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EDITOR'S WELCOME



Dear Canadian Allergy & Immunology Community,

Welcome to our final issue of *Canadian Allergy & Immunology Today* in 2022! The year has flown by and we are all thankful to be able to see our colleagues again at meetings and conferences and to have the chance to reconnect.

In this final issue of the year our articles cover a broad range of topics that we hope you will find helpful. We discuss current pharmacological and non-pharmacological therapies for chronic cough and we take an in-depth look at the systemic management of atopic dermatitis using new and emerging therapies. We also examine burdens, barriers, and potential for solutions of Canadian Indigenous peoples with atopic dermatitis and the importance of identifying dermatological emergencies in out-patient care.

As always, we hope you find these articles informative and helpful. We are grateful for your continued readership, and we look forward to another great year in 2023. To all our authors past and future, we say 'thank you' for the incredibly high quality of your submissions.

We would also like to acknowledge the support of our Canadian manufacturers who have demonstrated a commitment to credible and relevant medical education through their support of this journal.

Please let us know how we are doing by suggesting topics and feel free to share our registration link at canadianallergyandimmunologytoday.ca with your peers so that, they too, can subscribe to future issues!

Wishing you and your families a wonderful and peaceful holiday season.

Best wishes,

Vipul Jain, MD Nikhil Joshi, MD Jason Ohayon, MD Susan Waserman, MD

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SYSTEMIC MANAGEMENT OF ATOPIC DERMATITIS: NEW AND EMERGING THERAPIES

1. ATOPIC DERMATITIS

Atopic dermatitis, also known as atopic eczema (hereafter referred to as eczema) is the most common chronic inflammatory skin disease worldwide and, together with associated allergies, asthma, allergic rhinitis (with or without nasal polyposis), and eosinophilic esophagitis, atopic disorders represent a growing source of patient morbidity and health care cost globally.[1,2] The incidence of eczema spans all age groups, but in over 80% of cases it manifests during infancy or early childhood; interestingly, there is now recognition that a significant number of patients suffer from adult-onset, chronic-persistent, and/or late-relapsing disease.[1,3,4] Eczema is a complex disease with extreme heterogeneity, including highly variable penetrance, clinical phenotypic presentations (ethnicity, age and temporal factors), and natural history across the lifespan. The term endotype has been introduced to describe potential variance in therapeutic responsiveness and etiology, particularly with respect to genetic and immunologic profiling, as well as environmental triggering.[1,4–6] Notably, the range of treatment options available for patients with atopic disorders is changing rapidly, especially for eczema.[7] In this review, we provide a brief overview of targeted systemic therapeutic options for patients with eczema and atopy (**Table 1**).

2. WHO QUALIFIES FOR SYSTEMIC THERAPY?

A detailed approach to the management of eczema is beyond the scope of this review; however, our group has published a systematic review and quality assessment of existing guidelines for reference.[8] Management options range from skin-directed (topical corticosteroids, calcineurin inhibitors, PDE4 inhibitors, as well as phototherapy) to systemic agents, based on extent, severity, and type of disease.[1,5,8] Notably, assessment of disease is challenging, as highly-detailed full body skin examinations are required for validated disease assessment, including the primary outcome measure, the Eczema Area and Severity Index (EASI).[9] A stepwise approach to management of refractory or more severe disease generally focuses on systemic agents to induce itch remission rapidly, a core factor to drive improvement in quality of life. Objectively, a current target for eczema control is an EASI of <7; however, patient reported outcomes for itch and quality of life, such as the Dermatology Life Quality Index (DLQI), should strongly influence this target.[1,8, 9, 53] The importance of these subjective measures is highlighted when considering the temporal instability of the disease and the barriers to accessing specialized care and objective measures during flares. For individuals with refractory or extensive eczema affecting more than ten percent corporeal surface area, or special sites such as the hands or face, antimetabolite immunosuppressive agents have long been used, despite being off-label.[1,5,8,10,11] Therapeutic switches for ensuring safety of continuous immunomodulation for long-term maintenance of remission are now preferred management, as targeted therapies are considered to minimize the risk of adverse effects across the lifespan.[1,5,8,11] Patients and providers alike are increasingly seeking direct access to targeted agents when able. Broadly, targeted agents approved for eczema are categorized into biologics (monoclonal antibodies) and small molecule inhibitors.

3. WHAT TRADITIONAL IMMUNOSUPPRESSANTS ARE USED FOR ECZEMA?

Traditional immunosuppressive antimetabolites remain in frequent use despite being off- label in Canada in large part due to health system cost considerations.[5,8,11] Selection of these agents is based on individualized efficacy and safety considerations, while adhering to international management guidelines and requirements for screening and monitoring. Usage varies according to expertise, access to monitoring, as well as regional or national health system factors.

Cyclosporine is an effective small molecule calcineurin inhibitor that prevents IL-2 transcription resulting in reduced effector T cell function. Cyclosporine has long been approved by the European Medicines Agency (but not the FDA or Health Canada for refractory eczema.[11,12] It has been considered a first-line agent for adults with severe disease in European guidelines due its rapid onset; patients can achieve 51% and 72% improvement of eczema at week 2 and 12, respectively.[13] However, cyclosporine

should be administered in 3–6-month intervals for a maximum of 2 years to minimize side effects such as hypertension, nephrotoxicity and risk of malignancy or infection.[11,14,15] Unfortunately, relapse and rebound is common following cyclosporine discontinuation; therefore, careful tapering and/or switching to maintenance therapies is needed.[11,14]

Unlike cyclosporine, methotrexate works slowly, and patients often take as long as 8-12 weeks before responding optimally; however, methotrexate is generally considered a safer option for long-term maintenance.[5,11,14] This antifolate antimetabolite inhibits synthesis of DNA and RNA.[16–19] Up to 60% of patients can achieve improvement of disease whilst on methotrexate as part of a monotherapy or combination therapy regimen.[20,21] Methotrexate usage must be weighed against its teratogenic and hepatic adverse effects.[11,14] Mycophenolate mofetil and azathioprine are less commonly used systemic immunosuppressants for eczema patients but may be used as adjuncts or when cyclosporine and/or methotrexate are contraindicated.[11,14,20,22] While systemic glucocorticoids are a recognized rescue therapy for moderate-to-severe eczema, their usage is restricted to short-term management of acute flares due to their unfavorable safety profile with prolonged treatment.[11,14] Importantly, the cumulative risk of rescue corticosteroids must be considered across the lifespan.

