Adverse events associated with aesthetic injectable treatments

by

Kaitlyn M. Enright BSc, MSc, PhD Candidate

Department of Experimental Surgery

McGill University, Montreal

Quebec, Canada

Submitted: December 2023

A thesis submitted to McGill University in partial fulfillment of the requirements of a Doctoral (PhD) degree in the specialty of Experimental Surgery.

Table of contents

List of abbreviations

Adverse event	AE
Adverse reaction	AR
Botox	BTX
Botulinum neurotoxin	Abo-, inco-, ona-
Electronic database capture	EDC
Global Registry of Adverse Clinical Events	GRACE
Hyaluronic acid	HA
International Council for Harmonisation	ICH
Safety Task Force	STF

Abstract

English

This chapter book begins with an overall discussion of the field of aesthetic medicine, with a focus on soft tissue injectables [e.g., hyaluronic acid (HA) fillers]. In particular, this book evaluates adverse events (AEs) associated with the use of aesthetic injectables. Following a general introduction to the topics of interest (Chapter 1), Chapter 2 summarizes a 53-year retrospective analysis of MedEffect^{TM}, Health Canada's AE reporting database. Incidence rates of AEs associated with different injectable products (e.g., HA versus neurotoxins) are calculated, using data from this review. Chapter 3 focuses on an in-depth discussion of the findings presented in Chapter 2 and develops next steps in the investigation. In Chapter 4, a thorough systematic review of the literature is reviewed for methods of preventing, managing, and treating AEs. All recommendations are graded on a scale from very low to high, based on the quality of their supporting evidence, and resulting models are developed for use in clinical practice. However, it is concluded that the majority (> 85%) of recommendations proposed to date are of very low to low (GRADE D or C) quality, relying solely on expert opinion or studies with severe limitations, and often lack direct evidence. This chapter ends with a call-to-action, encouraging investigators to develop evidence-based AE prevention, management, and treatment strategies. As an early means of responding to this call-to-action, a Safety Task Force (STF) is developed and described in Chapter 5. A STF meeting was held and brought together a group of dermatologists, plastic surgeons, and injectors from other specialities to review and discuss current safety-related issues associated with aesthetic injectables. By the end of this meeting, the STF has agreed upon a list of priorities (i.e., areas of concern in the aesthetic industry) and methods of addressing them. The STF concluded that the development of a global AE registry

necessitates the development of evidence-based AE protocols. Therefore, in Chapter 6 we report the results of a prospective study wherein the Global Registry of Adverse Clinical Events (GRACE) was developed and validated. Finally, in chapter 7 future aims and plans for improving patient safety in the field of aesthetics are outlined.

Français

Ce chapitre commence par une discussion générale sur le domaine de la médecine esthétique, en mettant l'accent sur les produits injectables pour les tissus mous [par exemple, les produits de comblement à base d'acide hyaluronique (AH)]. Ce livre évalue en particulier les événements indésirables (EI) associés à l'utilisation des produits injectables à visée esthétique. Après une introduction générale aux sujets d'intérêt (chapitre 1), le chapitre 2 résume une analyse rétrospective sur 53 ans de MedEffect^{TM}, la base de données de notification des EI de Santé Canada. Les taux d'incidence des EI associés à différents produits injectables (par exemple, l'AH par rapport aux neurotoxines) sont calculés à l'aide des données de cette analyse. Le chapitre 3 se concentre sur une discussion approfondie des résultats présentés au chapitre 2 et développe les prochaines étapes de l'enquête. Dans le chapitre 4, une analyse systématique approfondie de la littérature est réalisée pour trouver des méthodes de prévention, de gestion et de traitement des EI. Toutes les recommandations sont classées sur une échelle allant de très faible à élevée, en fonction de la qualité des preuves qui les étayent, et les modèles qui en résultent sont développés pour être utilisés dans la pratique clinique. Cependant, il est conclu que la majorité (> 85 %) des recommandations proposées à ce jour sont de qualité très faible à faible (GRADE D ou C), s'appuyant uniquement sur des avis d'experts ou des études très limitées, et manquant souvent de preuves directes. Ce chapitre se termine par un appel à l'action, encourageant les chercheurs à développer des stratégies de prévention, de gestion et de traitement de l'EA fondées sur des données probantes. Pour répondre à cet appel à l'action, un groupe de travail sur la sécurité

(Safety Task Force, STF) a été mis en place et décrit au chapitre 5. Une réunion du STF a été organisée et a rassemblé un groupe de dermatologues, de chirurgiens plasticiens et d'injecteurs d'autres spécialités afin d'examiner et de discuter des questions de sécurité actuelles liées aux produits injectables à visée esthétique. À l'issue de cette réunion, le STF s'est mis d'accord sur une liste de priorités (c'est-à-dire de sujets de préoccupation dans le secteur de l'esthétique) et sur des méthodes pour les aborder. Le STF a conclu que la mise en place d'un registre mondial des EI nécessitait l'élaboration de protocoles d'EI fondés sur des données probantes. C'est pourquoi le chapitre 6 présente les résultats d'une étude prospective dans laquelle le registre mondial des événements cliniques indésirables (GRACE) a été développé et validé. Enfin, le chapitre 7 présente les objectifs et les projets futurs pour l'amélioration du domaine de l'esthétique.

Acknowledgements

I am grateful for the supervision, advice, and unwavering support given by the thesis supervisors, advisors, and members of the review committee. I am also appreciative of the support offered by my research funders, including McGill University and the Fonds de recherche du Québec. I would be remiss to fail to highlight the fact that this project would not have been made possible without the individual contributions of many clinician-investigators who participated in the GRACE Portal. Lastly, I would like to thank my colleagues and research team members, for the time I will cherish having worked together.

Contribution to original knowledge

All elements of this thesis are considered original scholarship and provide distinct contributions to knowledge.

Contribution of Authors

Chapters 1 -3, 5-7: Kaitlyn M. Enright confirms responsibility for chapter conception and design, literature review, statistical analyses (where applicable), interpretation of findings, and drafting of the manuscript. All authors [Kaitlyn M. Enright (student) and Drs. Andreas Nikolis and John. S. Sampalis (research supervisors)] revised it critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Chapter 4: Kaitlyn M. Enright, John S. Sampalis, Sebastian Cotofana, Mirko S. Gilardino, Demetrios Rizis, and Andreas Nikolis made substantial contributions to the study conception, design, acquisition of data, and/or analysis and interpretation of data. Andreas Nikolis and Kaitlyn M. Enright were responsible for the study conception and design, Kaitlyn M. Enright acquired data and performed the analysis under the supervision of John S. Sampalis, and all authors were involved in the interpretation of data and discussion of clinical impact. Kaitlyn M. Enright was involved in drafting the manuscript and all other authors revised it critically for important scientific/medical content. All authors have given final approval of the published version. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Chapter 1: Introduction

The field of aesthetic medicine

The field of aesthetics is one of the fastest growing medical fields to date, with over 30 million procedures performed worldwide in 2021.[1] Although both surgical and nonsurgical aesthetic procedures have seen a significant increase in popularity over the last years, the number of non-surgical aesthetic procedures has more than doubled (+54.4%) in the last four years.[1] While there are some clear reasons why patients are turning to nonsurgical aesthetic procedures, including decreased cost and reduced recovery time, some other striking reasons include the desire to maintain/regain a youthful appearance, improve quality of life, and the desire to prevent signs of aging.[2-5]

Facial ageing

As the popularity of minimally invasive procedures grows, so does anatomical research investigating various areas and structures contributing to facial aging. For example, Cotofana and colleagues (2017) evaluated the anatomy of the forehead to better understand its various compartments and how they contribute to global and site-specific facial aging.[6] They specifically identified six fat-containing forehead compartments (three superficial and three deep) that contribute to aging of the forehead.[6] These authors also propose that an understanding of facial structural arrangement (i.e., five skin layers) is equally as important in identifying the underlying causes of facial aging. This five-layered arrangement is compared of the skin (layer 1), subcutaneous fat (layer 2), superficial muscle (layer 3), deep fat (later 4), and the deep fascia (layer 5).[7] Within each of these layers, there are various relevant factors contributing to significant signs of aging, including the development fine lines and winkles, bone resorption, loss of fat pads, hallowing of the contours of the face, changes in muscle tone (face and body),

and skin discoloration, among others.[8-11] Each of these factors occur in tandem, resulting in the appearance of an aged face.

Treatments for the ageing face

According to the International Survey on Aesthetic/Cosmetic Procedures (ISAPS), injectable products (e.g., neurotoxins, fillers, biostimulators, lypolytic products) lead the market with over 12 million procedures performed worldwide in 2021.[1] The specific choice of product should reflect the desires of the patient, the knowledge of the injector, and the impact certain patient factors may have on the outcome of the procedure. Each injectable is manufactured in a way to offer a product with unique properties and relatedly, that are suitable for their respective indications. For example, neurotoxins such as Botox (Onabotulinum toxin A – ONA, Allergan Aesthetics), Dysport (Abobotulinum toxin A – ABO, IPSEN Biopahrm LTD.), and Xeomin (Incobotulunum toxin A – INCO, Merz Pharmaceuticals) modulate muscle paralysis through the inactivity of key channels responsible for muscle contraction.[13-14] Biostimulators such as Sculptra (poly l-lactic acid, Dermik Labratories) and Radiesse (calcium hydroxyapatite, Merz North America, Inc. Merz Aesthetic) stimulate the immune system to produce and gradually replace lost collagen in the face or body.[15-16] Injectable products such as Kybella (Allegan Aesthetics), use the process of lipolysis to break down fatty tissue, and soft tissue fillers such as Restylane (Galderma) and Juvéderm (Allergan Aesthetics) use different gel formulations of hyaluronic acid (HA) to provide significant tissue lift or volume replacement to various areas of the face.[17-18] Each of the above-mentioned products possess specific properties that contribute to their respective outcomes and contribute to improving overall patient satisfaction.[19-25]

Adverse events

Although generally considered safe, adverse reactions (ARs) have been reported following the use of aesthetic injectables.[26-27] The term adverse [drug] reaction is defined by the ICH Harmonized Tripartite Guidelines as "all noxious and unintended responses to a medicinal product related to any dose" where there is reasonable possibility that the reaction is related to the administered product.[32] These reactions many be mild to severe in nature but are not considered life threating events. Conversely, a serious adverse [drug] reaction is defined as "any untoward medical occurrence at any dose that results death, is life threating, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect".[32] Due to the limited nature of this body of work, we will only be discussing adverse reactions (mild to severe) in the context of aesthetic injectable products. Mild to moderate adverse reactions for aesthetic injectible products include pain and tenderness, swelling, bruising, erythema (redness), firmness, lumps and bumps or nodules, itching and skin discoloration and, are generally transient in nature. While most ARs are considered mild to moderate in nature and generally resolve on their own, some ARs are more severe and warrant medical intervention (e.g., repeated hyaluronidase injection, antibiotics, corticosteroid administration).[28-31, 33-36] These include ARs such as bacterial infection, abscess or biofilm formation, vascular occlusion, tissue necrosis, visual impairment, blindness, hypersensitivity reaction, or severe inflammatory nodule formation.[34,36-38]

Whether mild, moderate, or severe in nature, all ARs should be assessed until resolution to ensure that current and newly approved products remain safe for patients seeking minimally invasive aesthetic procedures. As the popularity of these procedures grows, it is imperative that injectors understand the potential risks and benefits associated with each product or treatment.[1]

For this reason, the overall objectives of this body of work are to: i) provide an overview of various ARs associated with aesthetic injectable, including their incidence rates and methods for their prevention, management, and treatment; and ii) introduce and implement methods of improving AR reporting. The endpoints related to meeting our first objective include conducting a systematic review of Health Canada's current AE database, and the relevant scientific literature. The endpoints related to meeting our second objective include: a) designing and developing an online registry capable of accurately capturing and collecting information related to AEs following the use of aesthetic injectables; b) confirming the scientific validity of the above-mentioned AE registry through a prospective, multi-center research study; and c) increase outreach strategies and implement the AE registry within aesthetic clinics throughout Canada.

References

1. International Society of Aesthetic Plastic Surgery (ISAPS). (2021). ISAPS international survey on aesthetic/cosmetic procedures performed in 2021. https://www.isaps.org/media/vdpdanke/isaps-global-survey_2021.pdf
2. Maisel A, Waldman A, Furlan K, et al. Self-reported Patient Motivations for Seeking Cosmetic Procedures. *JAMA Dermatol*. 2018;154(10):1167-1174. doi:10.1001/jamadermatol.2018.2357
3. Ramirez SPB, Scherz G, Smith H. Characteristics of Patients Seeking and Proceeding with Non-Surgical Facial Aesthetic Procedures. *Clin Cosmet Investig Dermatol*. 2021;14:197-207. Published 2021 Mar 1. doi:10.2147/CCID.S296970
4. Sobanko JF, Taglienti AJ, Wilson AJ, et al. Motivations for seeking minimally invasive cosmetic procedures in an academic outpatient setting. *Aesthet Surg J*. 2015;35(8):1014-1020. doi:10.1093/asj/sjv094
5. Dadkhahfar S, Gheisari M, Kalantari Y, Zahedi K, Ehsani A, Ifa E. Motivations and characteristics of patients seeking minimally invasive cosmetic procedures in two Iranian dermatology centers: A cross-sectional study. *Int J Womens Dermatol*. 2021;7(5Part B):737-742. Published 2021 Jul 18. doi:10.1016/j.ijwd.2021.07.001
6. Cotofana S, Mian A, Sykes JM, et al. An Update on the Anatomy of the Forehead Compartments. *Plast Reconstr Surg*. 2017;139(4):864e-872e. doi:10.1097/PRS.0000000000003174
7. Cotofana S, Schenck TL, Trevidic P, et al. Midface: Clinical Anatomy and Regional Approaches with Injectable Fillers. *Plast Reconstr Surg*. 2015;136(5 Suppl):219S-234S. doi:10.1097/PRS.0000000000001837

8. Swift A, Liew S, Weinkle S, Garcia JK, Silberberg MB. The Facial Aging Process From the "Inside Out". *Aesthet Surg J*. 2021;41(10):1107-1119. doi:10.1093/asj/sjaa339
9. Farage MA, Miller KW, Elsner P, Maibach HI. Characteristics of the Aging Skin. *Adv Wound Care (New Rochelle)*. 2013;2(1):5-10. doi:10.1089/wound.2011.0356
10. Cotofana S, Fratila AA, Schenck TL, Redka-Swoboda W, Zilinsky I, Pavicic T. The Anatomy of the Aging Face: A Review. *Facial Plast Surg*. 2016;32(3):253-260. doi:10.1055/s-0036-1582234
11. Freytag L, Alfertshofer MG, Frank K, et al. Understanding Facial Aging Through Facial Biomechanics: A Clinically Applicable Guide for Improved Outcomes. *Facial Plast Surg Clin North Am*. 2022;30(2):125-133. doi:10.1016/j.fsc.2022.01.001
12. Devgan L, Singh P, Durairaj K. Minimally Invasive Facial Cosmetic Procedures. *Otolaryngol Clin North Am*. 2019;52(3):443-459. doi:10.1016/j.otc.2019.02.013
13. Nestor MS, Arnold D, Fischer DL. The mechanisms of action and use of botulinum neurotoxin type A in aesthetics: Key Clinical Postulates II [published correction appears in J Cosmet Dermatol. 2021 Apr 12;:]. *J Cosmet Dermatol*. 2020;19(11):2785-2804. doi:10.1111/jocd.13702
14. Samizadeh S, De Boulle K. Botulinum neurotoxin formulations: overcoming the confusion [published correction appears in Clin Cosmet Investig Dermatol. 2018 Dec 14;11:629]. *Clin Cosmet Investig Dermatol*. 2018;11:273-287. Published 2018 May 30. doi:10.2147/CCID.S156851
15. Vleggaar D, Fitzgerald R, Lorenc ZP. Composition and mechanism of action of poly-L-lactic acid in soft tissue augmentation. *J Drugs Dermatol*. 2014;13(4 Suppl):s29-s31

16. Loghem JV, Yutskovskaya YA, Philip Werschler W. Calcium hydroxylapatite: over a decade of clinical experience. *J Clin Aesthet Dermatol*. 2015;8(1):38-49.
17. Muskat A, Pirtle M, Kost Y, McLellan BN, Shinoda K. The Role of Fat Reducing Agents on Adipocyte Death and Adipose Tissue Inflammation. *Front Endocrinol (Lausanne)*. 2022;13:841889. Published 2022 Mar 24. doi:10.3389/fendo.2022.841889
18. Walker K, Basehore BM, Goyal A, et al. Hyaluronic Acid. [Updated 2023 Mar 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482440/
19. Fagien S, Bertucci V, von Grote E, Mashburn JH. Rheologic and Physicochemical Properties Used to Differentiate Injectable Hyaluronic Acid Filler Products. *Plast Reconstr Surg*. 2019;143(4):707e-720e. doi:10.1097/PRS.0000000000005429
20. Rohrich RJ, Bartlett EL, Dayan E. Practical Approach and Safety of Hyaluronic Acid Fillers. *Plast Reconstr Surg Glob Open*. 2019;7(6):e2172. Published 2019 Jun 14. doi:10.1097/GOX.0000000000002172
21. Sundaram H, Cassuto D. Biophysical characteristics of hyaluronic acid soft-tissue fillers and their relevance to aesthetic applications [published correction appears in Plast Reconstr Surg. 2013 Nov;132(5):1378]. *Plast Reconstr Surg*. 2013;132(4 Suppl 2):5S-21S. doi:10.1097/PRS.0b013e31829d1d40
22. Heitmiller K, Ring C, Saedi N. Rheologic properties of soft tissue fillers and implications for clinical use. *J Cosmet Dermatol*. 2021;20(1):28-34. doi:10.1111/jocd.13487
23. Scaglione F. Conversion Ratio between Botox®, Dysport®, and Xeomin® in Clinical Practice. *Toxins (Basel)*. 2016;8(3):65. Published 2016 Mar 4. doi:10.3390/toxins8030065

24. Nikolis A, Enright KM, Lazarova D, Sampalis J. The Role of Clinical Examination in Midface Volume Correction Using Hyaluronic Acid Fillers: Should Patients Be Stratified by Skin Thickness?. *Aesthet Surg J Open Forum*. 2020;2(1):ojaa005. Published 2020 Feb 6. doi:10.1093/asjof/ojaa005

25. Akinbiyi T, Othman S, Familusi O, Calvert C, Card EB, Percec I. Better Results in Facial Rejuvenation with Fillers. *Plast Reconstr Surg Glob Open*. 2020;8(10):e2763. Published 2020 Oct 15. doi:10.1097/GOX.0000000000002763

26. Povolotskiy R, Oleck NC, Hatzis CM, Paskhover B. Adverse events associated with aesthetic dermal fillers: A 10-year retrospective study of FDA Data. *The American Journal of Cosmetic Surgery*. 2018;35(3):143-151. doi:10.1177/0748806818757123

27. Cohen JL, Hicks J, Nogueira A, Lane V, Andriopoulos B. Postmarket Safety Surveillance of Delayed Complications for Recent FDA-Approved Hyaluronic Acid Dermal Fillers. *Dermatol Surg*. 2022;48(2):220-224. doi:10.1097/DSS.0000000000003350

28. Van Dyke S, Hays GP, Caglia AE, Caglia M. Severe Acute Local Reactions to a Hyaluronic Acid-derived Dermal Filler. *J Clin Aesthet Dermatol*. 2010;3(5):32-35.

