



Superior skin clearance (PASI 100) demonstrated vs. Tremfya

Percentage of patients achieving
PASI 100 at week 12, NRI*

Taltz, 41%, Tremfya, 25%;
 $p < 0.001$

NRI=non-responder imputation.

Indication:

Taltz is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Relevant warnings and precautions:

- Infections including tuberculosis
- Serious hypersensitivity reactions (including anaphylaxis)
- Patients with inflammatory bowel disease
- Immunizations
- Pregnant and nursing women
- Fertility
- Geriatrics

For more information:

Please consult the product monograph at www.lilly.ca/taltzpm/en for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece. The product monograph is also available by calling us at 1-888-545-5972.

Reference: 1. Blauvelt A, Papp K, Gottlieb A, et al. A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe plaque psoriasis: 12-week efficacy, safety and speed of response from a randomized, double-blinded trial. *Br J Dermatol.* 2019; DOI:10.1111.bjd.18851.

* IXORA-R: 24-week, multicentre, randomized, double-blind, parallel-group study. Patients were randomized to Taltz (n=520), 160 mg at week 0, 80 mg Q2W to week 12, then 80 mg Q4W, or Tremfya (n=507), 100 mg at week 0 and 4, then 100 mg Q8W. The primary endpoint was the proportion of participants achieving 100% improvement from baseline in Psoriasis Area Severity Index (PASI 100) at week 12.



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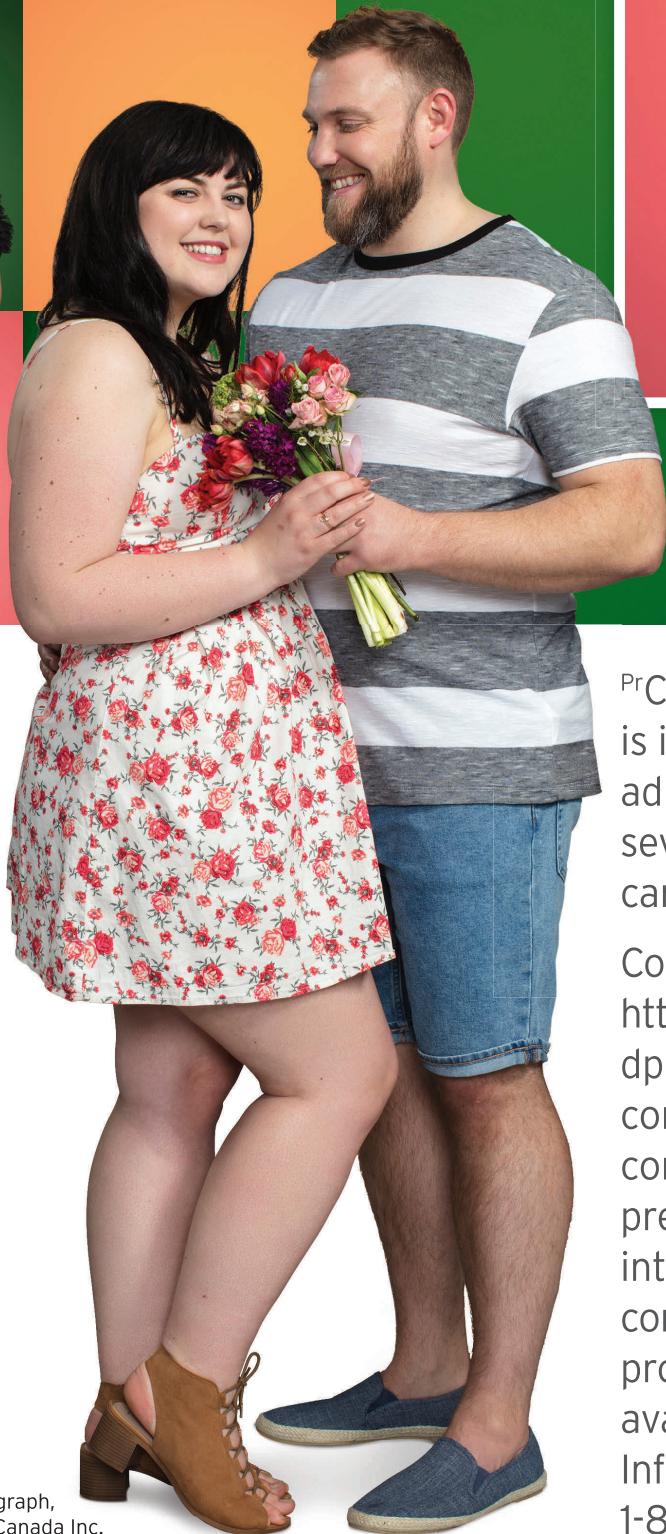
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Reference:

1. CIMZIA® Product Monograph,
November 13, 2019. UCB Canada Inc.



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patients with
moderate to severe
plaque psoriasis¹**

PrCIMZIA® (certolizumab pegol) is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy.¹

Consult the product monograph at <https://health-products.canada.ca/dpd-bdpp/index-eng.jsp> for the complete list of indications, contraindications, warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use. The product monograph is also available through Medical Information Services at 1-866-709-8444.



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The *Journal of Cutaneous Medicine and Surgery* (JCMS) is a bimonthly refereed journal which aims to reflect the state of the art in cutaneous biology and medical and surgical dermatology by providing original scientific writings, as well as complete critical reviews of the dermatology literature for clinicians, trainees, and academicians. The journal endeavours to bring readers cutting-edge dermatologic information by featuring scholarly research and articles on issues of basic and applied science and in-depth reviews, all of which provide a theoretical framework for practitioners to make sound practical decisions. The evolving fields of dermatology and dermatologic surgery are highlighted through these articles.

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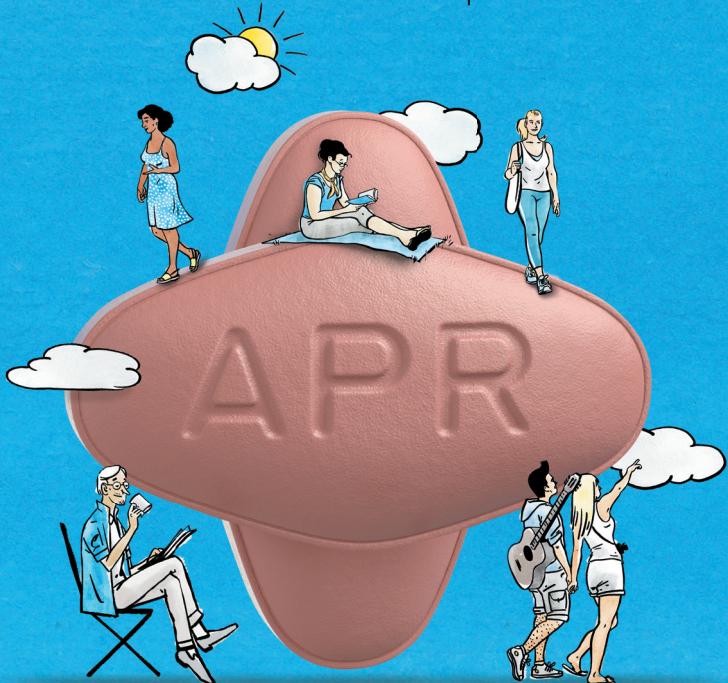
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OTEZLA® (apremilast) is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. OTEZLA, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response, intolerance, or contraindication to a prior disease-modifying anti-rheumatic drug (DMARD).¹

Consult the Product Monograph at <https://www.amgen.ca/products/~media/FB841218E06B4508B0E7213BC578E641.ashx> for important information on contraindications, conditions of clinical use, warnings, precautions, adverse reactions, drug interactions, dosing instructions, and dosage adjustments in patients with severe renal impairment.

The Product Monograph is also available by calling us at 1-866-502-6436.

References:

1. OTEZLA® Product Monograph. Amgen Canada Inc. January 22, 2020.
2. Amgen Canada Inc. Data on file (JAN2020 MedReg Letter).

PR-OTZ-CAN-000020



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 **Pr**
SILIQ[®]
(brodalumab injection)
210 mg/1.5 mL

IN MODERATE TO SEVERE PLAQUE PSORIASIS

HER GOAL: COMPLETE CLEARANCE

Help her reach it with SILIQ^{®†}

PASI 100 RESPONSE ACHIEVED

Complete clearance (PASI 100 response) achieved in plaque psoriasis with SILIQ vs. ustekinumab at Week 12[‡]

44% vs. 22%

p<0.05 (primary endpoint)

Indication and clinical use:

SILIQ (brodalumab) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

No dose adjustment is recommended in geriatric patients.

Not indicated in children < 18 years of age.

Contraindication:

- Crohn's disease

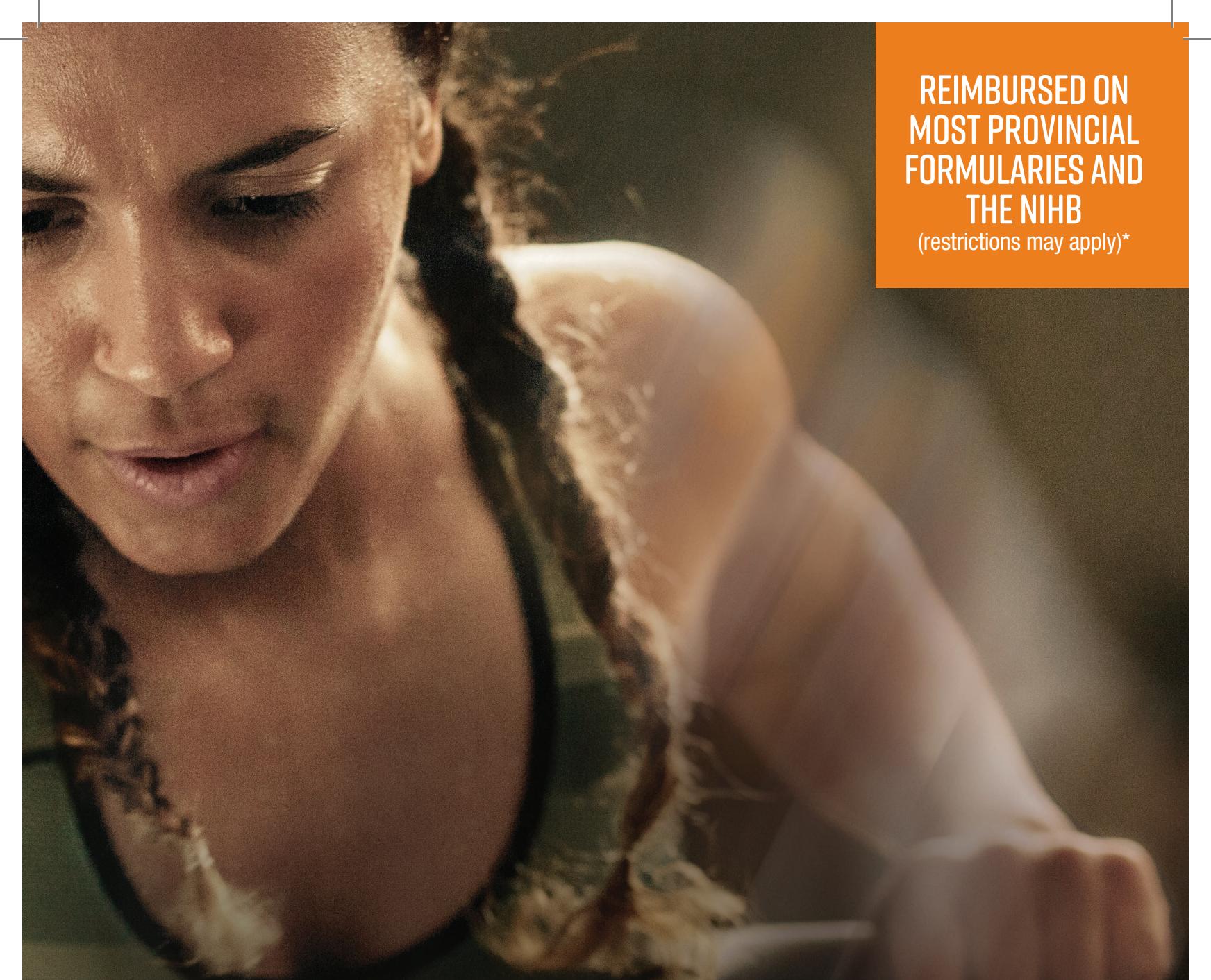
Most serious warnings and precautions:

Suicidal ideation and behaviour: Suicidal ideation and behaviour, including completed

suicides, have occurred in SILIQ patients. A causal association with SILIQ has not been established. Weigh the potential risk/benefit in patients with a history of depression, suicidal ideation, or behaviour, prior to prescribing. Refer patients with new or worsening suicidal ideation and behaviour to a mental health professional. Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behaviour, new onset or worsening depression, anxiety, or other mood changes. Because of this risk, if an adequate response to SILIQ has not been achieved within 12 to 16 weeks, consider discontinuing therapy.

Other relevant warnings and precautions:

- Prescribers are to register in the SILIQ Patient Support Program before prescribing SILIQ, be educated on the appropriate use of SILIQ, and educate patients on benefits and risks of treatment, especially the risk of suicidal ideation and behaviour.
- Discontinue SILIQ if the patient develops Crohn's disease while taking SILIQ.
- SILIQ may increase risk of infections.
- Exercise caution when considering the use of SILIQ in patients with a chronic infection or a history of recurrent infection.
- Evaluate patients for tuberculosis (TB)



**REIMBURSED ON
MOST PROVINCIAL
FORMULARIES AND
THE NIHB**
(restrictions may apply)*

1ST AND ONLY BIOLOGIC THAT SELECTIVELY BINDS TO AND BLOCKS IL-17 RECEPTOR A[§]

prior to initiating SiliQ treatment. Do not administer SiliQ to patients with active TB. Initiate treatment for latent TB prior to administering SiliQ. Monitor SiliQ patients for signs and symptoms of active TB.

- Live vaccines should not be given concurrently with SiliQ. Patients may receive inactivated or non-live vaccinations.
- Discontinue and initiate appropriate therapy if anaphylactic or other serious allergic reaction occurs.
- No adequate and well-controlled studies

have been conducted in pregnant women.
• Caution in nursing women.

For more information:

Please consult the Product Monograph at https://pdf.hres.ca/dpd_pm/00051682.PDF for important information relating to adverse reactions, drug interactions, and dosing information that has not been discussed here. The Product Monograph is also available by calling 1-800-361-4261.

NIHB: Non-Insured Health Benefits Program; PASI: Psoriasis Area Severity Index; IL-17: interleukin-17; SC: subcutaneous

*Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, Québec, Saskatchewan.

Please refer to the respective formularies for coverage information.

†Fictitious patient. May not be representative of all patients.

‡AMAGINE-2 study: A randomized, double-blind, active comparator trial assessing the efficacy and safety of SiliQ in adult patients with moderate to severe plaque psoriasis, defined as a minimum body surface area of 10%, a PASI score ≥ 12 , a static Physician's Global Assessment score ≥ 3 on a severity scale of 0 to 5 in the overall assessment, and who were candidates for systemic therapy or phototherapy. Patients received either SiliQ (210 mg SC at Weeks 0, 1, and 2, followed by the same dose every two weeks through Week 12; n=612), ustekinumab (45 mg SC for patients ≤ 100 kg, or 90 mg SC for patients > 100 kg at Weeks 0, 4, and 16, followed by same dose every 12 weeks; n=300), or placebo (n=309).

§Comparative clinical significance is unknown.

References:

1. SiliQ (brodalumab) Product Monograph, Bausch Health, Canada Inc., June 7, 2019.
2. Data on file, Bausch Health, Canada Inc.



PROGRAMME DE SANTÉ DE LA PEAU

CHERCHEZ LE LOGO!

Le Programme de santé de la peau est une initiative de l'Association canadienne de dermatologie qui aide les consommateurs à choisir, pour la peau, les cheveux et les ongles, des produits qui sont sains. Appuyé par des dermatologues certifiés, le Programme de santé de la peau offre des conseils d'experts portant sur des habitudes dermatologiques meilleures et optimales.

Le sceau de reconnaissance du programme identifie les produits non parfumés, peu irritants, qui ne contiennent pas d'allergènes de contact les plus courants et sont non comédogènes.



dermatology.ca/skin-health-program



SKIN HEALTH PROGRAM

LOOK FOR THE LOGO!

The Skin Health Program is a Canadian Dermatology Association initiative that helps guide consumers to select healthy skin, hair and nail products.

Backed by certified dermatologists, the Skin Health program provides expert advice for better and best dermatological practices.

The program's seal of recognition identifies products that are: fragrance-free, have a low potential for irritation, do not contain the most common contact allergens and are non comedogenic.



dermatology.ca/skin-health-program

Programme de santé de la peau

Produits reconnus



Reconnu
Santé de la peau
CDA-ACD

LES PRODUITS RECONNUS SATISFONTENT AUX CRITÈRES SUIVANTS :

- ✓ Faible risque d'irritation
- ✓ Sans parfums ou non-parfumé
- ✓ Ne contenant aucun des allergènes les plus courants
- ✓ Non comédogène

- Avène Eau Thermale
- Bioderma Sensibio H2O
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- CeraVe crème hydratante
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- Cetaphil Lotion hydratante
- Cetaphil Lotion hydratante ultra DailyAdvance
- Cetaphil Nettoyant doux moussant
- Cetaphil Nettoyant doux pour la peau
- Cetaphil nettoyant pour la peau grasse
- CW Beggs & Sons Anti-rides Defense Yeux
- CW Beggs & Sons Après-rasage Peau sensible
- CW Beggs & Sons Crème À Raser Hydratante
- CW Beggs & Sons Crème Ultra-hydratante Peau sèche
- CW Beggs & Sons Exfoliant Visage
- CW Beggs & Sons Exfoliant Visage Anti-brillance+
- CW Beggs & Sons Gel Yeux Énergisant
- CW Beggs & Sons Hydratant Anti-brillance+
- CW Beggs & Sons Hydratant Anti-rides Défense
- CW Beggs & Sons Hydratant Énergie+
- CW Beggs & Sons Hydratant Peau sensible
- CW Beggs & Sons Mousse à raser Peau sensible
- CW Beggs & Sons Nettoyant Visage Anti-brillance+
- CW Beggs & Sons Nettoyant Visage Énergie+
- CW Beggs & Sons Nettoyant visage Peau sensible
- CW Beggs & Sons Ultra-hydratant mains et corps
- Dermablend Camo Liquide Lissant Fond de Teint A Couvrance Moyenne
- Eucerin Lotion Hydratante Complete Repair 5% Urée
- Eucerin Lotion intensive Complete Repair 10% Urée
- Garnier Clean + Démaquillant Apaisant Lingettes Nettoyantes
- Garnier Clean + Gel Nettoyant Clarifiant Doux
- Garnier Clean + Lotion Nettoyante Démaquillante
- Garnier Moisture Rescue Lotion de Jour Hydratante Sans Parfum Peau Sensible
- Garnier SkinActive Eau Micellaire

- Garnier SkinActive Eau Micellaire (maquillage hydrofuge)
- Garnier SkinActive Eau Micellaire Matifiant Tout-En-1
- Garnier SkinActive Eau Micellaire Tout-En-1 Peau Sèches et Sensibles
- Garnier Skinactive Linglettes Micellaires Démaquillantes
- Garnier SkinActive Linglettes Micellaires Démaquillantes Hydrofuge tout-en-un
- La Roche-Posay Toleriane Sensitive
- L'Oréal Paris Revitalift Cicacream
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- L'Oréal Paris Revitalift Triple Power LZR Concentrate
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- Marcelle Mascara Xtension Skyline
- Marcelle Moussant Gel Nettoyant Ultradoux
- Marcelle New Age Uplift Crème Contour Des Yeux
- Marcelle New Age Uplift Crème De Jour Peaux Sèches
- Marcelle New Age Uplift Crème De Jour Tous Types De Peaux
- Marcelle New Age Uplift Crème De Nuit
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- Marcelle pour Thyme Maternité Crème Raffermissante et Tonifiante
- Marcelle pour Thyme Maternité Huile de Corps Hydratante
- Marcelle pour Thyme Maternité Hydratant Visage Soin Perfecteur + Éclat
- Marcelle pour Thyme Maternité Crème Triple Action pour Vergetures
- Marcelle Revival + Skin Renewal Serum Anti-Age 360 Redensifiant
- Marcelle Revival+ Advanced Crème Jour + Serum
- Marcelle Revival+ Advanced Crème Nuit + Serum
- Marcelle Tampons Démaquillant Pour les Yeux Express Hydrofuge - Sans Huile
- Marcelle Tampons Démaquillants Douceur pour yeux sensibles
- Marcelle Tampons Démaquillants pour les yeux sans huile
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- Marcelle Ultimate Power Volume Mascara
- Marcelle Ultimate Volume Infinity Mascara
- Marcelle Ultimate Volume Mascara
- Marcelle Ultimate Volume Nano Mascara
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- Marcelle Xtension Plus Curl Mascara
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 - ✓ Do not contain the most common allergens
 - ✓ Non-comedogenic
- | |
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Contents

Editorial

- Telehealth Goes Viral / La Télésanté Devient Virale 331
Kirk Barber

Original Articles

- Skin Manifestations in Pediatric Patients Treated With a TNF-Alpha Inhibitor for Inflammatory Bowel Disease: A Retrospective Study 333
Maria-Laura Cossio, Annie Genois, Prévost Jantchou, Afshin Hatami, Colette Deslandres, and Catherine McCuaig
- Epidemiology and Patient Distribution of Oral Cavity and Oropharyngeal SCC in Canada 340
Feras M. Ghazawi, Jessica Lu, Evgeny Savin, Andrei Zubarev, Peter Chauvin, Denis Sasseville, Anthony Zeitouni, and Ivan V. Litvinov
- Allergic Contact Dermatitis Secondary to Moisturizers 350
Stephanie R. Cohen, Jesús A. Cárdenas-de la Garza, Paige Dekker, Wasim Haidari, Sarah S. Chisolm, Sarah L. Taylor, and Steven R. Feldman
- Clinical and Laboratory Differences Between Early-Onset and Late-Onset Adult Atopic Dermatitis 360
Dae-Lyong Ha, Geun-Hwi Park, Hoon-Soo Kim, Hyun-Chang Ko, Moon-Bum Kim, Kyoung-Min Lim, and Byung-Soo Kim
- Utility of Preinjection Aspiration for Hyaluronic Fillers: A Novel In Vivo Human Evaluation 367
Jordan V. Wang, Ezra Hazan, Georgette Hattier, Richard L. Torbeck, Hooman Khorasani, and Nazanin Saedi
- Evaluation of Indoor Tanning Facilities in American Fitness Centers 372
Christina M. Huang and Mark G. Kirchhof
- The Impact of Suspension of Dermatology On-Call Services 380
Annie Langley and Mark G. Kirchhof



Review Articles

- Making Glove Decision Less of a White Knuckling Experience: A Systematic Review and Inventory of Glove Accelerator Contents 386
Kaitlyn M. Lopushinsky, Navjeet Gill, Whitney K. Shea, John F. Elliott, Sebastian Straube, and Marlene T. Dytoc
- Common Atopic Dermatitis Rating Scales: A Practical Approach and Brief Review 399
Yue Bo Yang, Charles W. Lynde, and Patrick Fleming



Visual Dermatology

- Visual Dermatology: Diffuse Cutaneous Mastocytosis With Bullous Lesions 405
Qi Tan and Jian Zhang
- Visual Dermatology: Nodular Scabies in an Infant 406
Qi Tan and Chun hua Tan
- Visual Dermatology: Black Chromhidrosis of the Bilateral Cheeks 407
Malika A. Ladha and Stewart Adams
- Visual Dermatology: Gulliver Sign: When Pyoderma Gangrenosum Soothes 408
Juan Jimenez-Cauhe and Pablo Fonda-Pascual
- Visual Dermatology: Acral Erythematous-purpuric Lesions During COVID-19 Pandemic 409
Giuseppe Ferrara and Daniel Morgado-Carrasco

Medical Letters

- The Novel Role of Antibiotic Treatment in the Management of Cutaneous T-Cell Lymphoma (CTCL) Patients 410
Michelle Le, Feras M. Ghazawi, Elena Netchiporuk, and Ivan V. Litvinov

SB206, a New Topical Nitric Oxide-Releasing Drug on the Horizon for the Treatment of Molluscum Contagiosum and External Anogenital Warts <i>Lina Belmesk, Ivan V. Litvinov, and Elena Netchiporouk</i>	412
Ultraviolet Radiation Seeking Behavior, Mediated by Endogenous β -Endorphin, Has Addictive Features <i>Lydia Ouchene, Anastasiya Muntyanu, and Elena Netchiporouk</i>	414
Cutaneous Manifestations of Coronavirus Disease 2019 (COVID-19) Infection—What Do We Know So Far? <i>Stephanie Ghazal, Ivan V. Litvinov, Naif Aljahani, Abdulhadi Jfri, and Elena Netchiporouk</i>	416
Patient-Driven Discontinuation of Apremilast During the COVID-19 Pandemic in Two Canadian Academic Hospital Clinics and One Community Practice <i>Jorge R. Georgakopoulos, Ron Vender, and Jensen Yeung</i>	418
Preliminary Data Suggests That Biologics in Dermatology Are Not Associated With Adverse COVID-19 Outcomes <i>David Nassim, Abdulhadi Jfri, Ivan V. Litvinov, and Elena Netchiporouk</i>	420
Patient-Driven Discontinuation of Dupilumab During the COVID-19 Pandemic in Two Academic Hospital Clinics at the University of Toronto <i>Jorge R. Georgakopoulos and Jensen Yeung</i>	422
Rate of Patient-Driven Biologic Treatment Discontinuation During the COVID-19 Pandemic in 2 Academic Hospital Clinics at the University of Toronto <i>Jorge R. Georgakopoulos and Jensen Yeung</i>	424

Letters to the Editor

The Need to Evaluate the Risks and Benefits Posed by Quebec Bill 43 Expanding Nurse Practitioners' Scope of Practice <i>Alex Derstenfeld, Neil H. Shear, Alexandra Mereniuk, Joel Claveau, Catherine McCuaig, and Ivan V. Litvinov</i>	426
The Need for a National Strategy on Artificial Intelligence in Canadian Dermatology <i>Ryan T. Lewinson and Isabelle A. Vallerand</i>	428

On the Cover



“Psoriasisiform eruption with weeping appearance in the retroauricular region” from Cossio et al. (pp. 333-339).

 An online CME course associated with this article and offering RCPSC Section 3 MOC credits is available at <http://www.dermatology.ca/jcmscme>. Material may include an expert interview podcast.

Official Publication of the

Telehealth Goes Viral

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In my March/April 2020 editorial, I opined that “Digital cameras have destroyed Medical Photography”. In the past 4 months, after looking at hundreds of poorly lighted and out of focus digital photographs submitted by patients, I suspect you may agree. However, a contrary opinion might say that digital photography has saved our specialty during these times of self-isolation and quarantine by allowing the capture of images that can be transmitted directly to our consulting rooms.

I have been practicing dermatology using virtual visits for the past 4 months. It is an experience that I am sure I share with most of you and I suspect you have the same mixed feelings. It is difficult to do well. I have yet to “see” a patient “on screen” where the virtual technology was any advantage in making a diagnosis when compared with a telephone conversation and some really good digital photographs. Neither approach is ideal, but the telephone and digital images are far superior in my hands. Allow me to share my experience in obtaining useful digital images from patients.

The 3 most important instructions I impart to patients who wish to send me photographs are:

1. Do not take the picture yourself.
2. Take the picture in daylight.
3. Brace the body part so it does not move.

These steps allow for good exposure and accurate focus. If I think that these instructions will be followed, I will then ask that the photographer:

4. Take a photograph of the spot/rash as close as they can (remaining in focus) and then “move out” for the next photograph and place the spot/rash on the body.
5. Check the images to make sure that they are in focus and “tell the story” before they send them to me. I will not wait for more photographs during the visit.

The single advantage that I see to a virtual visit via video is the ability to communicate “eye to eye” and share with our patients the confidence we have in our diagnosis and treatment plan. I had the opportunity to interview Dr Stephen Feldman, of Wake Forest School of Medicine, in preparation of an upcoming podcast (*JCMS* Editor’s Choice). During our discussion, we looked at the very real loss of true interpersonal contact when using virtual telehealth and how our interview technique will need to be adjusted in order to assure adherence to our treatment protocols.

Dr Regine Mydlarski and her co-authors in their article titled “Dermatologic Training and Practice in Canada: An In-Depth Review” in the May/June 2020 issue of *JCMS* lists one of their recommendations as:

The specialty committee should revise the discipline’s standards to make explicit the necessity, importance, and limitations of telehealth services and emerging technologies to the future of Dermatology by ensuring residents have exposure to telehealth in both the delivery of curriculum and training experiences in clinical consultation.

I expect they did not know how prescient they were being and how much COVID-19 would impact the rapid implementation of this recommendation. However, I do know that they understood that without proper funding for telehealth within the clinical fee code, all of this learning will have been wasted.

This pandemic has revealed many of the deficiencies in our care model but at the same time has provided us with the opportunity to rapidly assess the usefulness of telehealth for our specialty. Overall, I think this “experiment” has been a success. I know my patients are very happy and with the proper remuneration to provide this service, dermatologists will likely incorporate telehealth into their practices.

As always, dermatologists have proven themselves as innovators—if only we could convince government to value our innovations. Perhaps, our patients will have better luck now that they have experienced this new and user-friendly model of care.

Be good to each other.

READ WRITE REVIEW CITE



Kirk Barber, MD FRCPC FCDA
Editor-in-Chief, *JCMS*

La Télésanté Devient Virale

Dans mon éditorial de mars-avril 2020, j'affirmais que « Les caméras numériques ont détruit la photographie médicale ». Au cours des quatre derniers mois, après avoir analysé des centaines de photographies numériques mal éclairées et hors foyer soumises par des patients, je suppose bien que vous serez peut-être d'accord. Par ailleurs, on pourrait toutefois affirmer que la photographie numérique a sauvé notre spécialité en période d'isolement et de quarantaine en permettant de saisir des images qu'il est possible de transmettre directement à nos salles de consultation.

Je pratique la dermatologie virtuelle depuis quatre mois. C'est une expérience qui, j'en suis sûr, est la vôtre aussi pour la plupart et je soupçonne que les mêmes sentiments mitigés vous animent. Il est difficile de bien faire. Je n'ai pas encore « vu à l'écran » de patients pour lesquels la technologie virtuelle aurait plus aidé à poser un diagnostic qu'une conversation téléphonique et des photographies numériques vraiment bonnes. Ni l'une ni l'autre des méthodes n'est idéale, mais le téléphone et les images numériques sont de loin supérieurs entre mes mains. Permettez-moi de vous faire part de mon expérience lorsque j'ai réussi à obtenir des images numériques utiles de patients.

Les trois consignes les plus importantes dont je fais part aux patients qui veulent m'envoyer des photographies sont les suivantes :

1. Ne prenez pas la photo vous-même.
2. Prenez la photo de jour.
3. Appuyez la partie du corps afin de l'immobiliser.

Ces étapes permettent de produire une image bien exposée et mise au foyer. Si je pense que ces consignes sont suivies, je demande ensuite au photographe de :

4. prendre une photographie de la plaque ou de l'éruption en plan le plus gros possible (tout en demeurant au foyer), de « reculer » ensuite pour prendre la photographie suivante et de montrer l'endroit du corps où se trouve la plaque ou l'éruption;
5. vérifier les images pour s'assurer qu'elles sont au foyer et « révélatrices » avant de me les envoyer. Je n'attendrai pas d'autres photographies durant la consultation.

Le grand avantage que je vois à une consultation virtuelle vidéo, c'est la capacité de communiquer « face à face » et de partager avec nos patients notre confiance dans notre diagnostic et notre programme de traitement. J'ai eu la chance d'interviewer le Dr Stephen Feldman, de la Faculté de médecine de Wake Forest, dans le contexte de la préparation d'une balado-diffusion à venir (*Editor's Choice du JCMS*). Au cours de notre

discussion, nous avons abordé la perte très réelle de contact interpersonnel véritable en télésanté virtuelle et décrit comment nous devrons ajuster notre technique d'entrevue afin de garantir l'observation de nos protocoles de traitement.

Dans leur article intitulé « Dermatologic Training and Practice in Canada: An In-Depth Review » qui a paru dans le numéro de mai et juin 2020 du *JCMS*, la Dr Régine Mydlarski et ses coauteurs présentent une de leurs recommandations :

« Le comité de la spécialité devrait réviser les normes de la discipline afin de préciser clairement la nécessité, l'importance et les limites des services de télésanté et des technologies émergentes pour l'avenir de la dermatologie en veillant à ce que les résidents soient exposés à la télésanté à la fois au cours du cursus et pendant leur formation en consultation clinique. »

Je crois qu'ils ne savaient pas dans quelle mesure ils avaient preuve de prémonition et ne connaissaient pas l'ampleur des répercussions de la COVID-19 sur la rapidité de la mise en œuvre de cette recommandation. Je sais toutefois qu'ils comprenaient que sans un financement approprié pour la télésanté prévu dans le code des honoraires cliniques, tout ce savoir acquis aura été gaspillé.

La pandémie en cours a mis en évidence un grand nombre des lacunes de notre modèle de soin, mais elle nous a aussi permis d'évaluer rapidement l'utilité de la télésanté dans notre spécialité. Dans l'ensemble, je pense que cette « expérience » s'est révélée un succès. Je sais que mes patients sont très heureux et si ce service est dûment rémunéré, les dermatologues intégreront probablement la télésanté dans leur cabinet.

Comme toujours, les dermatologues se sont révélés innovateurs – si seulement nous pouvions convaincre le gouvernement d'attacher de la valeur à nos innovations. Nos patients seront peut-être plus chanceux maintenant qu'ils ont connu un modèle de soin nouveau et convivial.

Soyez bons les uns pour les autres.
LIRE ÉCRIRE REVOIR CITER



Kirk Barber, MD FRCPC FCDA
Rédacteur en chef, *JCMS*

Skin Manifestations in Pediatric Patients Treated With a TNF-Alpha Inhibitor for Inflammatory Bowel Disease: A Retrospective Study

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Maria-Laura Cossio^{1,2} , Annie Genois¹ , Prévost Jantchou³, Afshin Hatami¹, Colette Deslandres³, and Catherine McCuaig¹

Abstract

Background: Tumor necrosis factor (TNF) alpha inhibitors (anti-TNF) are effective in the treatment of inflammatory bowel disease (IBD) as well as psoriasis. Their increasing use has raised the identification of cutaneous side effects (CSEs). Evidence in children is limited.