4. WHAT TARGETED AGENTS ARE USED, AND WHEN?

A rapid pace of translational discovery has led to landmark shifts in the management of eczema over the last six years: there are now four on-label therapies with demonstrated efficacy in AD and that are safe for long-term maintenance of remission (**Table 2**). Patients and providers are thus seeking improved health trajectories across the lifespan, with increasing awareness of ameliorated outcomes, due to the capacity for targeted agents to selectively modulate branches of the immune system without broad immunosuppression, or while minimizing off-target effects to other organs. Health systems are recognizing these novel agents and balancing econometric evaluations against budget impact analyses.

a. Targeted Biologics: Monoclonal Antibodies

Biologics for eczema are proliferating; notably, these selective agents are injections. As the first targeted agent approved for eczema, dupilumab is licensed for use across the greatest number of atopic conditions and has the widest age range of regulatory approvals (**Table 2**).[23–25] This fully humanized monoclonal antibody targets the alpha subunit of IL-4 receptor (IL-4R)[26] blocking type 2 (IL-4 and IL-13) signaling, and significant skin clearance has been established in 3 pivotal trials for adults.[27,28] It has also been approved for children aged 6 to 11 years with uncontrolled eczema (**Tables 1 and 3**).[29,30] The FDA also accepted dupilumab for priority review for approval in children between the ages of 6 months and 5 years.[31] A phase 2/3 trial in this patient population found that 53% of such patients were able to achieve EASI75 at week 16 with dupilumab, versus 11% with placebo.[32] With a signal for conjunctivitis but otherwise minimal adverse effects, given its consistent safety profile for patients 6 years and older, dupilumab's strengths include efficacy over a range of other moderate-to-severe allergic diseases such as uncontrolled asthma and nasal polyps that may influence its selection in patients with these co-morbidities (**Table 1**).[33]

Tralokinumab is another selective and high-affinity human monoclonal antibody against IL-13, the dominant Th2 cytokine in skin. It was approved by Health Canada for adults with moderate-to-severe eczema in late 2021;[34,35] public reimbursement in Canada is pending.[31,32] In clinical trials, the majority of tralokinumab responders maintained their response through week 52 and there is some evidence for improved long-term response rates.[34–36] In pivotal trials, EASI75 at week 52 was maintained by 60% of treatment responders who continued tralokinumab (vs. 33% who transitioned from tralokinumab to placebo), after the week 16 primary endpoint in ECZTRA 1, and 56% who continued tralokinumab (vs. 21% who transitioned to placebo) in ECZTRA 2. Tralokinumab does not have any notable contraindications or additional safety monitoring requirements associated with its use for patients prior, during, or post initiation (**Table 3**).[36]

Of note, a recent Canadian literature review and expert clinical framework notes that exposure to dupilumab during pregnancy poses little risk to mother and fetus, with negligible absorption of dupilumab by infants who are breastfed by women taking dupilumab.[33]

b. Targeted Small Molecule Inhibitors: JAK1 Inhibitors (JAKi)

Biologic agents are appealing options for long-term maintenance due to their favorable safety profiles; however, their pharmacodynamics are slower than oral targeted agents. Patients suffering from moderate-to-severe eczema frequently require rapid rescue and remission of disease, as demonstrated by the prevalent use of systemic corticosteroids despite their broad adverse effect profiles. A new class of agents, the small molecule inhibitors of Janus kinases

(JAKi), control disease rapidly by interrupting signal transduction downstream of cytokine receptors;[1] JAKi are already used in rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis (**Tables 1,2**).[37,38] The JAKi of interest for eczema in North America (upadacitinib and abrocitinib) are oral small molecule inhibitors with predominant selectivity for JAK1.[5] JAK1 inhibitors are highly effective at blocking signaling downstream of the type 2 cytokines that contribute to eczema pathophysiology; they also interrupt signaling downstream of other cytokine families, including interferons, the gp130 receptor group, IL-10-related, and common gamma chain cytokines.[39,40] While serious adverse effects of special interest have been highlighted in patients with rheumatoid arthritis under combination treatment with the less selective JAK inhibitor (JAK1/3) tofacitinib, leading to blanket inclusion of black box warnings for the JAK class across all diseases, this data has not been extrapolated to selective JAK1 inhibition in patients with eczema.[41,42] Notably, a wide range of topical and oral inhibitors of JAK and related kinases are under active development for a wide range of dermatologic conditions, including vitiligo and alopecia areata, which are common underlying comorbid conditions in patients with severe eczema. [43]

Upadacitinib was the first approved JAKi for moderate-to-severe eczema in adults and adolescents (>12 years).[44,45] In phase 3 studies, patients treated with upadacitinib achieve rapid control as early as week 4, with 70% EASI75 and IGA-AD scores by Week 16 compared to placebo (**Table 4**).[46–48] Notably, patients experienced rapid improvements in itch beginning as early as 1-2 days following the first dose. At higher dosing (30 mg) upadacitinib achieved higher skin clearance compared to dupilumab after four months, with 60.6% versus 38.7% achieving 90% improvement in the EASI.[49] Routine blood work is recommended pre-treatment with monitoring at 3 months and as per care required (**Table 3**).[38] Non-live vaccination prior to therapy, followed by booster vaccination after two months is recommended, with stronger recommendations in patients who are at a greater risk for developing shingles, including patients of Asian ethnicity. Shared decision-making is needed to review timing and options for therapy modifications during vaccinations.[38] Upadacitinib should be prescribed with caution in patients with infection, hematologic disorders, history of clotting, and liver or kidney impairment, and is contraindicated during pregnancy and breastfeeding.[38]

Abrocitinib is a comparable JAK1 inhibitor recently approved by Health Canada, with small differences in adverse effect profiles including a slightly lower signal for acne.[50,51] Patients receiving abrocitinib also showed significantly greater improvements in their EASI75 and Investigator Global Assessment- Atopic Dermatitis (IGA-AD) scores compared with the placebo group across three pivotal registration studies (**Table 5**).[26,50] Unlike dupilumab and tralokinumab, upadacitinib and abrocitinib require additional safety considerations prior to and post initiation of therapy (**Table 3**).[37]

5. CHOOSING THE BEST SYSTEMIC ECZEMA THERAPY

The systemic therapy that best suits an individual's unique eczema presentation depends on multiple patient-specific factors, including age, underlying comorbidities, disease- and risk-factors, endotype variables and personal preferences, in addition to health system considerations related to reimbursement and access. However, only select therapeutic agents (cyclosporine, upadacitinib, abrocitinib, prednisone) have kinetics that are useful in achieving very rapid remission of eczema, while others (dupilumab, tralokinumab, methotrexate) have slower onset of action but also possess multiple years of data demonstrating durability of response over time with favorable safety profiles. In addition, restricted options are available for certain populations, including children and women of childbearing potential. For patients with health-related quality of life affected by comorbid atopic conditions like asthma and/or chronic rhinosinusitis with nasal polyps (CRSwNP), dupilumab remains advantageous (**Table 3**). Although tralokinumab may not be as efficacious as dupilumab at the time points considered here, it remains a viable alternative with fewer safety concerns than the JAK inhibitors and targets the key mediator in skin.[10,52] As more molecules progress through clinical development, including additional IL-13 inhibitors and biologics targeting OX40 or ligand co-stimulatory signaling, further research is required to determine how to personalize management approaches with the idealized aim to identify therapeutic approaches that may alter the natural history of disease.

The author wishes to acknowledge the contribution of Radia Kamal, Aashna Jain, and Valerie Jack for their help in the research and writing of this manuscript

		Children								Adolescent and Adult							
MOA	Rx	Children 6 months-5 years				Children 6-11 years				Adolescents 12-17 years				Adults			
		AD	Asthma	CRS wNP	EoE	AD	Asthma	CRS wNP	EoE	AD	Asthma	CRS wNP	EoE	Eczema	Asthma	CRS wNP	EoE
Anti-IL-4R alpha (IL4/IL13)	Dupilumab[1]	Pending*				✓! @	✓! @			✓! @	✓! @#		Pending	✓! @	✓! @#	✓! @#	@
Anti-IL-13	Tralokinumab[2]													✓! @			
Anti-JAK1	Upadacitinib[3]									✓! @				✓! @			✓**
Anti-JAK1	Abrocitinib[4]													✓!			