29. Funt D, Pavicic T. Dermal fillers in aesthetics: an overview of adverse events and treatment approaches. *Clin Cosmet Investig Dermatol*. 2013;6:295-316. Published 2013 Dec 12. doi:10.2147/CCID.S50546

30. Ahsanuddin S, Roy S, Nasser W, Povolotskiy R, Paskhover B. Adverse Events Associated With Botox as Reported in a Food and Drug Administration Database. *Aesthetic Plast Surg*. 2021;45(3):1201-1209. doi:10.1007/s00266-020-02027-z

31. Urdiales-Gálvez F, Delgado NE, Figueiredo V, et al. Treatment of Soft Tissue Filler Complications: Expert Consensus Recommendations. *Aesthetic Plast Surg*. 2018;42(2):498-510. doi:10.1007/s00266-017-1063-0

32. International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). (1994). ICH harmonized tripartite guideline – Clinical safety data management: definitions and standards for expedited reporting E2A. https://database.ich.org/sites/default/files/E2A_Guideline.pdf

33. Colon J, Mirkin S, Hardigan P, Elias MJ, Jacobs RJ. Adverse Events Reported From Hyaluronic Acid Dermal Filler Injections to the Facial Region: A Systematic Review and Meta-Analysis [published correction appears in Cureus. 2023 Jun 30;15(6):c125]. *Cureus*. 2023;15(4):e38286. Published 2023 Apr 29. doi:10.7759/cureus.38286

34. Witmanowski H, Błochowiak K. The whole truth about botulinum toxin - a review. *Postepy Dermatol Alergol*. 2020;37(6):853-861. doi:10.5114/ada.2019.82795

35. Lafaille P, Benedetto A. Fillers: contraindications, side effects and precautions. *J Cutan Aesthet Surg*. 2010;3(1):16-19. doi:10.4103/0974-2077.63222

36. Sorensen EP, Urman C. Cosmetic complications: rare and serious events following botulinum toxin and soft tissue filler administration. *J Drugs Dermatol*. 2015;14(5):486-491.

37. DeLorenzi C. New High Dose Pulsed Hyaluronidase Protocol for Hyaluronic Acid Filler Vascular Adverse Events. *Aesthet Surg J*. 2017;37(7):814-825. doi:10.1093/asj/sjw251

38. Haneke E. Managing Complications of Fillers: Rare and Not-So-Rare. *J Cutan Aesthet Surg*. 2015;8(4):198-210. doi:10.4103/0974-2077.172191

Chapter 2:

Adverse reactions associated with the esthetic use of soft tissue fillers and neurotoxins: a 53-year retrospective analysis of MedEffect™, Health Canada's reporting database

Authors: Kaitlyn M. Enright[a,b,c,] John Sampalis[d,e,f] and Andreas Nikolis[b,c,g]

Affiliations: [a]Department of Experimental Surgery, McGill University, Montreal, Canada; [b]Erevna Innovations Inc, Research Unit, Montreal, Canada; [c]Victoria Park Medispa, Montreal, Canada; [d]Department of Surgery and Medicine, McGill University and University of Montreal, Montreal, Canada; [e]Division of Surgical Research, Head Surgical Epidemiology, McGill University, Montreal, Canada; [f]JSS Medical Research, Montreal, Canada; [g]Centre Hospitalier de l'Universite de Montreal, Montreal, Canada

Note: Published in the Journal of Dermatological Treatment 2021, Vol. 32, No. 5, 538-543.
https://doi.org/10.1080/09546634.2019.1682501

Abstract

Introduction: This is the first study to evaluate Health Canada's national reporting database, MedEffect™, to assess the safety and efficacy of esthetic injectables.

Objective: Describe adverse reactions (ARs) associated with soft tissue fillers and neurotoxins.

Methods: Investigators reviewed MedEffect™ for reports associated with esthetic injectables from January 1, 1965, to March 31, 2018. Descriptive analyses of the reports were completed, including information on reporters', patients', and AR characteristics.

Results: A total of 1459 individual reports containing 5714 ARs were evaluated. The majority (n = 5705; 99.84%) of reported ARs were related to neurotoxins and only 0.16% (n = 9) were related to soft tissue fillers. Most reports were submitted by health professionals (n = 4930; 86%), indicated that the product was ineffective (n = 2428; 42.5%) and that the result of ARs were unknown (n= 4835; 84.6%).

Conclusions: ARs associated with the use of neurotoxins and soft tissue fillers are underreported in Canada. More complete and representative information regarding ARs is necessary for the development and validation of treatment algorithms and management strategies.

Introduction

Esthetic injections using products such as soft tissue fillers and neurotoxins represent one of the most common non-surgical procedures performed by cosmetic physicians. For example, the American Society of Esthetic Plastic Surgery (ASAPS) reports that 9.1 million treatments using esthetic injectables occurred in the United States (US) in 2015 (1). The use of these products is commonly indicated for the restoration of volume loss or the correction of folds and wrinkles. The safety and efficacy of soft tissue fillers and neurotoxins have been investigated in numerous clinical trials and are generally considered low-risk. However, several adverse reactions (ARs) have been attributed to these products. Examples include ARs related to the injection technique (e.g. bruising, swelling redness), delayed onset complications (e.g. infections, scarring, nodule formation), and more serious and persistent ARs (e.g. blindness, skin necrosis) (2–11).

Most recently, a review of the available US Food and Drug Administration data on adverse events related to soft tissue fillers has been completed (6). However, to the authors' knowledge, similar data within a Canadian population has yet to be evaluated. Such an analysis is valuable as this information could contribute to the development and validation of treatment algorithms and management strategies (12–14). Therefore, the objective of the current review was to describe ARs associated with soft tissue fillers and neurotoxins, as reported in a governing body's primary database.

Methods

The database

The investigators reviewed MedEffect™, Canada's online AR database (15). MedEffect™ is a publicly available database that contains information from the Canada

Vigilance Program, which is a post-market surveillance program that collects information relating to suspected ARs to health products. Such products include prescription medications, biologics, natural health products, radiopharmaceuticals, and medical devices. As the database is publicly available, voluntary reports of ARs can be submitted from multiple sources, including manufacturers, distributors, physicians, and patients. Only reports from market authorization holders are mandatory. Submitted reports are reviewed by Health Canada representatives, who code the ARs according to the clinically validated medical dictionary MedDRA version 21.0 (16). This coding ensures the standardized reporting throughout various sources (e.g. international languages). Reports include an array of information, including variables relating to patient characteristics (e.g. weight, height, gender), the reporter (e.g. manufacturer, distributor, physician, patient), the AR (e.g. MedDRA code, seriousness, duration, outcome), and the suspected health product.

As MedEffect™ is a publicly available database and does not include personal identifiers, the present retrospective review did not require approval from an institutional review board. This is in accordance with TCPS Article 2.2:

> "Research that relies exclusively on publicly available information does not require REB review when: (a) the information is legally accessible to the public and appropriately protected by law; or (b) the information is publicly accessible and there is no reasonable expectation of privacy."

Eligibility criteria

All reports submitted to MedEffect™ from its inception to the last available date at the beginning of data collection were evaluated. This resulted in a reporting period from January 1, 1965, to March 31, 2018 (53.79 years). The field prompts used to search the database are

presented in Table 1 and keywords used to search the database are presented in Table 2. Selected keywords were chosen based on: (i) a review of the relevant literature (e.g. consensus documents, manuscripts discussing management strategies, key reports describing the characteristics, and rates of ARs); (ii) brand and generic names of approved products in Canada, including their primary ingredients; and (iii) keywords drawn from the US National Library of Medicine's collection of Medical Subject Headings (MeSH). The tool 'MeSH on Demand' was used to select descriptors as key words for articles. This tool can automatically identify relevant MeSH terms from text such as abstracts or manuscripts. A senior plastic surgeon (AN) was consulted to resolve any discrepancies in keyword selection.

Only reports associated with the esthetic use of medical devices were included in the present analyses. Health products used for therapeutic indications were excluded, as previous reports have revealed that adverse events related to therapeutic treatments are 33-fold higher than those associated with esthetic procedures (5). This may be due to factors such as the use of different injection techniques, including larger product boluses, more injection sites, and more frequent treatments. Examples of therapeutic indications (excluded reports) included: pain, musculoskeletal stiffness, hyperhidrosis, muscle spasticity, rheumatoid arthritis, torticollis, Parkinson's disease, urinary incontinence, headache, hypertonia, blepharospasm, salivary hypersecretion, camptocormia, cerebral palsy, hypertonic bladder, anal fissure, and others. Included reports specified either skin wrinkles or a skin cosmetic procedure as an indication. Reports where the indication field was left blank, or the indication was marked as unknown were also excluded. Only injectable soft tissue fillers and neurotoxin products specified as being the suspected cause of the ARs were included. Reports where the role of such products was indicated

as concomitant were excluded, as the reporter's assessment of causality indicated that they were likely unrelated to the AR.

Statistical analyses

The investigators reviewed MedEffect™ to identify reports meeting eligibility criteria. All replicate events were consolidated into single events, then descriptive analyses of the resulting reports were performed. Reports were evaluated for reporter type, patient demographics, AR type, seriousness, outcome, and product description. The means and standard deviations (SD) were displayed for continuous, normally distributed variables; means and interquartile ranges (IQR) were presented for non-normally distributed variables; and frequencies were reported for categorical variables. The trend of reported ARs over time was displayed in a line graph along with their annual frequencies. All analyses were performed using Statistical Package for the Social Sciences (SPSS), Version 20.0 (Chicago, IL).

Results

At the time of these analyses (October 2018), MedEffect™ contained a total of 618,048 AR reports. As reports could have included multiple ARs, this resulted in a total of 1,048,576 ARs. Of these, a shortlist of 5626 reports and 88,171 ARs contained one or more keywords identified in Table 2. After consolidating replicate cases and applying the eligibility criteria, there were 1459 individual reports containing 5714 ARs remaining in the sample to be evaluated. The frequencies evaluated in our final sample accounted for 0.24% of all reports and 0.54% of all ARs in the population. The majority (i.e. 69.3%) of reports contained $\leq$ 2 ARs.

Report characteristics

The characteristics of AR reports relating to injectable soft tissue fillers and neurotoxin treatments are presented in Table 3.

Product description

Overall, 99.84% (n¼5705) of reported ARs were related to neurotoxins and only 0.16% (n¼9) were related to soft tissue fillers. All nine ARs were disclosed within a single report, while the ARs relating to neurotoxins were reported within 1458 individual reports. The key ingredients of suspected health products included botulinum toxins and hyaluronic acid. There were no reports associated with calcium hydroxylapatite, collagen, poly-Llactic or polymethylmethacrylate fillers.

Reporter type

Of all ARs, 2855 (49.6%) were reported by 'other' health professionals, 2067 (36.2%) by physicians, 805 (14.1%) by consumers or non-health professionals, and eight (0.1%) by pharmacists.

Patient demographics

Information on the patient's age was available for 4289 (75%) of ARs. An analysis of the available data revealed that patients had a mean age of 44.39 years (SD: 9.48). Information on the patient's weight was available for 255 (4.5%) of ARs. An analysis of the available data revealed that patients had a mean weight of 80 kg (176.37 lbs; 95% CI: 76.30–84.64 kg; IQR: 56 kg). Information on the patient's height was available for 152 (2.7%) of ARs. An analysis of the available data revealed that patients had a mean height of 168.27 cm (505 ft; 95% CI: 167.55–168.99 cm; IQR: 3.18 cm). Of patients experiencing ARs, 4900 (85.8%) were female and 360 (6.3%) were male. For 454 (7.9%) ARs, the sex of the patient was unknown or not specified.

ARs

In total, there were 280 different AR types reported. The three most common ARs related to drug effectiveness (n = 2428; 42.5%); off label use of a product (n = 918; 16.1%); and

therapeutic response decrease (n = 478; 8.4%). The MedDRA System Organ Class types for all reported ARs are presented in Table 4. The most common MedDRA System Organ Class types included general disorders and administration site conditions (n = 3227; 56.5%), and injury, poisoning, and procedural complications (n = 1687; 29.5%). A total of 683 (12%) ARs were considered serious. The outcome for the majority (n = 4835; 84.6%) of ARs were unknown, 599 (10.5%) did not recover/resolve, 241 (4.2%) recovered/resolved, and 39 (0.7%) were recovering/resolving at the time of report submission.

Reporting trends over time

The first AR associated with a neurotoxin was reported in 2005 and the first AR associated with a soft tissue filler was reported in 2014. As shown in Figure 1, the proportion of reported ARs increased over time, with a sharp increase in 2015.

Discussion

This study represents the first analyses of a post-market surveillance system for ARs associated with soft tissue fillers and neurotoxins, using a Canadian database. MedEffect^{TM} is one of the only large Canadian data sources available to manufacturers and distributors, health care providers, and consumers for reported ARs associated with medical devices (15). However, passive surveillance systems have been associated with underreporting (6,10). Contributing factors to the underreporting of ARs have been stipulated to include that health care providers and consumers are simply unaware of the existence of such a database, medical facilities, and individuals may not have time to submit reports, or users may only think serious ARs should be reported (10).

In order to estimate approximately how underreported the Canadian data are, we can look at the available data from the US, as unfortunately there are no official plastic surgery statistics

available in Canada. Nonetheless, comparable statistics are available from the ASAPS, who report that in 2015 there were 6.7 million treatments using botulinum toxins and 2.4 million treatments using soft tissue fillers (1). Since the Canadian population is approximately 1/10th of that of the US, it can be approximated that 670,000 botulinum toxin and 240,000 soft tissue filler treatments occur in Canada each year (17–20). While it remains possible that confounding factors (e.g. demographics of patients, training of health care professionals, physician density) vary between the two countries and as a result, that actual statistics remains a reasonable method of estimating the use of cosmetic injectables in Canada. For example, support for its accuracy comes from other industries where the 1/10 ratio is true, such as annual hospital admission rates (3 million versus 30 million), automotive sales (1,870,703 versus 17,274,250), and cigarette smoking (4 million versus 40 million). Therefore, in the absence of any official plastic surgery statistics in Canada, we base our estimates off of the US, plastic surgery statistics (21–26). Furthermore, it has been described that in the US, 1/3600 treatments result in a reportable AR (6). Therefore, it is estimated that roughly 67 AR reports should have been submitted in Canada each year, resulting in a total of 3551 reports relating to soft tissue fillers that should have been submitted to the database over the last 53 years. Notwithstanding, given that advances in esthetic injectables can be mostly attributed to the last 30 years, this data should be rightly skewed and not evenly distributed over each year (27,28).

Further support that ARs are being underreported comes from the finding that data submitted to various sources are not consistent. For example, Health Canada publishes a monthly e-notice, one of which indicated that they have received a total of 16 adverse incident reports describing ARs with dermal filler injections as of June 2016 (8). However, these reports were not available in the public database and as such, could not be evaluated in the present analyses. As a

consequence, the comparability of their contents to those of the reports in the public database are difficult to evaluate, as they are only available upon submitting an 'Access to Information' request to Health Canada; the results of which can take up to a year to receive. Therefore, the validity of the 16 adverse incident reports has not been ascertained.

A surprising finding of this evaluation was that only a single report relating to soft tissue fillers has been submitted to MedEffect^{TM} in the previous >53 years. This reflects an overly favorable safety profile for soft tissue fillers and if misinterpreted, can lead to unreasonable conclusions regarding the safety and efficacy of approved products in Canada (29–31). While ARs using these products are known to be rare events, the frequency reported in MedEffect^{TM} is clearly an inaccurate representation of incidence rates.

The reporting of ARs relating to neurotoxins are more common in the Canadian database than those for soft tissue fillers. However, given the relative rates reported in the USA, it is suspected that they are still being underreported (9). Moreover, the finding that there were no reports associated with calcium hydroxylapatite, collagen, poly-L-lactic or polymethylmethacrylate fillers is inconsistent with previous literature that has described increased rates of ARs associated with fillers other than hyaluronic acid products (31,32).

While the majority of reports included only incomplete information on patient demographics, the available data revealed that patient profiles were consistent with those typically seen in private clinical practice. For example, the gender ratios and the mean age of patients were consistent with those typically seeking esthetic treatments (1). For this reason, while there was a higher prevalence of women experiencing ARs than men, this is thought to be reflective of the greater proportion of women seeking these treatments and is likely not reflective of sex-related differences that would make women more susceptible to ARs.