Objectives: The objective of this study is to describe CSEs of anti-TNF treatment in a pediatric population with IBD.

Methods: This is a retrospective single-center study of children with IBD under anti-TNF treatment between 2013 and 2016. A total of 40 patients with CSEs related to anti-TNF were referred to our pediatric dermatology clinic. A control group was randomly selected from patients receiving anti-TNF for IBD, who were referred to the dermatology clinic for other conditions unrelated to anti-TNF.

Results: Of 343 patients with IBD, 40 (11.3%) presented CSEs potentially related to the treatment. No differences in sex, age, and underlying disease were found between those with and without CSEs. The most frequent CSEs were psoriasiform eruptions (41%) which were more exudative than usual, located especially in skin folds and on the scalp; skin infections (20%); and eczematous eruptions (10%). Only 5% of patients changed or discontinued the current anti-TNF because of CSEs.

Conclusion: This is one of the largest pediatric cohorts of IBD patients with CSEs. Psoriasiform eruptions were the most common CSEs, with predilection for skin folds and scalp, and frequent superimposed bacterial infection. Topical and/or systemic antibiotics were required in addition to topical corticosteroids in 25% of patients. The rate of discontinuation of anti-TNF therapy due to CSEs was low.

Keywords

inflammatory bowel disease, TNF-alpha antagonists, cutaneous side effects, psoriasis, children

Introduction

Antitumor necrosis factor (anti-TNF) alpha antibodies are effective in the treatment of several inflammatory diseases, such as rheumatoid arthritis (RA), psoriatic arthritis, psoriasis, ankylosing spondylitis, juvenile idiopathic arthritis (JIA), and inflammatory bowel disease (IBD).¹ The increasing use of anti-TNF for the last 15 years has been accompanied by cutaneous side effects (CSEs), including papulopustular, eczematous, lichenoid, or psoriasiform reactions, leukocytoclastic vasculitis, skin infections, lupus-like syndrome, and granulomatous reactions.^{2,3} According to the previous studies, CSEs of anti-TNF are usually of mild to moderate severity and resolve with short-term topical or systemic therapy. In the most severe cases, however, the biologic must be changed.² Cutaneous side effects, especially psoriasiform reactions and skin infections, are more frequent and severe in

patients treated with anti-TNF who have IBD compared to other inflammatory diseases.⁴

Most of the studies on anti-TNF adverse effects have focused on psoriasiform reactions, which have a frequency ranging from 1.7% to 35% in different series.⁵⁻¹⁰ Psoriasis is

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more commonly located on the scalp (sometimes evolving to severe alopecia) and skin-folds such as retroauricular and umbilical areas, often with crusting and weeping, differing from the classic dry plaque-type psoriasis.^{4,8,11,12} Psoriasisiform eruptions can appear at any moment after anti-TNF initiation, but IBD activity is in remission in most of the patients at the time of psoriasis onset,^{7,11} and fecal calprotectin levels are significantly lower in IBD patients with skin reactions.⁸ Classic psoriasis and IBD share common environmental, genetic, and inflammatory factors.^{4,13-15} Skin infections and eczematous reactions are second in frequency in both pediatric and adult populations using anti-TNF in IBD.⁶⁻¹⁰

Currently, there are no guidelines on the treatment of CSEs. The data in the pediatric population are primarily retrospective and are scarce regarding other CSEs than psoriasis. The prevalence of pediatric IBD in Canada is one of the highest in the world,¹⁶ and the number of children receiving anti-TNF has markedly increased in the recent years.¹⁷

Methods

We conducted a retrospective single-center study between November 2013 and June 2016 at Sainte-Justine University Hospital Center, in Montreal, Canada. Our Institutional Review Board approved the study. Patient data were obtained from medical records and a database maintained in the gastroenterology service.¹⁸ Of 343 patients 19 years of age and younger, with a diagnosis of Crohn's disease, ulcerative colitis, or unclassified colitis IBD according to the NASPGHAN/ESPGHAN criteria, receiving anti-TNF, 40 were referred to our pediatric dermatology clinic due to CSEs secondary to the anti-TNF. A control group was selected within a cohort of patients receiving anti-TNF for IBD, who were referred to the dermatology clinic for other conditions unrelated to anti-TNF. From 47 patients without CSEs seen in the clinic, 40 were randomly selected as controls.

Data collected included demographic characteristics, IBD phenotype, clinical characteristics of CSEs, details of anti-TNF alpha therapy (type and duration), delay between administration of anti-TNF and the onset of CSEs, personal and family history of eczema or psoriasis, clinical outcomes of CSEs (therapeutic strategies and response), and therapy changes based on skin manifestations.

The data are presented as mean \pm standard deviation (SD) for parametric distributions and median and interquartile range (IQR) for nonparametric distributions. Categorical variables are presented in absolute frequencies (*N*) and relative frequencies (%). Statistical analysis was performed using Student's *T*-test or Mann-Whitney U test or for quantitative variables, and Pearson's χ^2 test for categorical variables. The potential risk factors were estimated by fitting a binary regression to estimate the odds ratios (ORs) with 95% confidence interval (CI). Statistical significance was set at *P*-value $<.05$.

Results

A total of 343 patients younger than 19 years of age with a diagnosis of IBD using anti-TNF therapy were followed at our gastroenterology clinic over 2.5 years. From this group, 40 (11.3%) patients presented CSEs potentially related to the treatment, diagnosed by a pediatric dermatologist. From the total IBD population, 40 patients who were also seen in pediatric dermatology without CSEs in relation to anti-TNF were randomly selected as controls (see Table 1).

In the 40 patients with CSEs, 20 (50%) were females, and the median (IQR) age at the onset of CSEs was 15.4 (13.0, 16.9) years. The underlying IBD was Crohn's disease in 33 patients (82.5%), ulcerative colitis in 6 (15%) patients, and unclassified colitis in 1 (2.5%) patient, which is comparable to the total IBD population in our center (75.2% Crohn's disease, 17.4% ulcerative colitis, and 7% unclassified colitis). No differences were found in terms of age at the time of diagnosis of IBD and age at anti-TNF onset between the CSE group and the non-CSE group, and lower age at diagnosis of IBD and at anti-TNF onset were not found to be risk factors for developing CSEs (OR = 0.89; 95% CI: 0.77-1.04, *P* = .16 and OR = 0.91; 95% CI: 0.77-1.06, *P* = .22, respectively). The median (IQR) time between the onset of anti-TNF and the development of CSEs was 13.2 months (7.0 - 29.2 months). All patients from both groups (CSEs and controls) had received infliximab (IFX) as first biologic therapy, since this is the protocol for IBD in our institution. The majority remained on IFX alone, but a few patients were switched to adalimumab (ADA) at some point, which is comparable to the total anti-TNF population at our institution. In the group with CSEs, 33 (82.5%) were still on IFX, 6 (17.5%) of them on adalimumab (ADA), and 1 (2.5%) had changed to ustekinumab following CSEs.

In terms of risk factors for developing CSEs, family history of psoriasis showed a trend toward increased risk of CSEs that was not statistically significant (OR = 3.01; 95% CI: 0.75-12.61, *P* = .12). Unlike other cohorts, we did not find association between having Crohn's disease (OR = 1.37; 95% CI: 0.45-4.12, *P* = .58) or ulcerative colitis (OR = 0.71; 95% CI: 0.22-2.26, *P* = .56) and a higher risk of developing CSEs.^{7,8}

None of the patients with CSEs reported smoking. Since obesity is considered a risk factor for classic psoriasis, body mass index (BMI) was assessed, but no differences between the group with psoriasisiform eruptions and the group without CSEs were observed (the mean \pm SD BMI were respectively 16.5 ± 3.3 and 17.2 ± 3.4 ; *P* > .05).

From the 40 patients with CSEs, a total of 45 skin reactions were observed. A total of 5 patients experienced more than one type of skin manifestation, especially superinfection of psoriasisiform eruptions, with weeping impetiginized plaques of the scalp, retroauricular, and periorificial regions (Figures 1 and 2). From the total CSEs, 10 (22%) were skin infections, of which 9 (20%) were bacterial infections, most

Table I. Demographic Characteristics of Patients With and Without Cutaneous Side Effects.

	Patients with CSEs (N = 40)	Patients without CSEs (N = 40)	P-value
Sex (female)	20 (50%)	19 (47.5%)	.1.00
Age of onset of CSEs (median years, IQR)	15.4 (13.0, 16.9)	15.4 (14.0, 16.8) ^a	.51
Crohn's disease	33 (82.5%)	31 (77.5%)	.78
Ulcerative colitis	6 (15%)	8 (20%)	.77
Unclassified colitis	1 (2.5%)	1 (2.5%)	1.00
Age at IBD diagnosis (mean years ± SD)	11.8 ± 3.0	12.7 ± 2.8	.16
Age at anti-TNF alpha onset (mean years ± SD)	13.1 ± 3.2	13.9 ± 2.5	.22
Time between onset of anti-TNF alpha and development of CSEs (median months, IQR)	13.2 (7.0, 29.2)	13.0 (3.2, 25.7) ^b	.46
BMI (mean ± SD)	16.5 ± 3.3 ^c	17.2 ± 3.4	.37
Family history			
Psoriasis	8 (20%)	3 (7.5%)	.27
Eczema	6 (15%)	5 (12.5%)	.44
Personal history			
Psoriasis	2 (5%)	1 (2.1%)	.65
Eczema	6 (15%)	10 (25.0%)	.59

Abbreviations: BMI, body mass index; CSEs, cutaneous side effects; IQR, interquartile range; SD, standard deviation; TNF, tumor necrosis factor.

^aAge at the time of dermatology assessment.

^bTime between onset of anti-TNF alpha and dermatology assessment.

^cOnly the 20 patients with psoriasiform eruptions were analyzed.

of them caused by *Staphylococcus aureus*; 20 (44%) were psoriasiform eruptions (Figure 3); and 5 (11%) were eczematous eruptions. Less frequent CSEs included 3 (4.4%) type IV hypersensitivity reactions, 1 lupus-like photosensitivity, 1 urticaria, 1 alopecia areata, 1 hidradenitis suppurativa, 1 pyoderma gangrenosum, 1 granuloma annulare, and 1 acrocytosis. All the cases of psoriasiform or eczematous eruptions were diagnosed clinically. The most frequent sites of psoriasiform eruption were skin folds in 12 cases (60%) and scalp in 10 cases (50%) (Table 2).

From the 40 patients with CSEs, IFX was suspended in 2 (5%) cases due to severe psoriasiform eruptions, one of whom was changed to ustekinumab and the other case was switched to ADA. The other 38 patients responded well to the systemic and topical treatments prescribed, without requiring withdrawal of the current anti-TNF therapy. For the treatment of psoriasiform eruptions, all the patients (20/20) received topical corticosteroids; 15/20 (37.5%) received calcineurin inhibitors, 8/20 (20%) calcipotriol, and 3/20 (7.5%) salicylic acid. Of these 20 patients, 5 (25%) also received antibiotics (2 (10%) topical and 3 (15%) systemic) for superimposed bacterial infection. Systemic therapies added to the previous anti-TNF therapy for more severe psoriasiform eruptions included oral methotrexate in 2/20 (5%) and oral retinoids in 1 (2.5%) patient. Eczematous eruptions were treated with topical corticosteroids combined with topical calcineurin inhibitors in all (5/5) cases.

Cutaneous infections were treated with topical antibiotics in 5/9 (55%) cases; oral antibiotics in 3/9 (33%) cases; and both topical and oral antibiotics in 1 (11%) case. As mentioned above, 5/9 patients treated for infections were simultaneously treated with topical corticosteroids for their psoriasiform eruption.

Discussion

This cohort is one of the largest in the literature with CSEs due to anti-TNF in the pediatric population with IBD. Cutaneous side effects affected more than one-tenth of our total IBD population under anti-TNF therapy; psoriasiform eruptions were the most frequent manifestation, followed by skin infections and eczematous eruptions. These results, as well as the median age of onset of CSEs, are consistent with other pediatric studies.^{6,8}

Contrary to other previous research, we found no correlation between CSEs and age at onset of anti-TNF therapy.^{4-7,10} The reported data for adult patients suggested that CSEs were more frequent in female than males^{4,5,7,10}; however, our findings support the results of Mälkönen et al in a prospective study in pediatric population, who described no differences in the frequency of CSEs between genders.⁸ The mean latency period between the first dose of anti-TNF and the appearance of CSEs was 13 months, which is consistent with the previous studies that have reported a mean time ranging



Figure 1. Psoriasisiform eruption with weeping appearance in the retroauricular region.

from 11 months to 3 years.^{5-7,11} Psoriasisiform eruptions were the most frequent manifestation, affecting 5.8% of the



Figure 3. Psoriasisiform eruption on the scalp.



Figure 2. Weeping impetiginized plaques in the perioral region in a patient with a psoriasisiform eruption.

anti-TNF population, followed by skin infections at 2.9% and eczematous eruptions at 1.4%. These results are consistent with other major pediatric study by Sridhar et al who found an overall rate of cutaneous complications of 11.5%, psoriasisiform lesions 8.1%, skin infections 5.6%, and eczematous lesions 2.4%.⁶

In other cohorts, Crohn's disease has been described as a risk factor for CSEs compared to ulcerative colitis, however, our population did not demonstrate any significant propensity.^{7,8} The proportion of patients that were under IFX and ADA in the CSE group was comparable to the total anti-TNF population, and none of the drugs was associated with a higher risk of developing CSEs in our cohort.

Not many studies have reported the presence of personal or family history of psoriasis or eczema as a relevant risk factor for developing CSEs.⁴ We found a trend between the risk of CSEs and the family history of psoriasis that was not statistically significant. Both psoriasis and eczema are reported to be more prevalent in IBD patients compared to the general population, regardless of the use of anti-TNF.^{13,19} Furthermore, anti-TNF-induced CSEs exhibit higher levels

Table 2. Frequency of Cutaneous Side Effects.

Total patients with CSEs	40
Total number of CSEs	45
Psoriasisiform eruptions	20 (44%)
Skin folds	12 (60%)
Scalp	10 (50%)
Extremities	7 (35%)
Face	3 (15%)
Trunk	3 (15%)
Eczematous eruptions	5 (11%)
Skin infections	10 (22%)
Bacterial infections	9 (20%)
Herpes zoster (VZV)	1 (2.5%)
Type IV hypersensitivity reaction	3 (4.4%)
Urticarial reaction	1 (2.5%)
Alopecia areata	1 (2.5%)
Hidradenitis suppurativa	1 (2.5%)
Pyoderma gangrenosum	1 (2.5%)
Granuloma annulare	1 (2.5%)
Acrocyanosis	1 (2.5%)

Abbreviation: CSEs, cutaneous side effects.

of interferon-gamma activation by Th1 cells than classic psoriasis or eczema, and this indeed may be a major underlying mechanism in genetically predisposed individuals for the paradoxical onset of psoriasis, given anti-TNF agents are used to suppress psoriasis.^{15,20}

Like the previous reports, all our cases of psoriasisiform reactions were diagnosed clinically. In the literature, only a few have histopathological confirmation showing typical features of psoriasis, but others with spongiosis and/or lichenoid features, apoptotic keratinocytes, and a mononuclear inflammatory infiltrate.²¹ Immunohistochemical analyses have revealed increased expression of CXCR3+ infiltrating cells compared to classic psoriasis, although lower than the levels found in lichen planus or discoid lupus.²²

Other risk factors for CSEs, such as smoking, were not reported by any of our patients, unlike studies in the adult population.^{5-7,9,11,23} Body mass index was not associated with psoriasisiform eruptions in this series, unlike classic psoriasis.

Anti-TNF-induced psoriasisiform eruptions showed good clinical response to topical corticosteroids, calcineurin inhibitors, and/or calcipotriol. Only 3/20 patients required a systemic agent, 1 was switched from the initial anti-TNF drug, and 1 discontinued anti-TNF class (see the Results section). The psoriasisiform lesions observed in our cohort had predilection for the skin folds (45%) and scalp (35%), frequently with a striking weeping appearance,^{4,8,11,12,24} and required

topical and/or oral antibiotic treatment for superimposed bacterial infections in 25% of the cases, differing from classic plaque-type psoriasis described in IBD and non-IBD patients.²⁵ The pathogenesis of these cutaneous infections may involve both immunosuppression and the effect of Th1/Th17 inflammation on the skin barrier.⁶

Other CSEs observed in our cohort that have been described in case reports include alopecia areata and hidradenitis suppurativa. Alopecia areata has been described in patients treated with anti-TNF, but it may be an incidental autoimmune manifestation in patients with a chronic immune-mediated inflammatory disease, or a truly anti-TNF adverse reaction.^{26,27} Hidradenitis suppurativa has also been associated with IBD²⁸ and has been reported as a side effect of anti-TNF treatment.²⁹

The rates of switch and suspension because of CSEs in our series are lower than what retrospective studies have described in both adults and children,^{6,7,10} and much lower than a pediatric prospective cohort.⁸ In pediatric population, Sridhar et al reported switching the original anti-TNF in 18.2% of psoriasisiform eruptions and discontinuing the class in 9.1% of cases,⁶ while Mälkönen et al reported a higher frequency of definitive discontinuation of anti-TNF (17% of cases of skin lesions).⁸ These differences may be related to different methodologies (retrospective vs prospective), different population (younger age and different genetic backgrounds), and other factors such as time between onset of skin lesions and referral to dermatology, and adjuvant therapy (systemic retinoids or systemic methotrexate).

In the studies that reported switching the original anti-TNF to another, more than 50% experienced recurrence of psoriasis.^{6,7} Even if most patients were able to continue the initial anti-TNF despite CSEs, the necessity to discontinue the drug in the more severe cases represents a serious clinical challenge to both dermatologists and gastroenterologists. Frequently used therapies include topical corticosteroids and antibiotics, oral antibiotics (for skin infections), methotrexate, phototherapy, and other biologics.^{5,30} Among the latter, ustekinumab appears to be a good choice since it is approved for both Crohn's disease and psoriasis in adults.³⁰ Psoriasis and IBD share not only a Th1 but also a Th17 cell-mediated inflammatory pathogenesis. Interleukin 17 (IL-17) and 22 (IL-22), derived from Th17, are involved in the pathogenesis of anti-TNF-induced psoriasisiform reactions, and higher expression of Th17 cells has been observed in more severely affected patients, who respond well to the anti-IL-12/23 ustekinumab.^{30,31} However, exacerbation of the previous psoriasisiform reactions during ustekinumab therapy have been described.³² Vedolizumab, a gut-specific $\alpha 4\beta 7$ integrin inhibitor, approved for both Crohn's disease and ulcerative colitis, has shown promising results in a few cases of anti-TNF-induced psoriasis.³³⁻³⁵ As variants of the IL-23BR gene are associated with higher Th17 cytokine production and higher risk of severe psoriasisiform reactions in IBD

patients,^{9,30,36} other alternative may be specific anti-IL-23 agents such as guselkumab, which has shown efficacy in psoriasis, with less side effects dependent on the Th1 pathway inhibition.^{37,38}

This study has important limitations given it had a small number of patients, is retrospective, and did not include a control group without anti-TNF. Some of the skin manifestations observed may be attributable to the IBD itself and not necessarily to anti-TNF treatment.

The strength of our review is that it adds to the limited literature in the pediatric population with IBD and CSE. Our study confirms the frequency of such CSEs to be higher than 1 in 10 children. In addition, paradoxical psoriasis or eczema is often complicated by superimposed bacterial infection, which may require antibiotics in order to minimize the need to change the biologic. Larger prospective studies are mandatory to generate treatment recommendations or guidelines that would assist the clinicians in handling CSEs.

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Epidemiology and Patient Distribution of Oral Cavity and Oropharyngeal SCC in Canada

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Abstract

Background: Oral cavity cancers (OCCs) and oropharyngeal cancers (OPCs) continue to be a major source of morbidity and mortality worldwide requiring the shared effort of numerous specialists. Tobacco and alcohol consumption have long been identified as risk factors for both OCC and OPC. In addition, human papilloma virus (HPV) is gaining its position as the main causal agent for OPC.

Objective: The objective of this study is to analyze the epidemiology of OCC and OPC in Canada.

Methods: Data pertaining to the year of diagnosis, the patient's sex, age at the time of diagnosis, province/territory, city and postal code of oral cavity, and oropharyngeal malignancies diagnosed during 1992–2010 were extracted from the Canadian Cancer Registry and Le Registre Québécois du Cancer.

Results: In total, 21 685 OCC cases and 15 965 OPC cases were identified from 1992 to 2010. Of those, 84.97% were oral cavity squamous cell carcinomas (SCCs), 88.10% were oropharyngeal SCCs, and both had a significant male predominance. While oral cavity SCC incidence stabilized over the study period, oropharyngeal SCC continued to increase. Oral cavity SCC incidence increased with age, while oropharyngeal SCC incidence peaked in the 50- to 59-year age group. Detailed geographic distribution analysis of patients at the provincial/territorial, city, and postal code levels identified several patient clusters.

Conclusions: This work highlights important epidemiological differences in trends between oral and oropharyngeal cancers, identifies high-incidence postal codes for each malignancy, and correlates incidence/mortality with known risk factors including alcohol/tobacco use and HPV infections, therefore providing a comprehensive understanding of epidemiology for these cancers in Canada.

Keywords

oral cavity, oropharyngeal, malignancy, squamous cell carcinoma (SCC), Canada, epidemiology, incidence, mortality, smoking, alcohol, human papilloma virus (HPV)

Introduction

Oral cavity cancers (OCCs) and oropharyngeal cancers (OPCs) continue to be a major source of morbidity and mortality worldwide, requiring the shared effort of numerous specialists including otolaryngologists, oncologists, dentists, dermatologists, family physicians, and other specialists in oral medicine. Anatomically, the oral cavity and oropharynx are distinct regions that border each other but do not overlap.¹ Recent evidence supports that tumors arising at these 2 sites have differing etiopathogenesis, treatment, and prognosis.² Thus, in this study, we will compare and contrast findings for these two sites.

Tobacco and alcohol consumption have long been identified as risk factors for both OCC and OPC.^{3–5} In addition,

human papilloma virus (HPV) is now an established causal agent for OPC.⁶ Studies performed in the United States have identified important differences in demographic

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characteristics between OCC and OPC.⁷ Although studies have examined epidemiological differences in oral cavity and oropharyngeal carcinomas in certain Canadian provinces,⁸⁻¹⁰ analyses comparing and contrasting the distribution of the aforementioned malignancies in all Canadian provinces have yet to be performed.

The objective of this registry-based study is to provide a comprehensive description of the incidence and mortality trends for oral cavity and oropharyngeal squamous cell carcinomas (SCCs) across Canada during 1992-2010. These findings could help direct public health programs and provide physicians with data to complement their clinical expertise to help better identify patients at risk for these important malignancies.

Methods

This study was conducted in accordance with the CISS-RDC-668035 and 13-SSH-MCG-3749-S001 protocols approved by the Social Sciences and Humanities Research Council of Canada (SSHRC) and the Québec Inter-University Centre for Social Statistics (QICSS), respectively. This study was exempt from the McGill University Research Ethics Board review in accordance with the institutional policy. Incidence and mortality data for oral cavity and oropharyngeal malignancies were extracted from 3 distinct but complementary population-based cancer databases (Canadian Cancer Registry [CCR], Le Registre Québécois du Cancer [LRQC], and Canadian Vital Statistics [CVS]) using the previously reported and established methods.¹¹⁻³⁴

From the CCR and LRQC databases, demographic, geographic, and clinical information on patients diagnosed with cancer, including sex, year of diagnosis, age at the time of diagnosis, Forward Sortation Area (FSA) of residence, and the ICD-O-3 code of the tumor were extracted. In Canada, postal codes consist of letters and numbers (eg, H3G 1A4), where the FSA defines a geographic region in which all postal codes start with the same 3 entries. The CCR (2014 version) database provides data on all malignancies diagnosed in Canada from 1992 to 2013 except for those in the province of Quebec (QC). Information pertaining to QC cancer patients was retrieved from the LRQC which provides data from 1992 to 2010. Hence, our analysis was limited to the years 1992-2010 in order to include all 10 Canadian provinces and 3 territories.

Oral cavity and oropharyngeal SCC cases were defined based on the International Classification of Diseases for Oncology, Third Edition as the following: Verrucous carcinoma (ICD-O-3 code: 8051), Papillary SCC (8052), SCC, NOS (8070), SCC, keratinizing, NOS (8071), SCC, large cell, nonkeratinizing, NOS (8072), SCC, small cell, nonkeratinizing (8073), SCC, spindle cell (8074), SCC, microinvasive (8076), Lymphoepithelial carcinoma (8082), and

Basaloid SCC (8083). In addition, a few cases of Papillary carcinoma, NOS (8050), SCC, adenoid (8075), SCC, clear cell type (8084) were identified for oral cavity site, but not oropharyngeal. The 2018 updated ICD-O-3 table included histology codes 8085 and 8086 that encode HPV-positive and HPV-negative SCC, respectively. However, there is no available data on HPV-related types of SCC within the examined range of 1992 to 2010. Anatomical site codes used for the oral cavity and oropharynx were reported as in the previous studies (Supplemental Table S1).^{8,10}

Malignancy-associated mortality was performed by extracting data from the CVS database. Codes from the International Statistical Classification of Diseases and Related Health Problems, ninth revision (ICD-9) and tenth revision (ICD-10) were used for deaths between 1992-1999 and 2000-2010, respectively. Unfortunately, deaths are only reported by anatomical site and do not differentiate between different morphologies of cancers. Hence, we were unable to specifically analyze SCCs. Nevertheless, given that SCCs accounted for the great majority of all malignancies in the oral cavity and oropharynx, we proceeded with these analyses based on anatomical sites (Supplemental Table S2).

Raw data were rounded in accordance with the rules put forward by the SSHRC/Statistics Canada to maintain confidentiality. Each cell count was rounded, independent of other cells, to a lower or higher multiple of 5 using a random rounding system. Only counts of 0 and ≥ 5 could be released.

Unless otherwise specified, the Canadian Census of Population for 1996, 2001, 2006, and 2011 were used to calculate average population size during the associated time period. Forward Sortation Areas with population of <5000 individuals and cities with population of $<50\,000$ individuals based on the census data were excluded to reduce the likelihood that a few cases of malignancies within a scarcely populated area may artificially inflate or deflate the incidence or mortality rate. 95% Confidence intervals (CIs) for the incidence rates were calculated using exact Poisson tests for each geographic region. Statistical significance was defined by 95% CI not overlapping with that of the national average 95% CI. Geographic regions with statistically significant cancer rates were mapped using geographic information systems software.

Results

The clinical and demographic characteristics of Canadian oral cavity and oropharyngeal cancer patients were examined using 2 population-based health registries, namely the CCR and LRQC. In total, 21 685 cases of OCC and 15 965 cases of OPC were identified from 1992 to 2010. Of those, the majority were SCCs: 84.97% of oral cavity malignancies were oral cavity SCC and 88.10% of oropharyngeal malignancies were oropharyngeal SCC (Supplemental Table S2).

Demographic Characteristics of Canadian Oral Cavity and Oropharyngeal SCC Patients

Approximately 18420 patients were diagnosed with oral cavity SCC in Canada during the period 1992-2010. These cases predominantly consisted of SCC, NOS (8070), and SCC, keratinizing, NOS (8071) representing 73.28% and 19.89% of oral cavity SCC cases, respectively. Approximately 14055 patients were diagnosed with oropharyngeal SCC in Canada during the period 1992-2010 (Supplemental Table S2). Like oral cavity cancers, these cases predominantly consisted of SCC, NOS (8070), and SCC, keratinizing, NOS (8071) representing 76.06% and 12.17% of all oropharyngeal SCC cases, respectively.

The greatest proportion of oral cavity SCC were diagnosed in the eldest age group of ≥ 90 years, with the steepest rise in incidence in the 50- to 69-year age group. Conversely, oropharyngeal SCC incidence followed a normal distribution, with incidence peaking in the 60- to 69-year age group at 82.88 cases per million individuals per year (Figure 2).

Incidence of Oral Cavity and Oropharyngeal SCC Patients in Canada During 1992-2010

During 1992-2010, the crude mean incidence was 31.19 cases per million individuals per year for oral cavity SCC and 23.81 cases per million individuals per year for oropharyngeal SCC. Oropharyngeal SCC incidence increased over the course of the study period, rising from 15.16 cases per million in 1992 to 34.85 cases per million in 2010. On the contrary, oral cavity SCC incidence remained relatively stable over the same study period, from 33.84 to 34.99 cases per million over the study period (Figures 1 and 2).

Analysis by sex showed a considerably higher proportion of cases diagnosed in males compared to females, with a

sex-standardized rate ratio of 1.69:1 (male:female) for oral cavity and 3.26:1 for oropharyngeal SCC (incidence per million per year).

Geographic Distribution of SCC Cases in Canada by Province

The incidence rates analysis for Canadian provinces revealed notable trends. Nova Scotia (NS), Prince Edward Island (PE), British Columbia (BC), and Manitoba (MB) had significantly higher number of oral cavity SCC cases than the national average. On the other hand, Newfoundland and Labrador (NL), Alberta (AB), and QC had incidence rates significantly lower than the national average. As for the oropharyngeal SCC, New Brunswick (NB), BC, QC, and NS had significantly higher incidences than the national average, while Saskatchewan (SK), AB, Nunavut (NU), Ontario (ON), Northwest Territories (NT), and NL had lower rates (Table 1). Crude values for SCC incidences were then adjusted for age for every province. Indirect standardization was performed using Canada's 1992-2010 average population structure as a standard (Table 1).

Geographic Distribution of SCC Cases by City Across Canada

For oral cavity SCC, most high incidence cities were located in BC, a high incidence province (Supplemental Table S3). Ontario's oral cavity SCC incidence rate was similar to the Canadian average, likely owing to the fact that it houses a balance of both high and low incidence cities. Other provinces containing high oral cavity incidence cities included NB (Saint John) and MB (Winnipeg).

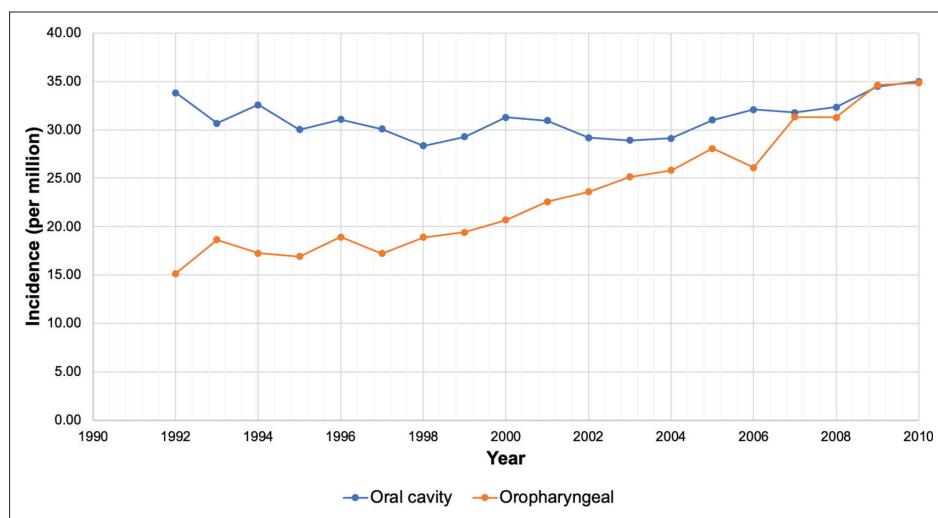


Figure 1. Oral cavity and oropharyngeal squamous cell carcinoma incidence per million between 1992 and 2010.

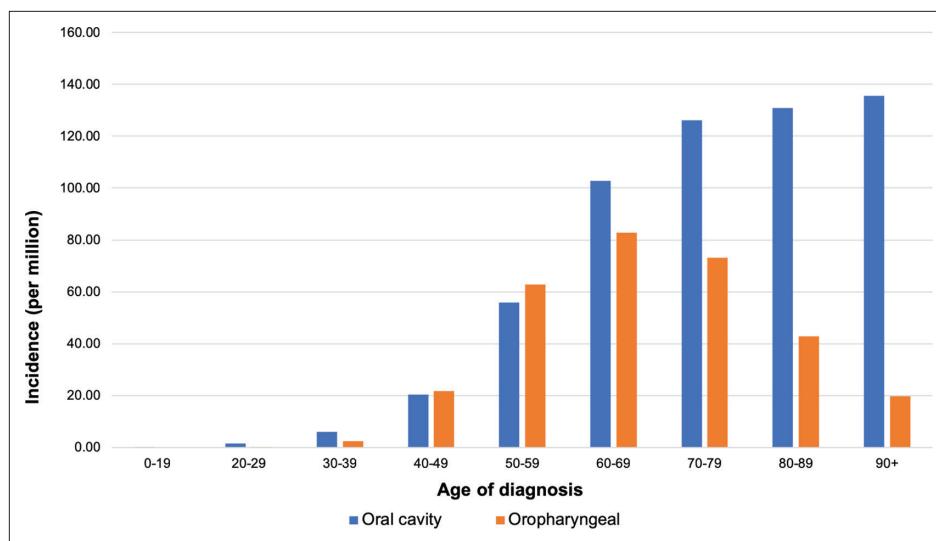


Figure 2. Incidence of oral cavity and oropharyngeal squamous cell carcinoma by age of diagnosis between 1992 and 2010.

For oropharyngeal SCC, once again, most high incidence cities were in BC, a high incidence province (Supplemental Table S4). Other high incidence cities were found in QC (Granby), ON (Sault Ste. Marie, Thunder Bay), NB (Moncton, Saint John), and NS (Cape Breton).

Geographic Distribution of SCC Cases by FSA Across Canada

The highest crude incidence rate for oral cavity SCC was 95.69 cases per million, in T2G and E2L, located in Calgary, AB, and Saint John, NB, respectively. The lowest crude incidence rate for oral cavity SCC was 7.97 cases per million individuals per year, in L6P, Brampton, ON.

The highest crude incidence rate for oropharyngeal SCC was 119.62 cases per million, in T2G, Calgary, AB, which was also a high incidence oral cavity SCC FSA. The lowest crude incidence rate for oropharyngeal SCC was 4.54 cases per million, in E0B, Bathurst, NB. (Complete FSA results are presented in Supplemental Tables S5, S6 and Supplemental Figures S1 and S2.)