Table 1. New systemic therapies approved for patients with Atopic Dermatitis (Eczema), considering other atopic disorders, as of April 2022.
CRSwNP (chronic rhinosinusitis with nasal polyposis)
! Approved by Health Canada as of April 2022
@ Approved by U.S. FDA
 # Approved as add-on maintenance treatment only
** Accepted for Priority Review by the U.S. FDA5*
*** Approved for moderate-to-severe ulcerative colitis, active psoriatic arthritis, and moderately to severely active rheumatoid arthritis*

Mechanism of Action	Therapeutic Name	Phase 2	Phase 3	FDA Approval	Health Canada Approval	Phase 4
Anti-IL-4R alpha (IL4/IL13)	Dupilumab	✓ !@# [1]	✓ !@# [2]	✓	✓	✓ !@# [3]
Anti-IL-13	Tralokinumab	✓ ! [4]	✓ !@ [5]	✓	✓	
	Lebrikizumab	✓ ! [6]	✓ !@ [7]			
Anti-IL-31	Nemolizumab	✓ !@ [8]	✓ !@ [9]			
Anti-JAK1	Upadacitinib	✓ ! [10]	✓ !@ [11]	✓	✓	
	Abrocitinib	✓ ! [12]	✓ !@ [13]	✓		
Non-Specific Anti-JAK1/2	Baricitinib	✓ ! [14]	✓ !@# [15]			

Table 2. New and emerging therapies in clinical development for the treatment of Atopic Dermatitis (Eczema) as of April 2022.[5]

Green *(Approved for use);* **Orange** *(Clinical development ongoing - Not approved);* **Yellow** *(Not filing for approval in North America)*

Disease Severity: M (moderate); MS (moderate-to-severe); S (severe)

Study Population: ! (Adult); @ (Adolescent); # (Children)

*Study status "Completed" unless labelled with any of the following: $ (Active, not recruiting); ^ (Active, recruiting); * (Terminated)*

[1] *Dupilumab Phase 2 Clinical Trials: NCT02407756[@#MS], NCT01859988[!MS], NCT02210780[!], NCT01639040[!MS], NCT01979016[!MS], NCT01548404[!MS], NCT03346434[#MS]*

[2] *Dupilumab Phase 3 Clinical Trials: NCT03346434[#MS], NCT01949311[$!MS], NCT02277769[!MS], NCT03912259[!MS], NCT02277743[!MS], NCT02260986[!MS], NCT02755649[!MS], NCT02395133[!MS], NCT03054428[@MS], NCT04678882[$@#MS], NCT03345914[#MS]*

[3] *Dupilumab Phase 4 Clinical Trials: NCT03293030[^!MS], NCT03667014[$!MS], NCT03389893[*!MS], NCT04358224[^!MS], NCT04447417[!@MS], NCT05203380[^@MS], NCT04823130[^!MS], NCT04033367[!MS], NCT04718870[#MS], NCT05265234[^!MS]*

[4] *Tralokinumab Phase 2 Clinical Trials: NCT04556461[$!MS], NCT02347176[!MS]*

[5] *Tralokinumab Phase 3 Clinical Trials: NCT05194540[^!@MS], NCT03587805[$!@MS], NCT03761537[!MS], NCT04587453[!MS], NCT03363854[!MS], NCT03526861[@MS], NCT03160885[!MS], NCT03131648[!MS]*

[6] *Lebrikizumab Phase 2 Clinical Trials: NCT02465606[!MS], NCT03443024[!MS], NCT02340234[!MS]*

[7] *Lebrikizumab Phase 3 Clinical Trials: NCT04250350[$@MS], NCT04178967[$!@MS], NCT04146363[$!@MS], NCT04250337[!@MS], NCT04626297[^!MS], NCT04392154[^!@MS], NCT05149313[^!@MS], NCT04760314[$!@MS]*

[8] *Nemolizumab Phase 2 Clinical Trials: NCT04921345[^#MS], NCT03921411[@MS], NCT01986933[!M,MS,S], NCT03100344[!MS], NCT04365387[^!@MS]*

[9] *Nemolizumab Phase 3 Clinical Trials: NCT03985943[$!@MS], NCT03989349[$!@MS], NCT03989206[^!@MS]*

[10] *Upadacitinib Phase 2 Clinical Trials: NCT02925117[!MS]*

[11] *Upadacitinib Phase 3 Clinical Trials: NCT03738397[!MS], NCT04195698[$!MS], NCT03569293[$!@MS], NCT03568318[$!@MS], NCT03607422[$!@MS], NCT03661138[$!@MS]*

[12] *Abrocitinib Phase 2 Clinical Trials: NCT03915496[!MS], NCT02780167[!MS]*

[13] *Abrocitinib Phase 3 Clinical Trials: NCT04345367[!MS], NCT03720470[!MS], NCT03796676[@MS], NCT03575871[!@MS], NCT03349060[!@MS], NCT03422822[$!@MS]*

[14] *Baricitinib Phase 2 Clinical Trials: NCT02576938[!MS]*

[15] *Baricitinib Phase 3 Clinical Trials: NCT03952559[^@#MS], NCT03559270[$!MS], NCT03435081[!MS], NCT03334422[!MS], NCT03334435[$!MS], NCT03733301[!MS], NCT03428100[$!MS], NCT03334396[!MS]*

	Dupilumab (Dupixent®)[1]	Tralokinumab (Adtralza®)[2]	Upadacitinib (Rinvoq®)[3]	Abrocitinib (Cibinqo®)[4]
Patient Population per Health Canada	6 years and older	18 years and older	12 years and older	18 years and older
Indications	Moderate-to-severe AD, asthma, severe chronic rhinosinusitis with nasal polyposis	Moderate-to-severe AD	Moderate-to-severe AD, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis	Moderate-to-severe AD
Contraindications	Hypersensitivity to dupilumab	Hypersensitivity to tralokinumab	Hypersensitivity to upadacitinib	Antiplatelet therapies except for low-dose aspirin during the first 3 months of treatment
Relative Contraindications and/or Black Box Warnings	Pregnancy	Pregnancy	Pregnancy; Breastfeeding; Active serious infection, hematologic disorders, severe renal and/or hepatic impairment, malignancy, thrombosis	Pregnancy; Breastfeeding; Active serious infection, hematologic disorders, severe renal and/or hepatic impairment, malignancy, thrombosis, major adverse cardiovascular events
Route of Administration	Subcutaneous Injection	Subcutaneous Injection	Oral	Oral
Mode of Action	Anti-IL-4R alpha (IL4/IL13)	Anti-IL-13	JAK1 Inhibitor	JAK1 Inhibitor
Adverse Events (based on product monograph, >1%)	a) Injection site reactions (9.7% dupilumab, 5.5% placebo) b) Conjunctivitis (9.7% dupilumab, 3.2% placebo) c) Oral herpes (3.6% dupilumab, 1.6% placebo)	a) Upper respiratory tract infections (ECZTRA 1/2: 23.8% 300 mg, 20.2% placebo; ECZTRA 3: 29.0% 300 mg, 15.1% placebo) b) Injection site reactions (ECZTRA 1 & 2: 7.3% 300 mg, 4.0% placebo; ECZTRA 3: 10.7% 300 mg, 0.8% placebo) c) Conjunctivitis (ECZTRA 1 & 2: 5.1% 300 mg, 1.8% placebo; ECZTRA 3: 11.1% 300 mg, 3.2% placebo)	a) Upper respiratory tract infection (25.4% 30 mg, 22.6% 15 mg, 16.5% placebo) b) Acne (15.1% 30 mg, 9.6% 15 mg, 2.2% placebo) c) Herpes simplex (8.4% 30 mg, 4.1% 15 mg, 1.7% placebo)	a) Nasopharyngitis (8.7% 200 mg, 12.4% 100 mg, 7.9% placebo) b) Nausea (14.5% 200 mg, 6.0% 100 mg, 2.1% placebo) c) Headache (7.8% 200 mg, 6.0% 100 mg, 3.5% placebo) d) Herpes simplex (4.2% 200 mg, 3.3% 100 mg, 1.8% placebo)
Serious Adverse Events of Special Intertest (based on product monograph)	N/A	N/A	Malignancy (0 patient on placebo, 2 on 15 mg, 7 on 30 mg) Serious Infections (5 patients on placebo, 26 on 15 mg, 30 on 30 mg) Thrombosis (2 patient on placebo, 1 on 15 mg, 1 on 30 mg)	Malignancy (0 patients on placebo, 4 on 100 mg, 2 on 200 mg) Serious Infections (2 patients on placebo, 18 on 100 mg, 16 on 200 mg) Thrombosis (0 patients on placebo, 0 on 100 mg, 5 on 200 mg) Major Adverse Cardiovascular Events (0 patients on placebo, 1 on 100 mg, 2 on 200 mg)
Recommended screening and monitoring Blood Work	N/A	N/A	Screening: HepB, HepC, TB, LFT, CBC, lipid panel Monitoring: CBC, LFT, lipid panel	Screening: HepB, HepC, TB, LFT, CBC, lipid panel Monitoring: CBC, LFT, lipid panel

