compared with placebo-treated patients, achieved an ACR20 response at week 24 (54%, 51%, and 29% versus 15 %).[30] Five-year data was recently published for the secukinumab FUTURE1 trial which shows ACR 20/50/70 data of 71.0%/51.8%/36.3% respectively for secukinumab treated patients.[31] The FUTURE1 trial showed that secukinumab inhibited structural joint damage through 24 weeks,[32] and delayed radiographic progression out to 3 years (data was only collected up to 3 years).[33] The SPIRIT-P1 trial looking at ixekizumab showed ACR 20/50/70 rates of 57.0/33.6/15.0 for the 80mg q4 week dosing at week 24 vs 31.1/4.7/0 for placebo (all statistically significant).[34] In biological-naive PsA patients from the SPIRIT-P1 trial, ixekizumab q2 week dosing or q4 week dosing achieved comparable ACR50 and ACR70 responses and delayed joint structural damage at 24 weeks irrespective of disease-modifying anti-rheumatic drugs (DMARD) or methotrexate use.

**Brodalumab** is a monoclonal antibody that blocks the IL-17 receptor ą subunit, effectively inhibiting IL-17a, -e and -f. In a phase II randomized, double-blind, placebo-controlled study in PsA, brodalumab 140 or 280 mg at week 1, 2, and then every 2 weeks, at 12 weeks achieved ACR 20 response of 37% and 39% respectively, compared to placebo 18%.[35] An ACR50 response in 14% of patients at both doses compared with 4% in the placebo group and ACR70 response in 5% of patients.[35] Similar rates of improvement were seen in biologic naïve and non-naïve patient groups. In the open extension of this study, the ACR50 response increased to 33%. However, brodalumab was not shown to be effective for dactylitis.[36]

**IL-23s and PsA**

Guselkumab is a human monoclonal antibody that binds to IL-23p19 subunit and inhibits the downstream signaling of IL-23. DISCOVER-2, a Phase III study, showed ACR20 of 64% at week 24. However, delay in radiographic bone progression was seen but only the 100mg every 4 week dosing (not 100mg every 8 week dosing as is currently approved for psoriasis).[37] Gulselkumab is thus the first IL-23 agent to show delayed radiographic progression in a large phase 3 cohort.

Risankizumab is a humanized monoclonal antibody that targets the IL-23p19 subunit and selectively inhibits IL-23. Phase II data showed promising results with an ACR20 up to 62% at week 16 in risankizumab-treated patients (150mg week 0, 4, 16) versus ACR20 of 36% in the placebo patients. As well, pooled rizankizumab treated patients showed no radiographic bone progression seen at week 24. Phase III studies are beginning in the near future.

Tildrakizumab is a humanized monoclonal antibody that binds to the p19 subunit of IL-23 with high affinity and inhibits downstream signaling of IL-23. A Phase IIb trial of 391 patients with PsA who had three or more tender or swollen joints were randomized to receive tildrakizumab 200 mg once every four weeks, 200 mg, 100 mg, 20 mg every 12 weeks, or placebo every four weeks. At week 24, a significantly greater proportion of patients receiving tildrakizumab achieved an ACR20 of 79.5% (at any dose) compared to placebo. However, the placebo score was elevated at 50.6% for reasons that remain unclear (Study presented at the European Congress of Rheumatology (EULAR) annual meeting in Madrid 2019).

**Conclusion**

The most recent biologics to come to market for the treatment of PsO have had highly efficacious results in clearing cutaneous disease, however, have potentially disparate abilities in treating joint disease. It is imperative for the dermatologist, who may be the first physician to suspect or diagnosis PsA, to

have a working understanding of the differences in biologic efficacy in PsA. Together with a rheumatologist, an appropriate management plan for patients with both PsO and PsA can be tailored.

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