Mortality Analyses From Malignancies Arising in Oral Cavity and Oropharynx

The national mortality rates for OCC and OPC between 1992 and 2010 were 13.35 and 5.84 deaths per million individuals per year, respectively. Of note, since ICD-9 and ICD-10 codes do not differentiate between the morphologies of cancers, the incidence rates at the specified sites are not limited to SCC. The increase in oral cavity SCC incidence rates with age was reflected in the corresponding increase in mortality rates. Oropharyngeal cancers demonstrated the steepest increase in mortality rate for the 60- to 69-year-old age

group. Although mortality rates fluctuated mildly over time, the general trend was a decrease in oral cavity malignancy-associated deaths (from 14.10 to 13.67 deaths per million) and an increase in oropharynx malignancy-associated deaths (from 5.46 to 6.91 deaths per million) (Supplemental Figures S3 and S4).

Crude OCC mortality rates did not reveal any provinces with significantly higher rates. However, when rates were adjusted for sex, NL, AB, NB, SK, MB, NS, BC, ON, and QC became significantly high. With age standardization, PE and Yukon also showed significantly higher mortality rates. This result further corroborated our incidence finding. Provinces/territories with significantly low oral cavity mortality rates included AB, NL, NT, and NU. This finding remains unchanged when adjusted for age, but when adjusted for sex, the results were reduced to only NT having significantly low mortality rates.

The only province with significantly high OPC mortality was QC, regardless of standardization by sex or age. Oropharyngeal cancer mortality was significantly lower in PE, SK, AB, BC, NL, and NT, regardless of standardization by sex or age (Supplemental Table S7).

Most cities with a significantly high oral cavity cancer mortality rates were also cities that had high SCC incidences, and most cities with significantly low oral cavity cancer mortality rates correspondingly had low SCC incidences. Exceptions to this trend were found in Saint John, NB and St. Catharines, ON cities, where high oral cavity SCC incidences were associated with lower oral cavity cancer mortality rates. Conversely, QC, Sherbrooke, Sudbury, Drummondville, Montreal, and Saint-Jerome cities had lower oral cavity SCC incidences, but high oral cavity cancer mortality rates. It is interesting to note that many of these cities are located in the province of QC. This inverse trend

Table I. Oral Cavity and Oropharyngeal Squamous Cell Carcinoma Crude Incidence Rates by Province.

Province	Population ^a	Cases	Oral cavity						Oropharyngeal					
			Crude			Age-adjusted			Crude			Age-adjusted		
			Incidence rate	Lower 95% CI	Upper 95% CI	Incidence rate	Lower 95% CI	Upper 95% CI	Cases rate	Lower 95% CI	Upper 95% CI	Incidence rate	Lower 95% CI	Upper 95% CI
Canada	31 087 000	18 420	31.19	30.74	31.64	14 070	23.82	23.43	24.22	17.47	23.08	19.78	17.11	22.67
Newfoundland and Labrador	536 000	255	25.04 ^b	22.06	28.31	25.09	22.06	28.31	205	20.13 ^b	-	-	-	-
Prince Edward Island	137 000	105	40.34 ^c	32.99	48.83	38.40	31.17	46.65	60	23.05	17.59	29.67	22.30	16.80
Nova Scotia	933 000	630	35.54 ^c	32.82	38.43	33.34	30.70	36.13	535	30.18 ^c	27.68	32.85	28.57	26.11
New Brunswick	750 000	440	30.88	28.06	33.90	29.38	26.62	32.31	400	28.07 ^c	25.39	30.96	26.90	24.25
Quebec	7 446 000	4 100	28.98 ^b	28.10	29.88	27.86	27.00	28.74	3 855	27.25 ^c	26.40	28.12	25.94	25.11
Ontario	11 868 000	7 230	32.06	31.33	32.81	32.34	31.60	33.09	4 960	22.00 ^b	21.39	22.62	22.22	21.61
Manitoba	1 158 000	790	35.91 ^c	33.45	38.50	35.58	33.13	38.16	500	22.73	20.78	24.81	23.24	21.26
Saskatchewan	1 010 000	565	29.44	27.06	31.97	28.42	26.06	30.88	345	17.98 ^b	16.13	19.98	18.25	16.38
Alberta	3 109 000	1 625	27.51 ^b	26.19	28.88	32.17	30.73	33.64	1 140	19.30 ^b	18.19	20.45	22.15	20.96
British Columbia	4 040 000	2 645	34.46 ^c	33.16	35.80	33.08	31.81	34.39	2 040	26.58 ^c	25.44	27.76	25.66	24.53
Yukon	31 000	20	33.96	20.74	52.44	45.50	29.78	65.75	15	25.47	14.24 ^d	42.01 ^d	30.22	17.92 ^d
Northwest Territories	42 000	15	18.80	10.51 ^d	31.00 ^d	34.49	22.80 ^d	50.04 ^d	10	12.53 ^b	6.00 ^d	23.05 ^d	20.55	11.81 ^d
Nunavut	28 000	-	-	-	-	-	-	-	5	9.40 ^b	3.03 ^d	21.93 ^d	21.72	11.07 ^d

Abbreviation: CI, confidence interval.

^aAll population numbers are rounded to the nearest thousand.

^bStatistically significant lower rates than the national average.

^cStatistically significant higher rates than the national average.

^dAdjusted for rare event.

was not observed with oropharyngeal carcinoma (i.e., no cities with significantly high oropharyngeal SCC incidences had significantly low oropharyngeal mortalities and vice versa) (Supplemental Tables S8 and S9).

Discussion

Oral cavity and oropharyngeal cancer incidence and prevalence vary markedly based on geographic localization.³⁵ This study presents the first comprehensive analysis of oral cavity and oropharyngeal SCC incidence and mortality in Canada during 1992–2010.

Combining oral cavity and oropharyngeal cancers, a total of 37 650 cases were detected in the Canadian population-based registries from 1992 to 2010, resulting in an incidence rate of 6.37 per 100 000 individuals. This value is strikingly lower than the average incidence rate of 11.2 per 100 000 in the United States, reported by the Surveillance, Epidemiology, and End Results database over the same time period.³⁶ However, such a significant difference may be expected—at least in part—considering that based on the 2010 study, the United States had more current smokers than Canada (39.4%, 25.9%).³⁷ In fact, the United States had ~1.52 times more than in Canada of current smokers (based on the 2010 study), which reasonably correlated with 1.76 times higher rate of combined oral and oropharyngeal cancers.

Studies from population-based registries in the United States have shown an increase in oropharyngeal cancers from 1997 to 2012,^{7,38} consistent with the increase in oropharyngeal cancers detected in our Canadian population. Hence, while absolute values may differ between the United States and Canada, the trends over time were similar. Such epidemiologic trends have also been observed in numerous other developed nations such as Portugal, the Netherlands, Korea, and Australia.¹ Oral cavity SCC incidence in Canada has stabilized, which differed slightly from the decline that was seen in the United States in recent years.³⁸

A distinct difference in incidence was noted based on the age of diagnosis for oral cavity cancers compared to oropharyngeal cancers. The higher incidence of oropharyngeal cancers in younger age groups is consistent with the previous research.⁷ Using sex-standardized rate ratios, our analysis shows a 1.69:1 male-to-female predominance for oral cavity and a 3.26:1 male-to-female predominance for oropharyngeal SCC, which is comparable to data in the United States showing 1.55:1 and 3.41 male-to-female ratio for oral cavity and oropharyngeal cancers, respectively.⁷ These gender disparities have been attributed to both behavioral and biological differences and are reviewed in detail in Woods et al.³⁹

The greatest risk factors for the development of oral cavity malignancies in the Western world are the consumption of tobacco and alcohol, with synergistic effects when their use is combined.³⁻⁵ With the increase in public awareness of the dangers of smoking and the institution of smoke-free legislation

and tobacco taxes over the past several decades, smoking rates have declined in Canada. In addition, Canada's consumption of alcoholic beverages increased until the 1980s, when it stabilized and began to decline.^{40,41} Since the occurrence of oral cavity cancer is usually observed after a latency period of 25 years,⁸ the stabilization in oral cavity SCC occurrences reflects the positive impact of provincial and federal efforts to decrease smoking and alcohol consumption.⁴²

In the United States, states with the highest smoking rates such as West Virginia, Kentucky, and Arkansas^{43,44} also have high rates of oral cavity and oropharyngeal cancers.⁴⁵ In addition, smoking rates among adults are highest in rural areas, with urban areas, small metropolitan areas, and large metropolitan areas exhibiting progressively lower rates.⁴⁶ Our study corroborates the latter findings, with the overwhelming majority of low SCC incidence cities being in metropolitan areas with population of over 100 000. Interestingly, smoking rates in ON remained below the national average from 1950 to 2011,⁴⁷ with the associated favorable oral cavity and oropharyngeal SCC incidence profile despite the longstanding dominance of the ON tobacco belt. This may point to the importance of public health measures put in place to counteract the province's large tobacco presence.

Due to the co-existence of other risk factors, it is difficult to directly correlate smoking trends across provinces to SCC incidence. Socioeconomic inequality has been demonstrated to result in differences in head and neck cancer incidence in the United States, Europe, and Canada, with disadvantaged areas consistently exhibiting higher rates of cancer than more prosperous areas.^{48,49} Rural populations are thought to be less exposed to antitobacco messages in the media and youth are more likely to have role models who are tobacco users.⁵⁰

In the last two decades, HPV has gained its position as the main causal agent for oropharyngeal carcinoma, especially in North America.^{6,51-53} Similar to how genital HPV infection is predominantly transmitted via sexual behaviors, increasing number of genital and oral sex partners is positively associated with the head and neck SCC.^{54,55} While HPV contributes to a large percentage of oropharyngeal cancers, its role remains limited for oral cavity and laryngeal cancers.⁵¹ Systematic testing of oral and oropharyngeal cancers for HPV status was not performed in the past during the period 1992–2010, and therefore, specific data are not available. However, testing of all SCCs for HPV status using the surrogate marker p16 is the current standard of care, as per the existing protocols and guidelines.⁵⁶ The observed increase in oropharyngeal SCC incidence in Canada is also mirrored by similar trends in other economically developed countries such as Japan, Australia, Denmark, the Netherlands, Slovakia, United Kingdom, United States, and Brazil.⁵⁴

Over the last decade, all provinces and territories have instituted HPV vaccination programs,⁵⁷ albeit with differences in coverage.⁵⁸ Since HPV infection usually takes more than 10 years to progress from infection to malignancy, it

remains too early to examine the effects of such vaccination campaigns on oropharyngeal SCC rates. However, a much higher incidence of oropharyngeal cancer in males compared to females points to the need to further target this population with public health initiatives. Incentivization and funding of HPV vaccines in this population that may be more susceptible to such infections may help stabilize this continuous increase in oropharyngeal cancer incidence.

We acknowledge several limitations of our study. The study is based on the evaluation of retrospective data from a national cancer registry with limitations that include misclassification bias and that not all relevant risk factors may have been identified and recorded in the registry. Further, information on individual case exposure to identified risk factors such as tobacco and alcohol consumption, HPV status of the cancer, and race of patients was not available. However, the 2018 update of the ICD-O-3 included new codes for HPV-positive and HPV-negative SCC, respectively. This update in the ICD-O-3 coding will enable future epidemiological studies to more accurately evaluate the role of HPV status of the cancer and the development of SCC and identify geographical clustering of HPV⁺ SCC cases and to confirm causality. Further, multiple Canadian provinces have a largely multicultural population, and the variation in oral/head and neck cancer occurrences around the world highlights the importance of examining ethnic differences. Socioeconomic status has also been linked to HPV⁺ head and neck cancers, and thus having such information could help to better characterize risk factors for these diseases.⁵⁹ Despite these limitations, this large registry-based study allowed for the detailed characterization of important epidemiologic trends in Canada.

Finally, it is important to highlight that as Canada's healthcare system is a single-tier (payer), which is funded and operated by the government, the data are collected with consistency, where each provincial and territorial cancer registry identifies tumors in its population by combining information from sources such as cancer clinic files, radiotherapy and hematology reports, records from inpatient hospital stays, outpatient clinics, pathology and other laboratory/autopsy reports, radiology and screening program reports, medical billing and hospital discharge administrative databases. The CCR/LRQC performs multiple rigorous processes to ensure accuracy including an internal record linkage to identify possible duplicate records. These measures allow for high rates of detection and diagnostic accuracy of incidence data recorded by the registries.

Indeed, several studies investigated the detection rates and accuracy of diagnostic data in the largest provincial branch of the CCR: the Ontario Cancer Registry (OCR) which collects data from the most populous province. In fact, a case ascertainment of ~99%, a detection rate (detecting and accurately assigning index tumor site) of 81.4% to 96%, and a confirmation rate (correctly assigning tumor site) of 90.9% were documented by several studies,⁶⁰⁻⁶² which confirms a

high quality of data and detection rates in the Ontario registry. According to the CCR, the process of data acquisition is consistent across all provincial and territorial registries and, therefore, we expect a high catchment rate and accuracy in the other registries, although this was not confirmed by studies, as in the Ontario registry.

In conclusion, this study identified and confirmed important epidemiological trends, allowing us to gain a more comprehensive understanding of oral cavity and oropharyngeal malignancies in Canada. Understanding the landscape of head and neck malignancies in Canada is crucial for informing the allocation of medical resources for the prevention, diagnosis, and management of these cancers.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

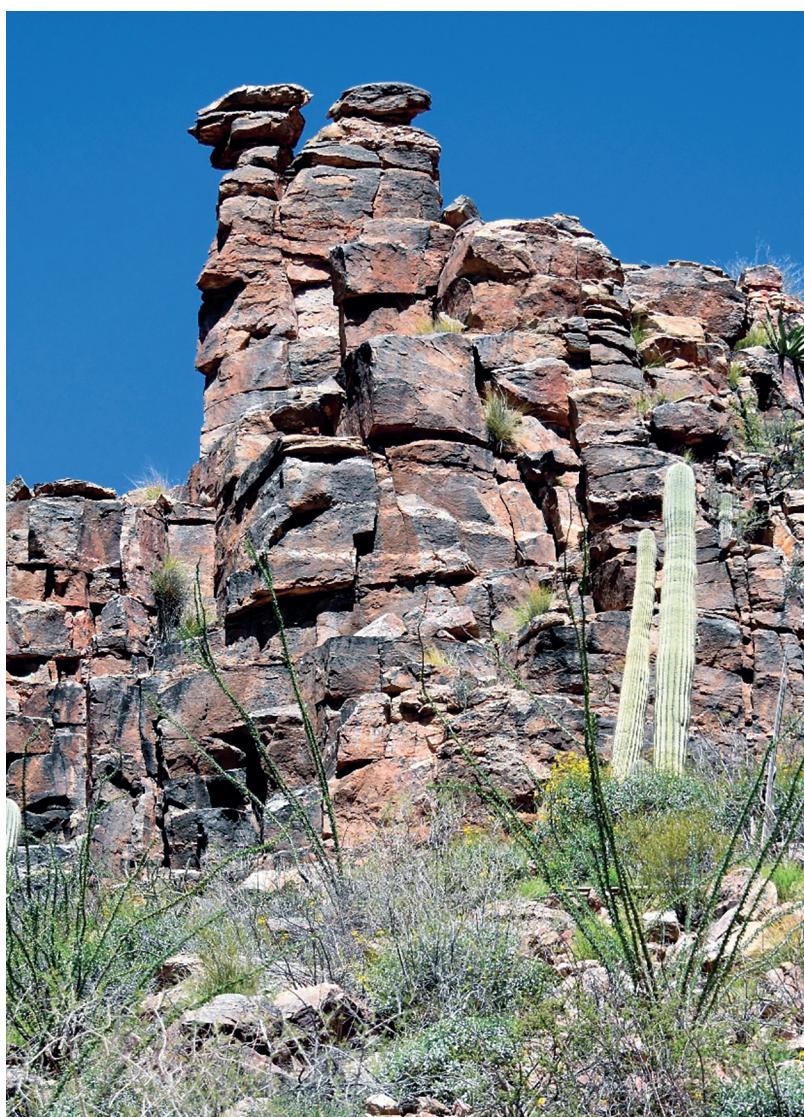
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Ventana Canyon, Tucson, AZ, USA

Photo by Patti Kubick Miller

Allergic Contact Dermatitis Secondary to Moisturizers

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Abstract

Background: Moisturizers are cosmetic products used routinely to manage various skin conditions. Even though moisturizers are often thought to have minimal or no adverse reactions, allergic contact dermatitis (ACD) to these products can develop in some cases.

Methods: We studied ingredients included in 3 of the most commonly used moisturizer brands, identified their presence in standard patch testing series, and evaluated their allergenic potential, categorizing the allergens as frequent or infrequent. The standard patch testing series used as reference were the Thin-layer Rapid Use Epicutaneous patch test (T.R.U.E. test), the North American Contact Dermatitis Group (NACDG) screening standard series, and the American Contact Dermatitis Society (ACDS) core allergen series.

Results: Aveeno, Cetaphil, and Cerave products had a total of 12, 14, and 9 potential allergens, respectively, the majority of which were infrequent and not included in standard patch testing series.

Conclusion: Being aware of the allergenic potential of commonly used moisturizers may help healthcare providers when evaluating patients with ACD. Further testing is recommended in a targeted manner when suspecting ACD with negative standard patch testing series or when ACD is refractory to treatment.

Keywords

allergens, natural ingredients, cosmetic products, patch testing

Introduction

Moisturizers are among the most common cosmetic products people use and are frequently recommended by dermatologists and physicians in general.¹ Although moisturizers are considered safe, immune-mediated reactions including allergic contact dermatitis (ACD) and contact urticaria can occur. Approximately 20% of the general population has a diagnosis of ACD; cosmetic products are involved in 8% to 15% of those cases.² Overall, the most frequent sensitizing allergens seen in ACD patients are nickel, fragrances, and preservatives.²⁻⁴

Recently, Chou et al and Xu et al studied the number of allergenic ingredients in moisturizers and matched them to the North American Contact Dermatitis Group (NACDG) standard screening series and to the American Contact Dermatitis Society (ACDS) core allergen series. These series include some of the most prevalent allergens in moisturizers. The allergens that were most frequently detected were fragrances, preservatives, and vitamin E derivatives.^{2,5} However, moisturizers tend to have long ingredient lists and many of their allergens are not included on either the NACDG

standard screening series or ACDS core series patch testing which jeopardizes the appropriate ACD diagnosis and treatment. Because of these, we decided to look at allergens that are not on any of the mentioned series.²

The frequency and economic burden of ACD caused by ingredients in moisturizers has been studied. Our study aimed to evaluate the allergenic ingredients in 2 moisturizer

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vehicles (1 cream and 1 lotion) of 3 common brands (Aveeno, Cetaphil, and Cerave) and their presence or absence in standard patch testing series.^{2,6,7}

Materials and Methods

Ingredient lists from a sample of Aveeno, Cetaphil, and Cerave moisturizers (1 cream and 1 lotion each) were collected from their official websites. Specific products were Aveeno Daily Moisturizing Lotion and Aveeno Positively Ageless Skin Strengthening Body Cream, Cetaphil Moisturizing Lotion and Cream, and Cerave Daily Moisturizing Lotion from Normal to Dry Skin and Cerave Moisturizing Cream. A systematic literature review was performed using the ingredient name on Medline (PubMed) database to find reports of ACD confirmed by patch test. A second search was employed with the ingredient name and the search terms were “allergy, allergen, dermatitis, or contact dermatitis.” If more than 500 references were obtained, only the second search was performed. The articles retrieved were screened for supplementary references that were not obtained in the initial search strategy. Allergens with 50 or more reported cases were labeled as frequent and the search was stopped. Otherwise, all other references were evaluated and included, when relevant, in the final analysis. Allergens with less than 50 cases were labeled as infrequent, and this cutoff point was chosen by the investigators a priori to help clarify the results. There is no classification system in the literature to categorize an allergen as frequent or infrequent. Additionally, as some allergens such as fragrances are highly prevalent causes of ACD, the search of those allergens would have been inordinately time-consuming. This classification denotes if an allergen is frequently or infrequently present as the culprit in case reports, series, or cohorts, and not actually in real-world use. Only case reports in humans were considered. Articles in English, Spanish, and French were evaluated for inclusion. Furthermore, standard patch testing series were reviewed to identify the presence or absence of the allergens in the moisturizers studied. The standard patch testing series used as reference were the Thin-layer Rapid Use Epicutaneous patch test (T.R.U.E. test), the NACDG patch testing series, and the ACDS core allergen series (Table 1).

Results

A total of 63 ingredients were identified among 6 products. The mean number of ingredients in each product was 19.1. Aveeno had 10 and 22, Cetaphil had 17 and 18, and Cerave had 24 and 24 ingredients in moisturizer lotion and moisturizer cream, respectively. A total of 11 ingredients were present in 2 or more brands (Table 2).

Aveeno products had a total of 12 allergens, 9 of which are not included in any of the series reviewed. We categorized 9 of these 12 allergens as infrequent allergens and 3 as

frequent allergens. Cetaphil products had a total of 14 allergens, 7 of which are not included in any of the series reviewed. We categorized 8 of these 14 allergens as infrequent allergens and 6 as frequent allergens. Cerave products had a total of 9 allergens, 5 of which are not included in any of the series reviewed. We categorized 6 of these 9 allergens as infrequent allergens and 3 as a frequent allergen (Table 3; Figure 1).

A total of 8 allergens were present in 2 or more brands, 4 of which are not included in any of the series reviewed. Among these 8 allergens, 5 were infrequent allergens and 3 were frequent allergens (Table 3).

Discussion

Moisturizers are over the counter products used in the treatment of xerosis and atopic dermatitis. Their active ingredients may act as humectants, emollients, and occlusive agents.¹ Dermatologists often recommend the use of moisturizers for other skin conditions such as contact dermatitis or ichthyosis.⁸ There is no clear superiority of any 1 moisturizing product, and the literature comparing the various products is limited.¹

The wide variety of moisturizers in the market with long ingredient lists and confusing marketing label strategies such as “dermatologist recommended,” “hypoallergenic,” “fragrance free,” “natural,” or even “gluten free” makes deciding which moisturizer is the right one a challenge for both patients and healthcare providers.⁵ We selected 3 moisturizer products which are commonly recommended for patients potentially at risk for ACD because of their low allergenic potential. However, our findings identified that these products do have potential allergens, some of which may be frequent. While ACD due to moisturizers may not be common, its incidence appears to be increasing and advising on their potential allergenicity could help in ACD management.^{9,10}

Studies have analyzed the characteristics in moisturizers to recognize their allergenic potential without any conclusion when it comes to deciding if there is a product “better” than the rest. A review paper on allergens in moisturizers based on their economic value found expensive moisturizers had more significant allergens than inexpensive moisturizers ($P = .003$).² Moreover, a Cochrane review on moisturizers for eczema treatment did not find any moisturizer to be superior to the others.¹¹ In another study of 174 best-selling moisturizers which counseled healthcare providers regarding how to help patients choose a product based on risk of allergenicity and irritancy while taking into account affordability, availability, and consumer preference, only 12% of the products were free of NACDG allergens.⁵

Patients in whom ACD secondary to moisturizers is suspected may undergo patch testing to try to identify the responsible allergen; however, many potential allergens

Table I. Comparison of Allergen List to Standard Patch Testing Series (American Contact Dermatitis Society Core Series, North American Contact Dermatitis Group Screening Standard Series, and Thin-layer Rapid Use Epicutaneous Test).

Allergen list from studied moisturizers	Presence of the allergen in standard patch testing series: ACDS core series, NACDG screening standard series, and T.R.U.E. test
Isopropyl palmitate	No
<i>Avena sativa</i> (oat) kernel flour	No
Butylene glycol	No
Tetrahydroxypropyl ethylenediamine	No
Fragrance	ACDS, NACDG, and T.R.U.E. test as <i>Myroxylon pereirae</i> —Balsam of Peru—and Fragrance Mix I and II
Chlorphenesin	No
<i>Lentinus (lentinula)</i> edodes extract (shiitake mushroom)	No
<i>Persea gratissima</i> (avocado) oil	No
Tocopheryl acetate (vitamin E)	ACDS and NACDG
Panthenol (dexpanthenol) (vitamin B5)	No
Stearyl alcohol	In ACDS as cetyl-stearyl alcohol
<i>Prunus amygdalus dulcis</i> (sweet almond) oil	No
Propylene glycol	ACDS and NACDG
Methylparaben and propylparaben	As paraben mix in T.R.U.E. Test, ACDS, and NACDG
Xanthan gum	No
Dimethicone	No
Glycerin (glycerol)	No
Petrolatum	Vehicle in many allergen formulations in 3 series
Cetyl alcohol (hexadecanol, palmityl alcohol)	In ACDS as cetyl-stearyl alcohol
Benzyl alcohol (phenylcarbinol, phenylethanol)	As benzyl alcohol in ACDS. As component of <i>Myroxylon pereirae</i> in T.R.U.E. Test, ACDS, and NACDG
Cetearyl alcohol (cetostearyl alcohol, cetylstearyl alcohol)	In ACDS as cetyl-stearyl alcohol
Phenoxyethanol	As phenoxyethanol in ACDS. As Methylbromo glutaronitrile/phenoxyethanol in NACDG
Disodium EDTA (ethylenediaminetetraacetic acid, edetate disodium)	No

Abbreviations: ACDS, American Contact Dermatitis Society; NACDG, North American Contact Dermatitis Group; T.R.U.E., Thin-layer Rapid Use Epicutaneous.

may not be present in common patch testing series. Many ingredients in cosmetic products that are not part of standard patch testing series are products labeled as “natural.” The majority of consumers and even some healthcare providers believe “natural” products are harmless ingredients and would not consider them to be a probable cause of contact dermatitis. However, in our report, 9 “natural” ingredients (including botanical extracts, oils, and vitamins) were evaluated, 6 of which had at least 1 case report of ACD confirmed by patch testing, but only 1 (tocopheryl acetate) was included in the common patch testing series reviewed. There is an increasing demand for “natural” products,¹² and manufacturers may have contributed to this demand by adding all sorts of plant extracts, essential oils, and other “natural” ingredients to their products.¹²

An example of a “natural” ingredient widely used in cosmetic products is dexpanthenol, a vitamin B5 derivative. While considered rare, ACD to dexpanthenol may be increasing due to the ongoing trend to use topical cosmetic products containing “natural” vitamin-derivative ingredients. However, dexpanthenol-associated ACD may be frequently overlooked because it is not included in the standard patch testing series. In a recent retrospective study of 2171 subjects with ACD who were patch tested with dexpanthenol, 26 (1.2%) had a positive reaction.¹³ In another trial, 3301 subjects were enrolled and 23 (0.7%) had a positive reaction to panthenol.¹⁴ In our report, dexpanthenol was classified as a frequent allergen due to the identification of more than 50 cases reported. Vitamin B5 derivatives are an example of allergens that can cause ACD

Table 2. Allergens in Aveeno, Cetaphil and Cerave Moisturizing Creams and Lotions.

Allergen	Product brand	Patch test series included	ACD cases	Frequent or infrequent
Isopropyl palmitate	Aveeno Daily Moisturizing Lotion and Aveeno Positively Ageless Skin Strengthening Body Cream	No	1 Case report ¹⁶	Infrequent
Avena sativa (oat) kernel flour	Aveeno Daily Moisturizing Lotion	No	6 Case reports ¹⁷⁻²⁰ 1 Trial in 302 children, 14.6% positive patch test and 19.2% skin prick test ²¹	Infrequent
Butylene glycol	Aveeno Positively Ageless Skin Strengthening Body Cream	No	8 Case reports with 1,3-butylene glycol ²²⁻²⁶	Infrequent
Tetrahydroxypropyl ethylenediamine	Aveeno Positively Ageless Skin Strengthening Body Cream	No	6 Case reports, 1 of them doubtful relevance ^{27,28}	Infrequent
Fragrance	Aveeno Positively Ageless Skin Strengthening Body Cream	ACDS, NACDG, and T.R.U.E. test as <i>Myroxylon pereirae</i> —Balsam of Peru—and Fragrance Mix I and II	Fragrance mix I was the second most common positive allergen in the North American Contact Dermatitis Patch Test in 2013-2014 and the third in 2015-2016 ^{29,30} Fragrance mix II was the 11th and 12th in the 2013-2014 and 2015-2016 reports, respectively ^{29,30}	Frequent
Chlorphenesin	Aveeno Positively Ageless Skin Strengthening Body Cream	No	7 Case reports ³¹⁻³⁶	Infrequent
Lentinus (lentinula) edodes extract (shiitake mushroom)	Aveeno Positively Ageless Skin Strengthening Body Cream	No	Multicenter study in 584 patients, 24 (4.1%) had positive patch test and 27 (4.4%) questionable/irritant reactions; authors discuss probable effect to irritant capacity of concentrations employed in patch test ³⁷	Infrequent
Persea gratissima (avocado) oil	Cetaphil Moisturizing Lotion	No	2 Case reports of occupational ACD with positive patch testing in workers involved in shiitake cultivation or handling ^{38,39}	Infrequent
Tocopherol acetate (vitamin E)	Cetaphil Moisturizing Lotion and Cream	ACDS and NACDG	4 Case reports with positive patch testing ⁴⁰⁻⁴²	Infrequent
Panthene (dexpantheno) (vitamin B5)	Cetaphil Moisturizing Lotion	No	>50 Reported cases confirmed by positive patch testing ^{43,44}	Frequent
Stearyl alcohol	Cetaphil Moisturizing Lotion	In ACDS as stearyl alcohol	10 Case reports ⁴⁴⁻⁴⁶	Infrequent
Prunus amygdalus dulcis (sweet almond) oil	Cetaphil Moisturizing Cream	No	1 Case report ⁶¹	Infrequent
Propylene glycol	Cetaphil Moisturizing Cream	ACDS and NACDG	>50 Reported cases confirmed by positive patch testing ^{29,62}	Frequent
Methylparaben and propylparaben	Cerave Daily Moisturizing Lotion from Normal to Dry Skin and Cerave Moisturizing Cream	As paraben mix in T.R.U.E. Test, ACDS, and NACDG	Considered together because parabens are routinely tested as paraben mix. >50 Reported cases confirmed by positive patch testing to paraben mix ⁶³	Frequent
Xanthan gum	Cerave Daily Moisturizing Lotion from Normal to Dry Skin and Cerave Moisturizing Cream	No	1 Case report ⁶⁴	Infrequent

(Continued)

Table 2. Continued

Allergen	Product brand	Patch test series included	ACD cases	Frequent or infrequent
Dimethicone	In all 3 brands	No	2 Case reports ^{65,66}	Infrequent
Glycerin (glycerol)	In all 3 brands	No	2 Case reports ^{25,67}	Infrequent
Petrolatum	In all 3 brands	Vehicle in many allergen formulations in 3 series	7 Case reports ⁶⁸⁻⁷⁴	Infrequent
Cetyl alcohol (hexadecanol, palmityl alcohol)	In all 3 brands	In ACDS as cetyl-stearyl alcohol	>50 Reported cases confirmed by positive patch testing ^{24,59,75-83}	Frequent
Benzyl alcohol (phenylcarbinol, Aveeno and Cetaphil phenylethanol)		As benzyl alcohol in ACDS. As component of Myroxylon pereirae in T.R.U.E. Test, ACDS, and NACDG	>50 Reported cases confirmed by positive patch testing ²⁴⁻²⁸	Frequent
Cetearyl alcohol (cetostearyl alcohol, cetylstearyl alcohol)	Cetaphil and Cerave	In ACDS as cetyl-stearyl alcohol	>50 Reported cases confirmed by positive patch testing ^{55,89}	Frequent
Phenoxyethanol	Cetaphil and Cerave	As phenoxyethanol in ACDS As Methylidibromo glutaronitrile/ 251 Chronic wound patients with signs of contact dermatitis, phenoxyethanol in NACDG	4 Case reports ⁹⁰⁻⁹³	Infrequent
Disodium EDTA (ethylenediaminetetraacetic acid, edetate disodium)	Cetaphil and Cerave	No	3 cases patch test positive for phenoxyethanol ⁹⁴	Infrequent
			7 Case reports ⁹⁵⁻¹⁰⁰	

Abbreviations: ACD, Allergic contact dermatitis; ACDS, American Contact Dermatitis Society; NACDG, North America Contact Dermatitis Group; T.R.U.E. Test, Thin-Layer Rapid Use Epicutaneous Test® (SmartPractice Denmark, Hillerød, Denmark).

Table 3. Ingredients: Allergens Comparison in Common Brands of Moisturizers.

Brand	Allergens:ingredients	Frequent allergens	Infrequent allergens	How many allergens in at least 1 patch testing?
Aveeno Daily Moisturizing Lotion	7:10	2	5	2/7 (28.57%)
Aveeno Positively Ageless Skin Strengthening Body Cream	11:22	3	8	3/11 (27.27%)
Cetaphil Moisturizing Lotion	12:17	5	7	6/12 (50%)
Cetaphil Moisturizing Cream	11:18	5	6	6/11 (54.54%)
Cerave Daily Moisturizing Lotion from Normal to Dry Skin	9:24	3	6	4/9 (44.44%)
Cerave Moisturizing Cream	9:24	3	6	4/9 (44.44%)

to cosmetics products but may be missed if standard series are used.¹⁵

Natural products mentioned in ingredient labels may also be employed as fragrances and be easily overlooked when analyzing labels; even in cases when manufacturing companies do list “fragrance mix” on the label, they are not required to disclose the components of the fragrance mix. In a prospective study of patients with ACD determined, 79% of subjects had a positive patch test to fragrance mix on the standard series, while 34% of subjects who tested positively on patch testing to Balsam of Peru also had positive patch testing to fragrances. As natural/herbal cosmetic products are becoming more popular and are being used interchangeably as fragrances, healthcare

providers are recommended to counsel patients with ACD to avoid all fragrances and plant extracts.¹²

Limitations of the present report include the analysis of only 6 products of 3 brands. Additionally, the low rate of patch testing to some of the mentioned ingredients might underestimate the actual number of ACD cases, while overestimating the role of allergens in the common patch test series. Further research aimed at determining the real prevalence of ACD to individual common moisturizer ingredients is needed; this may allow for accurate recommendation of a specific product.