Table 3. Comparison of targeted systemics approved in Canada for moderate-to-severe atopic dermatitis (AD) as of April 2022.

	MEASURE Up 1[6]		Measure Up 2[7]		AD Up[8]		HEADS UP[9]
Treatment (upadacitinib versus placebo)	% of patients to achieve EASI75	% of patients to achieve IGA of 0 or 1	% of patients to achieve EASI75	% of patients to achieve vIGA of 0 or 1	% of patients to achieve EASI75	% of patients to achieve IGA of 0 or 1	% of patients to achieve EASI75
15 mg	70%	48%	60%	39%	65%	40%	
30 mg	80%	62%	73%	52%	77%	59%	71%
Placebo	16%	8%	13%	5%	26%	11%	
Dupilumab 300 mg							61%

Table 4: Summary of primary endpoint results from the Measure Up 1 and 2, AD Up, and HEADS UP upadacitinib Atopic Dermatitis trials.
EASI75 (at least 75% improvement from baseline in Eczema Area and Severity Index)
IGA (Investigator Global Assessment)

	JADE MONO-1		JADE MONO-2		JADE COMPARE	
Treatment (abrocitinib versus placebo)	% of patients to achieve EASI75	% of patients to achieve IGA of 0 or 1 & 2-point reduction	% of patients to achieve EASI75	% of patients to achieve IGA of 0 or 1 & 2-point reduction	% of patients to achieve EASI75	% of patients to achieve IGA of 0 or 1 & 2-point reduction
100 mg	40%	24%	44%	28%	58%	36%
200 mg	62%	44%	61%	38%	70%	48%
Placebo	12%	8%	10%	9%	27%	14%
Dupilumab 300 mg					58%	36%

Table 5: Summary of primary endpoint results from the JADE MONO-1, JADE MONO-2, and JADE COMPARE abrocitinib atopic dermatitis trials.[10]
EASI75 (at least 75% improvement from baseline in Eczema Area and Severity Index)
IGA (Investigator Global Assessment)

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CURRENT PHARMACOLOGICAL AND NON-PHARMACOLOGICAL THERAPIES FOR CHRONIC COUGH

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INTRODUCTION

Chronic cough, defined as cough lasting 8 weeks or longer, affects approximately 10% of adults globally, but with large global variations with prevalence estimates ranging from 2-18%.[1] The prevalence of chronic cough in adults over the age of 45 in the Canadian Longitudinal Study of Ageing (CLSA) was 16%, the second highest in the world.[2] Interestingly, the prevalence and incidence is higher in English speaking compared with French speaking participants.[3] Cough is the leading cause for ambulatory and primary care visits to physicians and one of the most common reasons for referral to specialist care.[4,5] Chronic cough is associated with aging, smoking, higher body mass index, use of an ACE-inhibitor, and airways diseases. More recently, novel data has shown that symptoms of depression and psychological distress independently increase the risk of developing chronic cough by approximately 20%.[6] Data from clinical trials and observational cohort studies suggest that patients with chronic cough have a median cough frequency of 20 coughs/hr.[7] This may lead to distressing physical, psychological and social consequences such as urinary incontinence, exhaustion, fatigue, anxiety, frustration, embarrassment and social isolation, which all impairs quality of life.[8] Chronic cough can be challenging to treat, since most over-the-counter therapies are ineffective and current treatments for chronic cough are all considered 'off-label'.[9,10] Although most cases are due to a benign cause, chronic cough can represent a serious underlying condition. A recent Canadian consensus has identified a simplified approach which can aid in the management of chronic cough and provide treatment for refractory or unexplained chronic cough.[11] The guiding principles of this approach

include i) investigation to rule out serious underlying conditions, ii) objective testing to prevent over and under-diagnosis, iii) treatment of identifiable diseases and traits and iv) monitoring to ensure effectiveness of treatment, including minimization of side effects and appropriate titration of treatment.

WHAT IS REFRACTORY AND UNEXPLAINED CHRONIC COUGH?

After conducting a thorough history, examination, and appropriate investigations, an underlying disease may be detected in patients presenting with chronic cough. Treatment targeting this/these condition(s) may completely or partially resolve cough. In such cases, the chronic cough is considered 'explained' and a symptom of the underlying condition. In cases where an associated condition is found but does not fully resolve with appropriate treatment, the cough is considered to be "refractory chronic cough" (RCC). In cases where no underlying disease is identified, the cough is described as 'unexplained chronic cough'(UCC).[12] In patients with both RCC/UCC there are often clinical features of cough hyper-sensitivity syndrome.

WHAT IS COUGH HYPERSENSITIVITY SYNDROME?

Patients often describe sensations of 'tickle', 'irritation', or 'something stuck in the throat'. Cough is often triggered by changes in temperature, perfumes, aerosols, strong smells, talking, laughing, and singing.[13,14] Cough Hypersensitivity Syndrome is considered an umbrella term to describe the neuro-pathological mechanisms within the central and peripheral nervous system which may be implicated in RCC/UCC.[14] This has been described as "Cough Hypersensitivity Syndrome", as many patients cough after exposure to low levels of thermal, chemical, or mechanical stimulation.[14,15]

WHAT IS THE UNDERLYING NEUROPHYSIOLOGY CAUSING EXCESSIVE COUGH?

Cough can be under both voluntary and involuntary control, but the cough reflex is the archetypal airway defensive reflex to prevent aspiration of foreign bodies or inhalation of noxious chemicals like smoke. The vagus nerve projects sensory afferents to the upper and lower respiratory tract, which, when stimulated, transmits signals to the brainstem. These signals are projected to cortical neurons in the thalamus and primary somatosensory cortex. If the stimulus is great enough, coughing will occur via the spinal motor efferent nerves to the diaphragm, intercostal muscles, and glottis. Excessive cough in patients with RCC/UCC could thus be due to i) increased activation of the airway peripheral nerve terminals by chemical irritants/mucus/alarmins (e.g., extracellular ATP), ii) hypersensitivity and/or hyper-responsiveness of the afferent vagal nerve, brainstem, and higher cortical projections and iii) impaired voluntary control and/or descending inhibitory control pathways. Recent studies suggest patients with RCC have impairment in the descending inhibitory control neurons[16] and a relative lack of voluntary cough suppression[17] compared to healthy controls.