Limitations

Given the passive nature of this surveillance system, an evaluation of MedEffect™ cannot be used to determine valid national incidence rates. This limits the findings of the current study. Also, reporting from nonprofessionals may have resulted in erroneous reports. It is also important to note that the utility of a voluntary reporting system relies on the temporal relationship with exposure to the medical device under consideration (5).

Conclusions

Underreporting of ARs in Canada cannot be used in a systematic manner to detect and address safety concerns about medical devices. For this reason, several recommendations to government and industry regarding reporting guidelines require suggesting. For example, in order to improve AR reporting in Canada, Health Canada could: (a) develop a protocol for documenting follow up on ARs, for example, they could consider developing a tracking system to follow the outcome of reports submitted to MedEffect™; (b) ensure and document that manufacturers and distributors are meeting their mandatory reporting guidelines for submitting AR reports within a timely manner, including follow up with those who have submitted late or incomplete reports; and (c) enhance outreach strategies to reduce underreporting by health care professionals and consumers, which may prove to be the most effective strategy for increasing reporting. Overall, more accurate reporting is necessary to better understand ARs and develop prevention and management strategies.

Data availability

The dataset analyzed during the current study is available at: https://www.canada.ca/en/health-canada/services/drugs-healthproducts/medeffect-canada/adverse-reaction-database.html.

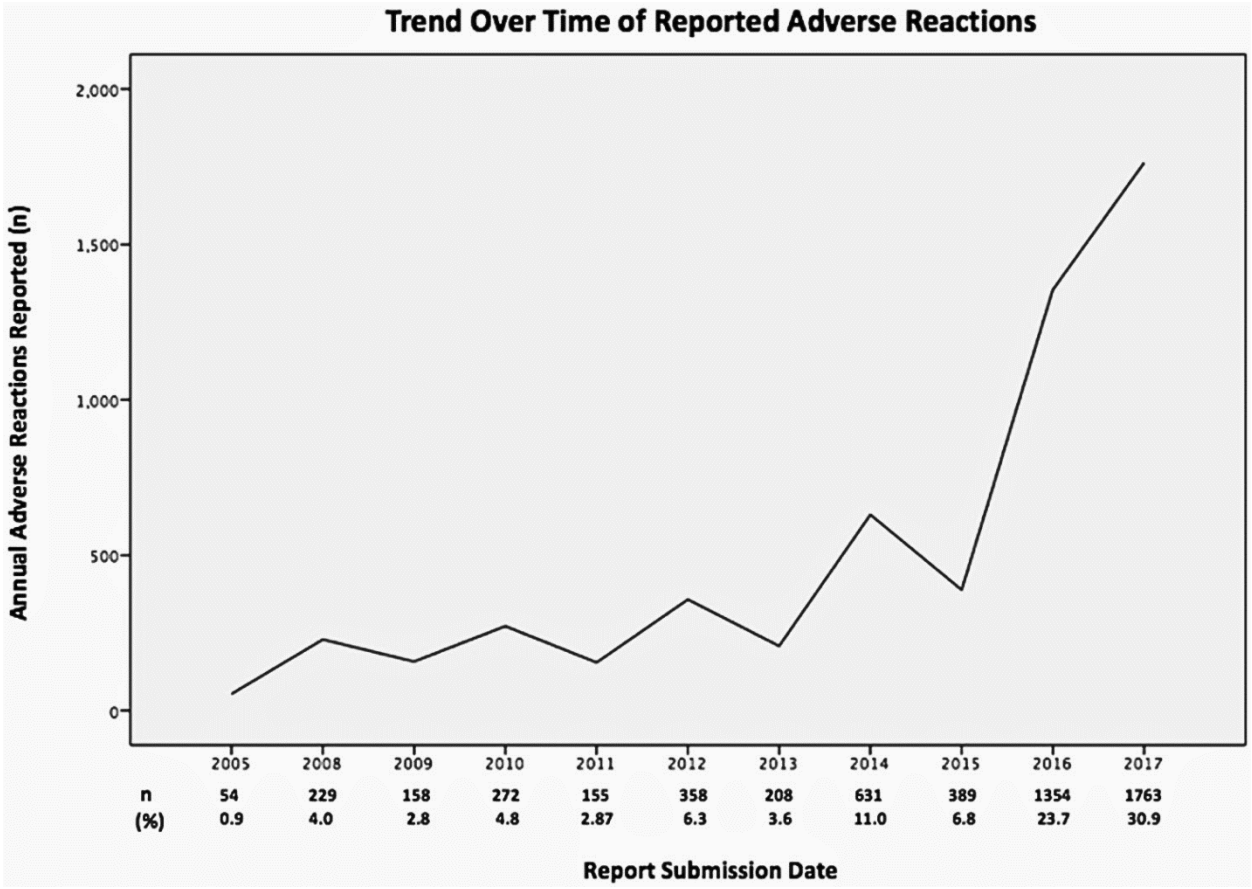


Figure 1. Trend over time of annual ARs related to soft tissue fillers and neurotoxins, as reported in MedEffect™ from 1965 to 2017. Completed annual data for 2018 were not available at time of data collection and are therefore not presented in this figure. AR: adverse reaction.

Table 1. Search criteria used for evaluating the MedEffect^{TM} adverse reaction database.

Section	Field question and response
1. Report search criteria	Initial received date from: 1965-01-01 to 2018-03-31
	Serious report? Select both
	Source of report? Select all
2. Patient search criteria	Gender? Select all
	Report outcome? Select all
	Age? From 0 years to all years
3. Suspect health product search criteria	Select: By brand name (or as applicable) by active ingredient
	Operator: Contains keyword search
Adverse reaction term search criteria	Select: All adverse reaction terms

Table 2. Keywords used to search reports in MedEffect™.

Keyword
Allergana
Aventis
Beloterob Botoxc
Botulinumd
Calcium hydroxylapatite
Collagen
Croma
Dermick
Dysporte
Emervelf
Galderma
Hyaluronic Acid
Juvedermg Merz
Poly-L-lactic
Polymethylmethacrylate
Princess
Radiesse
Restylanei
Sculptra
Xeominj

Table 3. Reporter, patient, and AR characteristics for reports associated with soft tissue fillers and neurotoxin injectable treatments, as reported in MedEffect™.

			ARs associated with injectable esthetic treatments, N¼5714 (%)
Reporter and patient characteristics	Reporter		
		Consumer or non-HCP	805 (14.1)
		Other HCP	2855 (49.6%)
		Physicians	2067 (36.2)
		Manufacturer or distributor	0
		Pharmacists	8 (0.1)
	Patient age	44.39 (SD: 9.48)	
	Patient sex		
		Female	4900 (85.8)
		Male	360 (6.3)
		Unknown	454 (7.9)
	Patient height		168.27cm (mean)
	Patient weight		80kg (mean)
AR characteristics	Serious AR		
		Yes	683 (12)
		Recovered/resolved	241 (4.2)

	Outcome	Recovering/resolving	39 (0.7)
		Recovered/resolved with sequelae	0
		Not recovered/not resolved	599 (10.5)
		Death	0
		Unknown	4835 (84.6)
	Suspected health product		
		Neurotoxin	5705 (99.84)
		Soft tissue filler	9 (0.16)

Table 4. The MedDRA System Organ Class types and frequencies associated with soft tissue fillers and neurotoxins.

MedDRA System Organ Class	**Frequency (n)**	**Percent (%)**
Blood and lymphatic system disorders	1	0
Cardiac disorders	19	0.3
Ear and labyrinth disorders	13	0.2
Eye disorders	131	2.3
Gastrointestinal disorders	82	1.4
General disorders and administration site conditions	3227	56.5
Hepatobiliary disorders	4	0.1
Immune system disorders	8	0.1
Infections and infestations	29	0.5
Injury, poisoning, and procedural complications	1687	29.5
Investigations	23	0.4
Metabolism and nutrition disorders	9	0.2
Musculoskeletal and connective tissue disorders	41	0.7
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1	0
Nervous system disorders	127	2.2
Product issues	113	2
Psychiatric disorders	36	0.6
Renal and urinary disorders	6	0.1

Reproductive system and breast disorders	3	0.1
Respiratory, thoracic, and mediastinal disorders	36	0.6
Skin and subcutaneous tissue disorders	107	1.9
Social circumstances	1	0
Vascular disorders	10	0.2

References

1. American Society of Aesthetic Plastic Surgery (ASAPS). Annual Statistics, 2015. [cited 2018 Oct 8]. Available at: https://www.plasticsurgery.org/documents/News/Statistics/2015/plastic-surgery-statistics-full-report-2015.pdf
2. Alijotas-Reig J, Fernandez-Figueras M, Puig L. Inflammatory, immune-mediated adverse reactions related to soft tissue dermal fillers. Semin Arthritis Rheum. 2013;43(2):241–258.
3. Alijotas-Reig J, Fernandez-Figueras MT, Puig L. Late-onset inflammatory adverse reactions related to soft tissue filler injections. Clinic Rev Allerg Immunol. 2013;45(1):97–108.
4. Bachmann F, Erdmann R, Hartmann V, et al. Adverse reactions caused by consecutive injections of different fillers in the same facial region: risk assessment based on the results from the injectable filler safety study. J Eur Acad Dermatol. 2011;25(8):902–912.
5. Batra R, Dover J, Arndt K. Adverse event reporting for botulinum toxin type A. J Am Acad Dermatol. 2005;53(6):1080–1082.
6. Chandawarkar AA, Provenzano DJ, Rad AN, et al. Learning curves: historical trends of FDA-reported adverse events for dermal fillers. Cutis. 2018;102(2):E20–E23.
7. Dayan S, Arkins J, Brindise R. Soft tissue fillers and biofilms. Facial Plast Surg. 2011;27(01):023–028.
8. Daines S, Williams E. Complications associated with injectable soft-tissue fillers: a 5-year retrospective review. Jama Facial Plast Surg. 2013;15(3):226–231.
9. Kazerooni R, Armstrong E. Botulinum toxin type A overdoses: analysis of the FDA adverse event reporting system database. Clin Drug Investig. 2018;38(9):867–872.
10. Povolotskiy R, Oleck N, Hatzis C, et al. Adverse events associated with aesthetic dermal fillers: a 10-year retrospective study of FDA data. Am J Cosmet Surg. 2018;35(3):143–151.

11. Zielke H, W€oLber L, Wiest L, et al. Risk profiles of different injectable fillers: results from the injectable filler safety study (IFS study). Dermatol Surg. 2018;34(3):326–335.
12. Emer J, Waldorf H. Injectable neurotoxins and fillers: there is no free lunch. Clin Dermatol. 2011;29(6):678–690.
13. Signorini M, Liew S, Sundaram H. Global aesthetics consensus: avoidance and management of complications from hyaluronic acid fillers-evidence- and opinion-based review and consensus recommendations. Plast Reconstr Surg. 2016;137(6):961–137.
14. Sperling B, Bachmann F, Hartmann V, et al. The current state of treatment of adverse reactions to injectable fillers. Dermatol Surg. 2010;36(Suppl 3):1895–1904.
15. Health Canada. 2011. Guidance document for industry: reporting adverse reactions to marketed health products. [cited 2018 Oct 8]. Available at http://epe.lac-bac.gc.ca/100/200/301/hcan-scan/guidance_doc_industry_reporting-ef/H164-33-2011-eng.pdf
16. Castillon G, Salvo F, Moride Y. The social impact of suspected adverse drug reactions: an analysis of the Canada vigilance spontaneous reporting database. Drug Safe. 2018;42(1):27–34.
17. Statistics Canada. Population estimates, quarterly. [cited 2018 Oct 15]. Available at https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000901
18. United States Census Bureau. National Population Totals and Components. [cited 2018 Oct 15]. Available at https://www.census.gov/data/datasets/2017/demo/popest/nationtotal.html
19. Kontis T, Rivkin A. The history of injectable facial fillers. Facial Plast Surg. 2009;25(02):067–072.
20. Narins RS, Mariwalla KB. History of fillers. Aesthet Dermatol. 2018;4:1–9.

21. Inpatient Hospitalization, Surgery, Newborn, Alternate Level of Care and Childbirth Statistics, 2017–2018. 2019. Available at https://www.cihi.ca/sites/default/files/document/dad-hmdbchildbirth-quick-stats-2017-2018-snapshot-en-web.pdf
22. Fast Facts on US Hospitals, 2019. 2019. Available at https://www.aha.org/statistics/fast-facts-us-hospitals
23. Canada-Flash report, Sales volume, 2018. 2019. Available at https://www.marklines.com/en/statistics/flash_sales/salesfig_canada_2018
24. USA-Flash report, Sales volume, 2018. 2019. Available at https://www.marklines.com/en/statistics/flash_sales/salesfig_usa_2018
25. Canadian Tobacco, Alcohol and Drugs Survey (CTADS): summary of results for 2017. 2019. Available at https://www.canada.ca/en/healthcanada/services/canadian-tobacco-alcohol-drugs-survey/2017-summary.html
26. Current Cigarette Smoking Among Adults in the United States. 2019. Available at https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm
27. Health Canada. Health Product InfoWatch – August 2016. [cited 2018 Sep 31]. Available at https://www.canada.ca/en/health-canada/services/drugs-health-products/MedEffectTMcanada/health-product-infowatch/health-product-infowatchaugust-2016.html
28. Narins RS, Jewell M, Rubin M, et al. Clinical conference: management of rare events following dermal fillers–focal necrosis and angry red bumps. Dermatol Surg. 2006;32(3):426–434.

29. Chiang YZ, Pierone G, Al-Niaimi F. Dermal fillers: pathophysiology, prevention and treatment of complications. J Eur Acad Dermatol Venereol. 2017;31(3):405–413.
30. Requena L, Requena C, Christensen L, et al. Adverse reactions to injectable soft tissue fillers. J Am Acad Dermatol. 2011;64(1):1–34.
31. Lemperle G, Gauthier-Hazan N, Wolters M, et al. Foreign body granulomas after all injectble dermal fillers: Part 1 –Possible causes. Plast Reconstr Surg. 2009;123(6):1842–1863.
32. Schlessinger J, Schlessinger D, Schlessinger B. Prospective demographic study of cosmetic surgery patients. J Clin Aesthet Dermatol. 2010;3(11):30–35.

Chapter 3: Methods of improving safety

As highlighted in the previous chapter, ARs associated with aesthetic injectables are significantly underreported.[1] This may be a result of multiple factors, including but not limited to, uncertainty of when reporting should be made (e.g., reporting only serious ARs versus ARs of all severities), or confusion regarding the responsibility of various sources of reporting (e.g., large institutions, medical spas, private clinics, consumers).[1-2] When evaluating the distribution of ARs reported to MedEffect™, there are significantly more reports associated with neurotoxins than soft tissue fillers. This apparent underreporting of ARs associated with soft tissue fillers can possibly be attributed to an overly presumed safety profile compared to neurotoxins such as Botox (BTX). While BTX is an agent that alters the normal and natural function of the nervous system through its action on ion channels leading to muscle weaking/paralysis, the mechanism of action of soft tissue fillers such as HA does not rely on impacting normal body systems. Thus, injectors may assume an increased safety profile of soft tissue fillers compared to neurotoxins[3-5].

With a growing number of products used for minimally invasive aesthetic procedures, and a large appeal of soft tissue fillers, it is especially important to understand the rheologic properties of each product and how the product itself, the injector and/or external factors may contribute to ARs. In the past, reporting of ARs has largely relied on passive, voluntary reporting. This is due, in part, to the fact that all currently approved products for sale and use have undergone significant and rigorous efficacy and safety testing (e.g., by Health Canada, the United States Food and Drug Administration, and/or the European Medicines Agency). However, product safety should not be determined by the results of these preliminary studies alone. Although clinical trials have investigated the safety an efficacy of many injectable products, its study designs are confounded by a typically short duration of follow-up and small sample sizes

that may preclude the identification of more serious or long term ARs.[6] Instead, active AR reporting could ensure the continued monitoring of the safety profile of injectable products across multiple patient, treatment, product, and extrinsic factors (e.g., bacterial or viral infection, medication including drugs and vaccines).[7] Active reporting may take many forms (e.g., providing patients with a short AR-related questionnaire at follow up visits, or encouraging patients to report ARs on their own, through government websites such as MedEffect™), but one method to ensure timely reporting in clinical settings could be with online applications or easily accessible, global or national databases.