Overall, many ingredients in common moisturizer brands have the potential to induce ACD. Healthcare providers struggle with the increasing trend of “natural” products which are commonly perceived as safe but present potential hazards. The challenge is that healthcare providers and patients with ACD rely on brands known for their low allergenicity potential; however, in our study, we determined that even ingredients in patient-friendly products need to be taken into account to avoid missing possible causes of ACD. However, while ACD reactions can be quite significant in individual cases, there are likely just a few case reports for each of the ingredients classified as infrequent allergens because they are rare causes of ACD. The NACDG reviews new allergens and their prevalence yearly removing some and adding others from their standard recommended panel. Further testing such as the Repeat Open Application Test (ROAT) or by using additional allergen panels and patients’ products can be considered when ACD is suspected but standard patch testing series results are negative or weakly positive, or when ACD is refractory to treatment. These tools are helpful for patients and physicians for those more rare allergens that may be missed with routine patch testing.

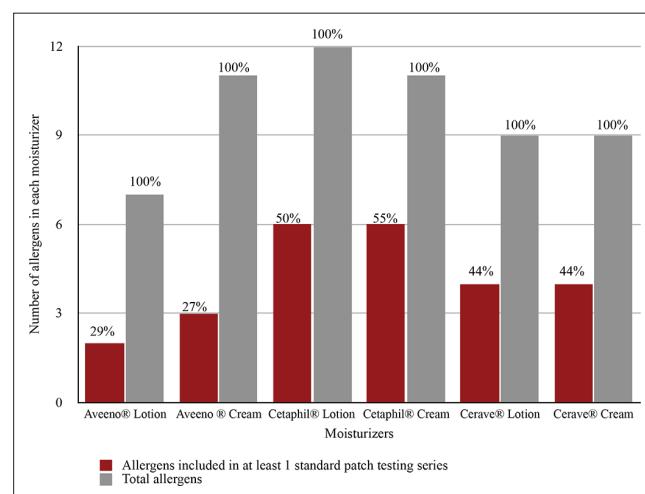


Figure 1. Number of allergens in moisturizers vs number of allergens included in patch testing series. Difference between number of known allergens per product and the actual number of allergens included in the patch testing series reviewed. An estimate of 58.8% of the allergens in the moisturizers we studied are not included in any of the patch testing series reviewed, regardless of the moisturizer brand or formulation.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this

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Clinical and Laboratory Differences Between Early-Onset and Late-Onset Adult Atopic Dermatitis

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Abstract

Background: Atopic dermatitis (AD) in adults is not uncommon, and its prevalence has been increasing in the recent decades. However, there is a paucity of data about the differences between early-onset and late-onset adult AD.

Objective: The objective of this study is to investigate the clinical and laboratory characteristics of adult AD, focusing on the differences between early-onset and late-onset adult AD.

Methods: We retrospectively reviewed the medical records and clinical photos of 214 adult AD patients (≥ 18 years of age) over a 3-year period. We classified the patients into 2 groups: early-onset (first onset of AD before 12 years of age) and late-onset (first onset of AD at 12 years of age or later).

Results: Among 214 patients, 151 patients (70.6%) belonged to the early-onset group (mean age 24.5 years), while 63 patients belonged to the late-onset group (mean age 29.5 years). An association with allergic asthma or rhinitis, a family history of atopic disease, elevated total serum IgE, and sensitivity to food allergens were more commonly seen in the early-onset group. The late-onset group had a significant likelihood of nonflexural involvement (38.1% vs 13.2%). There was no significant difference in the mean eczema area severity index score, eosinophil count, and sensitivity to aeroallergens between 2 groups.

Conclusion: Adult AD shows different clinical and laboratory characteristics depending on the age of onset. This study could help to create awareness about the heterogeneity of AD in adulthood and encourage further studies on clinical outcomes and different therapeutic methods depending on the age of onset.

Keywords

adult atopic dermatitis, atopic dermatitis, onset age, early-onset, late-onset

Introduction

Atopic dermatitis (AD) in adults is not uncommon, and its prevalence has been increasing in recent decades.¹ Atopic dermatitis usually presents in early childhood and goes into remission before puberty. However, in severe cases, AD persists until adulthood or presents later in life. A recent study revealed that AD has a prevalence of 2.1% to 4.9% in adults.¹⁻³

Atopic dermatitis typically has 3 phases: the infantile phase from 0 to 2 years of age, childhood phase between 2 and 12 years of age, and the adolescent or adult phase thereafter.^{2,4} Recent studies have reported a high prevalence of AD after 12 years of age and suggested that late-onset AD could be quite common.^{4,5} Late-onset AD could be difficult to diagnose, especially when the presentation differs from that commonly seen in childhood AD.⁶ However, there is a paucity of data about the differences between early-onset and late-onset adult AD. The aim of this study was to investigate

the characteristics of and differences between early-onset and late-onset adult AD.

Methods

The present study retrospectively reviewed the medical records and clinical photographs of adult AD patients treated in

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outpatient clinics during their initial visits at 2 Korean tertiary teaching hospitals (Busan and Yangsan Pusan National University Hospitals) from May 2014 to May 2017. In total, 214 adult patients (aged ≥ 18 years) diagnosed with AD using the Hanifin and Rajka criteria were included. The detailed medical histories and clinical photographs of the patients were reviewed extensively to exclude other cutaneous disorders. Patients with positive patch tests (TRUE test panels) for relevant allergens as determined by the history were excluded to rule out systemic contact dermatitis. We classified the patients into 2 groups: the early-onset group if the first onset of AD was before 12 years of age and the late-onset group if the first onset of AD was at 12 years of age or later.^{2,4,5}

Data for the patients' sex, age (at onset and at visit), eczema area severity index (EASI) score (at visit), treatment history, history of allergic asthma or rhinitis, family history of atopic disease, distribution of lesions (flexural only, flexural and other sites [face, hands, feet, extremities, and trunk], and nonflexural [sparring flexural] and other sites), and lesion morphology (typical lichenified, exudative eczematous, nummular, prurigo-like, follicular, and mixed pattern) were retrieved and assessed by 2 experienced dermatologists for reliability.

Laboratory data collected for each patient included the total serum immunoglobulin E (IgE) level (IU/mL), eosinophil count (%), and level of allergen-specific IgE against house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) and aeroallergens and food allergens with multiple antigen simultaneous test (MAST, Department of Laboratory Medicine, Pusan National University Hospital). The sensitivity to aeroallergens, food allergens, and house dust mites was analyzed in both the early-onset and late-onset groups as a large number of patients showed more than class 2 positivity to the allergen in their MAST results (classes 0-6).

All statistical analyses were performed using IBM SPSS (IBM SPSS Statistics, IBM Corporation, NY, United States), version 21. We used Pearson's χ^2 test and Fisher's exact test for the analysis of categorical variables and independent *t*-test for the analysis of measurement data. *P*-values $< .05$ were considered statistically significant.

Results

Two hundred and fourteen patients (140 males and 74 females; mean age 26.5 years [range 18-74]) were included in the study. Of these, 151 patients (70.6%) belonged to the early-onset group (mean age, 24.5 years) comprising 101 males and 50 females, while 63 patients (29.4%) belonged to the late-onset group (mean age, 29.5 years) comprising 39 males and 24 females.

The patient demographics are summarized in Table 1. The age at initial visit was significantly higher in the late-onset group (29.5 ± 7.2 years) than in the early-onset group (24.5 ± 7.1 years; *P*-value $< .001$). Sex-based analysis revealed a predominance of males, comprising 66.8% (101/151) of the early-onset group and 61.9% (39/63) of the late-onset group. However, sex predilection and mean EASI score did not show a significant difference between 2 groups (*P*-values = .529 and .626, respectively).

The ages at initial visit for AD are presented in Table 1 and Figure 1. The majority of the patients in the early-onset group (101/151, 66.8%) were in the age range of 18 to 25 years, followed by 47 patients (31.1%) in the age range of 25 to 40 years, 2 patients (1.3%) in the age range of 40 to 65 years, and 1 patient (0.6%) was more than 65 years. The late-onset group showed a different pattern of age distribution during the first visit compared to the early-onset group (*P*-value $< .001$). The largest proportion (40/63, 63.4%) of patients in the late-onset group was in the range of 25 to 40

Table I. Patient Demographics.

	Early-onset group (N = 151)	Late-onset group (N = 63)	P-value
Visit age (mean, SD, range)	24.5 ± 7.1 (18-74)	29.5 ± 7.2 (18-49)	<.001*
Onset age (mean, SD, range)	3.8 ± 2.9 (0-11)	18.3 ± 5.4 (12-37)	
Male (%)	101 (66.8%)	39 (61.9%)	.529†
EASI score (mean, SD, range)	9.9 ± 6.5 (1.8-41.2)	10.4 ± 7.9 (1.7-37.5)	.626*
Age			
18-25 (%)	101 (66.7)	20 (31.7)	<.001*
25-40 (%)	47 (31.1)	40 (63.4)	
40-65 (%)	2 (1.3)	3 (4.7)	
>65 (%)	1 (0.6)	0 (0.0)	

Abbreviations: EASI, eczema area and severity index; SD, standard deviation.
Statistical analysis was performed using *independent *t*-test and †Pearson's χ^2 test.

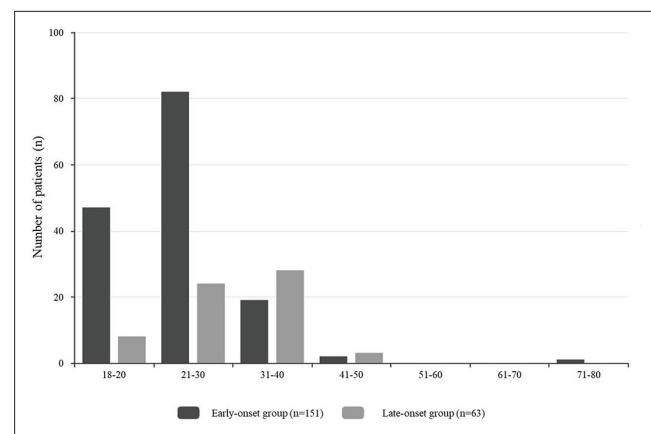


Figure 1. Distribution of patients according to age at initial visit.

years, followed by 20 patients (31.7%) in the range of 18 to 25 years, and 3 patients (4.7%) in the range of 40 to 65 years.

The details of the treatment modalities are summarized in Table 2. The largest proportion of patients in both the early-onset and late-onset groups used topical and systemic agents, including immune modulators (steroids or cyclosporine) for the previous and current treatment. In all patients using systemic agents, antihistamines were also used to control pruritus. There was no statistical difference in the treatment modalities between the early-onset and late-onset groups. However, systemic steroids with topical agents were most commonly used for the previous treatment for the early-onset and late-onset groups, whereas cyclosporine with topical agents was mostly commonly used for the current treatment for both groups.

The data of the association with allergic asthma or rhinitis are presented in Table 3. In the early-onset group, 13 patients (8.6%) had allergic asthma, 68 patients (45.0%) had allergic rhinitis, 11 patients (7.3%) had both allergic asthma and rhinitis, and 70 patients (46.3%) had either allergic asthma or rhinitis. In the late-onset group, 1 patient (1.5%) had allergic asthma, 16 patients (25.3%) had allergic rhinitis, 1 patient (1.5%) had both allergic asthma and rhinitis, and 16 patients (25.3%) had either allergic asthma or rhinitis. Associations

with allergic rhinitis and allergic asthma or rhinitis were more commonly seen in the early-onset than in the late-onset group (P -values = .009 and .006, respectively).

The details of patients' family histories of atopic diseases are presented in Table 3. The history of atopic diseases among the first-degree and second-degree relatives was analyzed in both groups. In the early-onset group, 45 patients (29.8%) had first-degree relatives, 21 patients (13.9%) had second-degree relatives, and 14 patients (9.2%) had both the first- and second-degree relatives with a history of atopic diseases. In the late-onset group, 10 patients (15.8%) had first-degree relatives, 7 patients (11.1%) had second-degree relatives, and 4 patients (6.3%) had both the first- and second-degree relatives with a history of atopic diseases. A family history of atopic diseases in first-degree relatives was more commonly seen in the early-onset than in the late-onset group (P -value = .039). However, a history of atopic disease in the second degree and both the first- and second-degree relatives did not reveal a significant difference between 2 groups (P -values = .662 and .445, respectively).

The data of distribution of the lesions are summarized in Table 4. Though flexural and other sites involvement was the most common one in both groups, the late-onset group had a significantly higher likelihood of nonflexural involvements (38.1% vs 13.2%, P -value < .001). Contrarily, the early-onset group had a significantly higher likelihood of only flexural involvement (18.5% vs 0%, P -value < .001).

The data of the morphology of lesions are summarized in Table 4. There was no significant difference in the frequency of typical lichenified (P -value = .763), exudative eczematous (P -value = 1.000), nummular (P -value = .321), prurigo-like (P -value = .067), follicular (P -value = 1.000), or mixed pattern (P -value = .554) lesions between the groups.

In the laboratory investigations, a higher total serum IgE was detected in the early-onset group (4709 ± 6474 IU/mL) than in the late-onset group (3825 ± 5961 IU/mL; P -value < .001; Figure 2(a)). The blood eosinophil count was similar in the early-onset and late-onset groups (8.7% vs 9.6%, P -value = .516; Figure 2(b)).

Table 2. Previous and Current Treatment.

	Early-onset group (N = 151)	Late-onset group (N = 63)	P-value [†]
Previous treatment			
Topical agents only	34 (22.5%)	22 (34.9%)	.087
Systemic steroids with topical agents	94 (62.3%)	35 (54.0%)	.363
Cyclosporine with topical agents	23 (15.2%)	6 (9.5%)	.838
Current treatment			
Topical agents only	31 (20.5%)	9 (14.3%)	.339
Systemic steroids with topical agents	8 (5.3%)	2 (3.2%)	.727
Cyclosporine with topical agents	112 (74.2%)	52 (82.5%)	.217

Statistical analysis was performed using [†]Fisher's exact test or Pearson's χ^2 test.

Table 3. Association With Allergic Asthma or Rhinitis and Family History of Atopic Disease.

	Early-onset group (N = 151)	Late-onset group (N = 63)	P-value [†]
Allergic asthma	13 (8.6%)	1 (1.5%)	.07
Allergic rhinitis	68 (45%)	16 (25.3%)	.009
Allergic asthma and rhinitis	11 (7.3%)	1 (1.5%)	.116
Allergic asthma or rhinitis	70 (46.3%)	16 (25.3%)	.006
First-degree relatives	45 (29.8%)	10 (15.8%)	.039
Second-degree relatives	21 (13.9%)	7 (11.1%)	.662
First- and second-degree relatives	14 (9.2%)	4 (6.3%)	.445

Statistical analysis was performed using [†]Fisher's exact test or Pearson's χ^2 test.

The test results for sensitivity to aeroallergens and food allergens are summarized in Table 5. The percentage of patients with sensitivity to aeroallergens was similar in the early-onset and late-onset groups (84.7% vs 74.5%, P -value = .085). However, the percentage of patients with sensitivity to food allergens was significantly higher in the early-onset (44.5%) than in the late-onset (13.7%) group (P -value < .001).

The results of sensitivity to house dust mites (*D. pteronyssinus* and *D. farinae*) are summarized in Table 5. The percentage of patients with sensitivity to each house dust mite

species was similar between the early-onset and late-onset groups (P -values = .678 and .529, respectively).

Discussion

Atopic dermatitis is a paradigmatic and complex disease with varied clinical characteristics and is accompanied by other atopic disorders such as allergic rhinitis and asthma, depending on the grade of sensitization.^{4,6} Recently, other studies have also suggested that adult AD appears to be more common than previously reported, as adult AD is now known

Table 4. Distribution of Atopic Lesions and Dermatitis Morphology.

	Early-onset group (N = 151)	Late-onset group (N = 63)	P-value [†]
Flexural only	28 (18.5%)	0	<.001
Flexural and other sites	103 (68.2%)	39 (61.9%)	.428
Face	88 (58.3%)	38 (60.3%)	.879
Hands	59 (39.1%)	32 (50.7%)	.130
Feet	40 (26.5%)	19 (30.2%)	.616
Extremities	25 (16.6%)	17 (27.0%)	.091
Trunk	22 (14.6%)	15 (23.8%)	.115
Nonflexural and other sites	20 (13.2%)	24 (38.1%)	<.001
Face	16 (10.6%)	18 (28.6%)	.002
Hands	12 (7.9%)	15 (23.8%)	.003
Feet	11 (7.3%)	14 (22.2%)	.004
Extremities	12 (7.9%)	19 (30.2%)	<.001
Trunk	13 (8.6%)	20 (31.7%)	<.001
Typical lichenified	84 (55.6%)	33 (52.3%)	.763
Exudative eczematous	22 (14.5%)	6 (9.5%)	1.000
Nummular	9 (5.9%)	2 (3.1%)	.321
Prurigo-like	4 (2.6%)	6 (9.5%)	.067
Follicular	9 (5.9%)	4 (6.3%)	1.000
Mixed pattern	23 (15.2%)	12 (19.0%)	.544

Statistical analysis was performed using [†]Fisher's exact test or Pearson's χ^2 test.

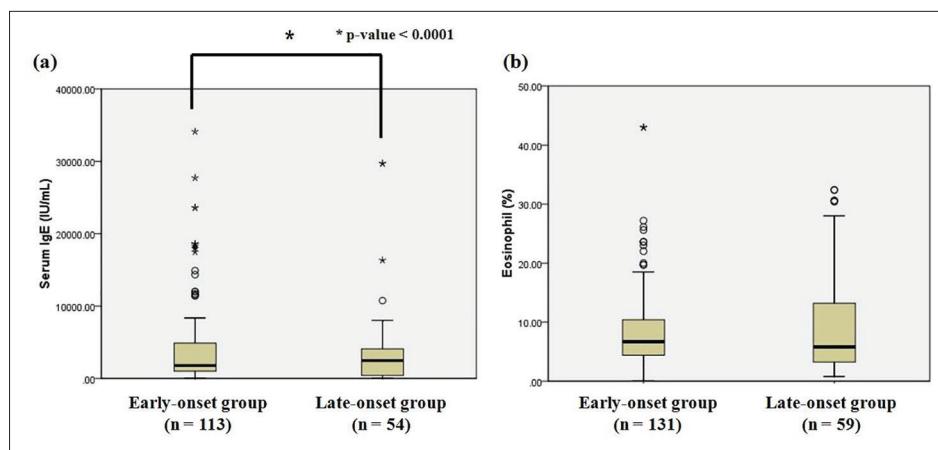


Figure 2. Laboratory assessments of patients with early-onset and late-onset atopic dermatitis. (a) Total serum immunoglobulin E (IU/mL), (b) The blood eosinophil count (%) of patients with early-onset and late-onset atopic dermatitis.

to persist since childhood or develop de novo in adults.⁷ However, much of the literature about AD is related to children, and the limited data about adult AD are regarding the prevalence of the childhood disease persisting in adulthood and not about late-onset AD. Moreover, studies investigating the differences between early-onset and late-onset adult AD are quite limited. Hence, we investigated the clinical and laboratory characteristics of adult AD, focusing on the differences between early-onset and late-onset adult AD.

The age at initial visit for AD was significantly higher in the late-onset than in the early-onset group. The largest proportion of patients in the early-onset group was in the age range of 18 to 25 years. The late-onset group showed a different pattern of age distribution, with the largest proportion of patients in the late-onset group being in the age range of 25 to 40 years. The early-onset group, which has a tendency of achieving remission before the age of 25 years, might have affected these findings. However, these results are based only on the initial visit and their clinical implications are difficult to identify.

In our study, the early-onset group had a higher incidence of concomitant allergic asthma or rhinitis, family history of AD, flexural only involvement, elevated total serum IgE, and sensitivity to food allergens. The prevalence of personal and/or family history of AD showed the importance of genetic factors and features in this disease.⁸ Although the William AD criteria^{9–11} merely suggested a link to family history of atopic disease in children under 4 years of age, our results revealed a presence of family history in 29.8% patients in first-degree relatives and 13.9% patients in second-degree relatives in the early-onset group. These results indicate that regardless of the age, family history is an important factor for AD, and genetic factors have a stronger contribution in the early-onset adult AD group.

In the previous reports, among atopic patients of all ages, those with AD tend to have the highest levels of IgE followed by atopic asthma, perennial allergic rhinitis, and seasonal allergic rhinitis.¹² In our study, the early-onset group had a higher incidence of allergic asthma, rhinitis, and elevated total serum IgE level than the late-onset group. These

Table 5. Laboratory Assessments (Multiple Antigen Simultaneous Test: Aeroallergen and Food Allergen, Specific Immunoglobulin E to House Dust Mites).

	Early-onset group	Late-onset group	P-value [†]
Aeroallergen	101/119 (84.7%)	38/51 (74.5%)	.085
Food allergen	53/119 (44.5%)	7/51 (13.7%)	<.001
<i>Dermatophagoides pterony</i>	104/151 (83.8%)	48/63 (81.3%)	.678
<i>Dermatophagoides farina</i>	106/151 (85.4%)	50/63 (84.7%)	.529

Patients (Positivity ≥2 + (class 0-6))

Statistical analysis was performed using [†]Fisher's exact test or Pearson's χ^2 test.

findings suggest that the early-onset AD can be more associated with allergic disease than the late-onset group. Previous reports revealed that it is difficult to differentiate between extrinsic and intrinsic AD based only on the clinical presentation, and only approximately 10% of the cases show a purely flexural distribution in adults.⁷ In our study, although all the patients showed flexural involvement, the early-onset group had a significantly higher likelihood of flexural only involvement in approximately 20% of patients, while the late-onset group had a significantly higher likelihood of non-flexural involvement. These findings could indicate a stronger genetic influence in the early-onset group and the relevance of extrinsic and intrinsic AD. A previous study about adult AD revealed that severe refractory AD is highly atopic with increased levels of total serum IgE and prominent IgE antibodies to aeroallergens, house dust mites, and food allergens, in contrast to moderate AD.¹³ Since the early-onset group showed a higher total serum IgE and sensitivity to food allergens than the late-onset group, AD in adulthood may show more heterogeneity, and there may be a stronger genetic influence and treatment resistance in the early-onset group patients.

This also leads to the conclusion that 2 variants of adult AD might exist: allergic and nonallergic. Similar to the previous study, the highest proportion of patients with the allergic variant of AD with high IgE serum levels, higher incidence of allergic asthma or rhinitis, and sensitization to allergens were seen in the early-onset group.¹⁴ On the contrary, the highest proportion of patients with the nonallergic variant of AD with low total IgE serum levels and lack of sensitization to allergens was present in the late-onset group. This finding indicates that common preventive measures, which are useful in childhood AD patients, especially the restriction of certain food items, most likely do not have any beneficial effect for adult patients.

Regarding the treatment modalities used, there was no significant difference between the early-onset and late-onset groups. The highest proportion of patients in both groups used topical and systemic agents (steroid or cyclosporine). Our study revealed no significant difference in the mean EASI scores in both groups, possibly because the study was conducted in a tertiary hospital and most patients had moderate to severe AD. There was also no significant difference in the dermatitis morphology and atopic comorbidities between 2 groups. Larger epidemiological studies are needed to confirm these differences between 2 groups.

Our study has several limitations. Although we used an arbitrary age cut-off of 12 years to classify the early-onset and late-onset groups, there are no established criteria for defining early-onset and late-onset AD. Since our study retrospectively reviewed the data from the initial visit, there is a possibility of recall bias, limited longitudinal data about disease progression, and historical patterns. In addition, since this study included patients diagnosed with AD based

on the Hanifin and Rajka criteria with detailed medical records to exclude other cutaneous disorders, this selection process might have caused a bias in the results.

In conclusion, this study showed that adult AD showed different clinical and laboratory characteristics depending on the age of onset. These findings could be helpful in understanding AD in adulthood, and they support the assumption of disease heterogeneity in AD. Since the number of adult AD patients is increasing, further studies on the underlying pathogenesis, clinical outcomes, and new treatment modalities considering the age of onset are necessary.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: This study was exempted from the requirement of ethics committee approval.

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Utility of Preinjection Aspiration for Hyaluronic Fillers: A Novel In Vivo Human Evaluation

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Abstract

Background: Hyaluronic acid (HA) fillers have increased in popularity. While complications are rare, practitioners should focus on their prevention. Preinjection aspiration remains controversial as an effective safety checkpoint.

Objectives: Our study investigated the utility of preinjection aspiration as a safety checkpoint for HA fillers through comparison of physiochemical and rheological properties in a novel in vivo human model.

Methods: An in vivo human model consisted of a cannula inserted into a peripheral vein. Preinjection aspiration was evaluated using syringes of 10 commonly used HA fillers. The time required to visualize a flash was recorded.

Results: Using a multivariable regression model, needle gauge, HA concentration, elastic modulus (G'), viscous modulus (G''), and complex modulus (G^*) had significant relationships with time to flash, whereas pullback volume did not. However, when comparing pullback volume using a more appropriate paired analysis, 0.5 cc pullback volume had a significantly decreased time to flash than 0.2 cc.

Conclusions: Preinjection aspiration for HA fillers has utility as a safety checkpoint. The times to visualize flashback decreased when using a human peripheral vein model compared to a previous in vitro model, suggesting that there may be real-time clinical utility of preinjection aspiration. Waiting times to visualize flashback may be affected by physiochemical and rheological properties. Additional studies would help to validate our results.

Keywords

filler, facial rejuvenation, hyaluronic acid, dermatology, patient safety

Introduction

Hyaluronic acid (HA) fillers have increased in popularity, especially for scar correction, rhytid augmentation, and volume rejuvenation. In 2018, more than 2.1 million procedures using HA fillers were performed in the United States.¹ Much of this popularity can be attributed to their ever-increasing diversity of applications, available reversibility, and historically low-risk profile.²

While complications are rare,³ knowledge regarding their prevention and management is crucial. Intra-arterial injection can cause visual impairment and local skin damage, including necrosis. In addition to having a good understanding of local vascular anatomy, preinjection aspiration is one method that has been proposed to decrease the risk of intravascular injection.⁴ However, its utility as a safety checkpoint continues to be controversial. While it can help to mitigate the risks of intravascular injection, adequate time must be allowed to visualize the flashback. Questions also remain as to whether vessel collapse would prevent a positive reflux and how the properties of HA

fillers, needle gauge, and injection volume affect the time needed for aspiration.⁵

HA fillers differ in their rheological properties, which describe how fillers behave under mechanical stress. The most commonly used rheological parameters are the elastic modulus (G'), viscous modulus (G''), and complex modulus G^* . G' describes its ability to restore shape after compression. G'' characterizes its resistance to dynamic forces. G^* reflects the total energy needed to deform the material. These properties are determined by several factors, such as the degree and

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technique of crosslinking, HA concentration, and HA substrate molecular weight.⁶⁻¹¹

The diversity of available HA fillers allows clinicians to tailor their approach to achieve the best cosmetic outcome for each clinical scenario. However, these rheological parameters may also affect the time needed to achieve a positive flashback during preinjection aspiration.

We had recently published an in vitro model to evaluate preinjection aspiration using physiochemical and rheological properties.¹² However, the times to visualize flashback were long, which was postulated to be from a lack of dynamic intravascular pressures. Here, we perform a similar study using a novel in vivo human model in order to shed additional light on this technique, which may help practitioners increase patient safety.

Materials and Methods

An in vivo model consisted of a synthetic plastic cannula (20 G, 1 in.) inserted into a peripheral vein located in the forearm of a willing author. A needle-accessible hub was attached, and air was removed from the system. Cannula patency was checked prior to each aspiration to avoid clotting. The needles of various syringes containing HA filler were primed and then each inserted separately. The plunger was pulled

back at volumes of 0.2 and 0.5 cc to mimic preinjection aspiration. In order to accommodate pullback volumes, some HA fillers had to be removed from the syringe. The plunger was held at this distance until flashback was visualized.

Syringes of 10 commonly used HA fillers were evaluated: Allergan (Pringy, France) Juvéderm Ultra Plus XC, Juvéderm Ultra XC, Juvéderm Volbella, Juvéderm Vollure, and Juvéderm Voluma; Galderma (Uppsala, Sweden) Restylane Defyne, Restylane Lyft, Restylane Refyne, and Restylane Silk; and Merz (Raleigh, NC, USA) Belotero Balance. Factory-provided needles were utilized to best approximate real-world injection conditions. Values for physiochemical and rheological properties at 0.1 Hz were gathered from previously published data.¹³

A multivariable regression model was utilized to evaluate factors influencing time to flash. Paired t-test was used to compare pullback volumes of each HA filler in order to control for outside variables. Two-sample t-test was used to compare changes in time to flash with varying HA concentration, G' , G'' , and G^* .

Results

For the 10 HA fillers, the time to flash varied (Table 1). The mean time to flash was 3.1 seconds with a maximum of 10.5 seconds. Using a multivariable regression model ($R^2 = .7638$;

Table 1. Time to Flash for Various HA Fillers.

HA filler	Needle gauge (G)	Pullback volume (cc)	Time to flash (s)	Rank (1 = greatest; 10 = least)		
				G'	G''	G^*
Belotero Balance	27	0.2	1.5	10	7	10
		0.5	0.5			
Juvéderm Ultra Plus XC	27	0.2	0.5	7	5	7
		0.5	0.5			
Juvéderm Ultra XC	30	0.2	9	8	8	8
		0.5	2.5			
Juvéderm Volbella	30	0.2	1	6	6	6
		0.5	0.5			
Juvéderm Vollure	30	0.2	1	4	3	4
		0.5	0.5			
Juvéderm Voluma	27	0.2	1	3	4	3
		0.5	0.5			
Restylane Defyne	27	0.2	8	5	9	5
		0.5	10.5			
Restylane Lyft	29	0.2	8	1	2	1
		0.5	4			
Restylane Refyne	30	0.2	9	9	10	9
		0.5	1			
Restylane Silk	30	0.2	1.5	2	1	2
		0.5	1			

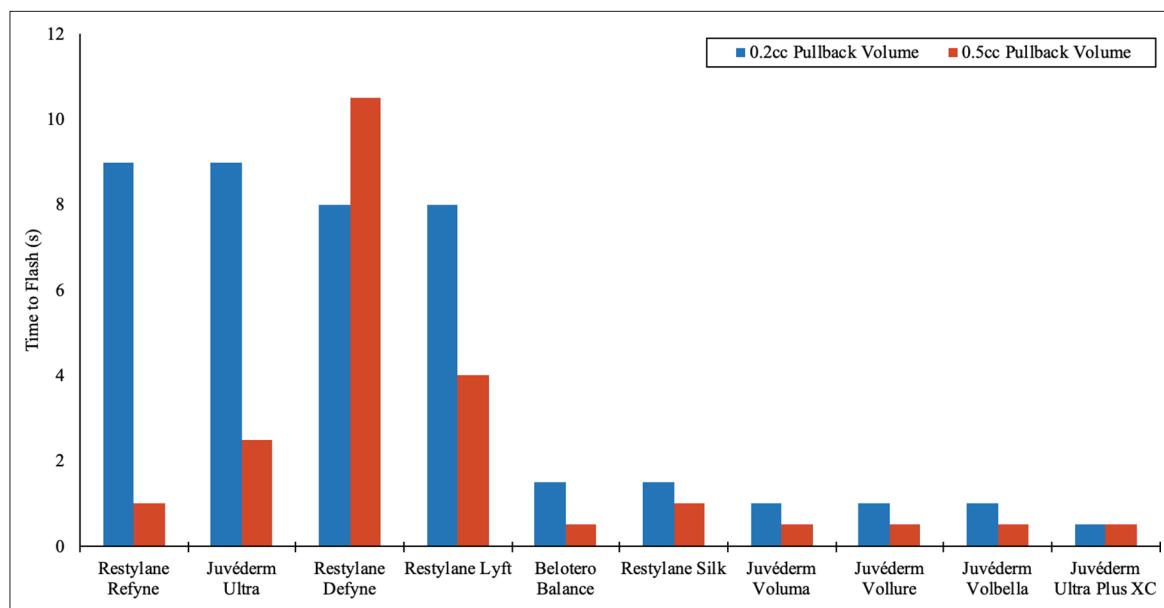


Figure 1. Time to flash for hyaluronic acid fillers comparing 0.2 versus 0.5 cc pullback volume.

$P = .0441$), $Y = -103.05 - 6.33A + 2.54B + 1.49C - 6.16D - 1.30E + 6.30F$, where Y = time to flash (seconds), A = pull-back volume (cc), B = needle gauge (G), C = HA concentration (mg/mL), D = G' (Pa), E = G'' (Pa), and F = G^* (Pa). Needle gauge ($P = .0085$), HA concentration ($P = .0050$), G' ($P = .0251$), G'' ($P = .0134$), and G^* ($P = .0247$) were shown to have significant relationships with time to flash, whereas pullback volume ($P = .1505$) did not.

However, when comparing pullback volume using a more appropriate paired analysis for each HA filler, 0.5 cc had a significantly decreased mean time to flash than 0.2 cc as expected (2.15 vs 4.05 seconds $P = .0483$). Only Restylane Defyne showed an increased time to flash with 0.5 cc pullback volume compared to 0.2 cc (Figure 1). A significantly greater decrease in time to flash was associated with $G' < 112$ Pa ($P = .0254$) and $G^* < 114$ Pa ($P = .0254$), while HA concentration and G'' showed no significant differences.

Discussion

Much of the appeal of HA fillers is in its reversibility. Even if injected intra-arterially, hyaluronidase does not need to be injected directly into the vessel for dissolution of the HA, as peri-arterial placement has been demonstrated to be effective in fresh human cadaver-sourced facial artery specimens.¹⁴ The same physicochemical properties that make HA fillers diverse also make the response and proper dosing of hyaluronidase highly variable between products.¹⁵ In a reported case, treatment with hyaluronidase following intra-ophthalmic artery injection with HA failed to restore vision despite restoring partial blood flow to the retina and choroid.¹⁶ Due to the variability in outcomes of hyaluronidase,

intravascular injection should be avoided at all reasonable costs. Our study demonstrates that the time to visualize flashback varies from product to product and provides an approximate range of time required to visualize flashback in a human peripheral vein model. This may or may not correlate with facial vasculature and real-world scenarios.