WHAT TREATMENTS ARE CURRENTLY USED FOR REFRACTORY OR UNEXPLAINED CHRONIC COUGH

There are currently no approved treatments for RCC/UCC, thus the therapies described below are considered 'off-label' (**Table 1**). The American College of Chest Physicians (ACCP) and European Respiratory Society (ERS) suggest speech and language therapy and neuromodulators should be considered as appropriate therapies/interventions for the treatment of RCC/UCC.

Speech and Language Therapy

Speech and language therapy provides a safe and effective adjunct or alternate therapy in patients who do not wish to take neuromodulator medications or for those who develop intolerable side effects.[18] However, access to adequately trained therapists in the management of RCC/UCC can be challenging, and patient compliance with exercises is difficult beyond the initial 4 visits that are recommended as part of the speech and language therapy care algorithm.

Treatment of Neuromodulation

Neuromodulator treatment includes low-dose morphine[19], gabapentin[20], and pregabalin[21]. All three therapies demonstrate improved symptom control and improved quality of life in randomised controlled trials; however, these trials have been small, and the doses used in the RCTs were associated with high rates of adverse events, such as dizziness, drowsiness, unsteadiness, and fatigue. One study using amitriptyline 10 mg at bedtime reported symptomatic improvement but lacked a placebo control or a validated tool to assess improvements in cough.[22] In clinical practice, most patients are unable to tolerate the high doses of neuromodulators used in RCTs, hence it is recommended to start gabapentin at 100 mg TID and titrate up to a maximum of 300 mg TID, or to start pregabalin at 50-75 mg BID and increase on a weekly basis up to 150 mg twice a day. The use of low-dose opioid therapy can be attempted after discussion with the patient on the potential benefits and harms of treatment. Low-doses, between 5-10 mg of slow- or modified-release morphine BID may be effective, and in those who achieve clinical response, the benefit is often apparent

within 3-7 days.[19] Another recent study showed that treatment for one week can reduce objective cough frequency by up to 72%.[23] Hence, if the patient does not demonstrate clinical benefit after a 1–2-week trial, low-dose morphine can be discontinued. If there is benefit, then the dose can be titrated to minimize side effects such as constipation, drowsiness, and sedation. A clinical audit in a tertiary cough clinic has shown that approximately 36% of patients demonstrate a complete or partial response to low-dose morphine and nearly two-thirds develop no side effects.[24] If cough severity improves and side effects are mild, changing the dose and timing may be useful. Alternative regimens include once daily dosing at night, alternate day dosing, or, when required, 3-4 hours before socializing, teaching or attending important public events. In patients who have been on treatment for longer periods, short periods 'off-treatment' can be carefully attempted to prevent tolerance.

WHAT DOES THE FUTURE HOLD FOR REFRACTORY AND UNEXPLAINED CHRONIC COUGH?

In the absence of any licensed treatments, new treatments are desperately needed for RCC/UCC. Over the last 7 years, there have been successful studies demonstrating blockade of P2X3 ion channels found on peripheral airways nerves may be a successful strategy to reduce coughs.[25-27] Gefapixant is an oral, non-opioid, peripherally acting P2X3 antagonist which met its primary outcome in two phase 3 studies at a dose of 45 mg BID. Subjects in these studies had been diagnosed with RCC/UCC for at least 1 year prior to study entry, showed no abnormalities on chest radiology contributing to the cough (within 5 years of the study and after the onset of chronic cough), and had cough severity visual analog scale scores of ≥ 40 mm at both the screening and baseline visits. The primary endpoint in both studies was 24-hour cough frequency and safety/tolerability. The placebo adjusted estimated relative reduction in cough frequency was approximately 18% in COUGH-1 and 15% in COUGH-2.[25] These reductions were lower than expected due the significant placebo effect, the reasons for which are yet to be fully understood. The most prevalent side-effect was taste disturbance which was experienced by 60% and 69% of subjects at the highest dose of 45 mg compared with 3% and 8% of subjects in the placebo arm in COUGH-1 and COUGH-2 respectively. The putative mechanism is due to cross-selectivity against the hetero-trimer P2X2/3 which is thought to transmit taste from the tongue. Nonetheless, gefapixant has now been approved in Japan and Switzerland and is currently under-review by the U.S Food and Drug Administration (FDA), Health Canada and European Medicines Agency (EMA). Another P2X3 antagonist is currently under development by Bellus Health with its lead molecule BLU-5937 recently passing phase 2b with a placebo run-in study showing an approximate 34% reduction in 24-hour cough frequency with only a 6% taste disturbance.[26] Another P2X3 antagonist, sivopixant did not meet its primary endpoint in the phase 2b dose-finding study, but the optimum dose is still unknown.[27]

CONCLUSIONS

Chronic cough is a common troubling symptom that can severely affect the physical, social, and psychological well-being of patients. Current guidelines recommend treatment of any identifiable conditions, but if the cough is refractory or unexplained, speech and language therapy along with neuromodulator treatment, such as low dose opioids, pregabalin, and gabapentin, can be trialed. Clinicians should monitor and minimize the dose and length of treatment with centrally acting neuromodulator treatment to limit side effects and tolerability in a respiratory or specialized cough clinic. Emerging therapeutic agents such as the novel oral P2X3 antagonists may provide hope to patients in the years to come.

Name/Dose	Mechanism	Pros	Cons
Speech Therapy	Teaches cough suppression, avoid triggers, laryngeal exercises, hydration	No side effects Patient led	Access, Cost, Requires patient motivation Limited subjective improvement beyond initial 3-4 month treatment period, operator dependent 1 study of 24-hr cough frequency
Low-Dose Morphine 5-10 mg M/R BID	mu-opioid receptors	Fast onset 1-2 week trial	Nausea, drowsiness, unsteadiness, stigma, constipation 1 RCT with subjective endpoint
Pregabalin 150 mg BID	$\alpha 2\delta$-2 subunit of presynaptic voltage-gated calcium channels	Can start very low doses and titrate up	Drowsiness, hallucinations, suicidal ideation, weight gain, hair loss, difficult weaning off, 150 mg BID rarely tolerated 1 RCT with speech therapy, no improvement on spontaneous objective cough frequency
Gabapentin 300 mgTID	$\alpha 2\delta$-1 and $\alpha 2\delta$-2 (low affinity)	Can start very low doses and titrate up	Unsteadiness, dry mouth, nausea, sleepiness 1 RCT with subjective endpoint Cough monitoring for 1-hour only
Amitriptyline 10 mg -25 mg OID	TCA, serotonin/ noradrenaline reuptake inhibitor	Might also help with depression, anxiety	Tremor, dry mouth, weight gain, 1 uncontrolled study with unvalidated subjective endpoint

Table 1: Current Guideline Recommended Treatment Options for Refractory and Chronic Cough. OID; once per day BID; twice per day, RCT; randomised controlled trial, TCA; tricyclic anti-depressant

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ATOPIC DERMATITIS AND CANADIAN INDIGENOUS PEOPLES: BURDENS, BARRIERS, AND POTENTIAL FOR SOLUTIONS

BACKGROUND:

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease worldwide.[1,2,3] AD begins before age five in 90% of cases[4] and is associated with the development of comorbid conditions such as infections, environmental allergies, food allergies, asthma, anxiety/depression, and abnormalities in sleep, growth, and development. While personal experience suggests that Canadian Indigenous peoples, including children and youth, are facing burdens associated with AD, formal research studies addressing the impact of AD and skin disease in general on Canadian Indigenous peoples are lacking.