Another element to consider when discussing ARs is the impact of certain patient factors that may be contributing to such events. When conducting clinical trials, the implementation of strict inclusion and exclusion criteria improves safety but narrows the population of under evaluation. Therefore, relationships between ARs and certain patient factors (medical/surgical history, concomitant medication, skin quality, concurrent aesthetic procedures) may not become apparent until explored in the general population. As the population of individuals seeking procedures using injectable products grows, a broader assessment of patient factors contributing to outcome and ARs should be explored. This would ensure safety across a wide range of individuals from varied populations. However to date, investigating patient factors has been underexplored. Yet, some early investigations by our research team have evaluated such factors. For example, we evaluated the beneficial effect of improving clinical outcomes by selection products based on patient factors such as skin thickness.[10]

Despite the fact that there have been considerable recommendations proposed for the use of soft tissue fillers, a systemic review of all recommendations must be undertaken to establish

evidenced-based universal models in which ARs related to injectable procedures are prevented, managed, and treated.[11-13]

References

1. Enright KM, Sampalis J, Nikolis A. Adverse reactions associated with the esthetic use of soft tissue fillers and neurotoxins: a 53-year retrospective analysis of MedEffect™, Health Canada's reporting database. *J Dermatolog Treat*. 2021;32(5):538-543. doi:10.1080/09546634.2019.1682501
2. Povolotskiy R, Oleck NC, Hatzis CM, Paskhover B. Adverse events associated with aesthetic dermal fillers: A 10-year retrospective study of FDA Data. *The American Journal of Cosmetic Surgery*. 2018;35(3):143-151. doi:10.1177/0748806818757123
3. Sundaram H, Liew S, Signorini M, et al. Global Aesthetics Consensus: Hyaluronic Acid Fillers and Botulinum Toxin Type A-Recommendations for Combined Treatment and Optimizing Outcomes in Diverse Patient Populations. *Plast Reconstr Surg*. 2016;137(5):1410-1423. doi:10.1097/PRS.0000000000002119
4. Lagueny A, Burbaud P. Mécanisme d'action, indication et résultats des traitements par la toxine botulinique [Mechanism of action, clinical indication and results of treatment of botulinum toxin
5. Walker, K. (2023, March 7). *Hyaluronic acid*. StatPearls – NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK482440/
6. Singh S, Loke YK. Drug safety assessment in clinical trials: methodological challenges and opportunities. *Trials*. 2012;13:138. Published 2012 Aug 20. doi:10.1186/1745-6215-13-13
7. Bachour Y, Kadouch JA, Niessen FB. The Aetiopathogenesis of Late Inflammatory Reactions (LIRs) After Soft Tissue Filler Use: A Systematic Review of the Literature [published correction appears in Aesthetic Plast Surg. 2021 Jun 21;:]. *Aesthetic Plast Surg*. 2021;45(4):1748-1759. doi:10.1007/s00266-021-02306-3

8. King M, Walker L, Convery C, Davies E. Management of a Vascular Occlusion Associated with Cosmetic Injections. *J Clin Aesthet Dermatol*. 2020;13(1):E53-E58.
9. DeLorenzi C. New High Dose Pulsed Hyaluronidase Protocol for Hyaluronic Acid Filler Vascular Adverse Events. *Aesthet Surg J*. 2017;37(7):814-825. doi:10.1093/asj/sjw251
10. Nikolis A, Enright KM, Lazarova D, Sampalis J. The Role of Clinical Examination in Midface Volume Correction Using Hyaluronic Acid Fillers: Should Patients Be Stratified by Skin Thickness?. *Aesthet Surg J Open Forum*. 2020;2(1):ojaa005. Published 2020 Feb 6. doi:10.1093/asjof/ojaa005
11. Moon H, Fundaro SP, Goh CL, Hau KC, Paz-Lao P, Salti G. A Review on the Combined Use of Soft Tissue Filler, Suspension Threads, and Botulinum Toxin for Facial Rejuvenation. *J Cutan Aesthet Surg*. 2021;14(2):147-155. doi:10.4103/JCAS.JCAS_119_20
12. Urdiales-Gálvez F, Delgado NE, Figueiredo V, et al. Preventing the Complications Associated with the Use of Dermal Fillers in Facial Aesthetic Procedures: An Expert Group Consensus Report. *Aesthetic Plast Surg*. 2017;41(3):667-677. doi:10.1007/s00266-017-0798-y
13. Urdiales-Gálvez F, Delgado NE, Figueiredo V, et al. Treatment of Soft Tissue Filler Complications: Expert Consensus Recommendations. *Aesthetic Plast Surg*. 2018;42(2):498-510. doi:10.1007/s00266-017-1063-0

Chapter 4: A Systematic Review of Methods for the Prevention, Treatment and Management of Adverse Events Following the use of Aesthetic Soft Tissue Fillers: A Call to Action

Authors: Kaitlyn M Enright[1], John S Sampalis[2], Sebastian Cotofana[3], Mirko S Gilardino[4], Demetrios Rizis[5], Andreas Nikolis[6].

Affiliations: [1]Erevna Innovations Clinical Research Unit, Westmount, Quebec, Canada; [2]Division of Surgical Research, McGill University, Montreal, Quebec, Canada**;** [3]Department of Clinical Anatomy, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, United States**;** [4]Division of Plastic & Reconstructive Surgery, Montreal Children's Hospital, McGill University Health Center, Montreal, Quebec, Canada**;** [5]Division of Plastic and Reconstructive Surgery, Hôpital Cité de la Santé, Laval, Quebec, Canada; Hôpital Charles-Le Moyne, Longueuil, Quebec, Canada**;** [6]Erevna Innovations Clinical Research Unit, Westmount, Quebec, Canada; Division of Plastic Surgery McGill University, Montreal, Quebec, Canada.

Note: Published in the Journal of Clinical and Experimental Dermatology and Therapies 2021, Vol. 6, Issue 02:172. www.doi.org/10.29011/2575-8268.100172

Abstract

Background: Signs of facial ageing can be safely and effectively treated using hyaluronic acid (HA) injectables. Despite the relatively high safety profile of HA soft tissue fillers, adverse events (AEs) are associated with their use. Various algorithms and guidelines have been created for the prevention, treatment and management of AEs. However, different expert recommendations are founded on varying levels of evidence, which should be taken into consideration when practicing evidence-based medicine.

Aims: i) Review methods for the prevention, management and treatment of AEs following the use of soft tissue fillers for facial aesthetic indications and ii) develop models for the prevention, treatment and management of AEs, based on the assignment of evidence level as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.

Methods: A systematic search of PubMed was conducted for the selection of articles (systematic reviews, meta-analyses, expert consensus statements, and guidelines) related to AEs following the use of soft-tissue facial fillers for aesthetic indications. Nonsystematic, exploratory searches of other search engines and sources were conducted where deemed appropriate.

Results: Fifty-four articles discussing thirty-four AEs were included in the present review. GRADE models for the prevention, treatment and management of these AEs were developed and presented. The majority (> 85%) of recommendations were of lesser quality [GRADE D (very low) or C (low)], with most complication guidelines relying on expert opinion lacking direct evidence, or studies with severe limitations.

Conclusions: This review provides a comprehensive summary of the quality of evidence supporting recommendations to AE prevention, treatment and management. Further research is required for validating these AE action protocols.

Introduction

Ageing is a multifactorial, three-dimensional and dynamic process caused by internal (biological) and external (environmental) factors [1,2]. With increasing age, an interplay of changes occurs in all anatomical structures, involving the skeleton, ligaments, muscles, adipose tissue and skin [3]. Some of the facial manifestations of ageing are a result of fat displacement, bone resorption and tissue atrophy that progressively lead to volume loss [4-6]. In turn, facial volume loss is responsible for many of the indications for which patients seek out aesthetic treatments, such as wrinkles, folds (e.g. nasolabial folds) [7] and tissue augmentation (e.g. midface, lips) [8-10].

Facial volume loss can be safely and effectively treated with the use of hyaluronic acid (HA) soft tissue fillers [10-12]. The latest report from the International Society of Aesthetic Plastic Surgery estimates that the number of treatments performed using these devices increased by 11.6% between 2017 and 2018, with 3,729,833 worldwide procedures completed [13]. In 2019, over 749,409 HA-based aesthetic procedures were performed in the United States (U.S.) alone [14]. Treatments using HA fillers are currently the second most popular non-surgical aesthetic procedure performed, following the use of neuromodulators [14]. Based on product, HA dominates the global dermal filler market, accounting for 77.2% of the market share [15]. With the increasing popularity of these procedures, the development of novel products and the expansion of indications, the number of treatments are likely to continue to increase. The growing demand for safe and minimally invasive aesthetic procedures, combined with the increasing geriatric population, will also continue to drive the growth of the global market which is projected to reach over 6 billion U.S., dollars by 2027 [15,16]. Concurrent with this growth,

the incidence of adverse events (AEs) following these treatments are predicted to increase as well [1].

Various AEs related to soft tissue fillers have been reported, ranging from mild injection site complications to severe complications [17]. Most immediate-to-short term AEs tend to be related to the injection technique rather than the devices themselves and frequently consist of erythema, edema and pain. Other early-onset AEs include hypersensitivity, infections, surface irregularities, vascular occlusion and more [18]. Delayed and/or chronic AEs may include foreign body granulomas or biofilms, among other complications [18,19].

Familiarity with the AEs possibly associated with HA fillers and guidance to their prevention, treatment and management are imperative to ensuring patient outcomes [15]. AEs can occur due to a variety of contributing factors, such as patient characteristics (e.g. concomitant conditions and/or medications), injection technique (e.g., needle versus cannula), injector's level of knowledge of anatomy and the biophysical properties of the injectate [19,20]. For example, the degree of crosslinking, gel calibration (particle sizing) and concentration of HA of different products affect therapeutic results [1,20,21]. Hence, achieving optimal outcomes with HA relies on an understanding of these concepts and approaches to AE prevention, treatment and management [1].

Many authors have proposed algorithms and/or created guidelines for the prevention, treatment (addresses the causative agent) and management (addresses the symptoms) of AEs related to HA soft tissue fillers [1,19,20]. However, different recommendations may be based on varying levels of evidence. Therefore, the purpose of this systematic review is to perform an evaluation of currently proposed methods for the prevention, treatment and management of AEs related to the use of HA soft tissue fillers for aesthetic indications, and to develop evidencebased

models established on the level of support for each recommendation. These schematics may be used by providers of aesthetic injectable treatments when practicing evidence-based medicine founded on some of the strongest knowledge currently available.

Materials and Methods

The following methods were created in consultation with the Preferred Reporting Items for Systematic Review and Meta- Analysis Protocols-2015 (PRISMA-P) checklist and patient, intervention, comparison, outcome (PICO) items [22,23]. The PICO framework was used to develop the search terms, which were also informed by relevant Medical Subject Headings (MeSH) [24]. As per the Cochrane Handbook suggestion, we altered the PICO model to P, I, S/T (i.e., study type or types of study) and O [25]. PubMed was searched using the following terms: (((hyaluronic acid) AND ((facial) OR (aesthetic)) AND ((safety) OR (adverse event) OR (complication) OR (side effect))). Systematic reviews, literature reviews, meta-analyses, expert consensus statements and guidelines related to AEs following the use of soft tissue facial fillers were selected. Broad and general search terms were chosen as there are relatively fewer publications of the aforementioned categories than individual studies. Inclusion criteria consisted of English language publications; free full-text availability; relating to products approved for use by the Food and Drug Administration and/or Health Canada; use for aesthetic indications, in healthy adults (i.e. above the age of 18 years); and a publication date in the preceding ten years (i.e. from January 2010 and May 2020), prior to the search date.

Exclusion criteria included articles on the topic of biostimulators (e.g. poly-L-lactic acid, calcium hydroxylpatite), neuromodulators (e.g. onabotulinumtoxinA, incobotulinumtoxinA, abobotulinumtoxinA) or treatments to anatomical areas outside of facial regions (e.g. neck, décolletage, body, hands); use for medical indications (e.g. lagophthalmos, eyelid malpositions,

orbital volume deficiency; post-traumatic facial disfigurement); use in immune-compromised individuals (e.g. human immunodeficiency virus-associated lipodystrophy); animal studies; and the following study designs: clinical trials, case report/series, cross-sectional analyses and registries. As the final step in the selection process, the systematic search was supplemented with non-systematic scoping methods for the inclusion of additional key references.

Two reviewers independently performed each stage of the review (screening, eligibility and inclusion) and extracted information using data extraction tables and quality appraisal forms. Variables for which data/information was sought included AE descriptions (signs, symptoms) and prevention, management and treatment strategies. The overall strength of the body of evidence presented in each publication, for each recommendation, was also assessed as per the ratings described by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group (Table 1) [26]. Each reviewer was trained on the GRADE Handbook before beginning their reviews. The model development group consisted of clinical and methodological experts, including three board-certified plastic surgeons with a combined total of over 40 years of injecting experience, a senior epidemiologist with substantial experience in the aesthetics field, an anatomist and clinical researchers specializing in the fields of aesthetics and dermatology.

Results

Number of articles: The search terms resulted in 878 texts; 94.65% (n = 831) of which were available in the English language. After applying the filters for publication year, full-text availability and article type, nineteen texts remained. The titles and abstracts of these nineteen texts were screened by the two reviewers and then the full texts were assessed according to the eligibility criteria. The reference lists of the eleven resulting texts were consulted, which resulted

in 447 references before the removal of duplicates. These additional 447 references were assessed using the same techniques as the original 878 texts that resulted from the search terms. A third reviewer resolved any disagreements. Following this methodology (Figure 1), 46 texts remained. Eight additional references were added to the collection, using non-systematic methods. Following this step, fifty-four texts were included in the present review (Table 2).

Article types: The vast majority of eligible articles included non-systematic reviews (37/54; 68.52%), followed by consensus recommendations (9/54; 16.67%). Systematic reviews (4/54; 7.41%) and guidelines (4/54; 7.41%) were infrequent.

Number of studies and subjects: Only reviews and systematic reviews reported the number of studies and/or subjects that were included in their analyses. The current analyses are therefore based on approximately 251 studies involving 3448 subjects treated with fillers, including 130 studies involving 401 subjects treated with HA (Table 2). However, it remains possible that reviews and systematic reviews may have considered duplicate studies/cases.

Adverse events: All AEs discussed within the included publications (N = 54) are presented in (Table 3). In total, thirty-four AEs were found to be associated with the use of aesthetic soft tissue fillers in the face. Many publications (35/54; 64.81%) examined multiple AEs, with the average number of AEs presented in a single article being 5.02 (SD: 5.56; Range: 1 to 23). Reviews (9/11; 81.82%) and consensus recommendations (2/11; 18.18%) made up all article types that reviewed >10 AEs (N = 11). The most frequently mentioned AEs were blindness/vision loss, disturbances, compromise or impairment (23/54; 42.59%); ischemia/vascular complications (21/54; 38.89%); nodules (18/54; 33.33%); and infection (18/54; 33.33%).

Quality of evidence: The prevention, treatment and management strategies presented in the included articles are summarized in (Figure 2) (parts a to z6vi). There were 8/34 (23.53%) AEs (i.e. abnormal sensation, anaphylactic shock, intra-cranial penetration, urticaria, nerve palsy, scarring, stroke and telangiectasia) for which there was only a single reference providing guidance on its prevention, treatment and/or management. “Common” AEs such as bruising and swelling were widely mentioned in the literature.

Overall, the quality of evidence in support of the proposed prevention, treatment and management techniques was poor; consisting largely of D (very low) and C (low) GRADE scores. Prevention and management techniques were described less often than treatment techniques; with 14/34 (41.18%) AEs having no provided prevention techniques, 21/34 (61.76%) AEs having no accompanying management techniques, and 5/34 (14.71%) AEs having no methods of treatment (i.e. abnormal sensation, bleeding, intra-cranial penetration, pain and stroke). There were only three strategies that met a GRADE A (high) quality of recommendation, each of which were preventative strategies. These included: i) knowledge of anatomy (e.g., knowing the location and depth of facial vessels and the common variations) and injection techniques are imperative; ii) injectors should wear gloves; and iii) skin should be disinfected (see Figure 2, parts i and t). A small subset (i.e. < 15%) of recommendations corresponded to B (moderate) GRADE scores, with the remaining ~85% being classified as either a C (low) or D (very low). Many of the D recommendations were founded strictly on expert opinion, with no accompanying supporting evidence.

Discussion

In this review, we aimed to summarize currently available data on the prevention, treatment and management of AEs related to HA soft tissue fillers. We then evaluated the quality

of evidence in support of each recommendation and assigned to it a corresponding GRADE score, accordingly [26-29]. Overall, thirty-four distinct AEs were identified as being associated with soft tissue fillers used for facial aesthetic indications, in the literature. When attempting to summarize prevention, treatment and management strategies for each AE, twenty-five (73.53%) AEs lacked information pertaining to at least one of the given care categories. Furthermore, almost a quarter of the AEs had but a single reference providing guidance. This review also demonstrated that there have been few advancements or changes to expert recommendations in AE action protocols in the last decade (e.g., High Dose Pulsed Hyaluronidase).45 This is a significant limitation of current guidelines, given product refinements over the last few years, and the increase in novice injectors and subsequent number of treatments being performed worldwide, all of which may effect AE risk [30,31]. Moreover, as there were relatively few AEs described in the literature until 2010,[35] updated guidelines would likely be more representative of real-world data.

In many aspects, standards in aesthetic medicine are set forth by health and safety legislation. However, currently there is no standard for handling AEs associated with the use of HA fillers. Practitioners in different medical fields are performing these procedures and they have varied educational backgrounds and levels of expertise [35]. Consequently, there is an urgent need to evaluate currently proposed guidelines in order to provide clinicians with guidance [20]. In fact, Signorini et al. (2016) [20], professed that complication management is the largest unmet need with HA fillers. In response to this call-to-action, the present review critically appraised the available evidence for validity, based on a hierarchy of strength.

Herein, it was found that a number of approaches alternative to established consensus have been published and most complication guidelines rely on expert opinion with no direct

evidence or very low quality studies with severe limitations. This poses a dilemma as a theory or conceptual model of therapy may be perfectly reasonable, but the resulting predictions it enables are limited, if not validated by research. Additional limitations of the current literature include: describing vague safety techniques (e.g. prevent AEs via "meticulous technique") or in insufficient detail for replication (e.g. suggesting topical steroids for reducing erythema [1,37], hyaluronidase for nodules, or antimicrobials for biofilms but not indicating specific products, doses, or frequency and duration of use; recommending to stop anticoagulant use prior to treatment in order to prevent bruising, but not specifying for how long beforehand [38], providing general safety measures for any/ all AEs, without relating the recommendations to any specific AE [39], referring to different AEs as if they are the same, when in fact they significantly differ based on etiology and thus, prevention, treatment and management (e.g. ecchymosis occurs because small veins and capillaries break under the skin, but a hematoma occurs when a collection of blood pools outside of a large blood vessel; yet some authors refer to them as if they were indistinguishable) [39], failing to make the distinction between treating AEs or their signs and symptoms (e.g. treatment of the emboli causing vascular complications versus the necrotic tissue that results from the interruption of blood flow); providing recommendations but limiting it to a certain anatomical area [40] and as mentioned, most importantly many authors provided no evidence to support their recommendations, or relied on case-control, or cohort studies, with a high risk of confounding bias, non-analytic studies (e.g. case reports, case series) or expert opinion; such are the lowest grades of study designs based on multiple grading schemes, even those not implemented herein [41]. Although, the authors do appreciate that the true rarity of some AEs may precede the ability to develop analytical studies. The literature is also fraught with inconsistencies in the language used, for example: nodules should not be

interchanged with the terms “lump”, “bump” or “contour irregularity”; nodules, papules and granulomas should be distinguished from each other as their etiology and treatment differ; “hypersensitive reactions” should be described by their symptoms, such as swelling and inflammation and may actually involve many AEs; swelling and inflammation are distinct AEs; some authors consider Tyndall effect as skin discoloration [42], but only changes to melanin should be considered in hyper/hypopigmented disorders; and vague terms such as “general”, “local” or “site reactions” should be avoided.