Previous studies have evaluated the time to flash using both in-vitro and animal models. In one study, red ink was aspirated from a cup into syringes of 17 different fillers.⁵ Reflux was considered positive if flash occurred in less than 10 seconds. In 8 of the 17 fillers, no flash was observed in the time allotted using needle gauges provided by the manufacturer. In the same study, five fillers that had positive flash were randomly selected and tested on the vein of a rabbit ear to assess whether the in vitro results were reproducible. All five products had positive flash. While the use of a rabbit ear vein likely better approximates the behavior of human vasculature than a cup, only five products were tested, and it is unclear whether the HA fillers that had a negative reflux test in vitro would have become positive in the animal model.

In our previous study using pressure-stabilized vacutainers,¹² whole blood was drawn into syringes containing 10 commonly used HA fillers using 0.2 and 0.5 cc pullback volumes. The time to flash varied with pullback volume with an average of 10.86 and 8.86 seconds for 0.2 and 0.5 cc pullback volumes, respectively. Increased pullback volume had a similar effect of decreasing the time to flash in this current in vivo human study. The maximum time to visualize flashback also greatly decreased to 10.5 seconds from greater than 30 seconds in the previous study.

This present study provides a more accurate assessment of real-time injection conditions. By inserting the cannula into a

peripheral vein, the contributions of both venous collapse and venous pressure could be accounted for. Using a cannulated vein more accurately mimics facial vasculature than previously studied models, and it ensures that the injection needle is truly within the vessel. The shorter times to visualize flashback compared to our in vitro model suggest that preinjection aspiration may have clinical utility. However, the practitioner must still be sure to use other safety techniques, including injecting smaller volumes to prevent vessel collapse due to volume effect if injected into surrounding tissue.

Although this study addressed many of the issues inherent to an in vitro study, there were several limitations. One limitation is that while numerous HA fillers were used, only one trial was performed for each filler at each pullback volume. A larger study with multiple trials would be needed to ensure reproducibility and increased power. Additionally, variables in our regression model are inherently related, which may lead to some degree of unavoidable collinearity. Nonetheless, we believe this provides the most accurate estimate by including so many relevant variables. This model utilized syringes that were inserted into a needle-accessible hub as opposed to directly into the vein. While this allows for a simple and reliable model for testing, this does not replicate real-world conditions. This study also evaluated a peripheral vein, which may not accurately reflect preinjection aspiration of an artery. However, venous pressures likely provide a more conservative estimate as the increased pressure of an artery would probably decrease the time needed to visualize flashback and would be less likely to be affected by vessel collapse. The caliber of the peripheral vein is also larger than facial veins, which may potentially affect time to flash. Therefore, our data offer directional information. It is also important to note that syringes from various manufacturers are different, especially in terms of internal diameter and length, which can impact the negative pressures generated by pullback.

Conclusion

Preinjection aspiration for HA fillers continues to be controversial as a safety checkpoint. Previous studies utilized in vitro and animal models, while our current study represents the only in vivo human model to analyze preinjection aspiration to our knowledge. Our results show decreased times to visualize flashback when inserted into a peripheral vein, suggesting that there may be clinical utility of preinjection aspiration for HA fillers as a safety checkpoint. Waiting times to visualize flashback may be affected by physicochemical and rheological properties. Additional studies are needed to validate the results of our small study.

Declaration of Conflicting Interests

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Gila Woodpecker (*Melanerpes uropygialis*)

Photo by Patti Kubick Miller

Evaluation of Indoor Tanning Facilities in American Fitness Centers

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Abstract

Background: Indoor tanning (IT) in fitness facilities encourages a misleading positive relationship between tanning and health. While IT in Canadian fitness facilities has been studied, American literature regarding this topic is lacking.

Objectives: The objective of this study is to evaluate availability, cost, reported risks, and adherence to legislation of IT in American fitness clubs.

Methods: This was a cross-sectional study utilizing a telephone questionnaire to survey gyms across all 50 states. The key term “fitness club” was searched in the *Yellow Pages* and 20 facilities from each state were randomly included into the study. Data were described descriptively and Pearson χ^2 tests were used to compare IT prevalence and rates of noncompliance between population groups. Regression analysis examined potential relationship between cost and prevalence of IT.

Results: Of the 1000 fitness clubs surveyed, 44.4% (444/1000) offered IT. The overall noncompliance rates for age, rest time, and eye protection were 13.8% (54/390), 26.0% (20/77), and 27.8% (85/225), respectively. The most common risk reported was skin cancer (61.6%), but many facilities were unsure of risks (27.0%) and some described no risk associated with IT (3.2%). The average cost for monthly unlimited tanning was 33 ± 13.96 USD. A state-to-state comparison showed a statistically significant inverse relationship between mean cost and prevalence of IT ($P = .013$, $[r] = -0.35$).

Conclusion: The prevalence and noncompliance rates of IT in fitness clubs contradict the healthy lifestyles they are working to promote. To limit harms, legislations should be standardized and more strictly enforced. Additionally, public education on IT risks and the use of higher costs may help minimize IT use.

Keywords

indoor tanning, skin cancer, public health

Introduction

Skin cancer is the most common type of malignancy worldwide, with a prevalence that is 5 times greater than breast or prostate cancer.¹ While melanoma is the most invasive one, the majority of skin cancers are nonmelanoma skin cancers (NMSCs). Ultraviolet (UV) radiation is a known carcinogen, as it is associated with up to 90% of NMSCs.^{2,3} With the current societal trends, UV exposure from indoor tanning (IT) devices has become more common. This is of concern as IT contributes an additional 419 000 NMSC cases in the United States annually.⁴ The risk of melanoma also increases considerably with every IT session.^{5,6}

Despite the known risks, a large proportion of individuals worldwide continue the practice of IT.⁷⁻⁹ In particular, adolescents remain a target population for the tanning industry. According to the 2015 Youth Risk Behavior Surveillance System, 15% of Caucasian high school girls and 16% of all 12th grade girls were found to be participating in IT.¹⁰ As evidence has shown that exposure to IT before the age 25 can

increase skin cancer risk by up to 102%,¹¹ the use of IT, particularly in youth, must be limited.

The health risks associated with early exposure to IT have led Brazil and Australia to ban IT altogether, and over 10 other countries, including 25 of the United States to prohibit minors under the age of 18 from IT.^{12,13} In addition to an age regulation, the US Food and Drug Administration proposed that IT facilities must also inform users about potential health risks.¹⁴

The availability of IT at fitness clubs is contradictory as it reinforces the misconception that tanning should be part of an everyday health and fitness routine. While IT has been

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studied in Canadian fitness clubs,¹⁵ there is a lack of literature in the United States, where there are over 36 000 fitness facilities.¹⁶ The purpose of this study was to evaluate IT in US fitness clubs, with a focus on availability, cost, regulations, safety measures, and reported risks.

Methods

Study Design

This was a cross-sectional study that utilized a telephone questionnaire to inquire about IT amenities in American fitness clubs and their adherence to State legislations. The Queen's University Health Science and Affiliated Teaching Hospitals Research Ethics Board approved this study (#6018854).

Participants

The Yellow Pages website (www.yellowpages.com) was used as a database to recruit fitness clubs. For each of the 50 states, "fitness club" was used as a key search term and the results were filtered by relevance. Twenty businesses from each state were then randomly generated to be included in the study. Dance studio, winter club, martial arts, kung fu, tai chi, tae kwon do, pilates, boxing, physiotherapy, spa, cross-fit, weight loss, personal training only, group class only, and women only results were excluded. Selected fitness clubs were then contacted via telephone by the principal investigator (PI) and asked questions from the questionnaire. If participation was declined, the telephone number was disconnected,

or there was no answer after 3 call attempts, alternative eligible fitness clubs were randomized into the study, until at least 20 gyms were reached from each state. The search strategy is illustrated in Figure 1.

Telephone Questionnaire

Each fitness club was surveyed from a consumer's perspective, with the purpose of the study not disclosed to the fitness club. This was undertaken to minimize the potential for bias and obtain truthful answers about IT policies and precautions. The PI was not blinded to the name or location of the fitness clubs. The telephone questionnaire consisted of a minimum of 2 questions (if the facility did not have IT) and a maximum of 9 questions (if the facility offered IT). The complete telephone questionnaire is found in Figure 2.

Outcome Measures

The presence, number, and type of tanning devices; future plans of investing in IT for facilities without IT; cost of monthly unlimited tanning; requirement of a gym membership for IT access; minimum age to tan; mandatory rest time between tanning sessions; requirement and/or supply of eye protection; and IT risks reported by the fitness center employee were recorded for each business location.

Tanning Legislation

Legislations governing minimum age, mandatory rest time between tanning sessions, and use of protective eyewear

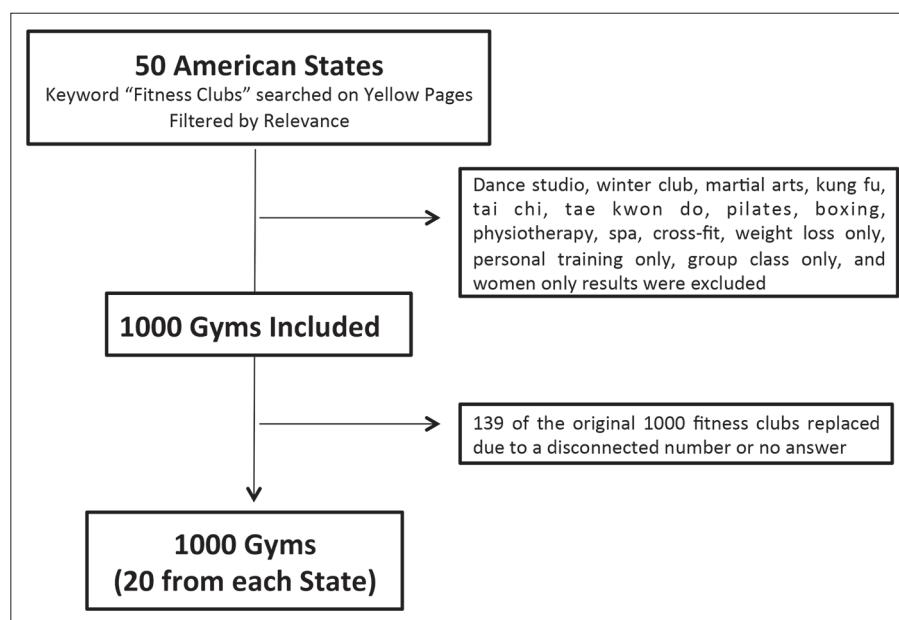


Figure 1. Search strategy.

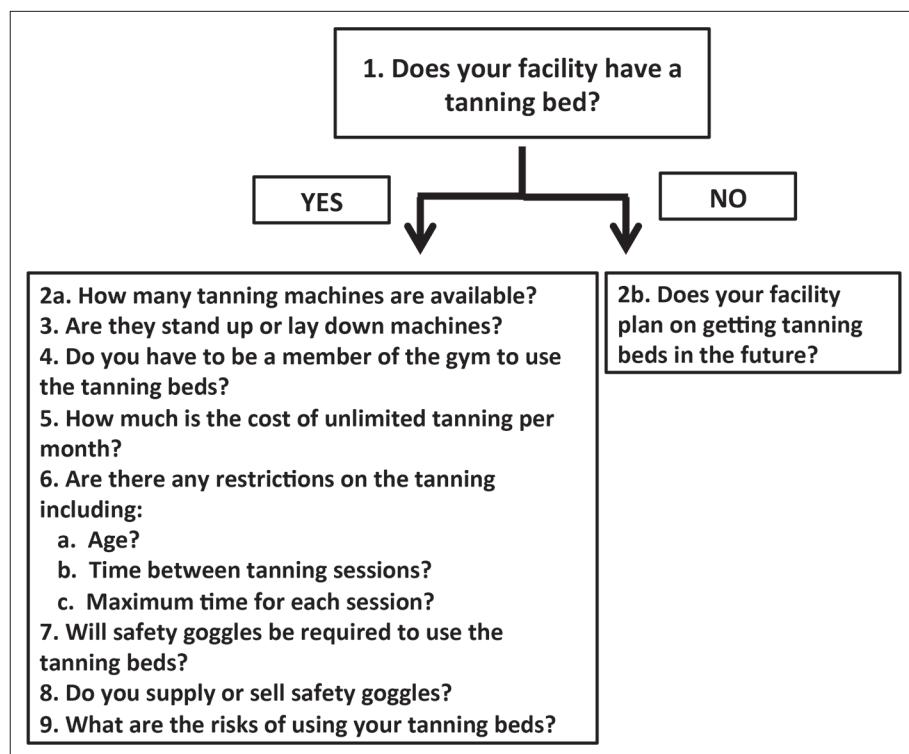


Figure 2. Standardized script used when calling fitness facilities.

were based on current laws as of July 2018. Noncompliance for each state was calculated independently, based on State policy (Supplemental Appendix).

Population Size Definitions

Fitness clubs were also analyzed based on population size. Small cities were defined as a population of fewer than 30 000 people. Medium and large cities were defined as regions with 30 000 to 99 999 and greater than 100 000 people, respectively.

Statistical Analysis

Data collected from the telephone questionnaire were compiled into a centralized database designed specifically for the study using Microsoft Excel. The data were summarized in table format using descriptive statistics (mean, standard deviation, and range). Pearson χ^2 tests were used to compare IT prevalence and rates of noncompliance between population groups. Regression analysis examined potential relationship between cost and prevalence of IT. Statistical significance was set at an alpha of 0.05.

Results

From the original list of 1000 fitness clubs surveyed, 13.9% (139/1000) were replaced due to a disconnected number or

no answer after 3 calls (Figure 1). There were no fitness clubs who declined to respond to questions asked of them. In total, 1000 fitness clubs, 20 from each state completed the telephone questionnaire. There were 43.9% (439/1000) of fitness clubs from small sized cities, 28.0% (280/1000) from medium sized cities, and 28.1% (281/1000) from large sized cities.

Overall, 44.4% (444/1000) of fitness clubs offered IT. Of the centers that did not, 3.4% (19/556) had plans to invest in IT devices in the future. There was an average of 2.62 ± 0.55 tanning machines per facility with IT. Of the facilities surveyed, there was a total of 1175 tanning devices, with 40.9% (481/1175) attributed to stand-up booths and 59.1% (694/1175) being lay down beds. Over half of the fitness clubs offered access to unlimited IT with the purchase of a gym membership. The cost for these memberships with unlimited IT per month ranged from 10 to 99 USD, and the average price was 33 ± 13.96 USD per month. The rates reported did not include activation or annual fees. Of all states, 88.0% (44/50) had a legal age requirement. Of those, 56% (25/44) of states required tanners to be at least 18 years old. There were 13.6% (6/44), 4.5% (2/44), 9.1% (4/44), and 15.9% (7/44) with a minimum age requirement of 14, 15, 16, and 17 years, respectively. The distribution of age legislation is illustrated in Figure 3. An asterisk (*) reports the states that allowed IT to minors below the minimum age if they had parental consent and/or accommodation. Twenty-four

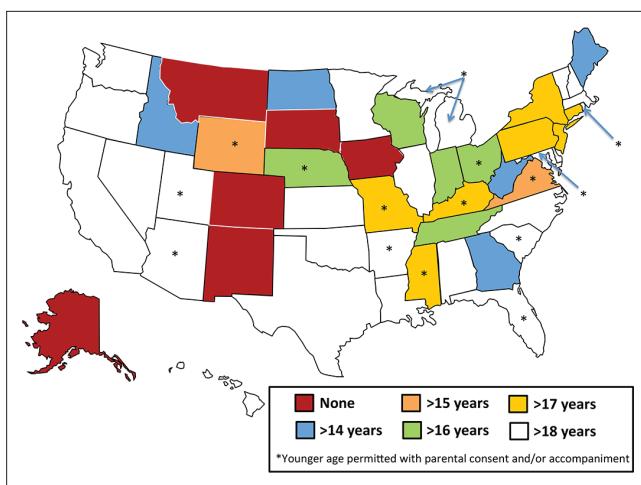


Figure 3. Age legislation by state.⁴¹

percent (12/50) of states mandated mandatory rest time between tanning sessions and 58% (29/50) established eye protection policies. Considering gyms with IT, it was determined that 13.8% (54/390) disregarded minimum age requirements. Additionally, 26.0% (20/77) were noncompliant to rest time between tanning sessions. There were also 38.2% (86/225) of fitness clubs who disregarded legislation on the requirement and/or supply of eye protection. A summary of data can be found in Table 1.

In terms of IT risks reported by fitness club employees, skin cancer (61.3%) and burns (36.5%) were the most prevalent ones. Of all employees, 27.0% were unsure of IT risks and 3.2% reported no risk associated IT. A combination of other risks including allergic reaction, drug reaction, infection, dry skin, rash, exacerbation of existing skin condition, and development/worsening of moles was described by 12.4% of employees. Premature aging/wrinkles (4.1%) and

eye damage (11.3%) were the least frequently reported risks (Figure 4).

When stratified based on population, the highest prevalence of IT was found in medium sized cities (48.2%), followed by small sized cities (43.5%), then large sized cities (42.0%) (Table 2). This difference, however, was not significant ($P = .294$). Moreover, violations of minimum age, rest time, and eye protection policies were not significantly different between various population sizes ($P = .368$, $P = .215$, and $P = .754$).

A state-to-state comparison revealed that Connecticut had the highest (70.0%), while Hawaii had the lowest (5.0%) prevalence of IT in fitness clubs. The average monthly cost for unlimited IT was highest in Hawaii (50 USD) and lowest in Connecticut (24 USD). However, the cheapest rate was 10 USD per month at single fitness clubs found in Arizona, New Jersey, and Oregon. The most expensive rate was 99 USD per month at a facility in Louisiana. A statistically significant inverse relationship was found between the prevalence of IT and cost ($P = .013$, $[r] = -0.35$; Figure 5). In gyms with IT, Colorado had the highest number of tanning equipment per facility (4.72), while Missouri, Montana, and Oregon had the lowest (1.88). The highest rate of noncompliance for minimum age, mandatory rest time, and eye equipment was found in Arizona (57.0%), Wisconsin (43.0%), and Minnesota (86.0%), respectively. Complete state-specific data can be found in Supplemental Appendix.

Discussion

Given the sparse data on IT in American fitness clubs, the present study provides novel insight on this topic. From our results, it was found that 44.4% (444/1000) of fitness clubs in the United States may have IT available to customers. The

Table 1. Summary of Data.

Gyms with IT, % (n)	44 (444/1000)
Gyms planning to invest in IT, % (n)	3.4 (19/556)
Number of tanning machines, mean (SD)	
Gyms with IT	2.62 (0.55)
Tanning beds	1175
Stand-up, % (n)	40.9 (482/1175)
Lay-down, % (n)	59.1 (705/1175)
Membership required for gyms with IT, % (n)	66.0 (293/444)
Cost/month for unlimited tanning (USD), mean, range (SD)	33, 10-99 (13.96)
Gyms not obeying state legislation, % (n)	
Age	13.8 (54/390)
Time	26.0 (20/77)
Eye protection (requirement and/or provide)	38.2 (86/225)

There were 42% (21/50) of states without legislation regarding eye protection, 12% (6/50) of states without legislation regarding minimum age, and 76% (38/50) of states without legislation regarding mandatory rest time between tanning sessions.

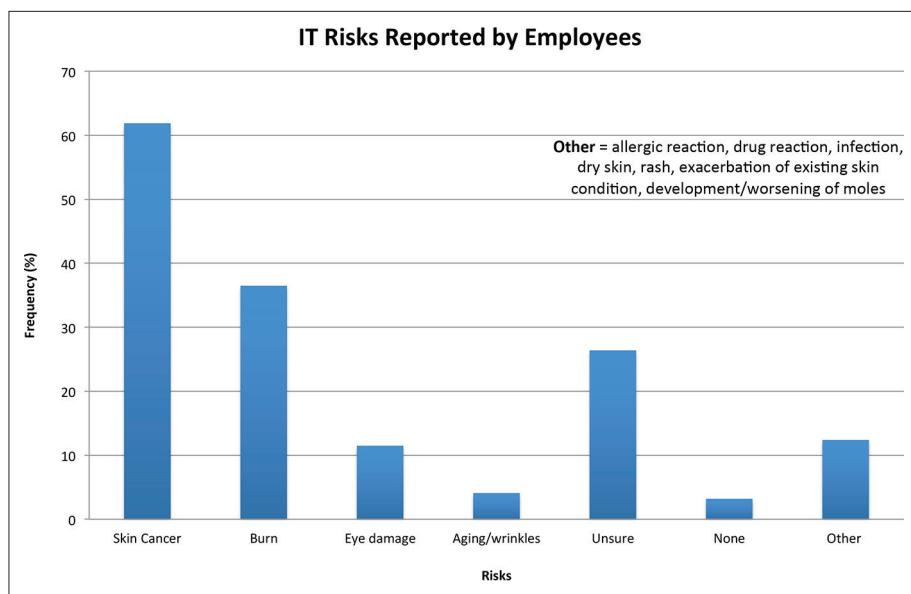


Figure 4. Risks of indoor tanning reported by employees.

prevalence of IT encourages the misconception that tanning is related to health and fitness. This trend was hypothesized to have originated from the fitness industry,¹⁵ where a darker skin tone gives bodybuilding athletes more muscle definition. Healthcare providers must work to terminate this mentality, as it is counterproductive to health and wellbeing.

In comparison with the results from a Canadian study of IT in fitness centers, the prevalence of IT was nearly identical (44.4% in United States vs 43.3% in Canada) but rates of noncompliance to age regulations were slightly higher (12.1% vs 8.0%).¹⁵ Another American study observed a more dramatic noncompliance rate for minimum age of 25%.¹⁷ However, this publication did not study IT exclusively in fitness clubs nor did it evaluate all 50 states. Furthermore, Culley et al visited 54 tanning businesses and reported that most violations were from age requirements.¹⁸ Despite the established age laws, the high rates of noncompliance found at fitness clubs may represent another avenue for continued IT in youth. With 6 states lacking any sort of legislature concerning age, the amount of youth with potential access to IT may be

underestimated. Regulation of IT is important in this population as intense UV exposure puts youth at higher risk of developing early onset skin cancer.¹⁹ The high noncompliance rate to age regulations in the United States may be attributed to the variation in legislation across the country. To improve adherence, State legislations should more consistent and more strictly enforced.

Another important result was that 26.0% of American fitness clubs were lenient about mandatory rest time between tanning sessions. Another group reported that only 5% of facilities in the United States followed recommended tanning schedules.²⁰ Additionally, this group determined that 100% of these facilities offered unlimited tanning packages.²⁰ It may be possible that the overuse of IT stems from the lack of rest time legislation, as only 24% of states have established laws for rest time. This may encourage the idea that time limits are less important for preventing harm. Thus, noncompliance rates should be interpreted with caution, as there are over 75% of states without rest time policies. Overexposure to UV radiation, regardless of age, is associated with increased risks of skin cancer.²¹⁻²³ This represents

Table 2. Prevalence and Compliance to Legislation Based on Population Size.

	Gyms with IT, % (n)	P value	Gyms with IT disobeying age restriction, % (n)	P value	Gyms with IT disobeying time restriction, % (n)	P value	Gyms with IT disobeying eye protection regulation, % (n)	P value
Pop. <29 999	43.5 (191/439)	.294	7.9 (15/191)	.368	4.8 (9/191)	.215	19.9 (38/191)	.754
Pop. 30 000-99 999	48.2 (135/280)		12.6 (17/135)		2.2 (3/135)		17.0 (23/135)	
Pop >100 000	42.0 (118/281)		10.2 (12/118)		6.8 (8/118)		20.3 (24/118)	

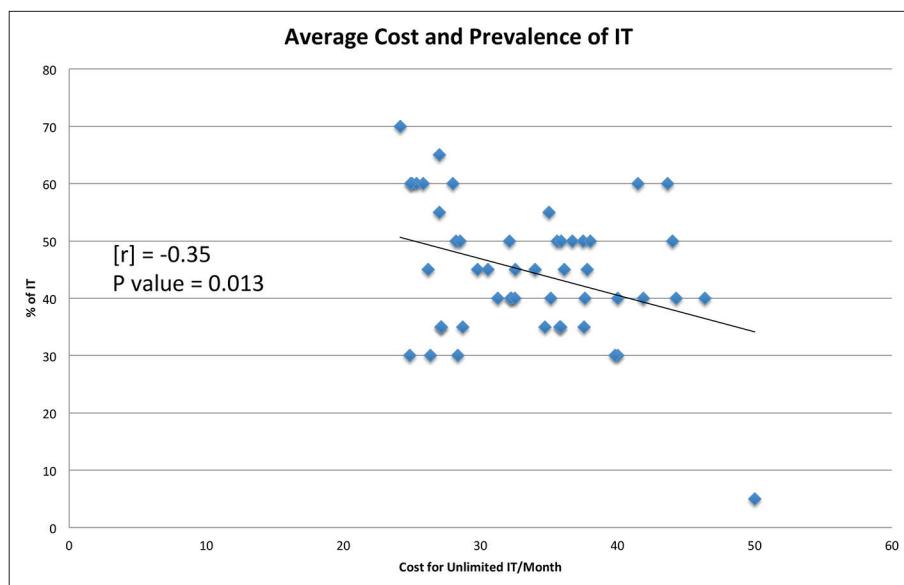


Figure 5. Relationship between cost and percentage of indoor tanning.

an area where further legislation might be important to mitigate the effects of IT.

Other key findings were that eye damage was not recognized as one of the main risks of IT and that a high proportion of facilities (38.2%) did not abide by eye protection laws. These results are alarming as the eyes are vulnerable to both short- and long-term damage from UV radiation. Ophthalmic injury from IT is common, as 40.3% of UV-induced corneal burns seen in the emergency room were from commercial tanning salons.²⁴ Repeated UV exposure to the conjunctiva can also result in thickening and hypervascularity.²⁵ Furthermore, UV exposure has been linked as a cause for cataract formation in both animal and human studies.²⁶⁻³⁰ Although harmful effects on the retina are minimal in the general population, individuals with disorders affecting UV absorption in the lens are at high risk of retinal damage.³¹ For these reasons, enforcement of eye protection policies must be improved to avoid further morbidity.

We found a significant inverse correlation between cost and prevalence of IT across the United States. This relationship may offer a potential solution for limiting the utilization of IT. From the efforts in regulating tobacco consumption, it was determined that a tax increase is the single most effective intervention for reducing the demands of a harmful product.³² Indoor tanning is comparable to tobacco use, as both activities are in high demand and have substantial consequences. Following the actions of tobacco regulators, a 10% federal excise tax was implemented on IT in the United States as part of the Patient Protection and Affordable Care Act in 2010.³³ This tax was intended to discourage the use of IT devices, and subsequently, reduce the development of skin cancers. Preliminary assessment of the tax found that 26% of tanning salons experienced a loss of clients.³⁴ However, tanning services within "qualified physical fitness

facilities" are currently exempt from this tax. Applying this excise tax to include tanning facilities in fitness clubs and potentially further amplifying the price may help drive the abandonment of IT in fitness clubs due to the fear of losing costumers and associated profits. Additionally, a price increase may have the highest impact in the younger population due to their limited incomes.³⁵ This barrier may further protect minors from the harms of IT.

Given our assessment of reported risks associated with IT, public awareness and education are needed to augment the strategies in place for IT risk reduction. We found that 27.0% of fitness club employees were unsure of IT risks and 3.2% reported no risk with IT, suggesting that they may be providing customers with misleading information. Furthermore, alongside employees, a previous study reported that over 33% of consumers were unaware of State legislation for IT.³⁶ Moreover, some believed IT to be beneficial to health.³⁷ Indoor tanning is popular among young females because of their belief that a tan makes them more attractive.^{38,39} Considering that only 4.1% of employees reported premature aging as a risk of IT, many tanners may be uninformed that IT is causing an effect opposite to that of creating younger and healthier-looking skin. The lack of knowledge on policies and risks of IT may contribute to availability and use of IT. Future revenues from the tanning excise tax should be used toward public health initiatives regarding IT to improve public education.

Although tanning in general can be harmful, those who tan at fitness clubs may be at higher risk, as compared to other indoor tanners. A study sampling 636 American indoor tanners reported that 24.2% have tanned at least once in a fitness facility, with 28.6% using gyms as their primary tanning location.⁴⁰ This group also found that people who tan in fitness clubs are significantly younger and

more active than other tanners. Not only does this finding emphasize the social misconception that tanning is linked with good health, it reiterates the fact that younger individuals are the most affected ones. Also of concern, gym tanners use the service 67% more frequently and may be at higher risk of developing tanning dependence.⁴⁰ This further highlights the need for increased awareness of the risks of IT to the public and gym owners.

Limitations

Although this study reports novel findings, it may have some limitations. The use of a telephone survey may have generated different results as compared to in-person requests. Second, appearances may influence the accessibility of IT to minors, as mature-looking youth may be able to bypass regulations more effortlessly. Conversely, direct requests may be handled more strictly with the requirement of photo identification for all customers. Next, depending on the position, authority, and experience of the employee that completed the telephone survey, answers may have varied. Finally, the unequal sample size from each population group may have influenced the power and significance of our results.

Future Directions

With data from two of the biggest countries in North America, it would be of interest to survey fitness centers from other continents to compare results. Also, as tanning taxes may affect the low- and middle-income populations the most, future studies can evaluate the relationship between social class and income with the use of IT. Additionally, to decrease confounding potential, a manager can be requested from each facility to fill out the survey in future studies.

Conclusion

The availability of IT at fitness clubs contradicts the healthy lifestyle they are working to promote. This study highlights the high prevalence and noncompliance rates of IT in American fitness facilities. To limit the harms associated with IT, legislation across all states should be more consistent and strictly enforced. Rest time policies should also be emphasized to reduce overexposure to IT. Likewise, the implementation of a higher tanning tax may help moderate the availability and demand of IT. Finally, public education initiatives surrounding IT should be considered to help to maximize IT control efforts.

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The Impact of Suspension of Dermatology On-Call Services

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Abstract

Background: Dermatological conditions are commonly seen in the emergency department and inpatient wards. The ability to access dermatology on-call services improves the accuracy of diagnosis and management of common and sometimes life-threatening conditions. Limitations of dermatologist availability led to the suspension of the dermatology on-call service for 3 months in Ottawa, Canada.

Objectives: Our objective was to assess the impact of this call suspension on patient care and the need for a dermatology on-call service at our hospital, as perceived by nondermatologist physicians at our center.

Methods: A survey was sent to all departments at The Ottawa Hospital, addressed to staff physicians and residents. Participation was entirely voluntary. Descriptive statistics were used to analyze survey responses.

Results: A total of 105 physicians completed the survey including staff physicians (85%) and resident trainees (15%). The most represented specialties were emergency medicine ($N = 21$), general internal medicine ($N = 19$), nephrology ($N = 17$), neurology ($N = 13$), and plastic surgery ($N = 13$). Over half of the respondents felt that the lack of dermatology on-call service impacted the care of their patients by a moderate or great extent. Over half reported performing dermatology-related clinical work during the call suspension and two-thirds of these individuals reported feeling uncomfortable or very uncomfortable doing so. Most (94%) participants felt that an on-call dermatology service was useful and 57% deemed it essential.

Conclusion: Our survey results demonstrate a significant impact of the suspension of a dermatology on-call service, as perceived by nondermatologist physicians. Hospitals need to recognize the importance of on-call dermatology consultations and provide support for divisions to enable this service to continue.

Keywords

accessibility, workforce, inpatient dermatology, on-call dermatology

Introduction

The scope of practice of dermatology is broad with several thousand diagnoses ranging from less acute entities that can be treated in an outpatient setting to more rare but serious and potentially lethal diagnoses requiring hospital admission and intensive dermatologic care and follow-up. Studies indicate that the presence of a dermatology on-call service improves the accuracy of diagnosis and management of admitted patients with studies consistently indicating a change in diagnosis and management in at least half of the cases.^{1–8} This not only improves patient care but also reduces health care costs by decreasing hospital length of stay and avoiding unnecessary hospital admissions.^{9–12}

In recent decades, dermatology has shifted to a primarily outpatient specialty with fewer dermatologists providing in-hospital consultations.^{13,14} With an aging population, increasing incidence of skin cancers and limited availability of dermatologists through much of Canada, wait lists are growing significantly and reaching exorbitant lengths of up to 2

years even in metropolitan centers such as ours. These increasing demands on community practices have limited the time and availability of practicing community dermatologists to cover on-call dermatology services such as in Ottawa, Canada, where the call service is primarily run by community-based practitioners. Limitations on the availability of dermatologists led to the unfortunate suspension of our dermatology on-call service for a 3-month period, January to March 2019. We sought to assess the impact of this call suspension on patient care, as perceived by nondermatologist physicians at our center.

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Methods

A survey was sent to all departments at The Ottawa Hospital, addressed to staff physicians and residents (Supplemental Material 1). As the study met published criteria for a quality improvement initiative as indicated by the REB at our institution, a formal REB application was not pursued. Participation was entirely voluntary, and consent to participate was implied through completion of the survey. Descriptive statistics were used to analyze survey responses. All variables assessed were categorical; summary statistics were therefore presented as counts and percentages. All data were tabulated, and calculations completed using Microsoft Excel.

The estimated number of missed consults during the call suspension was calculated based on the average number of reported missed consults (eg, the mean of 2.5 was used for respondents who selected the category of 1-5 consultations), multiplied by the number of respondents in each mutually exclusive category. The estimated number of times that dermatology-related clinical work was performed by nondermatologists during the call suspension was calculated using the average for the number of estimated times that dermatology work was performed (eg, the mean of 2.5 was used for 1-5 category), multiplied by the number of respondents in each mutually exclusive category.

Results

One hundred and five physicians completed the survey, most of whom were staff physicians (83%) with the remaining respondents being resident trainees. The most represented specialties were emergency medicine ($N=21$), general internal medicine ($N=19$), nephrology ($N=17$), neurology ($N=13$), and plastic surgery ($N=13$; Table 1).

Over half of the respondents felt that the lack of dermatology on-call service impacted the care of their patients by a moderate or great extent. This was most apparent among respondents from emergency medicine, internal medicine, and plastic surgery where respondents reported a moderate or great impact on patient care 81%, 79%, and 69% of the time, respectively. A greater proportion of residents reported a moderate or great impact on patient care (69%) compared to staff physicians (53%; Table 2).

Despite the call suspension, many physicians (58%) contacted a dermatologist to address clinical questions or obtain input on patient management during the call suspension, and usually, this was more than once (66% of the physicians who did contact dermatology during the call suspension). Eighty-one percent of respondents advised that they would have requested formal dermatology consultations if available, and most of these physicians indicated that 1 to 5 consults would have been requested during this 3-month time period (60%) but many physicians felt that 5 or more consults would have been necessary (21%; Table 3).