Canadian Indigenous* account for approximately 5% of the Canadian population.[5] Although Canadian Indigenous vary widely in geography, culture, language, and beliefs, they face common health disparities embedded in complex historical and social contexts related to factors such as colonization, intergenerational trauma from residential schools and institutionalization, racial segregation in the form of reservations, systemic racism, and being subjected to policies such as the 'Indian Act'.[6,7,8] This article reviews the burdens and barriers of AD in Canadian Indigenous by examining the literature, experiences of health care practitioners (HCPs), and media reports followed by proposing potential solutions to address such disparities.

BURDENS AND BARRIERS OF AD IN CANADIAN INDIGENOUS PEOPLES:

Cross-sectional and population-based Canadian studies demonstrate that AD is common among Canadian Indigenous children, but little is known about its prevalence in adults. According to the 2012 Regional Health Survey Ontario Final Report on Adults, Youth and Children Living in First Nations communities[9], the atopic triad (asthma, allergies and AD) were the top three reported conditions by children (age 0-11) and their caregivers in this population (**Table 1**). Asthma affected 15%, allergies affected 13%, and 'dermatitis/atopic eczema' affected 10% of those surveyed. Among Canadian Indigenous youth aged 12-18, the atopic triad was also among the most common conditions reported. In the same survey, skin disease data on adults was not available, although asthma and allergies were similarly identified as the most common chronic conditions (allergies affecting 23%, and asthma affecting 11%).

The British Columbia First Nations regional survey made similar findings[10], with the three most common health conditions in children being allergies (17%), asthma (12%), and 'dermatitis' (8%). Amongst youth, allergies (16%), and asthma (13%) were the top two most commonly reported conditions (AD data was not reported). In adults, there was no information on skin disease, although asthma was observed at higher than national average rates.

The 2018 national report of the compiled First Nations Regional Health Surveys[11] confirmed the high prevalence of the atopic triad among Canadian Indigenous children and youth: AD/eczema and asthma, respectively receiving treatment 69% and 64% of the time, were the top two chronic health conditions for which the highest percentage of First Nations children and youth reported receiving treatment (**Figure 2**) and for allergies, 38% of the

Chronic Health Condition	Boys (%)	Girls (%)	Total (%)
Asthma (n=753)	17.7	12.3	15.1
Allergies (n=749)	12.3	13.3	12.8
Dermatitis, atopic eczema (n=757)	10.1	10.9*	10.4
Chronic ear infections or ear problems (n=741)	7.7*	6.3	7
Speech/language difficulties (n=746)	8.3*	4.2*	6.3
Learning disability (n=744)	N/A	4.3*	4.2*
ADD/ADHD (n= 747)	3.8*	N/A	2.6*
Heart Condition (n=749)	1.6*	N/A	1.7*
Anxiety/Depression	N/A	N/A	1.0*

Table 1: First Nations Information Governance Centre/FNIGC (2012). First Nations Regional Health Survey (RHS) Phase 2 (2008/10) Ontario Region Final Report.

** High sampling variability; use value with caution*

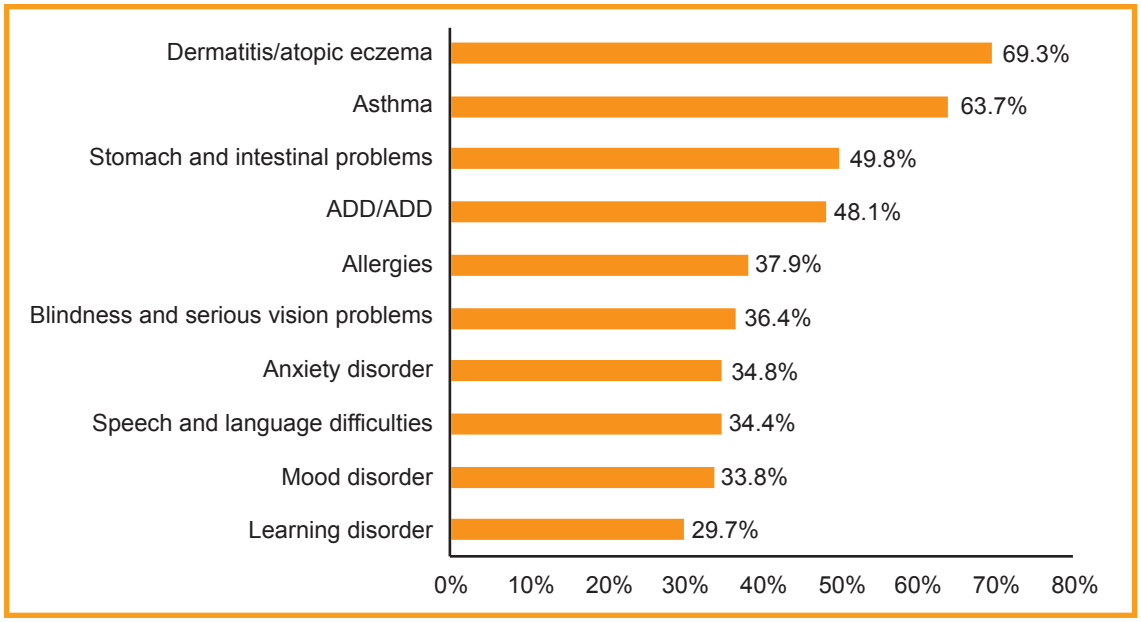


Figure 2: (FNIGC, 2018 'National Report of the First Nations Regional Health Survey Phase 3', Volume I, Figure 3.6).

time. These findings demonstrate the high burden and critical importance of these allergic diseases to Canadian Indigenous Peoples since patients and caregivers are seeking care despite the system-wide barriers and inequities. Barriers to care reported by all surveys included not only issues surrounding health care access, but also included elements related to social determinants of health such as transportation, cost, on-reserve housing conditions, water safety, and community infrastructure and implementation barriers. The limitations of these surveys include self-reported findings, sampling variability, and lack of understanding of the association between co-morbidities, outcomes and prognosis related to AD. Further research is needed in order to fully appreciate the scope of this problem.

The true prevalence of AD in Canadian Indigenous peoples may be under-estimated for a variety of reasons, including poor health care and specialist access, and due to under-representation in research engagement. A population-based survey of Indigenous children (n=182) conducted in 2014 in Labrador estimated the prevalence of AD to be 16.5%, with approximately two-thirds of cases being reported as moderate-to-severe.[12] In the north, recent cross-sectional surveys in Nunavut conducted within the last 5 years[13,14] demonstrated an overall higher prevalence of AD (range 8.6% to 25%) in both Inuit and mixed-ethnicity children (one parent Inuit), although these surveys were limited by small sample sizes. Additional efforts across multiple levels are required to better engage and empower the Canadian Indigenous community in research with the goal of optimizing health outcomes.

With regards to direct clinical experience, the first author (RA) has been conducting remote and northern outreach clinics around Saskatchewan in the form of in-person and virtual care/teledermatology for several years. She has observed a high and concerning burden of poorly controlled, functionally debilitating AD[15,16], particularly in the Indigenous pediatric population, which is often exacerbated by skin infections (eg. impetigo, MRSA [methicillin-resistant Staphylococcus aureus]). No systematic approach to the documentation of this observation exists, however, which addresses the direct clinical experience of HCPs in Indigenous skin health.

Perhaps most concerning are the media reports, mainly out of remote and northern Indigenous communities in eastern Canada, demonstrating potential for normalization of chronically infected and infested pediatric AD.[17-25] Many of these reports directly reference eczema/AD, impetigo, and scabies as poorly managed. As those with AD are at elevated risk for skin infections due to an impaired skin barrier and antimicrobial immune response, the challenges experienced by communities such as crowded housing on reserves, and lack of access to primary and specialist care may aggravate these issues and cause them to persist.