Currently and to the best of the authors’ knowledge, this is the most comprehensive review of the quality of evidence supporting recommendations to AE prevention, treatment and management. This review provides information on a large majority of currently known potential AEs of HA, where other authors have only considered a subset. For example, the majority of included articles only reviewed an average of ~five AEs, which often corresponded to specific anatomical regions; and the most comprehensive review evaluated twenty-three, whereas herein we describe thirty-four. Moreover, as some authors have only focused on either prevention, treatment or management strategies, we have summarized all three facets of patient care.

The methods employed herein included founding recommendations based on the strength of the supporting literature, using four levels of analyses. Strict inclusion and exclusion criteria were set, and the inclusion of articles and data extraction were performed in duplicate. The models we present were developed by a multidisciplinary expert group and have the potential to directly impact practice by offering aesthetic providers with evidence-based guidelines. Familiarity with the content of the models described herein are an essential requirement of any aesthetic practice and to upholding the integrity and responsibilities of clinicians performing injectable procedures.

Despite significant strengths of the current systematic review, there are some limitations to its methods. Given that PubMed was the only search engine searched systematically, it is possible that some relevant publications were not considered for inclusion. Furthermore, as non-English-language publications and texts related to products licensed outside of Canada and the United States were not considered, the international applicability of these findings are limited. There are hundreds of HA-based filler products available worldwide and counterfeit or illegally imported HA is widespread in some countries [43]. However, only approximately one-fourth of this amount is approved by the FDA and/or Health Canada [44]. Therefore, these findings may not be applicable to all soft-tissue fillers available on the world market. In addition, almost one-third of the AEs had but a single publication providing guidance on its prevention, treatment or management. Therefore, the resulting models are likely extremely limited. Lastly, no-to-small sample sizes and a lack of homogeneity in the included studies precluded any quantitative analysis of effect size, confidence interval estimates or a confirmation of the presence/ absence of statistical significance.

Conclusions and future research

Most complication guidelines for AEs related to HA soft tissue filler use rely on expert opinion with no direct evidence or very low-quality studies with significant imitations. Moreover, there have been few advancements or changes to expert recommendations in AE action protocols in the last decade, despite a growing number of novice injectors and treatments being performed, and varying product technologies entering the global market. Consequently, there is an increasingly urgent need to re-evaluate currently proposed guidelines in order to provide clinicians with more accurate guidance [20]. To date, the original call-to-action for increased evidence-based AE management by Signorini et al. (2016) [20] remains unaddressed.

In an early attempt to address this call-to-action, we first graded and summarized evidence-based methods for the prevention, treatment and management of AEs associated with the use of HA fillers for aesthetic facial indications. The findings of these quality assessments are summarized herein and provide a foundational framework for evaluating the current body of evidence. To further assess the quality of these methods, prospective studies are required to systematically evaluate outcomes following complication management. For example, a prospective registry could evaluate the true incidence rates of AEs, establish the real-world timeline between treatment exposure and signs and/or symptoms of late-onset AEs, establish standards (e.g., the mean number of hyperbaric oxygen sessions recommended for cases of vascular compromise, the ideal number and frequency of hyaluronidase sessions recommended to dissolve an emboli), and assess the suitability and applicability of the recommendations proposed to date. To the authors' knowledge, there exists only one such registry, the physician-researcher-initiated "Global Registry of Adverse Clinical Events (GRACE)', which is a multi-year, prospective AE registry (2018-2020; results in press). To increase participant engagement in these types of registries, governing bodies or specialty groups should consider developing public registries or online portals for tracking AEs. Following future research, modifications to the current AE prevention, treatment and management models may be required.

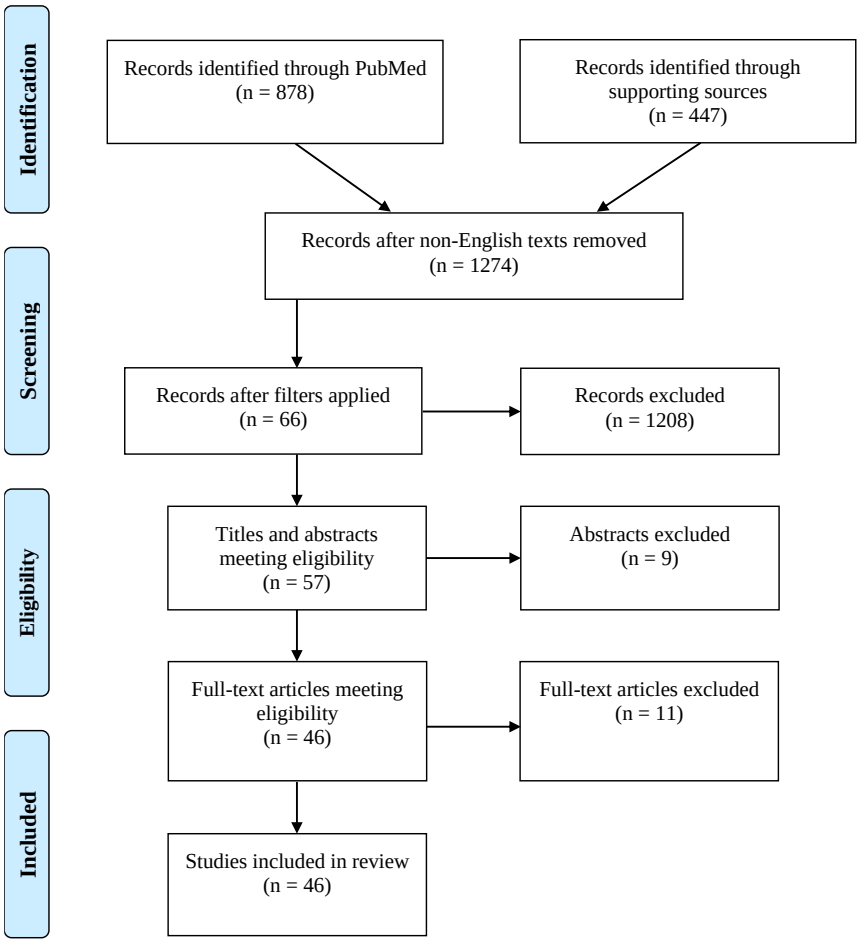


Figure 1. PRISMA flow diagram of the methods applied for assessing publications for inclusion in the present review.

Note: "Filters applied" included publication year, full text availability and article type. Supporting sources included the reference lists. PRISMA = Preferred Reporting Items for Systematic review and Meta-Analysis.

[Note: Due to the size of Figure 2 (parts A to ZVi), it has been moved to the appendix].

Figure 2. Models for the prevention, treatment and management of adverse events following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

TABLE 1. Strength of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[24]

Code	Quality of Evidence	Definition	Examples
A	High	Further research is very unlikely to change our confidence in the estimate of effect.	• Several high-quality studies with consistent results. • In special cases: one large, high-quality multi-center trial.
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	• One high-quality study. • Several studies with some limitations.
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	• One or more studies with severe limitations.
D	Very Low	Any estimate of effect is very uncertain.	• Expert opinion.

			• No direct research evidence. • One or more studies with very severe limitations.

Table 2. Publications included in the present review. *Note: References ordered by year and then author, in alphabetical order. Systematic reviews were differentiated by literature reviews based on: 1) presence of a focused research question versus broad overview of topic; ii) use of a systematic versus ad hoc search strategy and iii) assessment of the quality and validity of findings.*

Number	**Author(s)**	**Title**	**Journal/Index**	**Year**	**Article Type**	**Nº Studies** [All fillers (Hyaluronic acid)]	**Nº Patients** [All fillers (Hyaluronic acid)]
1	Mccann M.	Intravenous Hyaluronidase for Visual Loss Secondary to Filler Injection: A Novel Therapeutic Approach.	J Clin Aesthet Dermatol 12(12):25-27.	2019	Guideline	-	-
2	Chen YC, Wu HM, Chen SJ, et al.	Intra-arterial thrombolytic therapy is not a therapeutic option for filler-related central retinal artery occlusion.	Facial Plast Surg 34(3): 325–329.	2018	Review	6 (5)	15 (8)

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
3	Vedamurthy M.	Beware What You Inject: Complications of Injectables-Dermal Fillers.	J Cutan Aesthet Surg Apr-Jun;11(2):60-66.	2018	Review	-	-
4	Urdiales-Gálvez F, Delgado NE, Figueiredo V, et al.	Treatment of Soft Tissue Filler Complications: Expert Consensus Recommendations.	Aesthetic Plast Surg Apr;42(2):498-510.	2018	Consensus recommendations	-	-
5	Walker L, King M.	This month's guideline: visual loss secondary to cosmetic filler injection.	J Clin Aesthet Dermatol 11(5):E53–E55.	2018	Guideline	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
6	Delorenzi C.	New high dose pulsed hyaluronidase protocol for hyaluronic acid filler vascular adverse events.	Aesthet Surg J 13:814–25.	2017	Guideline	-	-
7	Ferneini EM, Beauvais D, Aronin SI.	An overview of infections associated with soft tissue facial. fillers: identification, prevention, and treatment.	J Oral Maxillofac Surg 75(1):160–166	2017	Review	7 (1)	140 (1)
8	Mundada P, Kohler R, Boudabbous S, et al.	Injectable facial fillers: imaging features, complications, and	Insights Imaging 8(6):557-572.	2017	Review	-	13

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
		diagnostic pitfalls at MRI and PET CT.					
9	Urdiales-Gálvez F, Delgado NE, Figueiredo V, et al.	Preventing the Complications Associated with the Use of Dermal Fillers in Facial Aesthetic Procedures: An Expert Group Consensus Report.	Aesthetic Plast Surg. 41(3):667-677.	2017	Consensus recommendations	-	-
10	Buhren BA, Schrumpf	Hyaluronidase: from clinical applications to	Eur J Med Res 13;21:5.	2016	Review	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
	H, Hoff NP, Bölke E, Hilton S, Gerber PA.	molecular and cellular mechanisms.					
11	Chiang YZ, Pierone G, Al-Niaimi F.	Dermal fillers: pathophysiology, prevention and treatment of complications.	J Eur Acad Dermatol Venereol Mar;31(3):405-413.	2016	Review	-	-
12	Ferneini EM,	An overview of vascular adverse events associated with facial soft tissue fillers:	J Oral Maxillofac Surg 74(8):1630–1636.	2016	Review	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
	Ferneini AM.	recognition, prevention, and treatment.					
13	Fitzgerald R, Bertucci V, Sykes JM, Duplechain JK.	Adverse reactions to injectable fillers.	Facial Plast Surg 32(5):532–555	2016	Review	-	-
14	Hwang CJ	Periorbital injectables: understanding and avoiding complications.	J Cutan Aesthet Surg 9(2):73–79.	2016	Review	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
15	Loh KT, Chua JJ, Lee HM, Lim JT, Chuah G, Yim B, Puah BK	Prevention and management of vision loss relating to facial filler injections.	Singap Med J 57(8):438–443	2016	Consensus recommendations	-	-
16	Signorini M, Liew S, Sundaram H, et al.	Global Aesthetics Consensus Group. Global Aesthetics Consensus: Avoidance and Management of	Plast Reconstr Surg Jun;137(6):961e-71e.	2016	Consensus recommendations	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
		Complications from Hyaluronic Acid Fillers-Evidence- and Opinion-Based Review and Consensus Recommendations.					
17	Wagner RD, Fakhro A, Cox JA, Izaddoost SA	Etiology, prevention, and management of infectious complications of dermal fillers.	Semin Plast Surg 30(2):83–86 676.	2016	Review	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
18	Belezany K, Carruthers JDA, Humphrey S, Jones DJ.	Avoiding and treating blindness from fillers: a review of the world literature.	Dermatologic Surg 41(10):1097–1117.	2015	Review	44 (23)	98 (23)
19	Bravo BS, Rocha CR, Bastos JT, Silva PM.	Comprehensive Treatment of Periorbital Region with Hyaluronic Acid.	J Clin Aesthet Dermatol 8(6):30-5.	2015	Review	-	-
20	Cohen BE, Bashey S, Wysong A.	The use of hyaluronidase in cosmetic dermatology: a review of the literature.	J Clin Investigat Dermatol 3(2):7.	2015	Review	(13)	(48)

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
21	Cohen JL, Biesman BS, Dayan SH, DeLorenzi C, Lambros VS, Nestor MS, et al.	Treatment of hyaluronic acid filler-induced impending necrosis with hyaluronidase: consensus recommendations.	Aesthet Surg J 35(7):844–849.	2015	Consensus Recommendations	-	-
22	De Boulle K,	Patient factors influencing dermal filler complications:	Clin Cosmet Investig Dermatol 8:205–214.	2015	Consensus Recommendations	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
	Heydenrych I.	prevention, assessment, and treatment.					
23	Funt D, Pavicic T.	Dermal fillers in aesthetics: an overview of adverse events and treatment approaches.	Plast Surg Nurs 35:13–32.	2015	Review	-	-
24	Lee JM, Kim YJ.	Foreign body granulomas after the use of dermal fillers: pathophysiology, clinical appearance, histologic features, and treatment.	Arch Plast Surg 42(2):232–239.	2015	Review	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
25	Rzany B, DeLorenzi C.	Understanding, avoiding, and managing severe filler complications.	Plast Reconstr Surg 136(5 Suppl):196S–203S	2015	Review	-	-
26	Carruthers JD, Fagien S, Rohrich RJ, Weinkle S, Carruthers A.	Blindness caused by cosmetic filler injection: a review of cause and therapy.	Plast Reconstr Surg 134(6):1197–1201	2014	Review	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
27	Kim JH, Ahn DK, Jeong HS, Suh IS.	Treatment algorithm of complications after filler injection: based on wound healing process.	J Korean Med Sci 29 Suppl 3(Suppl 3):S176-82.	2014	Review	-	-
28	Cavallini M, Gazzola R, Metalla M, Vaienti L.	The role of hyaluronidase in the treatment of complications from hyaluronic acid dermal fillers.	Aesthet Surg J 33(8): 1167–1174.	2013	Review	-	-
29	DeLorenzi C.	Complications of injectable fillers, part I.	Aesthet Surg J 33(4):561–575.	2013	Review	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
30	Dumitrașcu DI, Georgescu AV.	The management of biofilm formation after hyaluronic acid gel filler injections: a review.	Clujul Med 86(3):192-5.	2013	Review	(29)	(13)
31	Funt D, Pavicic T.	Dermal fillers in aesthetics: an overview of adverse events and treatment approaches.	Clin Cosmet Investig Dermatol 6:295–316.	2013	Review	-	-
32	Ginat DT, Schatz CJ.	Imaging features of midface injectable fillers and associated complications.	AJNR Am J Neuroradiol. 34(8):1488-95.	2013	Review	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
33	Ledon JA, Savas JA, Yang S, Franca K, Camacho I, Nouri K.	Inflammatory nodules following soft tissue filler use: a review of causative agents, pathology and treatment options.	Am J Clin Dermatol. 14:401–411	2013	Review	(12)	(48)
34	Ozturk CN, Li Y, Tung R, Parker L, Piliang MP, Zins JE.	Complications following injection of soft-tissue fillers.	Aesthet Surg J 33:862–877.	2013	Systematic Review	41(22)	61(32)

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
35	Kleydman K, Cohen JL, Marmur E.	Nitroglycerin: a review of its use in the treatment of vascular occlusion after soft tissue augmentation.	Dermatol Surg 38:1889–1897.	2012	Review	-	-
36	Lazzeri D, Agostini T, Figus M, Nardi M, Pantaloni M, Lazzeri S.	Blindness following cosmetic injections of the face.	Plast Reconstr Surg. 13:995–1012.	2012	Systematic Review	29(2)	32(2)

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
37	Bailey SH, Cohen JL, Kenkel JM.	Etiology, prevention and treatment of dermal filler complications.	Aesthet Surg J 31:110–121.	2011	Review	-	-
38	Dayan SH, Arkins JP, Brindise R.	Soft tissue fillers and biofilm.	Facial Plast Surg 27:23–28.	2011	Review	(13)	(40)
39	Funt DK.	Avoiding malar edema during midface/cheek augmentation with dermal fillers.	J Clin Aesthet Dermatol 4(12):32–36.	2011	Review	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
40	Kassir R, Kolluru A, Kassir M.	Extensive necrosis after injection of hyaluronic acid filler: case report and review of the literature.	J Cosmet Dermatol. 10:224–231.	2011	Review	(9)	(12)
41	Kim JE, Sykes JM.	Hyaluronic acid fillers: history and overview.	Facial Plast Surg. 27:523–528.	2011	Review	-	-
42	Requena L, Requena C, Christensen L, et al.	Adverse reactions to injectable soft tissue fillers.	J Am Acad Dermatol. 64(1):1–34.	2011	Review	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
43	Sturm LP, Cooter RD, Mutimer KL, et al.	A systematic review of dermal fillers for age-related lines and wrinkles.	ANZ J Surg 81:9–17	2011	Systematic Review	9(1)	2893(135)
44	Lafaille P, Benedetto A.	Fillers: contraindications, side effects and precautions.	J Cutan Aesthet Surg 3(1):16–19.	2010	Review	-	-
45	Rohrich RJ, Monheit G, Nguyen AT,	Soft-tissue filler complications: the important role of biofilms.	Plast Reconstr Surg 125:1250–1256.	2010	Review	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
	Brown SA, Fagien S.						
46	Vedamurthy M, Vedamurthy A, Nischal K.	Dermal fillers: do's and dont's.	J Cutan Aesthet Surg 3(1):11–15	2010	Review	-	-