Table I. Characteristics of Survey Respondents.

Characteristic	N (% by specialty or training level)
Specialty (N = 105 total)	
Emergency medicine	21 (20)
Internal medicine	19 (18)
Nephrology	17 (16)
Neurology	13 (12)
Plastic surgery	13 (12)
Endocrinology	5 (5)
Hematology	5 (5)
Geriatrics	5 (5)
Oncology	3 (3)
Gastroenterology	3 (3)
Infectious disease	1 (1)
Level of training	
Staff physician	89 (85)
PGY6	1 (1)
PGY5	2 (2)
PGY4	4 (4)
PGY3	3 (3)
PGY2	3 (3)
PGY1	3 (3)

Based on respondents' reported times that a consult would have been sought if available, we estimated a total number of missed consults being 328 during the call suspension. Although not formally asked, several respondents noted conditions for which dermatology consultations would have been sought. These included potentially lethal entities such as vasculitis, autoimmune connective tissue and blistering disorders, and calciphylaxis.

Over half of the respondents reported performing dermatology-related clinical work during the call suspension, with most physicians indicating 1 to 5 instances (41%) although several respondents reported performing this work 5 to 10 times (10%) and even 10 times or more (6%). The cumulative total number of times that dermatology-related clinical work was performed by nondermatologists during the call suspension was estimated to be 150. Two-thirds of respondents who performed this work reported feeling uncomfortable or very uncomfortable while doing so (Table 4).

The overwhelming majority (94%) of participants felt that an on-call dermatology service was useful and 57% deemed this essential. Although not formally asked, many respondents reported that the lack of dermatology in patient care contributed to prolonged hospitalizations and unnecessary admissions during the 3-month call suspension.

Table 2. Impact of Dermatology Call Suspension on Patient Care.

Survey responder characteristic	Moderate or great impact, N (%) by specialty or training level	Minimal or no impact, N (%) by specialty or training level
All specialties (N = 105 total)	59 (56)	46 (44)
Emergency medicine (N = 21)	17 (81)	4 (19)
Internal medicine (N = 19)	15 (79)	4 (21)
Nephrology (N = 13)	6 (35)	11 (65)
Neurology (N = 13)	4 (31)	9 (69)
Plastic surgery (N = 13)	9 (69)	4 (31)
Other specialties (N = 22 ^a)	7 (33)	14 (67)
Staff physicians (N = 88 ^a)	47 (53)	41 (47)
Residents (N = 16)	11 (69)	5 (31)

^aN = I did not comment on the level of impact.

Discussion

The results of our survey indicate a significant perceived impact of a 3-month suspension of the dermatology call service to nondermatologist physicians at our hospital. Many consultations were not accommodated, and a large amount of dermatology-related clinical work was performed by nondermatologist physicians who felt uncomfortable doing so, including for the management of potentially life-threatening conditions. Affected nondermatologist physicians overwhelmingly felt that this impacted the quality of patient care and probably led to prolonged and at times unnecessary hospitalizations.

To our knowledge, this is the first published report of the perceived impact of a suspension of a dermatology on-call service to other physicians in a tertiary care center. Previous work reveals improved quality of care and reduced health care costs when a dermatology on-call service is used. Dermatology involvement in the care of patients admitted for dermatological concerns results in an altered diagnosis at least 50% of the time, shown consistently across several studies.¹⁻⁸ Dermatology involvement also allows for shorter hospital lengths of stay,^{11,12} reduced rates of readmission,¹¹ and significant cost savings.¹² Li et al estimate that a dermatology consultation for presumed cellulitis could save 256

000 inpatient hospitalization days and \$210 million annually in the United States.¹²

Dermatologic care is an important component of overall inpatient medical care. Analysis from the American 2014 National Inpatient Sample revealed that 1 in 8 adults hospitalized in the United States in 2014 were diagnosed with a skin disease during admission, and that close to 650 000 admissions were principally for skin disease, equivalent to an estimated total cost of over 5 billion dollars.¹⁵ Conditions for which inpatient dermatology consultations are requested range from nonurgent chronic inflammatory dermatoses to potentially lethal dermatologic emergencies such as Severe Cutaneous Adverse Reactions (SCAR). In a 1-year retrospective review of dermatology consultations at the Mayo clinic, the most common consultation requests were skin infections, dermatitis, drug eruptions, chronic wounds and ulcers, cutaneous neoplasms, graft-vs-host disease, purpura, intertrigo, and urticaria.¹⁶

Dermatology on-call services have become less available in recent decades, with the specialty shifting to a primarily outpatient practice. Surveys in the United States indicate that few dermatologists (14%) spend more than 1 hour in the hospital per week.¹³ A recent study of dermatology in Ontario revealed a decrease in the number of dermatologists

Table 3. Missed Consults During Call Suspension.

Survey responder characteristic	Times during call suspension that consult service would have been used if available, N (%)				Times during call suspension that dermatology was contacted for advice, N (%)			
	10 or more	5-10	1-5	None	More than once	Once	Never	Not reported
All levels of training (N = 105)	2 (2)	20 (19)	63 (60)	20 (19)	40 (38)	21 (20)	42 (40)	2
Staff physicians (N = 89)	2 (2)	16 (18)	54 (61)	17 (19)	34 (38)	18 (20)	35 (39)	2
Residents (N = 16)	0 (0)	4 (25)	9 (56)	3 (19)	6 (38)	3 (19)	7 (44)	

Table 4. Dermatology-Related Clinical Work Performed by Nondermatologists During Call Suspension.

	Instances where dermatology work was performed by nondermatologists			
	10 or more	5-10	1-5	None
N (%)	6 (6)	11 (10)	43 (41)	45 (43)
Comfort level with performing above-mentioned dermatologic clinical work				
Very comfortable	N = 1	N = 1	N = 3	
Moderately comfortable	N = 2	N = 4	N = 9	
Uncomfortable	N = 2	N = 5	N = 30	
Very uncomfortable	N = 1			
Did not perform duties due to lack of comfort		N = 1	N = 1	

providing hospital inpatient services from 50 in 2009 to 37 in 2014.¹⁴ In many cities in Canada such as Ottawa, the dermatology call service is primarily run by community dermatologists who operate busy private practices. Increasing wait times of up to 2 years, large rosters and the challenges of running a small business have limited the time and availability of practicing community dermatologists to cover on-call services. On-call availability is more easily instituted when dermatologists are hired in academic salaried positions. A survey of the Society of Dermatology Hospitalists (SDH) in the United States, a group of over 100 dermatologists who perform in patient consultations at major American academic institutions, indicated that most “hospitalist dermatologists” worked on a fixed salary with an average of only 4 half-day clinics per week to allow adequate protected time for inpatient consultations.¹⁷ Community dermatologists operating on fee-for-service model and managing operational costs of a business face greater challenges providing hospital consultations that are more time consuming and poorly remunerated.

Another important factor contributing to limited in patient dermatology coverage is a shortage of board-certified dermatologists in Canada and an unbalanced geographic distribution of dermatologists.¹⁸⁻²⁰ The 1988 National Specialty Physician Review (NSPR) of the Royal College recommended a ratio of 1 dermatologist per 62, 650 population size,²¹ a number that is only met in Quebec.²⁰ Recent data for Ontario estimate 1.62 dermatologists per 100 000 people (equivalent to 1 dermatologist per 61 728 residents), although this varied significantly between rural and urban LHINs (0.47 and 1.96 per 100 000, respectively, or 1 dermatologist per 51 020-212 766 residents).¹⁴ Significant increases in enrollment of postgraduate dermatology trainees in recent years have not yet resulted in equivalent increases in the dermatology workforce. This may be due to several factors including retirements and changes in practice patterns of newer graduates who may have fewer average yearly patient visits per dermatologist and experience increasing demands for healthy skin concerns and cosmetic procedures.²⁰ The

previously recommended 1 dermatologist per 62, 650 is outdated²¹ and does not account for these demographic trends. Newer studies recommend an optimal ratio of 1:25 000 or 1:33 000,^{22,23} which is not met by any Canadian province or territory.²⁰

The value of a dermatology on-call service goes even beyond patient care, safety, and health care costs. This service is an irreplaceable learning experience for dermatology trainees as it provides exposure to rare conditions that may not be seen in clinics as well as acute dermatologic emergencies. Diagnosis and management of acute dermatologic presentations is integral to the development of a competent practicing dermatologist. Exposure and education in this setting as a trainee is necessary to obtain a comfort level that allows for ongoing work in inpatient dermatology once graduated.

The value of a dermatology on-call service is further highlighted by minimal teaching and exposure to dermatology during medical school and nondermatology residency training. Canada-wide surveys show that the average number of hours spent on dermatology in medical school is 10 to 20, or <1% of the total undergraduate medical curriculum.^{24,25} The limited teaching hours spent on dermatology do not reflect the growing prevalence of dermatological conditions in the population. Nondermatologist physicians such as emergency physicians and internal medicine specialists, the most affected specialties in our survey, are often the initial point of contact for patients with dermatologic conditions. They may sometimes be the only available treating physician given the shortage of dermatologists and hospital-based dermatology consultations in particular. Numerous surveys have shown that medical students and nondermatologist physicians do not feel comfortable with their level of dermatological knowledge and training.²⁶⁻²⁹ In addition to providing better support for ongoing dermatology inpatient care, we are also looking into how to better support dermatology education to the most affected specialties at our center. At present, the undergraduate medical curriculum in Ottawa has approximately 10 hours of dermatology instruction and 1 out

of 7 students have the opportunity to pursue a 1-week clinical dermatology rotation during their core clerkship.³⁰ The internal medicine curriculum in Ottawa has 1 hour of dermatology teaching per year and approximately 10 out of 100 residents have the opportunity to pursue a clinical elective at our center per year. The emergency medicine curriculum in Ottawa has no formal teaching from dermatology and no residents pursue electives with us.

The results from this study illustrate the importance of the dermatology on-call service in the hospital environment from the perspective of nondermatologist physicians. Dermatologists in the hospital are asked to consult on potentially life-threatening conditions like severe drug reactions, infections, neoplasms, autoimmune conditions, and unknown clinical entities with cutaneous manifestations. Having a dermatology on-call service improves the diagnosis and management of admitted patients leading to better outcomes and lower healthcare costs. During the suspension of the dermatology on-call service, over half the physicians surveyed noted that there was a moderate-to-great impact on the clinical care of patients. Of the survey respondents, 57% indicated that the dermatology on-call service was essential and 94% deemed it to be useful for patient care. These results confirm the need for continued support of a dermatology on-call service in hospitals and the important role of dermatologists in the care of admitted patients.

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Making Glove Decision Less of a White Knuckling Experience: A Systematic Review and Inventory of Glove Accelerator Contents

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Abstract

Background: Accelerators in medical gloves are a common cause of allergic contact dermatitis among healthcare workers.

Objective: A systematic review of medical and nursing literature, patch testing reports, and chemical analyses of gloves was conducted to assess accelerator contents reported in the literature and to identify accelerator-free gloves.

Methods: A systematic literature search was performed in OVID Medline and OVID EMBASE. Hand-searching of reference lists of articles in the field and author input generated the remainder of articles assessed.

Results: We present an inventory of accelerator contents of gloves and accelerator-free glove options as reported in the literature as a clinical reference tool to assist allergen-free glove selection for individuals suffering from allergic contact dermatitis due to rubber accelerators.

Limitations: Pertinent limitations of our review include lack of predefined study exclusion criteria and screening of the studies identified in the search by 1 review author only.

Conclusion: The glove inventory we provide summarizes the available literature regarding medical and surgical glove accelerator content, describing gloves both by brand and manufacturer as well as by accelerators.

Keywords

allergic contact dermatitis, medical and surgical gloves, rubber accelerators, healthcare workers

Introduction

Hand dermatitis has a lifetime prevalence of 20% and commonly affects healthcare workers (HCWs), laboratory workers, cleaning personnel, food service workers, hairdressers, tradespeople, construction workers, and homemakers. Allergic contact dermatitis (ACD) is a common occupational skin disease, which affects approximately 1% to 3% of the population and is associated with considerable financial cost and negative impact on quality of life.¹ In HCWs, ACD is commonly seen in the context of hand dermatitis due to rubber accelerators used in the manufacture of medical and surgical gloves. Rubber accelerators are catalysts used in rubber vulcanization, also adding durability and strength to rubber.²

Contact dermatitis is the most common cause of occupational skin disease, accounting for 90% to 95% of cases.³ The hands are the most frequently affected site, seen in 80% to 90% of contact dermatitis cases.⁴ Unfortunately, contact dermatitis is particularly prevalent among HCWs and is

often seen in association with the use of protective medical gloves. Medical gloves are class II medical devices used to prevent the transmission of diseases both to patients from

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HCWs and from patients to HCWs.⁵ For many HCWs, they are a daily necessity.

Allergic contact dermatitis is a type IV hypersensitivity reaction.⁶ This type of hypersensitivity reaction involves a T-cell response aimed at the allergen.⁷ Allergic contact dermatitis presents as a delayed reaction occurring after the skin has been sensitized to the allergen, and develops over the course of 12 to 72 hours. It differs from irritant contact dermatitis, which is related to the direct toxicity of agents to skin and can develop rapidly without prior sensitization.⁷ After sensitization to the allergen, further exposures reactivate the cell-mediated immune response and can present as erythema, pruritus, vesicles, fissures, or scaling. Allergic contact dermatitis accounts for approximately 20% of occupational contact dermatitis, while irritant contact dermatitis accounts for about 80%.⁴ In 1 study, up to 24% of HCWs reported glove-induced symptoms, with 10.5% testing positive for allergic contact dermatitis to rubber allergens on patch test.⁸

The cost burden associated with contact dermatitis is considerable. According to the American Academy of Dermatology, the total medical costs associated with contact dermatitis were estimated in 2017 to be over \$1.5 billion USD and lost productivity was estimated to cost \$699 million USD.⁹ Aside from the monetary costs associated with contact dermatitis, the burden of the disease on affected individuals may also be considerable. The modified Skindex-16 quality of life assessment tool has been used to study the impact of ACD on patients.¹⁰ The 4 scales in the assessment include emotions, symptoms, functioning, and occupational impact. Allergic contact dermatitis was found to have the greatest impact on the emotions scale, with individuals feeling frustrated and annoyed by their condition. In terms of symptoms, individuals with ACD reported being bothered most by itching, skin irritation, and disease persistence or recurrence. People with hand dermatitis had significantly worse scores on the occupational impact scale. In terms of functioning, individuals reported that it was significantly harder to work or do what they enjoy.¹⁰

Functional limitation is understandable in those with occupational hand ACD given the common clinical presentation as an eczematous eruption of erythematous papules or plaques, which may have secondary lichenification, fissures, and scaling. Glove-related ACD is often sharply demarcated at the wrists and confined to the area of exposure.

In glove-related contact dermatitis, rubber accelerators are the main culprits.¹¹ Natural rubber latex does not cause ACD, however latex-based gloves may contain rubber accelerators. It is important to note that the rubber accelerants, not the latex base, cause ACD. The most common causative agents include thiurams, carbamates, and mercaptobenzothiazoles.¹² Other causes of glove-related ACD include antioxidants, such as black rubber mix chemicals, which prevent degradation of glove material.¹¹ Thiurams and carbamates

are often found together in gloves as these 2 types of organic compounds form a redox pair. Allergic contact dermatitis to carbamates has increased in recent years as thiurams were replaced with carbamates in rubber vulcanization,² a process used to improve rubber elasticity and strength. Benzothiazoles, such as mercaptobenzothiazole, are heterocyclic aromatic compounds and are a common cause of hand or foot dermatitis.² Another accelerator implicated in glove ACD is diphenylguanidine, an organic compound with similar molecular structure to dithiocarbamates. Structural similarity has led to diphenylguanidine being included in the testing reagent for dithiocarbamate ACD in carba mix. Thus, positive patch test reactions to carba mix may have led to underdiagnosis of true diphenylguanidine ACD.² Dithiodimorpholine (DTDM) is another vulcanizing agent and is used in rubber tire, inner tube, footwear, and glove production. The majority of DTDM ACD cases are secondary to hand dermatitis. Since DTDM is not found on commonly used patch testing series, ACD to this allergen is likely underdiagnosed and it could be the culprit allergen in cases of hand dermatitis where other tested allergens were negative.¹³

Studies have shown trends of decreasing thiuram and mercaptobenzothiazole ACD, while the incidence of reactions caused by carba mix (including 1,3-diphenylguanidine [DPG], zinc dibutylthiocarbamate [ZDBC], and zinc diethyldithiocarbamate [ZDEC]) has significantly increased.¹⁴ Changing trends may be related to developments in glove manufacturing, including movement toward powder-free gloves. The accelerator content in powder-free gloves is significantly lower than in powdered gloves.¹²

The identification of the specific causative allergens is very difficult without patch testing. In their study, Siegel et al found that only 51% of subjects were able to correctly identify the gloves responsible for their ACD. The ability of individuals to identify the specific gloves responsible for eliciting their ACD may be complicated by the number of different glove brands used and the severity of the reaction. Furthermore, as ACD is a delayed reaction, it may be difficult for people to associate their symptoms with exposures to particular gloves.¹²

Allergen avoidance, following identification via patch testing, is the mainstay of ACD treatment and prevention. Identifying gloves that are free of particular accelerators can be challenging because accelerator contents can differ within a single manufacturer. Moreover, glove brands named similarly can have different accelerator contents. As well, there are no reporting requirements regarding rubber accelerators present in a given glove brand. This can make glove decisions difficult even for individuals with an identified accelerator ACD.¹⁵ In an effort to facilitate the appropriate selection of medical and surgical gloves for individuals suffering from accelerator ACD, we performed a systematic review and created an inventory of gloves described as accelerator-free as

well as accelerator contents of gloves reported in the literature.

Materials and Methods

Data Source

A systematic literature search in OVID Medline and OVID EMBASE was conducted from database inception to August 2018. We included studies that identified the rubber accelerator content in medical and/or surgical gloves, that described the methodology used to identify the accelerator content, and that were written in the English language. Further exclusion criteria, defined after the search stage, include glove brands with discrepancies between references regarding the accelerator contents and glove brands with more than 1 manufacturer. The database literature search did not undergo additional updates after August 2018. The terms searched in OVID Medline were “gloves, protective/ OR (protective gloves OR medical gloves OR examination gloves OR surgical gloves).kf,tw AND (hypersensitivity/ OR hypersensitivity, delayed/ OR hypersensitivity, immediate/ OR latex hypersensitivity/ OR dermatitis, allergic contact/ OR (contact dermatitis or allerg*).kf.tw”

The terms searched in OVID EMBASE were

“protective glove/ OR (protective gloves OR medical gloves OR examination gloves OR surgical gloves).kw.tw AND hypersensitivity/ OR allergic reaction/ OR delayed hypersensitivity/ OR occupational allergy/ OR skin allergy/ OR tissue reaction/ OR latex allergy/ OR (contact dermatitis or allerg*).kw.tw”

These search results were transferred to EndNote X8 software (Clarivate Analytics, Philadelphia, United States) for data management. Additional studies were identified through a manual search of reference lists of articles in the field and through suggestion by authors of this review.

Results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.¹⁶ We did not register a protocol for this systematic review.

Study Selection

After search results were generated, all references were deduplicated using EndNote X8 data management software. Full text access was obtained through University of Calgary Libraries online access, Pubmed free full text access, and Google Scholar free full text access. Reference titles and abstracts were screened for relevancy to the topic of “glove allergic contact dermatitis” and “rubber accelerators” by one of the authors (KL). Remaining references were read in full by one of the authors to identify those that reported testing accelerator contents of glove brands (KL).

To improve the accuracy of the screening and inventory compilation, all references were screened twice by the first

author (KL). Intra-observer reliability was not statistically assessed during this study. The other authors of this review identified further studies for assessment.

Quality and Validity

Study quality (risk of bias) and validity were not formally assessed. In order to be included in qualitative synthesis, studies were required to describe a methodology for identifying the accelerator content. Since the aim of this study is to delineate glove purchasing decisions for HCWs with rubber accelerator ACD, other types of gloves including industrial, chemical, and household glove brands were excluded for the lack of external validity. Exclusion criteria were determined at the search result stage because of aspects we did not anticipate when designing our search strategy.

Information Synthesis

Information was synthesized through the creation of a glove inventory categorizing gloves by glove brand and manufacturer and reported accelerator contents per article description. In cases of discrepancies between references regarding the accelerator contents of the same glove brand, the brand was excluded because of ambiguity and this is further elaborated in the discussion section. In cases where more than 1 glove manufacturer was attributed to the same glove brand, the glove brand was likewise excluded from the study. Glove manufacturers were not contacted. Meta-analysis was not deemed suitable for the data we had identified.

Results

Search Results

Our search of OVID Medline yielded 1218 hits, while the OVID EMBASE search yielded 419 hits. Another 200 potentially relevant articles were identified through other sources. Excluding duplicates, 1613 potentially eligible references were screened for relevancy to the topic of allergic contact dermatitis and information regarding glove accelerators. After screening, 1454 references were excluded due to lack of relevancy to the intended topic. After title and abstract screening, 159 full text articles were assessed for eligibility and 9 references were included in qualitative synthesis.^{1,11,15,17-22} A PRISMA diagram outlining our study selection is given in Figure 1.

The most common reason for exclusion was articles that did not test for accelerators or had insufficient glove manufacturer and brand information ($n = 94$).^{8,12,13,23-113} In cases where full text articles were not available, these studies were excluded ($n = 24$).¹¹⁴⁻¹³⁷ All non-English language literature was excluded from qualitative synthesis ($n = 20$).¹³⁸⁻¹⁵⁷ Articles that reported accelerator contents without providing a methodology to support their claims were also excluded

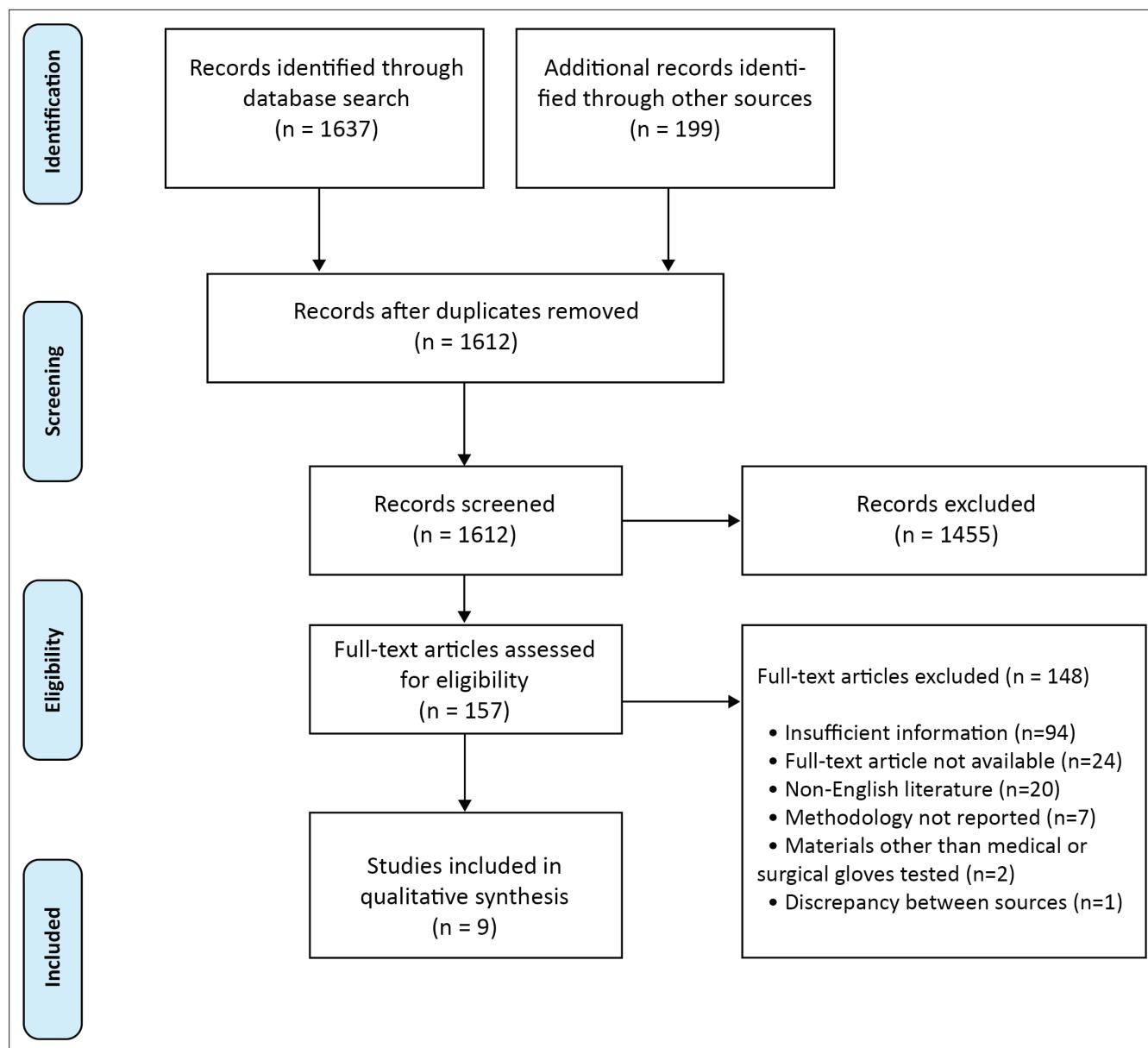


Figure 1. Study selection.

from qualitative synthesis ($n = 7$).^{2,158-163} It has been decided to exclude articles that did not provide a description of the methodology for the determination of glove accelerator contents to ensure that the references provided in the glove inventory employed adequate methods. Studies that tested accelerator contents in materials other than medical and surgical gloves were excluded ($n = 2$)^{164,165} as were studies with results that showed discrepancy compared to multiple other sources ($n = 1$).¹⁶⁶ A detailed list of excluded studies with the reasons for exclusion is provided in Supplemental Table 3.

The 9^{1,11,15,17-22} included articles were used to create the glove inventory presented in Table 1. In addition to this inventory of gloves containing the fewest number of

accelerators, we provide a full inventory of all gloves included in our review as reported in the literature in Supplemental Table 2.

Included studies differed in the methodology used to test accelerators and in the accelerators tested by each study. References included in qualitative synthesis employed various methodologies such as UV or mass spectrometry and high performance liquid chromatography (HPLC) analyses,^{11,17,19} or accelerator analysis reports from glove manufacturers.^{15,20} A detailed list of included studies with the study methodology is provided in Table 2. Contact information for glove manufacturers as listed in the reviewed literature is provided in Supplemental Table 3 to facilitate glove acquisition.

Table I. Inventory of Glove Brands with Minimal Accelerator Content.

Manufacturer	Brand	Powder status	Sterility	Material	References	TM	C	MCT	MM	MDT	BRM	NL	DPG	DTD
Allerderm Phoenix, AZ, United States	Allerderm Disposable Vinyl Gloves	Unknown Powder status	Nonsterile	Vinyl	Scheman et al ¹	-	-	-	-	-	-	-	Unknown	Unknown
Ansell Healthcare Products LLC Red Bank, NJ, United States	Conform NL (PVC)	Unknown Powder status	Nonsterile	PVC	Scheman et al ¹	-	-	-	-	-	-	Unknown	Unknown	Unknown
States (or) Iselin, MN, United States	Cur-Resistant Glove Liners (polyethylene fiber)	Unknown Powder status	Sterile	Polyethylene fiber	Scheman et al ¹	-	-	-	-	-	-	Unknown	Unknown	Unknown
	Micro-Touch Elite (PVC)	Unknown Powder status	Nonsterile	PVC/polyurethane free of accelerators and vulcanizing agents	Goodier et al ¹⁵ ; Scheman et al ¹	-	-	-	-	-	-	-	-	Unknown
	New Touch (PVC)	Unknown Powder status	Nonsterile	PVC	Scheman et al ¹	-	-	-	-	-	-	Unknown	Unknown	Unknown
	Synsation (PVC)	Unknown Powder status	Nonsterile	PVC	Scheman et al ¹	-	-	-	-	-	-	Unknown	Unknown	Unknown
Best Glove Best Manufacturing Company Menlo, GA, United States	RealFeel (PVC)	Unknown Powder status	Nonsterile	PVC	Scheman et al ¹	-	-	-	-	-	-	Unknown	Unknown	Unknown
Cardinal Health Dublin, OH, United States	Esteem Stretchy Synthetic with Neu-Thera (PVC)	Unknown Powder status	Nonsterile	PVC	Scheman et al ¹	-	-	-	-	-	-	Unknown	Unknown	Unknown
	Esteem Stretchy Synthetic (PVC)	Unknown Powder status	Nonsterile	PVC	Scheman et al ¹	-	-	-	-	-	-	Unknown	Unknown	Unknown
	Esteem NV Stretchy Synthetic (PVC/Nitrile blend)	Unknown Powder status	Nonsterile	PVC/nitrile blend	Scheman et al ¹	-	-	-	-	-	-	Unknown	Unknown	Unknown
	InstaGard Powder-Free Synthetic Exam Gloves (PVC)	Powder-free	Nonsterile	PVC	Scheman et al ¹	-	-	-	-	-	-	Unknown	Unknown	Unknown
	Low Dermatitis Potential Nitrile Exam	Unknown Powder status	Nonsterile	Nitrile	Goodier et al ¹⁵	-	-	-	-	-	-	Unknown	Unknown	-
ECI Medical Technologies Inc. Bridgewater, NS, Canada	Elastyfree	Unknown Powder status	Sterile	Unknown	Scheman et al ¹	-	-	-	-	-	-	Unknown	Unknown	Unknown
	Elastylite	Unknown Powder status	Sterile	Unknown	Scheman et al ¹	-	-	-	-	-	-	Unknown	Unknown	Unknown

(Continued)

Table I. Continued

Manufacturer	Brand	Powder status	Sterility	Material	References	TM	C	MCT	MM	MDT	BRM	NL	DPG	DTD
Medline Industries, Inc. Mundelein, IL, United States	Accutouch PF Vinyl Synthetic Exam Gloves	Powder-free	Nonsterile	Vinyl synthetic	Scheman et al ¹	-	-	-	-	-	-	-	Unknown	Unknown
	Aloetouch Ultra IC PF Stretch Synthetic Exam Gloves	Powder-free	Nonsterile	Synthetic	Scheman et al ¹	-	-	-	-	-	-	-	Unknown	Unknown
	Medline Advantage PF Stretch Synthetic Exam Gloves	Powder-free	Nonsterile	Synthetic	Scheman et al ¹	-	-	-	-	-	-	-	Unknown	Unknown
	Universal 3G PF Stretch Synthetic Exam Gloves	Powder-free	Nonsterile	synthetic	Scheman et al ¹	-	-	-	-	-	-	-	Unknown	Unknown
SmartPractice Phoenix, AZ, United States	FlexTec Vinyl Powder Free Exam Gloves	Powder-free	Nonsterile	Vinyl	Scheman et al ¹	-	-	-	-	-	-	-	Unknown	Unknown
	Pink Ribbon Vinyl Powder Free Exam Gloves	Powder-free	Nonsterile	Vinyl	Scheman et al ¹	-	-	-	-	-	-	-	Unknown	Unknown
	Royal Shield Vinyl Powder Free Exam Gloves	Powder-free	Nonsterile	Vinyl	Scheman et al ¹	-	-	-	-	-	-	-	Unknown	Unknown
	Royal Shield Vinyl Powdered Exam Gloves	Powdered	Nonsterile	Vinyl	Scheman et al ¹	-	-	-	-	-	-	-	Unknown	Unknown

Abbreviations: DPG, diphenylguanidine; DTD, dithiodimorpholine; MCT, mercaptobenzothiazole; MDT, mixed dialkyl thioureas; MM, mercapto mix other than mercaptobenzothiazole; NL, natural latex; PVC, polyvinyl chloride; TM, thiuram mix.

Table 2. List of Included Studies, Year of Publication, Country of Study, and Methodology.

Reference	First author	Year of publication	Country of study	Method
17	Brehler	2002	Germany	Rubber chemicals were analyzed by HPTLC and GC
11	Cao	2010	United States	Patch testing and HPLC
18	Crepéy	2018	France	Patch testing
19	Depree	2005	United States	HPLC
15	Goodier	2018	United States	Accelerator analysis reports from glove manufacturers
20	Heese	1991	Germany	Accelerator analysis reports from glove manufacturers
21	Rich	1991	United States	Patch testing
1	Scheman	2008	United States	Accelerator analysis reports from glove manufacturers
22	Storrs	1992	United States	Patch testing

Abbreviations: GC, gas chromatography; HPLC, high performance liquid chromatography; HPTLC, high performance thin-layer chromatography.

Discussion

The selection of appropriate gloves for the management of ACD, in terms of both function and accelerator contents, can be challenging for healthcare providers. Different materials, manufacturers, and brands of medical gloves demonstrate a wide range of accelerator contents. Medical gloves are available in various materials such as latex, nitrile, polyvinyl chloride (PVC), neoprene, as well as other less common elastomer materials such as polyisoprene, sensoprene, or polychloroprene. These materials have distinct functional differences and characteristic accelerator content profiles. For example, most nitrile gloves reported in the literature contain carbamates.^{1,15} Other authors suggest that PVC gloves are the only gloves consistently free of all rubber accelerators.²⁰ However, our inventory provides evidence that other materials can be used to make accelerator-free gloves including nitrile and neoprene.^{1,15} Our inventory displays accelerator contents of gloves reported in the literature to facilitate glove choice for individuals who are sensitive to one or more accelerators but do not require their gloves to be free of all accelerators (Table 1; Supplemental Table 2).^{1,11,15,17-22}

While compiling this glove inventory, it was interesting to note that studies showed vast differences in the accelerators tested. For example, thiurams,^{1,11,15,17,18,21,22} carbamates,^{1,11,15,17,19-22} and mercaptobenzothiazoles^{1,11,15,17,19-22} were tested by most studies; whereas thioureas,^{1,11,15,20} diphenylguanidine,^{11,15,18} and dithiodimorpholine¹¹ were less often tested. Another aspect of accelerator reporting that was heterogeneous between studies is the amount of manufacturer information provided. Some studies did not provide the manufacturer of the glove brands and were therefore excluded from qualitative synthesis for lack of reported detail. In other cases, references provided inconsistent information in regard to glove manufacturer contact information.