POTENTIAL FOR SOLUTIONS:

Although fully addressing the complex and deeply ingrained health disparities faced by Canadian Indigenous peoples is beyond the scope of this article, there are steps that HCPs can take to help alleviate this burden and contribute to both short- and long-term solutions. From a non-clinical standpoint, clinicians should seek out educational initiatives aimed at improving cultural sensitivity, such as online courses offered by the University of Alberta[26] and University of Saskatchewan.[27] From a

clinical standpoint, the management of common skin conditions encountered among Canadian Indigenous peoples, such as AD and impetigo, should be highlighted in medical curriculums, especially for nurses and primary care physicians who are at the frontlines of care in remote and northern communities. Access to specialists is generally limited due to long wait times and the lack of geographic dispersion among specialists in remote communities. In order to truly enhance Indigenous Health, a tailored approach to address the unique disparities that Indigenous Peoples face is needed. Other practical tips and calls to action include:

- ✓ Keeping AD skin care as simple as possible to assist patients and caregivers, such as using pictorial-based handouts (such as those offered by the Eczema Society).[28]
- ✓ Prescribing adequate-sized topical therapy (e.g. 454 gram tubes) rather than small quantities (e.g. 15 or 30 gram tubes) including repeat prescriptions to reduce trips to pharmacy, dispensing fees, and provide enough therapy to optimally manage disease.
- ✓ Becoming familiar with NIHB coverage for AD. Examples include that NIHB covers bland moisturizers through prescription for those with AD, and that biologic therapy with dupilumab for moderate-to-severe AD does not require trials of methotrexate or cyclosporine.
- ✓ Development and delivery of nursing-led therapeutic educational models for AD management is needed in both online and conventional frameworks.[29,30]
- ✓ Advocating for phototherapy services for AD and other skin disorders in high population catchment areas, such as northern Ontario, may alleviate burdens of immunosuppression from alternative agents such as methotrexate and cyclosporine.
- ✓ Advocating for telemedicine initiatives, which may improve health from a cost, quality, and access standpoint.[31,32]
- ✓ Development of a national, interdisciplinary focus group to tackle burdens of AD and communicable infectious disease in northern and remote Canadian Indigenous communities.[33,34]
- ✓ Indigenous community engagement and empowerment, as well as Indigenous authorship is strongly needed in inter- and transdisciplinary research initiatives. The AAAAI/ACAAI approach has prioritized this in developing AD guidelines[42]
- ✓ National summits to increase awareness, HCP engagement, and direct perspective on interdisciplinary action plans.

CONCLUSIONS:

Although more information is needed, the current literature, multiple lines of evidence (i.e., clinical experience of HCPs, media reporting, and limited scientific reports) demonstrate the depth of impact of AD in Canadian Indigenous populations. The literature suggests that the atopic triad, starting with AD, represents the most common set of chronic health conditions seen in Indigenous children and youth. Especially when moderate-to-severe, those suffering from AD have been documented to face physical, mental, emotional, psycho-social and financial burdens due to their disease.[35,36] Thus, strategies must be implemented to tackle AD in these populations. Given the recent calls to action by the Truth and Reconciliation report,[37] the United Nations Declaration on the Rights of Indigenous peoples,[38] concerns for mass gravesites on residential school grounds, and the Pope's acknowledgement of cultural genocide, urgent calls to action must be heeded and acted upon. More research and information on AD is needed in Canadian Indigenous adults, and transdisciplinary research and integrated knowledge transfer approaches involving a wide variety of stakeholders, including Indigenous community members, with the ultimate goal of tangible health outcomes are needed.[39-41] A systematic scoping review of North American Indigenous skin and atopic disease led by the authors of this review, RA and DC, is currently underway, which may further shed light on regional and national issues in this field.

Footnotes: *The Canadian Constitution of 1982 defines "Aboriginal" peoples of Canada to encompass First Nations, Metis, and Inuit. Terms such as the use of "Indian" and "Eskimo" are considered outdated.

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IDENTIFYING DERMATOLOGICAL EMERGENCIES IN OUT-PATIENT CARE: WHEN TO BE WORRIED

INTRODUCTION

Dermatological emergencies require early identification and must be addressed immediately. According to a study from 2005, dermatological concerns constitute 15-20% of visits to family physicians and emergency departments. Understandably, different cutaneous manifestations may be challenging to categorize as the presentation of various lesions may overlap with respect to the diagnosis. It is essential for physicians providing outpatient care to consider that although lesions may only appear to be manifesting on the skin, systemic involvement may be a factor or may follow depending on the pathology of the underlying illness. As physicians seeing patients in outpatient care settings may be the first point of contact for patients, familiarity with the identification of specific lesions, the timeline of their occurrence, signs and symptoms at presentation, and their causes are valuable information needed to determine the urgency of their patients' situation. This article identifies some common lesions of concern that may require closer attention and some of the dermatological emergencies associated with these lesions.

PRESENTING LESIONS OF CONCERN

Morbilliform eruption

Morbilliform refers to a lesion that resembles measles in its morphology and distribution.[2] Morbilliform eruptions can be described as symmetrical, erythematous blanching macules and papules.[3]

Palpable purpura

Palpable purpura is usually the consequence of vascular inflammation in the skin and extravasation of blood, and can be described as firm, raised palpable discoloration of the skin or mucous membranes, which can be several centimeters in diameter.[4] Patients with purpuric rashes and febrile or signs of toxicity require emergent evaluation.[5]

Petechiae

Petechial rashes are associated with several causes, including trauma, hematological abnormalities, and infection resulting in hemorrhage into the dermis.[6] They can affect the skin and mucous membranes and are characterized as non-blanching pin-point spots, measuring less than 2 mm in size.[6] The characteristic difference between purpura and petechiae is that petechiae spots measure less than 2 mm.

Violaceous lesions

The term violaceous refers to a bluish-purple colour and can characterize many lesions, some of which may not necessarily be an emergency. When seeing a violaceous lesion, it is essential to recognize that these lesions may potentially indicate early signs of necrosis or hemorrhage.

Bulla

Bulla refers to blisters which are greater than 5 mm in diameter. The rapid evolution of skin lesions to bulla can be cause for concern.

Table 1 provides a summary of these above-mentioned lesions of concern and the dermatological emergencies associated with them.

STEVENS-JOHNSON SYNDROME (SJS)/ TOXIC EPIDERMAL NECROLYSIS (TEN)

SJS and TEN are variants of a single entity which are distinguished by whether they involve less than 10% of the total body surface area or greater than 30%, respectively.[7] They begin as acute medical emergencies characterized by peeling of the skin that subsequently progresses to potentially life-long consequences (pigmentation, xerosis, alopecia, etc.). SJS and TEN are associated with systemic symptoms, multi-organ involvement, and mucocutaneous manifestations. The incidence of SJS/TEN is approximately 4–6 cases per million person/year. The mortality rate for SJS is approximately 5% and approximately 40% for TEN. Analysis has shown that 50% of cases of SJS and 80–90% of cases of TEN are caused by medication use (**Table 2**) and occur 4 to 21 days after initiating the implicated medication. Systemic symptoms occur 1-3 days before mucocutaneous lesions and are characterized by fever, malaise, cough, rhinorrhea, and difficulty swallowing.[8] Cutaneous lesions of SJS and TEN generally appear first on the face and thorax, followed by symmetrical spreading to other parts of the body. Early cutaneous lesions begin as erythema and rapidly