Table 3. Adverse events (AEs) following the use of aesthetic soft tissue fillers in the face, according to a systematic review of the literature. AEs are presented in alphabetical order. *Note: There were 8/46 (17.39%) articles that referred to "general" or "local" AEs, which presumably refer to the so-called "injection site reactions" that form part of the normal sequalae following breaking the dermis with injections (e.g., bleeding, bruising, edema).*[39] *However, given the vagueness of these terms, they are not included in the above table.* [a] *Includes articles focusing on non-specific arterial locations.* [b] *Includes central retinal and retinal artery occlusion and retinal embolus.* [c] *Includes "lumps", "bumps" asymmetries and overcorrection.* [d] *Excludes Tyndall effect.* [e] *Includes vascular compromise, infarction, embolism, occlusion and injection.*

Identification Number	Adverse Event	Number of References [N = 46; n (%)]
1	Abscess	5 (10.87)
2	Abnormal sensation (e.g., dysesthesias, paresthesia, anesthesia)	1 (2.17)
3	Allergic/hypersensitivity/inflammatory reactions	5 (10.87)
4	Anaphylactic shock	1 (2.17)
5	Angioedema	2 (4.35)
6	Arterial compromise/occlusion/injection[a]	3 (6.52)
7	Biofilm	12 (26.09)

8	Blindness/Vision loss, disturbances, compromise or impairment[b]	17 (36.96)
9	Bleeding	2 (4.35)
10	Bruising/Ecchymosis	11 (23.91)
11	Contour irregularities[c]	13 (2.17)
12	Dyspigmentation/Hyperpigmentation/Discoloration[d]	3 (6.52)
13	Edema/Swelling	13 (28.26)
14	Erythema	5 (10.87)
15	Foreign body granuloma/Granulomatous reaction	11 (23.91)
16	Hematoma	4 (8.70)
17	Herpetic outbreak	2 (4.35)
18	Hypertrophic scarring	2 (4.35)
19	Infection	15 (32.61)
20	Intra-cranial penetration	1 (2.17)
21	Ischemia/Vascular complications[e]	17 (36.96)
22	Urticaria (hives)	1 (2.17)
23	Migration of filler material	5 (10.87)

24	Necrosis	10 (21.74)
25	Neovascularization	2 (4.35)
26	Nerve palsy	1 (2.17)
27	Nodule	16 (34.78)
28	Pain	1 (2.17)
29	Papules/Papulopustular lesions	2 (4.35)
30	Pruritus	1 (2.17)
31	Scarring	1 (2.17)
32	Stroke	1 (2.17)
33	Telangiectasia (spider veins)	1 (2.17)
34	Tyndall effect	6 (13.04)

References

1. Urdiales-Galvez F, Delgado NE, Figueiredo V, Lajo-Plaza JV, Mira M et al. (2017) Preventing the Complications Associated with the Use of Dermal Fillers in Facial Aesthetic Procedures: An Expert Group Consensus Report. Aesthetic Plast Surg 41: 667-677.
2. Wong CH, Mendelson B (2015) Newer Understanding of Specific Anatomic Targets in the Aging Face as Applied to Injectables: Aging Changes in the Craniofacial Skeleton and Facial Ligaments. Plast Reconstr Surg 136: 44S-48S.
3. Cotofana S, Fratila AA, Schenck TL, Redka-Swoboda W, Zilinsky I, et al. (2016) The Anatomy of the Aging Face: A Review. Facial Plast Surg 2016: 32: 253- 260.
4. Coleman SR, Grover R (2006) The anatomy of the aging face: volume loss and changes in 3-dimensional topography. Aesthet Surg J 26: S4- S9.
5. Wulc AE, Sharma P, Czyz CN (2012) The anatomic basis of midfacial aging. In: Hartstein ME, Wulc AE, Holck DE, eds. Midfacial rejuvenation. Berlin: Springer.
6. Macierzynska A, Pierzchala E, Placek W (2014) Volumetric techniques: three-dimensional midface modeling. Postepy Dermatol Alergol 31: 388-391.
7. Sturm LP, Cooter RD, Mutimer KL, Graham JC, Maddern GJ (2011) A systematic review of dermal fillers for age-related lines and wrinkles. ANZ J Surg 81: 9-17.
8. Cotofana S, Schenck TL, Trevidic P, Sykes J, Massry GG et al. (2015) Midface: Clinical Anatomy and Regional Approaches with Injectable Fillers. Plast Reconstr Surg 136:219S-234S.

9. Stojanovic L, Majdic N (2019) Effectiveness and safety of hyaluronic acid fillers used to enhance overall lip fullness: A systematic review of clinical studies. J Cosmet Dermatol 18: 436-443.

10. Cohen JL, Dayan SH, Brandt FS, Nelson DB, Axford-Gatley RA et al. (2013) Systematic review of clinical trials of small- and large gel-particle hyaluronic acid injectable fillers for aesthetic soft tissue augmentation. Dermatol Surg 39: 205-231.

11. Bertucci V, Lin X, Axford-Gatley RA, Theisen MJ, Swift A (2013) Safety and effectiveness of large gel particle hyaluronic acid with lidocaine for correction of midface volume loss. Dermatol Surg 39: 1621-1629.

12. Wang C, Luan S, Panayi AC, Xin M, Mi B, et al. (2018) Effectiveness and Safety of Hyaluronic Acid Gel with Lidocaine for the Treatment of Nasolabial Folds: A Systematic Review and Meta-analysis. Aesthetic Plast Surg 42: 1104-1110.

13. International Society of Aesthetic Plastic Surgery (ISAPS). ISAPS International Survey on Aesthetic/Cosmetic Procedures performed in 2018.

14. The Aesthetic Society. Aesthetic Plastic Surgery National Databank Statistics 2019.

15. Funt D, Pavicic T (2013) Dermal fillers in aesthetics: an overview of adverse events and treatment approaches. Clin Cosmet Investig Dermatol 6: 295-316.

16. Fortune Business Insights. Dermal Fillers Market Size, Share & COVID-19 Impact Analysis, By Material (Hyaluronic Acid, Calcium Hydroxylapatite, Poly-L-lactic Acid, PMMA (Poly (methyl methacrylate)), Fat Fillers), By Product (Biodegradable and Nonbiodegradable), By Application (Scar Treatment, Wrinkle Correction Treatment, Lip Enhancement), By End User (Specialty & Dermatology Clinics, Hospital & Clinics), and Regional Forecast, 2020-2027.

17. Galadari H, Krompouzos G, Kassir M, Gupta M, Wollina U et al. (2020) Complication of Soft Tissue Fillers: Prevention and Management Review. J Drugs Dermatol 19: 829-832.
18. Abduljabbar MH, Basendwh MA (2016) Complications of hyaluronic acid fillers and their managements. Journal of Dermatology & Dermatologic Surgery 20: 100-106.
19. Philipp-Dormston WG, Bergfeld D, Sommer BM, Sattler G, Cotofana S et al. (2017) Consensus statement on prevention and management of adverse effects following rejuvenation procedures with hyaluronic acid-based fillers. J Eur Acad Dermatol Venereol 31: 1088-1095.
20. Signorini M, Liew S, Sundaram H, Boulle KL, Goodman GJ et al. Global Aesthetics Consensus: Avoidance and Management of Complications from Hyaluronic Acid Fillers-Evidence- and Opinion-Based Review and Consensus Recommendations. Plast Reconstr Surg 137: 961e-971e.
21. Hotta TA (2017) The Expanding Market of Health Canada-Approved Hyaluronic Acid-Injectable Dermal Fillers. Plast Surg Nurs 37: 25-31.
22. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A et al. (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 350:g7647.
23. Eriksen MB, Frandsen TF (2018) The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review. J Med Libr Assoc 106: 420-431.
24. Considine J, Shaban RZ, Fry M, Curtis K (2017) Evidence based emergency nursing: Designing a research question and searching the literature. Int Emerg Nurs 32: 78-82.

25. Lefebvre C, Manheimer E, Glanville J Chapter 6: Searching for Studies. In: Higgins JP, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Wiley Online Library. 2008:95-150.
26. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y et al. (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336: 924-926.
27. Goodman GJ, Magnusson MR, Callan P, Roberts S, Hart S et al. (2020) A Consensus on Minimizing the Risk of Hyaluronic Acid Embolic Visual Loss and Suggestions for Immediate Bedside Management. Aesthet Surg J 40: 1009-1021.
28. Beleznay K, Carruthers JDA, Humphrey S, Carruthers A, Jones D (2019) Update on Avoiding and Treating Blindness From Fillers: A Recent Review of the World Literature. Aesthet Surg J 39: 662-674.
29. Dayan SH, Arkins JP, Mathison CC (2011) Management of impending necrosis associated with soft tissue filler injections. J Drugs Dermatol 10: 1007-1112.
30. Swift A, von Grote E, Jonas B, Nogueira A (2017) Minimal recovery time needed to return to social engagement following nasolabial fold correction with hyaluronic acid fillers produced with XpresHAn technology. Clin Cosmet Investig Dermatol 10: 229-238.
31. Costa CR, Kordestani R, Small KH, Rohrich RJ (2016) Advances and Refinement in Hyaluronic Acid Facial Fillers. Plast Reconstr Surg 138: 233e-236e.
32. Segura S, Anthonioz L, Fuchez F, Herbage B (2012) A complete range of hyaluronic acid filler with distinctive physical properties specifically designed for optimal tissue adaptations. J Drugs Dermatol 11: s5-8.

33. Micheels P, Sarazin D, Tran C, Salomon D (2016) Effect of Different Crosslinking Technologies on Hyaluronic Acid Behavior: A Visual and Microscopic Study of Seven Hyaluronic Acid Gels. J Drugs Dermatol 15: 600-606.

34. Kablik J, Monheit GD, Yu L, Chang G, Gershkovich J (2009) Comparative physical properties of hyaluronic acid dermal fillers. Dermatol Surg 35: 302-312.

35. Bitterman-Deutsch O, Kogan L, Nasser F (2015) Delayed immune mediated adverse effects to hyaluronic Acid fillers: report of five cases and review of the literature. Dermatol Reports 7: 5851.

36. International Consortium of Investigative Journalists. The Implant Files: International Medical Devices Database.

37. McCann M (2019) Intravenous Hyaluronidase for Visual Loss Secondary to Filler Injection: A Novel Therapeutic Approach. J Clin Aesthet Dermatol 12: 25-27.

38. Bravo BS, Rocha CR, Bastos JT, Silva PM (2015) Comprehensive Treatment of Periorbital Region with Hyaluronic Acid. J Clin Aesthet Dermatol 8:30-35.

39. Vedamurthy M (2018) Beware What You Inject: Complications of Injectables-Dermal Fillers. J Cutan Aesthet Surg 11: 60-66.

40. Buhren BA, Schrumpf H, Hoff NP, Bolke E, Hilton S, et al. Hyaluronidase: from clinical applications to molecular and cellular mechanisms. Eur J Med Res 21: 5.

41. Harbour R, Miller J (2001) A new system for grading recommendations in evidence based guidelines. BMJ 323: 334-336.

42. Chiang YZ, Pierone G, Al-Niaimi F (2017) Dermal fillers: pathophysiology, prevention and treatment of complications. J Eur Acad Dermatol Venereol 31: 405-413.

43. Bellman B (2005) Immediate and delayed hypersensitivity reactions to restylane. Aesthet Surg J 25: 489-491.

44. Palm MD (2014) Filler frontier: what's new and heading West to the US market. Semin Cutan Med Surg 33: 157-163.

45. DeLorenzi C (2017) New High Dose Pulsed Hyaluronidase Protocol for Hyaluronic Acid Filler Vascular Adverse Events. Aesthet Surg J 37: 814-825.

Chapter 5: A global perspective on adverse events in aesthetics

After discovering that a significant portion (i.e., >85%) of AE guidelines lack supporting evidence, and that little-to-no advancement in the development of AE protocols has been made over the last decade, an expert committee was established to explore strategies for enhancing the aesthetic industry's safety standards. This committee, known as the Safety Task Force (STF), was formed by twelve experts from nine countries, each possessing valuable expertise in various aspects related to aesthetic injectables. Representatives from different countries included Andreas Nikolis, a Plastic Surgeon from Montreal, Canada; Katie Beleznay, a Dermatologist from Vancouver, Canada; Sebastian Cotofana, an Anatomist from Rochester, United States of America (USA); Rebecca Fitzgerald, a Dermatologist from Los Angeles, USA; Joel Coher, a Dermatologist from Greenwood Village, USA; Brian Biesman, a Facial Plastic Surgeon from Nashville, USA; Steven Weiner, a Plastic Surgeon from Santa Rosa Beach, USA; Meire Parada, a Dermatologist from Moema, Brazil; Won Lee, a Plastic Surgeon from Seoul, South Korea; Berthold Rzany, a Dermatologist from Vienna, Austria and Hugues Cartier, a Dermatologist from Arras, France. Despite their absence from this meeting, the safety task force comprises; Sabrina Fabi, a Dermatologist from San Diego, USA; Luiz Avelar, a Plastic Surgeon from Belo Horizonte, Brazil; Greg Goodman, a Dermatologist from South Yarra, Australia; Leoni Schelke, a Phlebologist from Amsterdam, Netherlands and Hang Wang, a Plastic Surgeon from Sichuan, China.

At a virtually held meeting, these experts in aesthetic medicine gathered to address AEs associated with injectables and develop a global consensus on methods to improve the safety of these treatments. Furthermore, during the meeting panellists discussed industry controversies related to the prevention, management, and treatment of AEs. Six key themes emerged from these discussions, as outlined below:

1) A global AE database is required to delineate the true incidence rates of AEs.
2) AE/vascular AE (VAE) management strategies need to be validated, with critical endpoints established.
3) Current hyaluronidase protocols need to be re-evaluated.
4) The use of ultrasound in AE prevention and diagnosis needs to be further explored.
5) The value of aspiration as a VAE preventative measure needs to be established.
6) The safety implications related to the use of different injection devices (i.e., cannulas versus needles) needs to be investigated.

Global AE database

To ensure patient safety, it is crucial for injectors to have access to clear guidelines for addressing AEs. To develop these protocols, a significant amount of information exchange is required among injectors and stakeholders, on a global scale. Such knowledge generation would allow correlations to be made between certain treatment factors and the occurrence and severity of AEs, such as product characteristics [e.g., manufacturing technology, cohesiveness, G', injection technique (e.g., linear threading, fanning, depot; depth; volume), AE progression timeline (e.g., identifying early signs and symptoms such as tissue conditions, including colour, texture, and molting), injectors' background, and other relevant factors.[1] During the meeting, 11/12 (91.60%) of the panelists were in favour of establishing an efficient and reliable method of gathering and exchanging such information via the development of a global AE registry. Key considerations related to difficulties in developing a global registry included standardizing information and terminologies across different countries and ensuring anonymity. Issues related to the credibility of the database were raised depending on whether it was sponsored by a pharmaceutical company versus a professional society or an independent group of physicians. Advisors agreed that the

database should be spearheaded by independent physicians, with support from professional societies. Most panelists (>75.00%) agreed that all injectable types (e.g., HA-based fillers, bio-stimulators, neurotoxins) should be included within the same database.

AE/VAE management

Possible AEs following a soft tissue filler injection have been documented elsewhere,[2] but may include swelling, bruising, hematoma, nodule, vascular occlusion, and tissue necrosis. While it has been proposed that aesthetic injections are generally associated with a low rate of AEs (i.e., less than 2%),[2,4] it has been established that the incidence rates of AEs are underreported.[3,4] Moreover, there has been little to no progress made over the last decade in the recommendations for AE prevention, management, and treatment (e.g., DeLorenzi's High Dose Pulsed Hyaluronidase protocol)[2], despite the growing number of injections being performed each year (i.e., 30.3% increase since 2020). Underreporting of AEs is problematic because it leads to incomplete and inaccurate data, which affects the ability to identify patterns, trends, or potential risk factors associated with specific products or injection techniques. Consequently, developing evidence-based guidelines and recommendations for AE prevention and management remains challenging, and often relies on expert opinions, which result in ongoing debates.

Managing complications related to VAEs (e.g., loss of vision, skin necrosis) was a significant point of interest during the panel discussion. The experts thoroughly reviewed previous incident reports and discussed strategies to reduce the risks associated with vascular occlusion. They emphasized the significance of early detection and prompt intervention as crucial steps for minimizing adverse outcomes. In managing VAEs, several vital considerations were discussed. One participant (8%) emphasized the importance of not overlooking the use of steroids to diminish the inflammatory component of the injury[5], and expressed his approval that many advisors selected

steroids as a treatment option. Additionally, another expert mentioned success in using hyaluronidase for non-HA-related VAE, particularly in cases where patients were not scarred. It was highlighted that differentiating the phase of the VAE is crucial to determining whether hyaluronidase should be employed. While VAE can be treated without hyaluronidase, it was noted that hyaluronidase's popularity has risen significantly in recent years. Following the use of hyaluronidase, experts expressed varying opinions on the rank order of useful interventions. Aspirin was suggested as the first option, followed by hyperbaric oxygen therapy (HBO), steroids, nitropaste, heparin, and finally lidocaine and exosomes as the last resorts. All panelists (100%) agreed that ultrasound was a useful tool for confirming a VAE had occurred. In determining critical endpoints for managing or treating a VAE, experts ranked the following indicators as essential: skin color and condition, and capillary refill. Most experts (7/12; 58.33%) did not consider ultrasound findings to be a reliable endpoint capable of confirming VAE resolution.