The articles included in qualitative synthesis were limited to English language literature. As well, references were

required to describe glove brands by their accelerator content, list the corresponding manufacturer, and provide some description of how the accelerator content was assessed. The requirement for such a methodological description may have limited the number of included studies in our review because references that did not describe their methodology may still have reported glove accelerator content correctly. However, without described methods, it is unclear whether the reported glove accelerator contents are reliable.

To our knowledge, this review and glove inventory provides the most comprehensive and current list of glove options for those with rubber accelerator-induced ACD. We have included all rubber accelerators reported in the references used in the glove inventory to provide detailed information for glove purchasing decisions. We also have included other patch test allergens including latex and black rubber mix which are less commonly associated with glove-related ACD but are common medical and surgical glove components. Our glove inventory is limited by the amount of detail provided in the included studies, and because not all common rubber accelerators are reported by each study, our glove inventory is unable to display all accelerators for each glove brand. However, it provides what we believe is the best summary of the available literature at present. There are 389 glove brands outlined in our inventory, representing glove ACD literature published as early as 1991.

This review is subject to a number of limitations. First, our workflow deviated from the standard methodology for a systematic review in that only 1 author screened the potentially eligible studies and we did not register a protocol for this systematic review. Second, we did not have predefined study exclusion criteria. Furthermore, some readers may view the lack of prior registration of our review as a limitation. Moreover, most of the information on gloves included in this inventory were provided by 2 main sources^{1,15}; therefore, errors in methodology or data of the sources could impact the overall accuracy of this review. Finally, some of

the studies included in our glove inventory were published many years prior to our review, with the oldest references published in 1991.^{20,21} This could mean that the glove brands described by these sources are no longer available for ordering or that the accelerator contents of some glove brands have changed since the time that the study in question was published.

Finally, when compiling this review, we identified examples of gloves where 2 manufacturers appear to produce gloves of the same or a similar brand name although the accelerator contents may differ. It is unclear why different glove manufacturers may share a glove brand name as we did not contact these glove manufacturers. For example, “TriFlex” and “Triflex” glove brands are marketed by Baxter Pharmaseal²¹ and CardinalHealth,^{15,20} respectively, and differ in both glove material and accelerator content. As well, in the case of “Triflex,” Heese et al²⁰ report this brand as PVC accelerator-free gloves, whereas Goodier et al¹⁵ report this brand as latex gloves containing carbamates. These 2 examples of discrepancies between seemingly identical products could cause danger to consumers who order this glove brand without knowing about the inconsistency in the literature. This risk for ordering error is the main reason that glove brands with discrepancies in accelerator content or material were excluded from our glove inventory. On the one hand, the complexity of glove options gives consumers more choice based on function and sensitivity to accelerators. However, on the other hand, the intricacies of glove brands and accelerator contents can lead to inadvertent exposure to accelerator allergens if users are not able to obtain the necessary information for safe glove purchasing decisions.

Conclusion

Glove-induced allergic contact dermatitis is a common occupational disease often caused by rubber accelerators. The selection of gloves free of offending agents can be difficult due to the wide variety of accelerators used in glove materials, challenges in obtaining accelerator content from manufacturers, and changes in brand accelerator contents over time. To our knowledge, our review represents the most comprehensive and current inventory in the literature. With our inventory of glove accelerator contents and accelerator-free glove options, we hope to facilitate safer and smarter glove purchasing decisions for those who have delayed-type hypersensitivity to rubber accelerators. While we attempted to be accurate and complete in our description of glove accelerator content, we cannot guarantee the accuracy and completeness of the data presented. Readers should do their own due diligence and verify the information on glove accelerator content before making clinical or glove purchasing decisions.

Authors' Note

The authors Navjeet Gill and Whitney K. Shea share second authorship.

The authors Sebastian Straube and Marlene T. Dytoc share senior authorship.

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Supplemental Material

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Common Atopic Dermatitis Rating Scales: A Practical Approach and Brief Review

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Abstract

Atopic dermatitis (AD) severity measurement scales are important in clinical trials as objective outcome measures and are often required for government and private insurance plans. These scales are sometimes underused by clinicians due to a variety of factors including time constraints and lack familiarity. We conducted a literature review on the most commonly used AD measurement scales and provide succinct user guides and scoring explanations, advantages and disadvantages, and interscale comparisons.

Keywords

atopic dermatitis, eczema, SCORAD, EASI, IGA, SASSAD, POEM-PO-SCORAD, patient reported outcomes

Methods

We first conducted a broad search of PubMed using combinations of keywords such as “atopic dermatitis,” “rating scales,” “outcome measures,” and “clinical trials” to identify scales to be included in our review. We then conducted a targeted literature search for each scale through PubMed and Google. We also searched for review articles limited to January 1, 2009 to February 20, 2019 on validity, and interscale comparisons of various atopic dermatitis (AD) scoring instruments. Finally, articles concerning interscale comparisons and validity studies for individual scales were obtained from a combination of scanning reference lists of review articles and keyword searches on PubMed.

Atopic Dermatitis Scales

Eczema Area and Severity Index (EASI). The Eczema Area and Severity Index (EASI)¹ (Supplemental Material) was adapted from the Psoriasis Area and Severity Index in 1998. The EASI is calculated from summing 4 separate scores of the (1) head/neck, (2) upper extremities, (3) trunk, and (4) lower extremities. For each of the 4 anatomical regions, the score formula is $S*A*M$. “S” is the congregate score from the severity of 4 signs: erythema, edema/papulation, excoriation, and lichenification, graded on a discrete scale from 0 to 3, where 0 = absent, 1 = mild, 2 = moderate, and 3 = severe, giving S a maximum of 12. A representative region for evaluation within each anatomical region is chosen for each sign. “A” represents the area to which AD affects the body, yielding a maximum of 6 points: 0 = 0%, 1 = 1% to 9%, 2 = 10%

to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, and 6 = 90% to 100%. “M” is a multiplier, which is 0.1, 0.2, 0.3, and 0.4, respectively, for the aforementioned anatomical regions in those greater than or equal to 8 years and 0.2, 0.2, 0.3, and 0.3, respectively, for those less than 8 years. The final EASI score is calculated based on the sum of the scores from the 4 anatomical regions and yields a maximum of 72 (Table 1).

The pivotal validation study² for the EASI in 2001 involved 2 cohorts of 10 adults and 10 children less than 8 years with AD, scored by 15 dermatologists. Interobserver reliability yielded an R -hat convergence score of 0.71 (fair-good range). Intra-observer reliability was deemed fair-good to excellent, with points differing on average 0.5 points on the EASI.² Similar trends have been replicated in subsequent studies regarding inter- and intrarater reliability.^{3,4} Eczema Area and Severity Index is a comprehensive and systematic AD outcome instrument, with a total of 9 validation studies since 2013⁵ spanning ages of 0 to 70, mild, moderate, and severe AD, and taking place in secondary and tertiary care centers.⁵ Eczema Area and Severity Index has been validated

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Table 1. Identifying Characteristics, and Signs/Symptoms/Domains Covered in the Scoring Atopic Dermatitis, Eczema Area and Severity Index, Investigator's Global Assessment, Six Area, Six Sign Atopic Dermatitis, Patient-Oriented Eczema Measurement, and Patient-Oriented Scoring Atopic Dermatitis as Atopic Dermatitis Measurement Scales.

	SCORAD ¹⁶	EASI ¹	IGA ^a	SASSAD ¹⁷	POEM ⁶	PO-SCORAD ¹⁹
Year of creation	1993	1998	-	1996	2004	2011
Formula	A/5 + 7B/2 + C	Sum of 4 S*A*M	-	6 Area 6 sign	7 Question	A/5 + 7B/2 + C
Signs, symptoms, and area of AD						
Extent of area of AD	*	*	-	*		*
Erythema	*	*	-	*		*
Edema/papulation	*	*	-			*
Oozing/crusts	*		-	*	*	*
Excoriations	*	*	-	*		*
Lichenification	*	*	-	*		*
Flaking			-		*	
Cracking			-	*	*	
Bleeding			-		*	
Dryness/scaling	*		-	*	*	*
Pruritus	*		-		*	*
Sleep loss	*		-		*	*

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; POEM, Patient-Oriented Eczema Measurement; PO-SCORAD, Patient-Oriented Scoring Atopic Dermatitis; SASSAD, Six Area, Six Sign Atopic Dermatitis; SCORAD, Scoring Atopic Dermatitis.

^aMathematical multiplication.

¹As described, IGA is an umbrella term for over 20 global assessments, each scale including its own unique combination of signs, symptoms, and domains. However, the most commonly used characteristics used are erythema, papulation/edema, oozing/weeping, and crusting.¹⁴

for content validity,^{6,7} construct validity,⁸ internal consistency,⁹ intra/interobserver² reliability, and sensitivity to change (Table 2).^{9,10} A limitation of the EASI often cited in the literature stems from an unclear interpretability.² However to mitigate this, follow-up studies have correlated EASI scores to clinically relevant definitions of AD; 0 to 1 = clear/almost-clear, 1 to 7 = mild, 7 to 21 = moderate, 21 to 50 = severe, and 50+ = very severe.¹¹ Another limitation often cited is the EASI's intermediate interobserver reliability especially compared to the later discussed Scoring Atopic Dermatitis (SCORAD) scale. Feasibility is another barrier to use in clinical practice as the EASI takes an average of 6 minutes to administer, and hence, the EASI has been more utilized in research settings. Nevertheless, the EASI is one of the most well-validated and comprehensive AD rating scales³ and is often still used as an outcome measure in the current clinical trials despite its shortcomings.

Investigator's Global Assessments (IGAs). Investigator's Global Assessment (IGA) scores are widely used outcome instruments in published clinical trials of AD.^{12,13} In such scoring systems, an investigator applies an ordinal scale often ranging from 4-point to 7-point scales, scoring various AD signs/symptoms based on attached descriptions. The most commonly scored criteria among IGAs include erythema, papulation/edema, oozing/weeping, and crusting.¹⁴ Rarely,

excoriation, scaling, and lichenification are used.¹⁴ It should be noted that IGA is an umbrella term for the over 20 variant IGA scales (including the commonly used Physician's Global Assessment) which exist in the published literature.¹⁴ Investigator's Global Assessments are the simplest and least time-consuming outcome measurements for AD, and this is their main advantage relative to other AD instruments; however, they have several drawbacks. First, there is a lack of standardization of global assessments, as the vast array of scales differ in their maximum points, descriptions, and signs/symptoms assessed. This proves difficult for interstudy or interclinician comparisons. Second, unlike more systematic scales such as EASI, most IGAs fail to account for the extent of area affected by AD, detracting from their comprehensiveness. Third, IGAs lack validation studies^{5,14} despite their frequency of use as an outcome instrument in the literature,¹¹ partly because of their volume, diversity, and lack of standardization. This questions their reliability as AD tools in research and in clinical practice. Standardization of IGAs and then subsequent validation is needed.¹⁴ Nevertheless, IGAs are often used as an outcome measure in recent years due to their ease of administration. Of particular note, the validated IGA (vIGA)(Supplemental Material) is being utilized in JAK1/2 inhibitor (Baricitinib) phase 3 clinical trials from Eli Lilly with results to follow from the BREEZE-AD trials.¹⁵

Table 2. Validity Measure Definitions and Literature Pertaining to the Scoring Atopic Dermatitis, Eczema Area and Severity Index, Investigator's Global Assessment, Six Area, Six Sign Atopic Dermatitis, Patient-Oriented Eczema Measurement, and Patient-Oriented Scoring Atopic Dermatitis as Atopic Dermatitis Measurement Scales.

Validity outcomes ²³	SCORAD	EASI	IGA ^a	SASSAD	POEM	PO-SCORAD ^c
Construct validity						
The extent to which an instrument adequately measures disease, or to which a test measures what it claims	+ ¹⁰	+ ⁸	n/a	+ ⁷	+ ⁶	n/a ^b
Content validity						
The extent to which the measure represents every single element of a construct	+ ⁴	+ ^{6,7}	n/a	+ ⁷	+ ⁶	n/a ^b
Intrarater reliability						
The extent of agreement between the same investigator's measurements	n/a	+ ²	n/a	n/a	+ ⁶	n/a
Inter-rater reliability						
The extent of agreement between different investigator's measurements	+ ¹⁶	+ ²	n/a	+ ¹⁸	Not needed	Not needed
Sensitivity to change						
The ability of an instrument to measure a change in state, regardless of whether the change is relevant or meaningful to the decision-maker	+ ¹⁰	+ ^{9,10}	n/a	n/a	+ ⁶	n/a
Total validation studies (December 2013) ⁵	26	9	n/a	5	2	2

Abbreviations: EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; POEM, Patient-Oriented Eczema Measurement; PO-SCORAD, Patient-Oriented Scoring Atopic Dermatitis; SASSAD, Six Area, Six Sign Atopic Dermatitis; SCORAD, Scoring Atopic Dermatitis.

+ There is at least one or more validation studies confirming this aspect of validity

^aAs described, IGA is an umbrella term for over 20 global assessments, with the individual scales lacking validation studies.

^bThere is a lack of support in the literature or no studies for this aspect of validity.¹⁹

^cThe PO-SCORAD is correlated to the SCORAD ($r = 0.67, P < .0001$).¹⁹ However, independent validation studies are lacking at this time and are a limitation of the scale.

Scoring Atopic Dermatitis. The SCORAD¹⁶ (Supplemental Material) was developed in 1993 by the European Task Force on Atopic Dermatitis and is the most widely referenced AD scoring instrument in the literature^{12,13} despite that its use in recent literature has declined in favor of EASI and IGA. The SCORAD is calculated using the formula $A/5 + 7B/2 + C$. “A” represents a congregate score representing the amount of body surface area affected by AD, using the *rule of nines* where the head/neck = 9 points, upper limbs = 9 points each, lower limbs = 18 points each, anterior trunk = 18 points, back = 18 points, genitals = 1 point, and palms including digits = 1 point each, or the *handprint method*, where one fully extended palm including digits = 1 point. The rule of nines is used to score “A” in children under 2 years except with the head/neck worth 17 points, lower limbs 15 points each, and palms not scored. “B” is the intensity score and encompasses 6 signs: erythema, edema/papulation, oozing/crusts, excoriations, lichenification, and dryness. Each sign is scored from 0 to 3, where 0 = absent, 1 = mild, 2 = moderate, and 3 = severe, and the total score is added for a maximum of 18. A representative average area is chosen to evaluate each sign, allowing a maximum of 6 unique areas when calculating “B.” An intra-observer standard deviation (SD) of 0.84 ($P > .05$) and interobserver SD of 0.92 ($P < .01$) were noted for a

mean “B” score of 5.0.¹⁶ “C” is a symptoms score calculated from the patient’s perception of their pruritus and sleep loss from the last 3 days/night, worth 10 points each giving “C” a maximum of 20. Originally, the SCORAD was statistically evaluated by 10 trained investigators based on a set of 10 slides, and then through a subsequent multicenter study of 88 patients¹⁶; however, much of the validation of the SCORAD came in later independent studies. Currently, compared to other AD scoring instruments, the SCORAD is the most validated^{5,11} with 26 supporting studies in the literature since 2013, spanning cohort ages of 0 to 74 years, mild, moderate, and severe AD, and situated in primary, secondary, and tertiary care centers.⁵ The SCORAD has been validated for content⁴ and construct validity,⁵ interobserver reliability,¹⁶ and sensitivity to change.¹⁰ However, a limitation is that it has not shown intra-observer reliability^{5,16} in contrast to the EASI which has.¹ Despite a major critique of SCORAD being its prolonged time of administration and resulting loss of practicality, the SCORAD remains the most thorough and systematic AD rating scale and is often the standard to which new AD rating scales are compared.

Six Area, Six Sign Atopic Dermatitis (SASSAD). The Six Area, Six Sign Atopic Dermatitis (SASSAD)¹⁷ score (Supplemental

Table 3. Top 10 Cited Atopic Dermatitis Rating Scales From 2010 to 2015.¹²

AD rating scale	No. of uses in the literature (2010-2015)
Severity Scoring of Atopic Dermatitis (SCORAD) ¹⁶	79
Investigator's Global Assessment (IGA)	29
Eczema Area and Severity Index (EASI) ¹	28
Affected Body Surface Area	9
Objective Scoring Atopic Dermatitis (SCORAD)	8
Patient-Oriented Eczema Measurement (POEM)	8
Hand Eczema Severity Index (HECSI)	5
Visual Analogue Scale (VAS) severity	3
5-Point physicians Global Assessment	2
Six Area, Six Sign Atopic Dermatitis (SASSAD)	2

Abbreviation: AD, atopic dermatitis.

Material) was created in 1998 by the British Association of Dermatologists. The SASSAD is derived from the sum of 6 different scores pertaining to the head/neck, trunk, hand, feet, arms, and legs. For each of these anatomical regions, 6 domains are assessed: erythema, exudation, excoriation, dryness, cracking, and lichenification from a scale of 0 to 3, where 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The score from each anatomical region can yield a maximum of 18, and the summed SASSAD score yields a maximum of 108. The SASSAD is better validated than IGAs, with 5 validation studies in the published literature since 2013⁵ spanning an age range of 0 to 67 years, mild, moderate, and severe AD, and occurring at secondary and tertiary care centers. Six Area, Six Sign Atopic Dermatitis shows good evidence of content⁷ and construct validity⁷ and interobserver reliability¹⁸; other aspects of validity require further investigations.⁵ To bolster the SASSAD's credibility as an AD rating instrument, data from a study of 55 children with AD at an academic centered score with multiple AD scales showed a significant EASI and SASSAD correlation of $r = 0.84$ and SCORAD and SASSAD correlation of $r = 0.92$. In comparison to other AD instruments, the SASSAD is similar to the SCORAD and EASI in that it is reasonably well validated, comprehensive, and standardized accounting for 6 AD signs as well as body area. However, similar to IGAs, it is less time-consuming to administer and is more suitable for use in clinical practice. However, we speculate that because the SASSAD represents somewhat of a middle-ground in terms of the advantages and disadvantages of AD-rating scales, it is not commonly used as an outcome measurement in the literature or in the clinical practice (Table 3) as there are better options for scales in terms of simplicity and validity.

Patient Reported Outcomes (PROs). Patient reported outcomes (PROs) are patient self-administered scales that are gaining ground in AD clinical trials. They have some utility in clinical practice due to their ease of use, potential

correlations with the established AD scales,^{10,19} and prospects of higher frequency of treatment/disease monitoring. The Patient-Oriented Eczema Measure (POEM)⁶ (Supplemental Material) contains 7 questions, in domains related to pruritus, sleep loss, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness. Each question is scored to a maximum of 4, based on the number of days in a week the patient has had symptoms, yielding a maximum POEM score of 28. The original POEM validation study followed an 18-week AD RCT with 435 patients; from this, a reliable content and construct validity,⁶ and intra-observer reliability (mean difference between scores 0.04; SD = 1.32) was noted. In terms of sensitivity to change, all POEM signs showed marked decreases throughout the RCT.⁶ However, the literature pertaining to validation of the POEM outside the original publication is scarce. The PO-SCORAD¹⁹ is scored with an identical structure to the SCORAD, except it is done so from the patients' perspectives. Patients are instructed to color the amount of area on a body diagram affected by the AD when calculating "A," and the signs used to calculate "B" are written in layman's terms. Patient-oriented SCORAD score shows significant correlation to SCORAD score ($r = 0.67$; 96% CI 0.62-0.72, $P < .0001$)¹⁹ at baseline in a study of 471 patients consulting for AD in hospitals across 9 European countries. Further validation studies also show a significant relationship between SCORAD and PO-SCORAD.²⁰⁻²² Indeed, PROs are advantageous because of their ease of administration, as well as their comprehensiveness in signs/symptoms. However, as they are relatively new, their current downfall is a lack of independent validation studies.

Conclusion

Currently, over 60 AD severity measurement scales have been reported in the literature^{4,12} with the 10 most referenced scoring systems accounting for >75% of citations (Table 3). Although SCORAD and EASI are by far the most widely

used and validated, they are time consuming and difficult to understand. In contrast, IGAs are simple and easy to administer but come with the trade-off of a lack of validity, comprehensiveness, and standardization. The SASSAD represents a middle ground for comprehensiveness and efficiency and is reasonably validated in the literature. Patient reported outcomes are efficient to administer in practice and are comprehensive, but currently lack validity. Therefore, at present, there is no gold standard for AD measurement instruments, each with their own unique advantages and disadvantages. As severity measurements are often required for government and private insurance plans, clinicians may find themselves using a variety of scales. We hope that this educational review acts as a concise reference for dermatologists and other clinicians to quickly familiarize themselves with their required AD scoring instrument, and to realize their advantages, drawbacks, and interscale comparisons.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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Visual Dermatology: Diffuse Cutaneous Mastocytosis With Bullous Lesions

Qi Tan^{1,2}  and Jian Zhang^{1,3}

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Cutaneous examination revealed a 1-year-old male child with multiple bullae and erosions on the trunk (a). Regular rubbing of affected skin areas resulted in urtication (Dariers sign) (b). The histopathological examination and Toluidine blue staining studies were consistent with diagnosis with bullous mastocytosis.

Bullous mastocytosis is a form of diffuse cutaneous mastocytosis that typically arises during the early stages of life without other organ mast cells infiltration.¹

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Visual Dermatology: Nodular Scabies in an Infant

Qi Tan^{1,2}  and Chun hua Tan^{1,3}

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A 3-month-old male child presented with erythematous nodules on the lower abdomen and scrotum. His mother had papular and crusted lesions distributed on the body. The biopsy examination showed a predominant eosinophils and lymphocytes infiltrated. The diagnosis of nodular scabies was made.

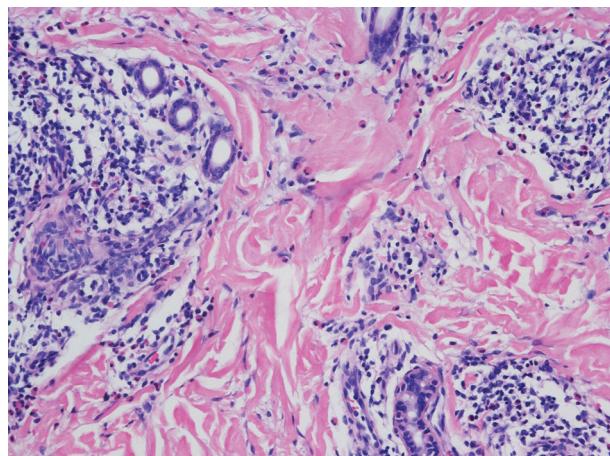
Nodular scabies is a hypersensitivity reaction to scabietic infestation characterized by persistent pruritic nodules and may be differentiated from Langerhans cell histiocytosis, insect bite reaction, non-Langerhans cell histiocytosis, lymphoma, or urticaria pigmentosa.¹

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Visual Dermatology: Black Chromhidrosis of the Bilateral Cheeks

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Malika A. Ladha¹  and Stewart Adams¹



A 39-year-old female presented with asymptomatic, daily black secretions to her bilateral cheeks, exacerbated by temperature increase or physical activity. Initial examination did not reveal any cutaneous findings. Upon manual expression, discrete pinpoint black droplets appeared on her bilateral malar cheeks (online supplemental Video 1), spanning approximately 0.5 cm (Figure 1). Her work-up revealed a normal blood cell count, coagulation profile, bilirubin level, and negative homogenetic acid urine test. She was diagnosed with chromhidrosis.

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Supplemental Material

Supplemental material for this article is available online.

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Visual Dermatology: Gulliver Sign: When Pyoderma Gangrenosum Soothes

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Juan Jimenez-Cauhe¹  and Pablo Fonda-Pascual¹



Pyoderma gangrenosum (PG) is an ulcerative skin disease with a high inflammation burden that cannot be contained by healing tissue, giving the typical undermined border. Gulliver sign was proposed by Landis et al¹ as a hallmark to recognize that the inflammation of PG has been controlled, and the suggested point to begin tapering corticosteroids. When this occurs, the edges of PG become more even with perilesional skin, and re-epithelialization is observed as string-like growths from the border to the ulcer bed (star).

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Visual Dermatology: Acral Erythematopurpuric Lesions During COVID-19 Pandemic

Giuseppe Ferrara¹ and Daniel Morgado-Carrasco²

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Cutaneous manifestations can be present in 20% of patients with coronavirus disease 2019 (COVID-19). The most commonly reported lesions are erythematous rash and widespread urticaria.¹ Chicken pox-like vesicles and purpuric rash mimicking Dengue have also been described. Recently, numerous unconfirmed highly suspicious COVID-19 patients (mostly children and young individuals) have presented with self-healing painful erythematous violaceous papules/plaques on acral locations (most frequently on the feet) in Italy. These lesions seem to be related to COVID-19.

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The Novel Role of Antibiotic Treatment in the Management of Cutaneous T-Cell Lymphoma (CTCL) Patients

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Michelle Le¹, Feras M. Ghazawi², Elena Netchiporouk¹, and Ivan V. Litvinov¹

Keywords

cutaneous T-cell lymphoma (CTCL), signal transducer and activator of transcription (STAT), antibiotics, treatment, *Staphylococcus aureus* enterotoxin

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of non-Hodgkin lymphomas with Mycosis Fungoïdes (MF) and Sezary syndrome (SS) being most prevalent.^{1–3} Signal Transducer and Activator of Transcription (STAT) signaling has previously been shown as a critical operative pathway in CTCL tumor cells.⁴ Early studies have suggested the influence of the microenvironment, namely, bacterial toxins, on STAT signaling which may accelerate progression of the disease.⁴ Patients with advanced stages of CTCL are frequently colonized with *Staphylococcus aureus* (SA), and its infection constitutes a major source of morbidity and mortality.^{1,4} It has been proposed that in malignant and benign infiltrating T lymphocytes, SA enterotoxin can bind to V β chains of the T-cell receptor (TCR) as a superantigen leading to increased inflammation that is protumorigenic. Specifically, SA enterotoxins have been shown to stimulate cross talk between nonmalignant infiltrating and malignant T-cells that promotes interleukin-2 (IL-2)-dependent proliferation of malignant T-cells.⁵ Prior studies concluded that SA enterotoxins may generate a tumor promoting inflammation, where CD4/CD8 T-cell responses from infiltrating benign lymphocytes to SA can inadvertently enhance neoplastic progression in MF/SS.¹

A recent study published in *Blood*¹ demonstrated the clinical benefit of short-term, aggressive antibiotic therapy on disease activity in advanced-stage CTCL patients colonized by SA. In this study, 8 patients with advanced refractory CTCL, but no obvious signs of infection or sepsis, were treated with intravenous (IV) cefuroxime and metronidazole for 10 days followed by oral amoxicillin/clavulanic acid dosing for 14 days. Marked clinical improvement with a significant decrease in skin disease burden was noted 1 to 2 months after antibiotic treatment in all patients. Clinical improvement correlated with a decrease of disease activity in situ, where immunohistochemistry results of skin biopsies taken before and 2 months after antibiotic treatment demonstrated a decrease in cell proliferation, expression of IL-2 receptor- α

(IL2R- α), and tyrosine-phosphorylated STAT3 (pY-STAT3) following therapy. T-cell receptor β chain sequencing revealed significant decrease of the dominant TCR clonotype in 5/6 patients, 60 days after antibiotic initiation. Normalization of mRNA expression profiles in skin lesions were also confirmed following antibiotic therapy demonstrating a decrease in IL-2 signaling and STAT activation. *Ex vivo* experiments demonstrated that SA enterotoxins derived from CTCL skin lesions induced the expression of pY-STAT3 and IL2R- α in malignant and nonmalignant T-cells. These observations suggest that SA and its toxins activate STAT3 signaling, increase expression of the IL-2R, and stimulate proliferation of CTCL tumor cells. Antibiotic treatment can effectively eradicate this stimulus, normalize tumor microenvironment, and inhibit disease activity in the skin.¹ Although this study had a relatively small sample size and a short follow-up time, it provides a promising basis for the use of antibiotics as an adjuvant therapy to reduce the burden and possibly progression of CTCL, especially during disease flares.

Based on these observations, larger clinical trials are warranted to further validate the use of antibiotics in the management of CTCL. Overall, this study reflects the clinical importance of the microbiome in CTCL patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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SB206, a New Topical Nitric Oxide-Releasing Drug on the Horizon for the Treatment of Molluscum Contagiosum and External Anogenital Warts

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Lina Belmesk¹ , Ivan V. Litvinov¹, and Elena Netchiporuk¹

Keywords

dermatology, molluscum contagiosum, wart, HPV, antiviral drug

Molluscum contagiosum (MC) and warts are the most common viral skin conditions seen in dermatology and primary care setting. While benign in nature and usually self-remitting, both are contagious, long-lasting (months-years), cosmetically disfiguring, and potentially stigmatizing.¹ Current treatments are either office-based destructive regimens (e.g., cryotherapy and laser) or home-applied topical irritants/toxins (e.g., cantharidin, podophyllotoxin, and imiquimod) and are limited due to their relative lack of efficacy and/or unfavorable side-effect profiles. The Cochrane review published in 2017 assessing the effectiveness of all available treatment options for MC concluded that there was not enough evidence to recommend *any* of the currently available treatment options.²

Berdazimer sodium (SB206), a nitric oxide (NO)-releasing macromolecule formulated in an alcohol-based gel co-administered with a carboxymethyl cellulose hydrogel, has been recently developed as an alternative for the management of MC, external genital warts (EGW), and perianal warts (PAW). NO inhibits DNA replication in several viruses including, human herpesviridae family, human papillomavirus (HPV), and MC.^{1,3} The results of a 12-week phase 2 dose-finding study of SB206 compared to vehicle in children with MC were recently published.¹

A total of 256 nonimmunocompromised children, ≥ 2 years of age, were randomized to receive vehicle ($n = 66$), SB206 4% ($n = 47$), 8% ($n = 48$), 12% ($n = 47$) twice daily (BID), or 12% daily (QD) ($n = 48$) for 12 weeks. The age, disease severity (MC lesion count), and presence of atopy were well distributed across treatment and placebo groups. In the intention to treat design, 18.2% (12/66) of vehicle patients achieved complete clearance (CR) of all MC lesions compared with 10.6% (5/47), 33.3% (16/48), 27.7% (13/47), and 37.5% (18/48) of SB206 4%, 8%, 12% BID and 12% QD patients, respectively. Reduction of MC papules was seen as early as 1 week. While no serious adverse events occurred, up to 40% to 50% of SB206-treated patients had

site-related adverse reactions which lead to treatment discontinuation in 7 patients. Irritation and/or eczematous reaction around MC papules is often clinically viewed as the “beginning of the end (BOTE)” sign and may in fact be desirable portraying immune recognition of MC virus and impeding resolution.⁴ While the efficacy falls significantly short of CR in all patients, investigators propose that patients with local reaction may in fact present the BOTE sign. SB206 12% applied QD has currently entered a phase 3 clinical trial.

Another phase 2b, double-blind, randomized, dose-escalation, multicenter trial showed that SB206 was moderately effective in patients with EGW/PAW caused by HPV types 6 and 11.⁵ A total of 108 nonimmunosuppressed adults with 2 to 20 EGW/PAW were randomly assigned to SB206 4% QD or BID, 8% QD, 12% QD, or vehicle. Primary end point, to achieve CR at week 12, was achieved in higher proportion of patients in the SB206 group compared to vehicle; SB206 12% (33.3%), 4% QD (20.8%), 8% QD (14.3%) vs vehicle (4.3%) ($P = .01$). It has recently been demonstrated that NO inhibits HPV DNA replication by reducing the activity of E6 and E7 oncoproteins, impairing the S-phase progression and causing DNA damage.³ This particular effect is of utmost interest as E6 and E7 oncoproteins play a key role in HPV-induced carcinomas.³

Declaration of Conflicting Interests

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Ultraviolet Radiation Seeking Behavior, Mediated by Endogenous β -Endorphin, Has Addictive Features

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Keywords

tanning addiction, UVR seeking behavior, β -endorphin, opioid, vitamin D

Previous studies have indicated that individuals using indoor tanning meet the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for addiction disorder with regard to ultraviolet radiation (UVR).¹ In addicted individuals, UVR exposure triggered the reward-responsible striatal dopaminergic reflux, as demonstrated by the single photon emission computerized tomography (SPECT).² Co-occurrence of tanning addiction with mood disorders and substance abuse was recently demonstrated in a large cross-sectional study of adolescents.³ In this study, for each additional substance abused, tanning addiction increased by 67%.³

Upon exposure to UVR, epidermal keratinocytes induce the transcription of pro-opiomelanocortin, which is cleaved into melanocyte stimulating hormone, responsible for skin tanning, and the endogenous opioid β -endorphin, which binds to μ -opioid receptor. β -Endorphin regulates pleasure, mood, and analgesia and chronic exposure can lead to tolerance and physical dependence.⁴

Fell et al have performed a study with mice to evaluate if UVR exposure results in opioid-related behavior (alteration in nociceptive threshold, tolerance, place avoidance/preference, and dependence) mediated by β -endorphin level.⁴ In their experiment, mice received 50 mJ/cm² of UVR type B (UVB) 5 days per week for 6 weeks, a dose that was estimated to correspond to 20 to 30 minutes of sun exposure for a fair-skin individual. Mechanical and thermal nociceptive thresholds were measured over 6 weeks. After 1 week of UVB exposure, circulating plasma β -endorphin levels and consequently mechanic and nociceptive pain thresholds were significantly elevated in UVR exposed compared to control mice. Administration of naloxone, an opioid antagonist, 15 minutes prior to nociception testing overturned the UVR-induced increase in pain-related threshold, regardless of plasma β -endorphin levels. Moreover, repeated UVR exposure induced opioid mediated behavior in mice, such as rigidity and elevation of the tail, a phenomenon also elicited by exogenous opioids.

Interestingly, naloxone administration following UVR exposure induced signs of opioid withdrawal in mice. Ultraviolet radiation-exposed mice tended to avoid environments where naloxone was administrated. These behavioral changes were not observed in neither the control mice nor the β -endorphin knockout mice. The authors demonstrated that the withdrawal signs and aversion behavior were the result of systemic β -endorphin acting on the central nervous system, which implies that the skin-derived β -endorphin crosses the blood brain barrier. Results also established the occurrence of tolerance, as increasing doses of morphine were needed in UVR-exposed mice to achieve equivalent thermal analgesia.