Lesion	Differential Diagnosis
Morbilliform Eruption	TEN/SJS DRESS Rickettsial infections Viral infection
Palpable Purpura	Meningococcemia Disseminated gonococcal disease Endocarditis Henoch-Schönlein purpura (HSP) Rocky mountain spotted fever
Bulla(e)	Bacterial infection (impetigo, cellulitis) Viral infection (HSV, hand-foot-mouth) TEN/SJS Mucous membrane pemphigoid Meningococcemia Necrotizing fasciitis Staphylococcal scalded skin syndrome
Petechiae	Purpura fulminans Disseminated intravascular coagulopathy (DIC) Thrombotic Thrombocytopenia Purpura (TTP)
Violaceous	Necrotizing fasciitis

Table 1: Lesions of Concern and Possible Dermatological Emergencies[5,16]; courtesy of Rao, MD and Motamedi, MD

Drug Class	Drug Name
Xanthine oxidase inhibitors	Allopurinol
Antibiotics	Trimethoprim-Sulfamethoxazole other sulfonamide antibiotics Aminopenicillins Cephalosporins Quinolones
Aromatic anticonvulsants	Carbamazepine Phenytoin Phenobarbital
Oxicam NSAIDs	Diclofenac Etodolac Indomethacin Ketorolac Nabumetone Sulindac

Table 2: Drugs with a "high" risk of inducing SJS/TEN[17]; courtesy of Rao, MD and Motamedi, MD

progress into a blistering, maculopapular eruption followed by skin sloughing.[8] Early identification of signs and symptoms is paramount to reducing mortality, as increased mortality is associated with the involvement of a large proportion of total body surface area.[9] However, prodromal symptoms that initially present may be considered typical influenza-like symptoms, which patients may not consider as necessitating the need to visit their primary care provider. For this reason, patients who present with systemic illness, symmetrical and diffuse erythema after recently starting a medication must be immediately evaluated for SJS/TEN. Management of SJS or TEN requires a multidisciplinary approach. The implicated drug, should be discontinued, and immediate intensive care support initiated.

DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

DRESS is a morbilliform drug eruption that causes an array of clinical symptoms involving multiple organ systems and the skin. Its reported incidence is estimated at more than 10 cases per million per year and current research is not conclusive on whether a racial predilection exists for the diagnosis of DRESS. The median age at diagnosis is approximately 51 years for men and 55 years for women with less than 10% of patients being younger than 20 years.[10] As the name suggests, the offending trigger in DRESS is a medication; high-risk culprits are listed in **Table 3**. The symptoms of DRESS are latent and may begin anywhere from 2 to 3 weeks after initiating the offending drug. Patients usually present with a widespread pruritic, maculopapular, morbilliform rash, symmetric across the trunk and extremities. Other clinical symptoms include facial edema, enlarged lymph nodes, and a fever of >38oC.[10] The overlapping presentation of DRESS and SJS/TEN is undeniable. However, the key to the differential diagnosis between these illnesses is that patients with DRESS usually do not have mucosal surface and palm involvement. The rash in DRESS patients is also pruritic, whereas, in SJS/TEN, this is not the case.[11]

DRESS management includes the immediate cessation of the instigating medication, supportive care, and inpatient monitoring depending on the severity of the symptoms. Symptom relief involves the use of systemic corticosteroids, which commonly result in dramatic improvements.[10]

Carbamazepine
Phenytoin
Phenobarbital
Zonisamide
Mexiletine
Lamotrigine
Dapsone
Salazosulfapyridine
Allopurinol
Minocycline
Abacavir
Nevirapine

Table 3: Drugs with a "high" risk of inducing DRESS[10]; courtesy of Rao, MD and Motamedi, MD

MENINGOCOCCEMIA

Meningococcemia is a severe and life-threatening infection caused by meningococci bacteria (*Neisseria meningitidis*). Although meningococcemia can affect patients of any age, the greatest number of reported cases are in children < 1 yr and adolescents between the ages of 16 and 23 years of age.[12] Clinical manifestations of meningococcemia involve multiple organ systems. In the early stage, symptoms can include an upper respiratory tract infection (URTI), fever, headache, vomiting, lethargy, and in 70% of cases, a non-blanching petechial/purpuric rash, commonly on the trunk or extremities.[12] Meningococcemia is a medical emergency, and therefore if it is suspected, immediate hospital referral is necessary.

NECROTIZING FASCIITIS (NF)

Necrotizing fasciitis (NF) describes a group of relatively uncommon, but life-threatening infections of the skin, soft tissues, and muscles. The annual incidence of NF is estimated at 500–1,000 cases and its prevalence globally has been reported to be 0.40 cases per 100,000 population with a reported predilection for men, with a male-to-female ratio of 3:1.[13] Early identification of NF can result in the salvage of soft tissue, the reduced chance or extent of amputation, and possibly reduced mortality for patients. Breakage of the skin, whether it be from a laceration, burn, or surgical procedure, is strongly associated with NF.[13] Any age group is susceptible to NF; however, those > 50 years of age are more likely to be affected due to the increased prevalence of co-morbidities in this age group, including diabetes and other vascular diseases.[13] In its early stage, NF may be resemble a soft-tissue infection, such as cellulitis. However, with NF, the infection initially occurs in the fascia. Therefore, margins of the erythema, which lend to the suspicion of a soft-tissue infection, are usually ill-defined with NF. As a result, the pain in the area extends and is much more exaggerated than what clinicians would expect to see with a soft-tissue infection.[14] If left unaddressed or in the case of the lack of clinical response to treatment, a violaceous dusky lesion begins to form about 3 to 5 days after initial symptoms appear, followed by bulla formation and necrosis. Patients may also present with signs and symptoms of septic shock such as being febrile, tachycardic, and hypotensive.[15] The hallmark feature of NF is pain that is disproportional to cutaneous symptoms. Patients who present in this manner and present with other systemic symptoms, including malaise, lethargy, and disorientation, should be assessed immediately.[15] NF is a rapidly progressing infection; prompt identification and the use of anti-microbial therapy are necessary. Patients with suspected NF should be hospitalized. The monitoring of other organ systems is essential to controlling the severity and progression of the infection.[15]

SUMMARY AND CLINICAL PEARLS

This article has identified a small number of diseases that would constitute a dermatological emergency. However, identifying lesion types and the significance of their distribution pattern is important, particularly when those lesions occur abruptly. Clinicians should take care to note some of the presenting symptoms discussed here, the drug products that may induce certain conditions (SJS/TEN/DRESS) and refer patients for hospitalization as required.

Important considerations when assessing a patient who reports unusual and abrupt cutaneous lesions

- ✓ Abrupt cutaneous lesions accompanied by signs of cognitive impairment and multi-system involvement commonly constitute an immediate need for urgent care
- ✓ Patients who are on immunomodulating medications or have a chronic illness that makes them immunosuppressed may be more susceptible to hypersensitivity reactions and aggressive infections
- ✓ Lesions that distribute symmetrically and begin as erythema with rapid (1-2 days) progression into maculopapular rashes followed by (2-3 days) bullae formation require immediate attention
- ✓ Pain which is out of proportion in areas of suspected subcutaneous infection should be thoroughly worked up
- ✓ Failure of conventional treatments and escalated worsening of symptoms should be indicative of the need for urgent care
- ✓ A thorough history of new medications started within the last several weeks should be taken when morbilliform eruptions are present
- ✓ Timing can be crucial for improved outcomes; if a patient's onset of symptoms has been > 48 hours and they or their family report rapid debilitation in health, an immediate need for hospitalization is required

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