Current hyaluronidase protocols

During the meeting, there was a significant focus on assessing hyaluronidase protocols for treating patients with vascular occlusion. The group examined cases of hypersensitivity reactions and delayed inflammatory responses resulting from the use of HA-based fillers. These discussions aimed to optimize the use of hyaluronidase as an intervention to reverse AEs safely and effectively. It was emphasized that standardized protocols are necessary for consistent outcomes. Most advisors agreed that DeLorenzi's high-dose hyaluronidase approach published in 2017, is the most effective method for treating VAE. This protocol has been widely accepted due to its impressive efficacy and safety in managing vascular occlusions.

The use of ultrasound

The use of ultrasound in preventing and managing AEs sparked discussion among panelists. Some specialists presented evidence that ultrasound can be used as a diagnostic tool to detect early signs of AEs, such as filler migration or granulomas. However, others expressed concerns regarding its cost-effectiveness and accessibility, highlighting the need for additional research to determine its practicality in regular practice. Key considerations highlighted during the discussion included the dependency of ultrasound's preventative benefits on the operator's experience. The advisors mentioned that one of the barriers to its use is the time required for training on the machine and technology. As the risk of vascular occlusion is rare[6], one advisor (8%) strongly believed that ultrasound will not significantly lower incidence rates and questioned its worth as a preventive measure. Nevertheless, many advisors reported using ultrasound for "riskier" injections, such as those performed in the glabellar region and lips. At the end of the meeting, debates surrounding the implementation of ultrasound as a preventative measure and in management strategies persisted, emphasizing that further research and validation are necessary.

Aspiration as a VAE preventative measure

As a safety measure, practitioners can withdraw the plunger of the syringe to check for blood prior to injection, indicating that the needle tip is placed in an artery and should be moved. This process is referred to as "aspiration". The use of aspiration as a safety measure in conducting aesthetic injectable treatments was debated among the panelists, with 9/12 (75.00%) supporting the use of this technique. The duration of aspiration varied, with 7/12 (58.33%) panelists suggesting ~10 seconds, with the remainder (5/12; 41.66%) proposing 5-7 seconds as being sufficient. Priming needles prior to aspiration was found to be unnecessary by 9/12 (75.00%) panelists. Skepticism existed about the usefulness of aspiration when used with high-viscosity gels,

which can lead to false negatives. Anatomical sites found most suitable for aspiration included the deep pyriform area, temples, nose, chin, nasolabial area, tear troughs, and jawline. It was concluded that the usefulness of aspiration in preventing VAEs be investigated in controlled trials, as it remains a debatable topic.

The use of cannulas versus needles

Some panelists (7/12; 58.33%) reported preferring the use of cannulas over needles, due to their perceived safety (i.e., cannulas are blunt, whereas needles are sharp). Anatomical areas wherein cannulas were most cited to be used included the forehead, tear troughs, cheeks, nasolabial folds, jawline, temporal regions, chin, and nose. Findings from the first randomized-controlled study investigating the safety and efficacy of cannula versus needle was reviewed. In this recently published manuscript (2023), our team demonstrated that the frequencies of AEs following HA injections into the infraorbital regions differ based on whether a needle or cannula was used to perform the injections. Treatments using needles resulted in greater rates of ecchymosis, while cannulas were associated with a greater risk for edema.[7] Given these findings, a discussion of when to use either device ensued. For example, it was suggested that deep injections into the bone could minimize edema, as the muscle could act as a camouflaging agent. Also, injectors should evaluate whether a patient presents with an expanded venous plexus, as this may increase the risk of bleeding regardless of the device used. It was concluded that ultimately, both patient anatomy and injection technique contribute to the development of AEs.

Discussion and conclusions

During the meeting, it was emphasized that a significant deterrent to developing AE protocols is the absence of an effective system for monitoring, recording, and sharing information about AEs when they occur in routine clinical practice. This lack of a reliable tracking mechanism

hinders access to accurate data and obstructs decision-making processes necessary for enhancing patient care.

Ensuring patient safety requires clear AE guidelines for injectors, necessitating global information exchange. This will enable correlations to be made between AEs and various treatment, patient, and injector factors. During the STF meeting, most of the panelists (11/12; 91.66%) supported the development of a global AE database, which may provide the data necessary to address other key themes, such as validating AE/vascular AE (VAE) management strategies, re-evaluating current hyaluronidase protocols as they are currently being used in practice, evaluating the use of ultrasound in real-world cases, and the effects of aspiration and different injections devices (needle versus cannula) on AE rates. In the following chapter, we present the development and design of such an AE database, entitled the Global Registry of Clinical Adverse Events (GRACE Portal).

References

1. Wollina U, Goldman A. Correction of tear trough deformity by hyaluronic acid soft tissue filler placement inferior to the lateral orbital thickening. Dermatol Ther 2021;34(5):e15045.

2. Kaitlyn M. Enright, John Sampalis & Andreas Nikolis (2019): Adverse reactions associated with the esthetic use of soft tissue fillers and neurotoxins: a 53-year retrospective analysis of MedEffect™, Health Canada's reporting database, Journal of Dermatological Treatment, DOI: 10.1080/09546634.2019.1682501

3. Rzany, B., & DeLorenzi, C. (2015). Understanding, Avoiding, and Managing Severe Filler Complications. Plastic and Reconstructive Surgery, 136, 196S–203S. doi:10.1097/prs.0000000000001760

4. Urdiales-Gálvez, F., Delgado, N.E., Figueiredo, V. et al. Treatment of Soft Tissue Filler Complications: Expert Consensus Recommendations. Aesth Plast Surg 42, 498–510 (2018). https://doi.org/10.1007/s00266-017-1063-0

5. Beer K, Downie J, Beer J. A treatment protocol for vascular occlusion from particulate soft tissue augmentation. J Clin Aesthet Dermatol. 2012 May;5(5):44-7. PMID: 22808309; PMCID: PMC3366448.

6. Beleznay K, Humphrey S, Carruthers JD, Carruthers A. Vascular compromise from soft tissue augmentation: experience with 12 cases and recommendations for optimal outcomes. J Clin Aesthet Dermatol. 2014 Sep;7(9):37-43. PMID: 25276276; PMCID: PMC4174919.Enright KM,

7. Nikolis, A, Enright, KM, Berros, P, Sampalis, JS. Safety of infraorbital hyaluronic acid injections: Outcomes of a meta-analysis on prospective clinical trials. J Cosmet Dermatol. 2023; 22: 2382-2390. doi:10.1111/jocd.15925

8. Sampalis JS, Cotofana S, Gilardino MS, Rizis D, et al. (2021) A Systematic Review of Methods for the Prevention, Treatment and Management of Adverse Events Following the use of Aesthetic Soft Tissue Fillers: A Call to Action. Clin Exp Dermatol Ther 6: 172. DOI: 10.29011/2575-8268.100172

9. DeLorenzi C. New High Dose Pulsed Hyaluronidase Protocol for Hyaluronic Acid Filler Vascular Adverse Events. Aesthet Surg J. 2017 Jul 1;37(7):814-825. doi: 10.1093/asj/sjw251. PMID: 28333326.

10. Moradi A, Shirazi A, David R. Nonsurgical Chin and Jawline Augmentation Using Calcium Hydroxylapatite and Hyaluronic Acid Fillers. Facial Plast Surg 2019;35(2):140-8.

11. Pierre, Sébastien PhD*; Liew, Steven MD†; Bernardin, Aude PhD*. Basics of Dermal Filler Rheology. Dermatologic Surgery 41():p S120-S126, April 2015. | DOI: 10.1097/DSS.0000000000000334

Chapter 6: The Global Registry of Adverse Clinical Events (GRACE©): A prospective, multicenter observational cohort study with thirty-month follow-up

Authors: Kaitlyn M. Enright[a,b,c,] Andreas Nikolis[b,c,g] and John Sampalis[d,e,f]

Affiliations: [a]Department of Experimental Surgery, McGill University, Montreal, Canada; [b]Erevna Innovations Inc, Research Unit, Montreal, Canada; [c]Victoria Park Medispa, Montreal, Canada; [d]Department of Surgery and Medicine, McGill University and University of Montreal, Montreal, Canada; [e]Division of Surgical Research, Head Surgical Epidemiology, McGill University, Montreal, Canada; [f]JSS Medical Research, Montreal, Canada; [g]Centre Hospitalier de l'Université de Montreal, Montreal, Canada

Acknowledgements: We would like to thank the following clinician-investigators for participating in the present study: Drs. Demetrios Rizis, Martin Braun, Lisa Kellett, Sean Rice, Jack Kolenda, Andrei Metelitsa, Zaki Taher, and Chantal Chiasson.

Note: To be submitted to Plastic Surgery (the official journal of the Canadian Society of Plastic Surgeons).

Abstract

Background: A review of Health Canada's post-market surveillance database has revealed that the reporting of adverse events (AEs) following injectable treatments for aesthetic indications are significantly underreported. To increase reporting, investigators have recently developed a novel Electronic Data Capture (EDC) system: The Global Registry of Adverse Clinical Events (GRACE)©.

Objective: To identify the true incidence of AEs associated with injectable treatments.

Methods: Aesthetic physicians from ten Canadian sites were recruited. Demographic and clinical data were recorded within the database, which included over fourty-five patient variables.

Results: Data was collected from July 2019 to December 2021 (thirty months). Throughout the active phase of the trial, 123,124 injectable treatments were conducted. One-hundred and eleven patients, experiencing a total of 235 AEs, were entered into the portal. This equated to an AE incidence rate of 0.19% (235/123,124), per treatment. Thirty unique products were associated with AEs, including two biostimulators, three neurotoxins, and twenty-five hyaluronic acid-based fillers. In total, there were 112/235 (47.66%) mild AEs, 88/235 (37.45%) moderate AEs, and 35/235 (14.90%) severe AEs. The most common complication (n = 48/235; 20.43%) was swelling, with a prevalence of 0.04%. Of the documented AEs, only five were reported to other sources, including one case being reported to Health Canada and four cases to the respective product manufacturer.

Conclusions: The initial feasibility of a registry assessing safety outcomes following injectable treatment has been demonstrated. Findings support that the implementation of the GRACE Portal is an effective outreach strategy for increasing AE reporting by health care professionals. Our

data represent a more accurate depiction of the safety profile of approved aesthetic injectables in Canada.

Introduction

The rates of adverse events (AEs) following injectable treatments are widely varied within the literature[1-13]. As can be seen in Table 1, which displays the summary results of fourteen studies reporting AEs rates, there is a widely variable range of rates depending on the source document. For example, a common AE following injection is erythema and this has been reported to occur in as little as 0.004%[14] to as high as 100%[7] of treated patients. The disparity between reported prevalence rates may be due to many contributing factors. Some may include variations in the record keeping practices of different clinics (e.g., many may not record immediate local site reactions to the injection technique as AEs and instead only report late onset and/or chronic AEs) and insufficient follow up with patients (e.g., requiring that patients follow up with the clinic may result in an under reporting of minor AEs and only allow for the practitioner to become aware of more stressing AEs experienced by patients). Moreover, the disparity between the prevalence observed during clinical examination and those documented suggests that AEs are being significantly under reported. For example, as transient local site reactions to injections are a part of the normal immune response to injury[15], it seems intuitive that in the majority, if not in all patients, physicians should observe one or a combination of any of the following: erythema, edema, inflammation, redness, soreness. However, some sources report very rare occurrences of an acute immune response (e.g., 0.06, 0.15[16]). Providing a distinct overview of the specific symptoms experienced by patients also becomes less discernable depending on the language used in the literature. Oftentimes, authors do not report the individual rates of specific AEs (e.g., erythema, edema) and instead report an overall rate for all “local site reactions” or “immune responses”[16-18]. This contributes to the uncertainty regarding the exact prevalence rates of specific symptoms. Furthermore, given the large number

of injectable treatments performed (i.e., 5,638,320 injections in the United States in 2013[19]), it is evident from current databases that AEs are being underreported. For example, a search of the "Canada Vigilance Adverse Reaction Online Database" revealed that only 10 cases of AEs were reported for the millions of treatments performed. Furthermore, since 2010 Health Canada has only received 48 adverse incident reports of pain, edema, nodules, abscesses, lip necrosis, partial loss of vision and vascular compromise suspected of being associated with the use of dermal fillers[20,21].

Given the observable underreporting of AEs and the variation in rates currently reported, the establishment of an easily accessible online AEs registry could provide the observational platform required to collect and evaluate data on the incidence of AEs following injectable treatments. Furthermore, this AEs registry would also provide the preliminary data required to create algorithms or protocols for managing AEs and standardizing care. In consideration of the above, the present manuscript described the development and validation of an AE database.

Research question

What is the true incidence of AEs associated with aesthetic injectable fillers, in routine clinical practice?

Objectives

To describe AEs following treatment with injectable fillers and to provide standard guidance on their avoidance and treatment.

Methods

Portal design and development

Major milestones in the development of the AE registry are depicted in Table 2. The portal was constructed specifically for observational research as a cost-effective management

tool. The design supports simple delivery models that are scalable, flexible and have the potential for international dissemination. Moreover, the registry consists of a transparent, uncomplicated user-face (Appendix 3). Data collection occurs through electronic clinical report forms (eCRFs), which are form-like web pages. Through eCRFs, sites submit patient, treatment, and AE data to the central database. The eCRFs have the same structure and design as typical paper-based CRFs from which their content was based. The eCRFs are organized into sections: i) Patient Information; ii) AE Information; and iii) Follow Up Visits. This structure introduces automation to the AE reporting process by providing a platform that intuitively breaks the procedure down into its primary steps. As the main outcome variables of interest are AEs, reporting is an event-centered process, rather than a visit centered one. A flexible visit structure ensures users can individualize the number of follow up visits and only have to enter data for visits that actually occur.

Throughout the data entry process, intuitive prompts will help physicians move swiftly through the entry procedures. Mouse overs will provide definitions of terms to ensure consistency of imputed data across all sources. Individual sites will be able to generate their own reports and data extracts and the Super Admin (study sponsor) can generate reports and data extracts for all sites. This feature will eliminate data transcription and iterations and ensure adverse events and product quality data capture is made easy.

A differential product analysis (results on file) demonstrated that at the time of development, there were no EDC systems specifically designed for AE data capture. This fact illuminated many purpose-driven limitations to the available platforms. Therefore, the GRACE Portal platform includes a purpose-built system design (e.g., risk based remote monitoring, back-up and disaster recovery) and efficient eCRF design (e.g., proper data element identifiers, robust

use of edit checks and electronic prompts for missing or inconsistent data). These features eliminate a high percentage of possible errors from manual inputting and save money on monitoring travel expenses for source verification site visits. Upon entry of an AE, the system automatically creates and records a link to the appropriate International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) code and term, to ensure consistent reporting between physicians and sites. Also, our software is the first and only EDC to subsequently provide links between the reported AE and current, real-time guidelines to standards of treatment and consensus documents on how to address the AE. At the final visit, a page displays a summary of all entries for that patient. At this point the physician can make any necessary changes, then they will e-sign and date stamp the record to archive it. No further changes to the patient's data can be made after this point, unless the monitor issues a query.

Regulatory requirements

Many features of the portal have been designed with certain international and national regulatory requirements in mind. For example, our registry design conforms to the following privacy and security standards:

- ***Health Insurance Portability and Accountability Act (HIPAA):*** The *Privacy Rule*, or Standards for Privacy of Individually Identifiable Health Information, which establishes the national standards for the protection of certain health information. *The Security Rule*, or The Security Standards for the Protection of Electronic Protected Health Information, which establishes a national set of security standards for protecting certain health information that is held or transferred in electronic form.

- ***FDA 21CFR Part 11(Code of Federal Regulations Title 21):*** In accordance with this regulation, which states general provisions for electronic records and signatures, our registry contains e-signatures, an audit trail, data validation and access management.
- ***ISO (The International Organization for Standardization) 9001:2015*****:** Which states the requirements for a quality management system to include documented information, planning, responsibilities of management, management of resources, measurements, analysis and improvement of the system through activities like internal audits and corrective and preventive action.
- Ensuring our system design is in accordance with standards listed in items 1 through 3 also warrants Good Clinical Practice (GCP/GxP) compliancy.
- The specific components of our innovative platform ensure that the goals of "reliability, quality, integrity, and traceability" mentioned in the 2013 FDA eSource Requirements Guidance document can be achieved.

Patient confidentiality: As the registry only requires data from the physician(s) or site(s), the data will be anonymized and de-identified at source. No individually identifiable health information or "protected health information" as defined by HIPAA and its implementing regulations will be collected. After the initial patient file is created, the physician may keep adding data to the registry by using an automatically assigned subject number.

Data encryption: As data will be anonymized and de-identified at source, the use of encryption is not required. However, in the event that patients' personal information must be retained (e.g., date of birth, physician and geographical location more specific than province, disease), the platform will be equipped with encryption capabilities. In these cases, the NHS

benchmark: AES256 standard for Encryption will be used. The data will be encrypted using AES256 in a separate portal.

SSL certificate: Secure Sockets Layer (SSL) certificates are small data files that digitally bind a cryptographic key to an organization's details. When installed on a web server, it activates the padlock and the https protocol and allows secure connections from a web server to a browser. Our software will utilize SSL certificates to secure data transfer and logins. The SSL certificates will provide secure, encrypted communications between the internet browser and database.

Risk plan for ensuring data quality: Our standard operating procedures will ensure that site quality checks are routinely performed to reveal information such as time since last patient entry, open queries and total queries. "Delinquent" sites will first be put on a watch list that will trigger a call from the Sponsor. Should delinquency continue, a site visit may be justified to further train staff or review source documents and speak with investigator to resolve any issues. This step wise process will better allocate resources to delinquent sites.