In humans, a recent study demonstrated that whole-body UVB exposure leads to mood improvement in healthy adults.⁵ Albers et al showed that exposure to blue light at 453 nm increased β -endorphin production by skin keratinocytes concomitantly with increase in plasma β -endorphin levels.⁶ Similarly, the administration of opioid antagonists reduced UVR-seeking behavior and induced withdrawal symptoms in frequent tanners.⁷

This endogenous opioid response is hypothesized to be the result of an evolutionary adaptation for eliciting sun-seeking behavior to prevent life-threatening vitamin D deficiency.² According to this hypothesis, vitamin D repletion would help reduce addiction to tanning and abrogate opioid-mediated addictive features. While so far there is no experimental evidence to support this hypothesis, low vitamin D levels in humans are known to be associated with lower pain

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threshold and higher exogenous opioid requirements,⁸ and in murine model, vitamin D supplementation decreased drug addiction through regulation of dopaminergic circuits.⁹

Considering the skin cancer epidemic and the opioid crisis, further research exploring the protective effects of universal vitamin D supplementation is needed. Until then, we should recommend maintaining healthy vitamin D levels through the use of inexpensive and safe oral supplements.

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Cutaneous Manifestations of Coronavirus Disease 2019 (COVID-19) Infection—What Do We Know So Far?

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Abdulhadi Jfri², and Elena Netchiporouk²

Keywords

coronavirus, COVID-19, cutaneous manifestations, skin involvement

In March 2020, the World Health Organization declared coronavirus 2019 (COVID-19) a pandemic. In addition to fever, respiratory symptoms, gastrointestinal symptoms, and anosmia, skin manifestations of COVID-19 have been characterized.

The first cohort of 88 patients in Italy described cutaneous involvement in $n = 18$ (~20%) of hospitalized COVID-19 patients. The most common involvement was diffuse erythematous rash ($n = 14$) followed by acute urticaria ($n = 3$). Few patients developed chicken pox-like vesicles and a dengue-like petechial eruption. These morphologic findings were not surprising as they are typical of viral exanthems. The rash coincided with the onset of symptomatic disease ($n = 8$) or developed after hospitalization ($n = 10$). There was no correlation between the rash and disease severity.¹

Later on, several case series described specific skin findings as manifestations of a general hypercoagulable state in severely ill patients. Indeed, systemic coagulopathy has been described as a prominent feature in severe cases of COVID-19 leading to stroke, pulmonary artery thrombosis, and myocardial infarction. A case series from China reported vasculopathic skin lesions in 7 patients, representing 21% of critically ill COVID-19 patients hospitalized at the time. Lesions ranged from acral cyanosis to dry gangrenes. The authors suggested that progression of ischemic cutaneous changes correlated with poor outcome. In fact, the median time from limb ischemia to death from circulatory failure in 5 patients was 12 days. This vascular damage could be caused by direct injury of vascular endothelium by the virus, which could lead to disseminated intravascular coagulation (DIC), antiphospholipid syndrome, and vasculitis mimics. In fact, 4/7 patients received a diagnosis of DIC.² Another case series from the United States reported purpuric skin involvement in 3 severely ill COVID-19 patients, specifically retiform purpura on the buttocks, dusky purpuric patches on the palms and soles, and livedo reticularis on the chest and limbs. In these cases, skin and lung biopsies revealed thrombogenic vasculopathy and deposits of C5b-9 and C4d complement

proteins. This was consistent with generalized activation of both alternative and lectin pathways of complement, suggesting that critically ill patients can suffer thrombotic microvascular injuries involving lungs, skin, and possibly other organs.³

While vasculopathic skin lesions in COVID-19 patients were mainly reported in severely ill adults, a surge in “blue” or so-called “COVID” toes has been described in otherwise well children with symptoms suggestive of COVID-19, but in whom the infection was not always proven.⁴

The largest, country-wide Spanish study including 375 COVID-19-infected patients (confirmed or presumed case) focusing on specific skin changes was published. The authors classified cutaneous features into 5 categories based on their morphology: (1) pseudo-chilblain (19%, hand and/or feet), (2) vesiculobullous (9%, generalized and/or acral, occasionally hemorrhagic), (3) urticarial lesions (19%, generalized or acral-limited), (4) maculopapular eruptions (47%, pityriasis rosea-like, erythema multiforme-like, or pseudovesicular), and (5) livedo or necrosis (6%, truncal or acral purpuric lesions suggestive of vaso-occlusive disease).⁵ Of these, vesiculobullous eruptions appeared early in the course of COVID-19 (15% in preclinical phase), pseudo-chilblain appeared late, while others appeared concurrently with systemic symptoms. Overall prognosis varied based on the morphology, with pseudopernio having a mild disease vs patient with morphologies suggestive of vascular occlusion (eg, livedo) having severe disease with higher risk for intensive

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care admission and mortality (10%). Patients with other morphologies had an interim disease severity.

COVID-19 cutaneous presentations can be highly variable. Because they can precede other symptoms and/or manifest in mild/asymptomatic cases, they could be the only clue to the diagnosis and thereby crucial to be recognized promptly by dermatologists to avoid community propagation of COVID-19. Importantly, in many cases there is an acral predilection of skin involvement, and morphologies suggestive of vaso-occlusion such as livedo or purpura could warrant a rapidly progressive/life-threatening disease.

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Peregrine Falcon (*Falco peregrinus*) in Central Park, NY, USA

Photo by Patti Kubick Miller

Patient-Driven Discontinuation of Apremilast During the COVID-19 Pandemic in Two Canadian Academic Hospital Clinics and One Community Practice

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Jorge R. Georgakopoulos¹ , Ron Vender^{2,3} , and Jensen Yeung^{1,4,5,6}

Keywords

COVID-19, psoriasis, apremilast, dermatology

Since the first reported cases in December 2019, coronavirus disease 2019 (COVID-19) has now become a worldwide pandemic.¹ Dermatologists have been forced to adopt a new model of care that includes in-person services reserved for emergent cases and telemedicine through various measures to provide continuity of care.² During this unprecedented time, patients have begun questioning whether or not they should discontinue the use of biologics for cutaneous diseases because of COVID-19 fears. However, a biologic alternative for treatment of moderate-to-severe psoriasis, apremilast, may be overlooked by patients. In this study, we aimed to quantify and understand rates of patient-driven discontinuation of apremilast for moderate-to-severe psoriasis during the early stages of the COVID-19 pandemic in Canada.

Following research ethics approval, a multicenter retrospective study was undertaken of all patients from two tertiary academic hospitals in Toronto, Canada, and one large community dermatology practice in Hamilton, Canada, currently on apremilast for moderate-to-severe psoriasis as of February 1, 2020. Primary outcome was the percent of patient-driven discontinuation of apremilast due to COVID-19 concerns. All patients included had no symptoms and had not been in close contact with anyone who had a confirmed diagnosis of COVID-19. The Patient Support Program (PSP) case manager for apremilast (Innomar Strategies Inc.) provided all reported data, but had no involvement in study design, data interpretation, or manuscript preparation. In Canada, the vast majority of patients receiving apremilast are enrolled in a PSP and decisions to withhold apremilast by clinicians are almost always reported to the PSP. The 3 sites used for data collection, however, have a 100% enrollment rate and 100% reporting rate. Data were collected from February 1, 2020 (total Canada-wide data of 5 documented cases of COVID-19 and 0 associated deaths) until April 15,

2020 (total Canada-wide data of 28 351 cases of COVID-19 and 1056 associated deaths).³

Of the 188 patients on apremilast as of February 1, 2020, 0 (0%) had discontinued treatment prior to April 15, 2020, due to COVID-19 concerns. These results suggest that patients on apremilast do not appear to be withholding treatment currently due to COVID-19 concerns. This is likely multifactorial including strong clinician support in answering patient concerns, PSPs encouraging patients to follow-up with their dermatologist prior to discontinuing treatment, and low rates of upper or lower respiratory tract infections long term. Phase 3 randomized controlled trials (RCTs) have demonstrated that lower respiratory tract infections are rare with both the short- and long-term use of apremilast.⁴ Alternatively, upper respiratory tract infections have been well documented in RCTs.⁴ While this may be seen as a deterring factor for patients during COVID-19, we believe the low overall rates and strong patient education about potential side effects at the time of treatment initiation may be reducing patient fear.

A limitation of this study includes the potential of not reporting their treatment discontinuation to the PSP or their

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dermatologist. Ultimately, it is unclear at this time whether or not dermatology patients should be discontinuing their immunosuppressive or immunomodulatory treatments. Each clinic is likely taking their own approach as no evidence-based data are available to guide recommendations during COVID-19. Our clinicians continue to educate patients on a case-by-case basis and have provided telemedicine support for patients on apremilast with COVID-19 concerns. Joint decisions on discontinuation or temporarily holding treatment are made after lengthy discussions between the dermatologist and patient. We hope the reported data here can offer our dermatologists expert-based approach in handling apremilast to help guide recommendations during this unique clinical landscape.

Ethics approval

Ethical approval was granted by the Research Ethics Board at Sunnybrook Health Sciences Centre (190-2016) and Women's College Hospital (2016-0072-E).

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Yeung has been a speaker, consultant, and investigator for AbbVie, Allergan, Amgen, Astellas, Boehringer Ingelheim, Celgene, Centocor, Coherus, Dermira, Eli Lilly, Forward, Galderma, GSK, Janssen, Leo, Medimmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB, Valeant, and Xenon. Dr Vender has been a speaker, consultant, advisory board member, and investigator for AbbVie, Actelion, Amgen,

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Preliminary Data Suggests That Biologics in Dermatology Are Not Associated With Adverse COVID-19 Outcomes

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Keywords

COVID-19, SARS-CoV-2, immunosuppressive agents, biologics, immunomodulators

The coronavirus disease 19 (COVID-19) pandemic has been a leading cause of death across many countries in 2020.¹ Most COVID-19 patients requiring hospitalization have comorbidities, such as hypertension, chronic cardiopulmonary disease, or immunosuppression.² The pressing question for dermatologists is whether our patients receiving biologics are at a higher risk of severe COVID-19 infection?

The immune response to COVID-19 virus appears to follow two phases.³ During the incubation period and early disease stage, interferon signaling and adaptive immunity preclude disease from progressing. If and when this immune response is impaired, the virus may cause significant organ dysfunction leading to a cytokine storm.³ This subsequent inflammatory surge may have a dual effect as a double-edge sword and is a matter of active research. It is plausible that suppressing cytokine storm with broad-spectrum anti-inflammatory therapies could dampen viral clearance and increase organ damage.⁴ However, most of the biologic agents used in dermatology immunomodulate rather than immunosuppress patients. For this reason, the Canadian Dermatology Association and the American Academy of Dermatology (AAD) suggest continuing biologic therapies for psoriasis, atopic dermatitis, and chronic spontaneous urticaria during the pandemic.

A multicenter retrospective study investigated the rate of death and hospitalization related to COVID-19 during the peak of the Italian pandemic in 5206 psoriasis patients treated with one of the following biologic agents: TNF-alpha, IL-17, IL-12/23, or IL-23 inhibitor.¹ Importantly, none of the treated patients died. Only 4 required hospitalization and all had typical COVID-19 risk factors (eg, hypertension, age ≥ 60 , diabetes, obesity, or renal failure). While the study was limited due to the lack of a comparison group and an unknown number of total COVID-19 infections in the country (as population-based testing was not performed), it remains very encouraging since many patients with severe psoriasis are known to have comorbidities that are often associated with poor COVID-19 disease outcome.¹

Furthermore, a prospective study conducted in New York, NY, assessed the rate of hospitalization in patients with immune-mediated inflammatory diseases (IMIDs) including psoriasis, who were treated with biologic agents or immunomodulatory therapies and in whom COVID-19 was either confirmed or highly suspected. Out of the 86 patients included in the analysis, 38 were taking TNF-alpha, 6 were taking IL-12/23, 6 were taking IL-17, and 3 were taking IL-23 inhibitors. Only 14 out of 86 patients required hospitalization, while 1 required mechanical ventilation. In this group, most patients had additional metabolic syndrome, had advanced age, had ≥ 2 immunosuppression therapies, or were pregnant. The authors commented that the rate of hospitalization was not different from the city's reported average. The only study death occurred in a patient who was not on any immunosuppressive therapies. While the major limitation of the study was the small number of patients, it is reassuring that IMID patients constitute a very small fraction of hospitalized COVID-19 patients.²

The data on dupilumab and omalizumab are even more scarce, but it is generally accepted that both drugs do not have immunosuppressive potential and are not associated with a risk of severe infection.⁵ In a report of 30 atopic dermatitis patients treated with dupilumab in Northern Italy, none tested positive for COVID-19, despite being in a high risk of contagion area.⁶

The preliminary data on patients receiving biologic therapies for skin diseases during the pandemic are reassuring. Two

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global registries, the PsoPROTECT (Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of Covid-19 infection—<https://psoprotect.org/>) and SECURE-AD (Surveillance Epidemiology of Coronavirus Under Research Exclusion-Atopic Dermatitis—<https://www.covidderm.org/>), have begun patient recruitment and rely on the contribution of the entire dermatology community to deliver robust results. Similarly, AAD has created a similar registry, where cases can be entered—<https://www.aad.org/member/practice/coronavirus/registry>.

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Patient-Driven Discontinuation of Dupilumab During the COVID-19 Pandemic in Two Academic Hospital Clinics at the University of Toronto

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Keywords

COVID-19, psoriasis, dupilumab, dermatology

Treatment modalities for moderate-to-severe atopic dermatitis (AD) are greatly limited for patient's refractory to topical therapy. Dupilumab, a fully human monoclonal antibody that binds specifically to the IL-4R α subunit of the receptor complexes for IL-4 and IL-13, is the only government-approved biologic for AD. As such, the maintenance of its efficacy is critical for patient care. With the global spread of coronavirus disease 2019 (COVID-19), dermatology clinics have seen an increase in patient fear with use of biologic agents. Patient safety, efficacy following temporarily discontinuing treatment, and lack of available data to guide clinical judgment all impact a dermatologist's ability to offer recommendations. As such, we aimed to quantify the percent of patients discontinuing dupilumab due to patient-driven COVID-19 concerns to help guide care during this time.

Following research ethics approval, a multicenter retrospective study was undertaken of all patients from two tertiary academic hospitals in Toronto, Canada, on dupilumab for moderate-to-severe AD as of February 1, 2020. Primary outcome was the percent of patients who temporarily discontinued dupilumab prior to April 15, 2020, due to COVID-19 concerns. All patients included had no symptoms and had not been in close contact with anyone who had a confirmed diagnosis of COVID-19. The Patient Support Program (PSP) Case Manager for dupilumab provided all reported data, but had no involvement in study design, data interpretation, or manuscript preparation. All patients in our clinics are enrolled in a PSP at the time of treatment initiation and all decisions to discontinue dupilumab are reported to the PSP. February 1, 2020 (5 cases and 0 associated deaths Canada-wide), until April 15, 2020 (28 351 cases and 1056 associated deaths Canada-wide) was set as the time period as this represents the early stages of the COVID-19 pandemic in Canada.¹

Of the 162 patients on dupilumab, 1 (0.62%) had temporarily discontinued treatment due to patient-driven

COVID-19 concerns. The one individual was a 21-year-old male who had been on dupilumab for 2 months prior to stopping. These results suggest that patients with moderate-to-severe AD do not appear to be discontinuing dupilumab during the early stages of COVID-19. At this time, there are no evidence-based guidelines released from the dermatology community instructing clinicians on whether or not a biologic agent should be held during COVID-19. This is in part due to the lack of available data on the susceptibility of contracting COVID-19 for patients on a biologic for AD or other inflammatory disorders. Dupilumab data are grossly limited to isolated case reports, including that by Ferrucci et al who reported 2/245 (0.82%) patients on dupilumab for AD contracted COVID-19.² It is well known that patients with immune suppression, whether due to their illness or secondary to treatment, are at greater risk of bacterial and opportunistic infections. SOLO 1 and SOLO 2 randomized controlled trials demonstrated that rates of upper respiratory infections are similar between dupilumab and placebo, with no reports of more serious lower respiratory tract infections.³

A limitation of this study includes the risk of not capturing patients who temporarily discontinued dupilumab without contacting their dermatologist or PSP to suspend delivery of treatment. Overall, rates of dupilumab discontinuation appear to be low during the early stages of the evolving COVID-19 pandemic. Our understanding

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and ability to educate patients is limited since the strongest available data are obtained from randomized controlled trials, which cannot be extrapolated to the current healthcare landscape. Our clinicians have elected to encourage continuation of treatment and provide telemedicine support or emergent in-person visits for AD patients with therapy concerns. This has contributed greatly to the low rates of dupilumab discontinuation seen in our clinics.

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Rate of Patient-Driven Biologic Treatment Discontinuation During the COVID-19 Pandemic in 2 Academic Hospital Clinics at the University of Toronto

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Keywords

COVID-19, psoriasis, biologics, dermatology

Biologics have become a staple of treatment for cutaneous disorders. Patients have grown to put strong faith in these therapies due to their proven efficacy and safety profiles.^{1,2} However, the current coronavirus disease 2019 (COVID-19) pandemic has brought biologic safety to the forefront of our daily care. For reasons of suboptimal data, fear among patients with respect to the use of these agents during this unprecedented time is growing. As such, we aimed to further understand the impact COVID-19 has had on the use of biologics for moderate to severe psoriasis within dermatology.

Following research ethics approval, a multicenter retrospective review was undertaken of all patients from 2 tertiary academic hospitals in Toronto, Canada currently on a biologic agent for psoriasis as of February 1, 2020. Inclusion criteria were patients 18 years of age or older with moderate to severe psoriasis treated with either adalimumab, brodalumab, certolizumab, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, or ustekinumab. In total, patients from 8 prescribing dermatologists were included. Primary outcome was the percent of patients who suspended their biologic due to patient's COVID-19 concerns. These patients had no symptoms of COVID-19 and had no close contact with anyone who had a confirmed diagnosis of COVID-19. Data were retrospectively obtained from Patient Support Program (PSP) Case Managers of all major suppliers of biologic agents for psoriasis. In Canada, almost 100% of biologic patients are enrolled in PSPs. For some patients who contacted our clinic directly and discontinued their biologic, the PSP would have been notified. Data were collected up until April 15, 2020, a little more than 1 month since COVID-19 was declared a global pandemic by the World Health Organization. Starting point for data collection regarding patient's temporary discontinuation of biologics was completed from February 1, 2020 (5 documented cases and 0 deaths in Canada) until April 15, 2020 (28 351 cases and 1056 deaths).

Of the 1390 patients currently on a biologic agent for psoriasis, 7 (0.5%) have discontinued treatment temporarily due to COVID-19 concerns. Of the 7 patients who discontinued treatment, 5 (71.4%) were male, mean age was 58.0 ± 9.2 years and 1 (14.3%) patient also had psoriatic arthritis (Table 1). Rates of suspension for each biologic included adalimumab (2/221, 0.9%), brodalumab (0/20, 0%), certolizumab (0/21, 0%), etanercept (0/313, 0%), guselkumab (3/250, 1.2%), infliximab (1/43, 2.3%), ixekizumab (0/118, 0%), risankizumab (0/70, 0%), secukinumab (0/90, 0%), and ustekinumab (1/244, 0.4%). Mean duration of biologic treatment prior to discontinuation was 59.6 ± 43.8 months. In our entire cohort, there have been no reported cases of individuals who suspended their biologic due to contracting COVID-19. All 7 patients stopped treatment due to fear that they were at increased risk of falling ill with COVID-19 while on therapy.

At this time, there is no consensus on whether or not biologics should be held while COVID-19 continues to spread. As highlighted by Lebwohl et al, randomized controlled trials in the pre-coronavirus era demonstrated that respiratory infection rates were comparable to placebo.³ A limitation of this study includes the potential for missing a rare group of patients who have not enrolled in a PSP and we are not aware

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Table I. Demographics of Psoriasis Patients Who Have Discontinuation Biologic Treatment due to COVID-19 Concerns.

Biologic	Gender	Age (y)	Diagnosis	Duration (mo)
Adalimumab	Male	46	Psoriasis	92
	Female	65	Psoriasis and psoriatic arthritis	83
Guselkumab	Male	56	Psoriasis	19
	Female	64	Psoriasis	24
Guselkumab	Male	67	Psoriasis	23
Infliximab	Male	63	Psoriasis	133
Ustekinumab	Male	45	Psoriasis	43

Abbreviation: COVID-19, coronavirus disease 2019.

Biologics reviewed included adalimumab, brodalumab, certolizumab, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, and ustekinumab.

of their biologic discontinuation. Furthermore, some patients might not have contacted their PSP or our clinics to express their fear surrounding biologic use during COVID-19 and temporarily decided to hold their dose. In our clinics, physicians have provided telephone visits to patients who contacted the PSPs or our hospital nurses in order to address their COVID-19 concerns. This has greatly contributed to the low rates of biologic discontinuation during this unprecedent time (7/1390, 0.5%). Some dermatologist may be more inclined to recommend discontinuing biologics due to lack of available data, which is not the case with our group of clinicians. We hope that the results of this study can provide further information for dermatologist as they navigate patient concerns during this time. Arranging telehealth support for patients on biologics may greatly alleviate fear surrounding COVID-19, ultimately altering their treatment pathway.⁴

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The Need to Evaluate the Risks and Benefits Posed by Quebec Bill 43 Expanding Nurse Practitioners' Scope of Practice

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Dear Editor,

Once more, our medical community is faced with legislative changes requiring urgent consideration.

On October 9, Quebec Health Minister Hon. Danielle McCann presented Bill 43, which is set to institute a broad expansion of nurse practitioners' (NP) scope of practice in the province; the stated objective of said legislation is to increase access to care. At present, NPs in Quebec are only authorized to treat 6 enumerated chronic conditions with physician oversight. However, the proposed Bill 43 does away with physician involvement and grants NPs the ability to diagnose and treat "common illnesses" as well as perform invasive procedures. "Common illnesses" are defined as those which (i) are present with recognizable signs and symptoms, (ii) have recognized diagnostic criteria, and (iii) are present in the absence of significant clinical deterioration. Thus, "common illnesses" not only comprise the vast majority of dermatological disease, but the majority clinical diagnoses in medicine. Indeed, the minister confirmed this stating that Bill 43 would place 80% of all medical needs within the purview of NPs practice. Moreover, following the presentation of Bill 43, the government announced that it would aim to increase the number of NPs by 400% in Quebec by 2024. Despite uncertainty as to the final letter of the law, we consider Bill 43's implications for patient care in the dermatological context.

Bill 43 allows for Quebec NPs to assume clinical responsibility for dermatological disease and perform invasive procedures without formal dermatological training. Indeed, in order to become an NP in Quebec, one must obtain a bachelor and master's degree in nursing, a diploma in a complementary field of medical science and undertake a 910 to 980 hours (roughly 1.5 years) of internship training. However, a review of nursing programs across the province revealed that none include courses by university affiliated dermatologists nor courses devoted to dermatological diagnoses and treatments (excluding wound care). Thus, the knowledge and skill of NPs in the dermatological context necessarily rests on the experience they may acquire through clinical practice. Indeed, this variability in training and experience raises concerns for patient safety and public health.

Another concerning aspect of Bill 43 is that it may create yet greater delays for patients requiring dermatological care

affecting their prognoses and clinical outcomes. Under the proposed legislation, NPs may only refer patients to general practitioners, not specialists. Hence, patients presenting to NPs with pathologies requiring the urgent attention of a dermatologist, such as melanoma, may face additional delays as they would need to consult a generalist before receiving a consultation from a dermatologist. Although Bill 43, and others alike, may intend to increase access to care, they may inadvertently hinder access to appropriate care in some instances. Furthermore, recently established and provincially administered Centre de répartition des demandes de service (CRDS) specialist referral system is already strained with thousands of consultations for dermatology. The key to addressing the existing backlog of referrals to dermatology would be not to place more consultations into the CRDS system, but ensure better triaging and recognition of potentially life-threatening skin pathologies by referring to appropriate health providers, which is not addressed by this piece of legislation.

Also, should Bill 43 be implemented, Quebec NPs may choose to depart from clinical practice in favor of cosmetic medicine as several have done in Ontario following similar legislative changes. As discussed extensively in a previous letter,¹ NPs practicing cosmetic medicine without even minimal formal training not only raise concerns for patient safety but detract from governments' stated mission of increasing access to care. Indeed, Bill 43 would supersede the current restriction in Quebec whereby NPs may only perform, and not alter, cosmetic treatment plans established and overseen by a physician trained in cosmetic medicine. As such, enactment of Bill 43 would see Quebec NPs now licenced to perform minor operations without physician oversight, in stark contrast with the near universal requirement of physician oversight across the rest of North America to insure safety. Moreover, unlike Ontario, Quebec does not have overarching legislation preventing NPs from providing nontherapeutic treatment for financial gain. As such, should Bill 43 come into effect, NPs may freely migrate toward cosmetic practice increasing the risk associated with the aforementioned non-essential minimally invasive procedures and undermine the government's attempts to increase access to care.

As governments across Canada continue to expand the scope of allied health professionals, we must be mindful of the effects on our patients in the future. As Bill 43 has yet to

be enacted, physicians and affected stakeholders alike should consider engaging legislators and authorities to consider the perils noted above with view to amendment before Bill 43 is enshrined into law.

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SUPPLEMENTARY MATERIALS

The use of online-only supplementary files is available and encouraged for use by JCMS authors. These files may include more detailed methods, extended data sets/data analysis, surveys, forms, tables or additional figures, and other supporting material that is not essential for inclusion in the full text of the manuscript but would nevertheless benefit the reader. In addition, other material, including video clips and podcasts, that enhance or extend the context of the paper beyond that which can appear in print are welcome. Supplementary files are peer reviewed. Complete guidelines for Supplementary Files are available on the journal website.

The Need for a National Strategy on Artificial Intelligence in Canadian Dermatology

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In 2017, a *Nature* publication forever changed the future of dermatology, where scientists and dermatologists at Stanford University showed that artificial intelligence (AI) algorithms can classify melanoma from dermoscopic images with the same accuracy as 21 board-certified dermatologists.¹ Since then, there has been an explosion of AI-based dermatology research ranging from detection of keratinocyte cancer,² prediction of future events such as skin cancer³ and adverse cutaneous drug reactions,⁴ and identification of risk factors for atherosclerosis in psoriasis patients.⁵ Indeed, dermatology is ripe for AI technology given our specialty is visually-based with high case volumes for collection of training data. In Canada, this dermatology AI boom has sparked the creation of AI-driven dermatoscopes and medical records systems (MetaOptima Technology Inc.) and noninvasive skin biopsy technology (Elucid Labs Inc). Established skincare brands and new tech start-ups have ventured into the world of AI as well, where AI is being applied toward acne diagnosis (La Roche-Posay) and customized skin care and beauty regimens (PROVEN Skincare) to name only a few examples. It is strikingly clear that it is no longer a question of whether AI will impact the clinical practice of dermatology, but how.

Of course, with the arrival of AI in dermatology, a number of questions remain: How will AI be integrated into dermatology practice? Will it be used for diagnosis, treatment selection, and prognostication? How do we ensure AI is developed for clinically useful applications? Who will regulate the technology? Who carries the liability if the AI is wrong? What if there is a data breach? How will this impact training of dermatologists? Will AI replace the job of a dermatologist? After all, while a dermatologist may see and learn from over 100 000 cases in a lifetime, an AI system can learn from this many cases in hours, weeks, or months. To appreciate the implications of these questions, it is essential to understand how AI works and what its limitations may be. While a full description is beyond the scope of this article, we strongly recommend that dermatologists develop a basic understanding of machine learning principles (for a topical overview with clinical relevance, see Rowe, Academic Medicine 2019⁶; for more technical overview, see the online tutorial from Towards

Data Science,⁷ and the textbook “Neural Networks and Deep Learning”⁸ among other sources).

The process of developing and training an AI system is susceptible to many potential sources of error that are not readily apparent to those unfamiliar with AI. As striking support of this fact within the realm of dermatology, consider the recent systematic review published February 2020 in the *BMJ*⁹: authors evaluated smartphone-based AI apps for skin cancer detection that had received CE marketing (an implication that the apps conform to health and safety standards) and found many apps were not reliable in the detection of skin cancer, suggesting a risk to the public. However, not all AI are created equal – many AI technologies do not carry the same patient risks and indeed some applications have the potential to significantly improve clinical practice and patient outcomes. While there are many sources of error to consider in AI,^{10–12} these errors can be greatly reduced by appropriate design, development, testing, and implementation of AI. Therein lies the importance in recognizing the difference between quality AI that is clinically useful and AI that is potentially misleading or harmful.

In light of the rapidly increasing number of potential applications of AI in dermatology, and the inherent limitations and dangers of inappropriate AI, the American Academy of Dermatology (AAD) released a position statement in 2019 highlighting seven important considerations on AI for dermatologists¹³: (1) **model development** should include high-quality data that is representative of the population on which the AI is intended, and models should be validated extensively before clinical deployment; (2) **clinical deployment** of AI should allow for easy integration into clinical workflows, and models should continue to be extensively evaluated, iterated, and monitored in the clinical setting including through clinical trials of efficacy and patient safety, identifying situations where model bias and error can occur; (3) **post-marketing surveillance** includes continued measurement of outcomes relevant to physicians, patients, and health systems including cost, quality of care, safety, and clinical impact; (4) **engagement** of physicians and patients to assess their expectations, fears, and knowledge of AI and to help guide development of AI applications toward areas of need and utility; (5)

education of patients as to when and how AI will be used in improving their dermatological care, and education of physicians on the limitations of AI and its appropriate uses; (6) **privacy and medical-legal issues**, such as protecting patient health information during development and deployment of AI applications and in determining responsibility in AI error between the physician and AI manufacturer/distributor; (7) **advocacy** by physicians and patients to collaborate with policymakers to promote high-quality, clinically useful, and inclusive AI applications.

Presently, the Canadian Dermatology Association does not have a statement or action plan on AI in dermatology. While adoption of the AAD position statement is possible, differences in healthcare systems, billing practices, legal systems, and policymaking in Canada warrant consideration for developing a Canadian standard. It seems essential that Canadian dermatologists become familiar with AI in a general sense, much like we have familiarity with other tools in our diagnostic and therapeutic arsenal. For instance, we do not simply take a punch biopsy and blindly await a black-box answer—we have an understanding of why that biopsy was done, what we and the board-certified pathologist are looking for on histology, and what limitations that diagnostic technique may have. The same should be true for AI applications, where it is insufficient to simply allow a technology to make a decision on our behalf without having an understanding of whether it is useful for a given patient, what that technology might be doing, and what its strengths and limitations might be. By having this understanding, it will allow Canadian dermatologists to be at the forefront of AI in Canadian medicine, where we can collaborate with industry, academia, patients, and policymakers to actively guide, assist, implement, and regulate the research and development of dermatological applications of AI with the goal of reducing costs, improving clinical workflow, patient outcomes, and safety.

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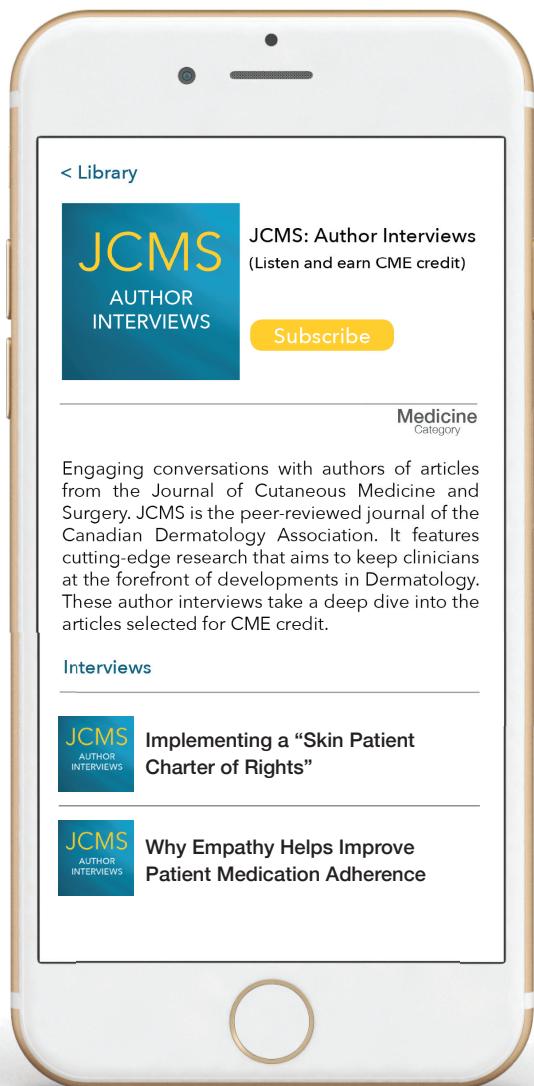
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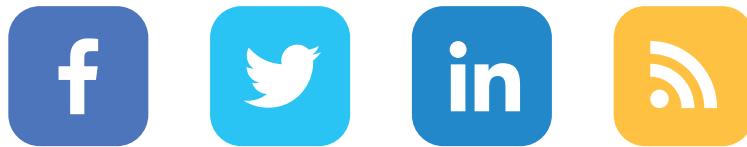
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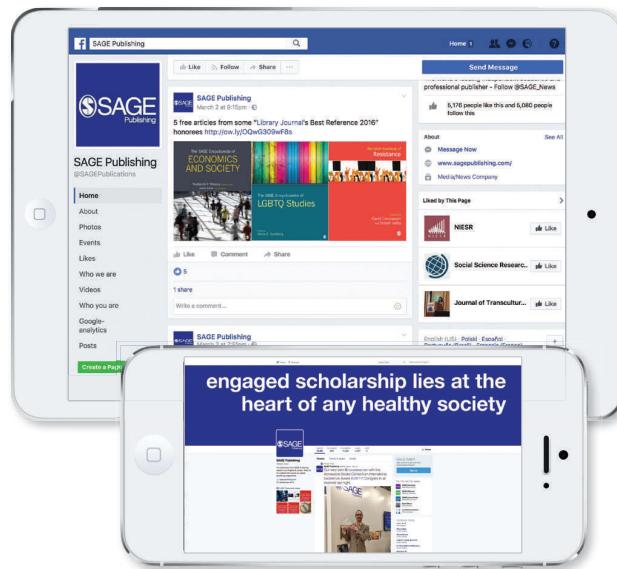


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