AE coding and terminology: Our platform is equipped with a medical dictionary for AE coding and terminology. This feature improves the dissemination potential of research conducted using our software and also simplifies and quickens the task of reporting AEs to regulatory bodies. The system includes pre-coded colloquial terms which maps back to the appropriate ICD-10 terms and codes. Future versions may also include the MedRA coding dictionary but given the price of obtaining and maintaining a MedRA subscription for system developers (e.g., $3,000 USD per year), the creators are making the first version of our EDC system using the freely available ICD-10 codes and terms.

Technical requirements: The system will be accessible online via Chrome and Safari web browsers. Providing a web-based solution (in comparison to a desktop application) circumvents

the installation process and expedites updates to software for users. The portal will initially be available on Windows and Mac. After an initial trial period, the possibility and benefit of making the program tablet and/or phone compatible will be evaluated.

Given that this EDC software is a cloud-based system, it lives on the internet (unlike on-premise solutions). This allows flexibility as the central server can be located anywhere in the world and the software can still be accessible to anyone with internet access. This makes our system more functional, affordable (since the same software base code can be used by all customers) and allows for more frequent updates. There is no need for customers to build and maintain an on-premise IT infrastructure that requires data centers, real estate to house them or skilled professionals to operate them. Also, the fact that very little user training is required and that training can be done remotely eases and minimizes the costs associated with the process of initial setup and facilitates penetration into various graphical regions.

Moreover, the GRACE Portal contains some exclusive and uncommon system features, including:

- Being the only system that provides guidance and consensus information upon AE reporting.
- Data encryption of identifying and protected health information.
- Contains an uploading tool for any associated images (available when confirmation that a signed photo release form has been obtained) or documents (e.g., lab results) that may need to be attached to individual records.
- Flexible visit structure, which is a feature many other EDC programs do not offer – which triggers many queries or missing data fields and causes problems during data analyses.

- Pre-coded colloquial terms within the system – easy terminology which maps back to appropriate ICD-10 terms.
- Ease of use and simple interface: existing software may be difficult to support technically or the creation of study-specific eCRFs may require advanced programming and coding knowledge.

Portal validation

***User acceptance testing*:** After completing the design and development of the GRACE portal, we approached colleagues to engage in user acceptance testing. These included evaluations related to the likeability of the user-face, its ease of use, the need to include or exclude certain variables and the phrasing and interpretations of questions.

Pilot Study: Aesthetic physicians from three Quebec clinics were invited to participate in the registry's validation. Over a three-month period, physicians were asked to report all AEs related to neurotoxins or soft tissue fillers. Variables of interest included sociodemographic data, product type, AE location, duration, intensity and outcome. Data quality was evaluated by assessing completeness and accuracy (defined as internal consistency within the registry record and alignment with the patient's source medical record). After revisions based on user feedback, Version 5.0 of the registry was deployed as the final version used in the pan-Canada study.

Study design

Plastic surgeons, dermatologists, and general aesthetic practitioners were invited to participate in the registry. All participants were required to have a minimum of five years of experience performing aesthetic injectables. The participants were selected to have a range of clinic sizes, levels of experience, relevant specialties (i.e., facial plastics, aesthetics, dermatology), and to ensure regional representation. The physicians were asked to report any

AEs related to filler injections that occurred throughout the thirty-month data collection period. The proposed registry focused on information regarding AEs obtained from observational methods. All AEs related to the use of soft tissue fillers for aesthetic purposes in the face and neck area were included. There were no other patient-related inclusion or exclusion criteria. Assessments included clinical events (e.g., venous occlusion, skin necrosis) and patient symptoms (e.g., pain). Personal data, prior injectable filler treatments, reaction type, location, duration, intensity and outcome were also recorded.

Recruitment consisted of all patients presenting with an AE following treatment with injectable products. No randomization or control group was present. The duration of treatment and number of visits varied based on the attending physician's direction. Data related to treatments conducted within the first 27-months of study startup were assessed. Safety data were collected for an additional three months, to allow for sufficient follow-up of subjects treated near the study end date.

Ethical considerations

This study received approval by a central research ethics board (REB; Institutional Review Board Services) and, where applicable, also local REB approval (HREBA). The IRBs determined that the Canadian privacy requirements for a waiver of consent were met. The study was carried out in accordance with Health Canada regulations, 21 CFR parts 56 and 312.3 and 45 CFR 46, good clinical practices (e.g., ICH GCP Guidelines), Alberta Health Information Act, and the Tri-Council Policy Statement for Ethical Conduct of Research Involving Humans, as appropriate to the research. Copies of the REB certifications and a description of the research were sent to the Office of the Information and Privacy Commissioner (OIPC).

Waiver of Informed Consent

As this research involved secondary use of information originally collected for charting purposes, it would have been impracticable to conduct this study without a waiver for informed consent. Therefore, the researchers requested a waiver of consent that was in accordance with the standards described by the Government of Canada and the Canadian Institute of Health Research. The waiver of consent was further justified because the research involved no risk to patients, the lack of the patient's consent was unlikely to adversely affect the welfare of the patients (as they are treated as per routine care) and the study did not involve administering a therapeutic intervention, but rather evaluated information after patients had been routinely treated by their attending physicians. Furthermore, this research satisfied all of the criteria in Article 5.5 Parts A to F regarding researchers who use secondary data without informed consent. It also conformed to industry standards whereby no consent is obtained as this was a limited data set and does not include identifiable information.

Sample size and recruitment

Given the study design (i.e., capturing all available cases in the population), no traditional sample size calculation was able to be performed. However, based on previous reports regarding the incidence rates of rare AEs in patients following injectable treatments (e.g., 0.004% for necrosis),[1-14] it was expected that data relating to ~200 AEs would be entered.

It was estimated that approximately ten Canadian sites would participate in the study. Recruitment of study sites was determined following the administration of a site feasibility questionnaire (Appendix 2).

Procedures

Physicians accessed the portal via an online platform, after successful completion of the site screening questionnaire. Each user was provided with a unique username and password. Regular on-site monitoring was conducted throughout the data collection period (~every 6 months), to ensure accuracy of the data entered into the portal with source documents maintained by the participating physicians. Following each monitoring visit, sites were provided with a monitoring report, which outlined any data queries that needed clarification/correction. All data was queried prior to data analyses.

Results

Study centers

In total, ten sites participated in the present study. These sites were location in Quebec (n = 3), Ontario (n = 3), New Brunswick (n = 1) and the West Coast [British Columbia, Alberta, Manitoba (n = 3)]. Participating physicians had an average of 15.20 (Range: 9 to 20) years of experience performing aesthetic injectables.

Adverse events

Throughout the active phase of the trial, 123,124 injectable treatments were conducted. One-hundred and eleven patients, experiencing a total of 235 AEs, were entered into the portal. This equated to an AE incidence rate of 0.19% (235/123,124), per treatment. Thirty unique products were associated with AEs, including two biostimulators, three neurotoxins, and twenty-five hyaluronic acid-based fillers. In total, there were 112/235 (47.66%) mild AEs, 88/235 (37.45%) moderate AEs, and 35/235 (14.90%) severe AEs. The most common complication (n = 48/235; 20.43%) was swelling, with a per-treatment prevalence of 0.04%. Of the 235

documented AEs, only five (2.12%) were reported to other sources, including one case being reported to Health Canada and four cases to the respective product manufacturer.

Discussion

Innovative solution for improving health outcomes

One of the strongest breakthroughs in information and communication technology for the healthcare system was the introduction of electronic patient records. This is reflected in the increase of resources that the healthcare industry allocates to healthcare informatics from 2% of its revenues during the 1990s to 5% to 7% in more recent years[22]. Despite the fact that EDC systems have been available for over two decades, many clinical trials and practices are still mainly conducted collecting patient data using paper documents as the primary tool. In fact, it has been reported that in over 75% of practices, paper data collection is the main source of data acquisition[23]. A reason for this has been partially ascribed to the fact that standards have not been extended to facilitate data collection at the investigation site, as AE capture and reporting is one of the most time-consuming activities related to the conduct of trials and in clinical practice. Another reason relates to the fact that present technological applications often do not have adequate functionality to meet current needs. Therefore, there remains a high demand for an EDC system that is designed to be quick, easy to deploy, and simple to use.

Herein, we describe the development and validation of an electronic tool that can be used in clinic settings for real-time AE collection. The EDC software can offer several benefits including regulatory compliance, help organizations manage pharmacovigilance requirements, ensure data quality, integrity, and transparency, and improve patient safety. Our EDC system may also lower the costs of collecting, storing, and distributing clinical trial data, as well as modernizes the data collection process. To date, the platform has been validated through a pan-

Canadian observational study, with its initial deployment into ten medical-aesthetic clinics. Of note, the usefulness of the registry was evidenced by the significant increase in the number of AE reports submitted by sites, in comparison to reports submitted by the same sites via other means. For example, of the 235 documented AEs, only five (2.12%) were reported to other sources, including one case being reported to Health Canada and four cases to the respective product manufacturer.

Implications

The validation and implementation of the GRACE Portal offers many near and far-reaching benefits, including creating a cohort of subjects for future epidemiological, health services and outcomes research; enabling clinics to compare their performance with aggregated data; supporting clinicians in decision making and in quality improvement activities; helping decision-makers evaluate policies; and encouraging medical practice change and improved clinical outcomes. Herein, the true incidence of any AE following an aesthetic injectable treatment was found to be 0.19%, which is higher than previous reports. This finding stresses the importance of re-evaluating current AE protocols and validating treatment recommendations through clinical trials.

Limitations

There are inherent limitations to an observational study (e.g., lack of a control group, no standardization of assessments). However, this study represents a first attempt to provide the aesthetics industry with a landscape assessment (e.g., type of injector; experience and training of injectors; average number of procedures performed per year; types of products being used; geographical patterns in use, techniques, or AE rates) and delineate these data points in the field.

As such, an observation study design was appropriate for this initial probe and to inform the design of future studies.

The results of this study may not be generalizable to all aesthetic practitioners, clinics, or geographical locations. This may be due to differences in the training or experience of the injectors, should they significantly differ from those evaluated in this study. For example, incidence rates of AEs may be higher in a sample of nurses, or in non-regulated professions. Moreover, AE incidence rates are likely increased in clinics that illegally import and distribute products not currently approved for use in Canada. As this was a Pan-Canadian study, results could be dependent on the demographical distribution of patients in Canada. As such, the results may not be generalizable to clinics located in other countries. However, given the ease of implementing a virtual monitoring system, the GRACE Portal could be easily implemented into other countries. The GRACE Portal is HIPAA compliant and was designed to meet international standards regarding the use of health-related information.

Future Directives

Future directives include increasing outreach strategies to implement the GRACE Portal throughout Canada and internationally, creating algorithms or protocols for the management and/or treatment of AEs and standardizing care, and ultimately, contribute to the improvement of health care outcomes in aesthetic patients.

Intellectual property

The database was registered for copyright as per Canadian copyright laws under the registration number 1146604, on January 22nd 2018. The “GRACE” logo associated with the product and services was into the Trademarks Register of the Trademarks Office of the Canadian

Intellectual Property Office of Industry Canada. The portal logo has been designed as indicated below, using the following colour chart:

GRACE
GLOBAL REGISTRY OF ADVERSE CLINICAL EVENTS

Pantone: 647
HEX: 014A74
RGB: 1, 74, 116

HEX: 6DCBD2
RGB: 109, 203, 210

Figure 1. Flow chart of registry procedures.

Table 1. List of adverse events and their respective reported rates following treatment with injectable products.

Adverse Event	Rate
Erythema	0.07%; 10%; 12%; 100%
Edema	0.01%; 0.02%; 15%; 32%
Pain/Tenderness	
Bruising/hematoma	0.02%; 5%; 21%; 35%
Itching	
Infection/ Biofilms	0.04 to 0.2%
Papule formation	0.02%
Nodule/Abscess	0.02%; .025%; 0.05%; 0.07%; 12.4%; 56%; 60%
Lumps/asymmetries/contour irregularities (caused by technique and placement errors)	15%
Skin discoloration -Redness -Whiteness -Hyperpigmentation -Tyndall effect (blue bump)	0.09%
Vascular occlusion > tissue necrosis	0.004%
Immune reactions ex: granuloma	8%; 32%
Migration of implant material	
Scarring	
Herpetic outbreak	0.006%; 21%
Paresthesia	
Needle marks	
Under/over correction	
Any site reactions/immune responses reported	*0.06%; 0.15%; 13%; 51% 90.6% -93.5%*

Note: Many AEs were reported without their respective rates.

Table includes summary of results from references #1-14

Table 2. AE Registry Timeline and Milestones

	Timelines	**Milestones**
Project Planning: Month 0 - 6	Month Zero to Six	• Articulate the purpose/objectives of the registry; • Define the scope and rigor needed; • Assess the feasibility of a registry; • Define the data set, patient outcomes and target population; • Describe the health-related events under surveillance, including the case definition for each specific condition; • Cite any legal authority for the data management. • Develop a project plan and protocol including amendments and updates; • Identify key stakeholders; • Secure funding; • Describe the planned uses of the data from the system.
	Month Four to Six	• Build a registry team • Establish a governance and oversight plan.
Project Execution Month 6 - Year 3	Month Six to Twelve	• Ethics submission(s) • Set up private server • Portal design and development • Site initiation visits • Establish out of hours information line • Data collection begins.
	Years Two to Three	• Periodic critical evaluations of the registry by by internal review/advisory committee to ensure that the objectives are being met; • Registry adaptations based on critical evaluations; • Site visits;

		• Data collection completed; • Data analyses; • Results dissemination.

References

1. Alijotas-Reig J, Garcia-Gimenez V. Delayed immune-mediated adverse effects related to hyaluronic acid and acrylic hydrogel dermal fillers: clinical findings, long-term follow-up and review of the literature. J Eur Acad Dermatol Venereol 2008;22(2):150-61.
2. Alijotas-Reig J, Garcia-Gimenez V, Miró-Mur F, Vilardell-Tarrés M. Delayed immune mediated adverse effects of polyalkylimide dermal fillers: clinical findings and long-term follow-up. Arch Dermatol 2008;144(5):637-42.
3. Kerscher M, Bayrhammer J, Reuther T. Rejuvenating influence of a stabilized hyaluronic acid-based gel of nonanimal origin on facial skin aging. Dermatol Surg 2008;34(5):720-6.
4. Morris CL, Stinnett SS, Woodward JA. Patient-preferred sites of restylane injection in periocular and facial soft-tissue augmentation. Ophthal Plast Reconstr Surg 2008;24(2):117-21.
5. Sadick NS, Katz BE, Roy D. A multicenter, 47-month study of safety and efficacy of calcium hydroxylapatite for soft tissue augmentation of nasolabial folds and other areas of the face. Dermatol Surg 2007;33(Suppl 2):S122-S126.
6. Goldberg RA, Fiaschetti D. Filling the periorbital hollows with hyaluronic acid gel: initial experience with 244 injections. Ophthal Plast Reconstr Surg 2006;22(5):335-41.
7. Han SK, Shin SH, Kang HJ, Kim WK. Augmentation rhinoplasty using injectable tissue engineered soft tissue: a pilot study. Ann Plast Surg 2006;56(3):251-5.
8. Jacovella PF, Peiretti CB, Cunille D, Salzamendi M, Schechtel SA. Long-lasting results with hydroxylapatite (Radiesse) facial filler. Plast Reconstr Surg 2006;118(3 Suppl):15S-21S.
9. Jansen DA, Graivier MH. Evaluation of a calcium hydroxylapatite-based implant (Radiesse) for facial soft-tissue augmentation. Plast Reconstr Surg 2006;118(3 Suppl):22S-30S.

10. Roy D, Sadick N, Mangat D. Clinical trial of a novel filler material for soft tissue augmentation of the face containing synthetic calcium hydroxylapatite microspheres. Dermatol Surg 2006;32(9):1134-9.
11. Carruthers J, Klein AW, Carruthers A, Glogau RG, Canfield D. Safety and efficacy of nonanimal stabilized hyaluronic acid for improvement of mouth corners. Dermatol Surg 2005;31(3):276-80.
12. Carruthers A, Carruthers JD. Polymethylmethacrylate microspheres/collagen as a tissue augmenting agent: personal experience over 5 years. Dermatol Surg 2005;31(11 Pt 2):1561-4.
13. Jacinto SS. Ten-year experience using injectable silicone oil for soft tissue augmentation in the Philippines. Dermatol Surg 2005;31(11 Pt 2):1550-4.
14. Stupak HD, Moulthrop TH, Wheatley P, Tauman AV, Johnson CM. Calcium hydroxylapatite gel (Radiesse) injection for the correction of postrhinoplasty contour deficiencies and asymmetries. Arch Facial Plast Surg 2007;9(2):130-6.
15. Lowe NJ, Maxwell CA, Patnaik R. Adverse reactions to dermal fillers: review. Dermatol Surg 2005;31(11 Pt 2):1616-25.
16. Friedman, P. M., Mafong, E. A., Kauvar, A. N. B., et al. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. *Dermatol. Surg.* 28: 491, 2002.
17. Zielke H, Wölber L, Wiest L, Rzany B. Risk profiles of different injectable fillers: results from the Injectable Filler Safety Study (IFS Study). Dermatol Surg 2008;34(3):326-35
18. Sperling, B., Bachmann, F., Hartmann, V., Erdmann, R., Wiest, L., & Rzany, B. (January 01, 2010). The current state of treatment of adverse reactions to injectable fillers. *Dermatologic Surgery : Official Publication for American Society for Dermatologic Surgery [et Al.], 36,* 1895-904.
19. Hotta, T. A. (January 01, 2014). ASAPS (American Society of Aesthetic Plastic Surgery)--2013 Annual Statistics. Plastic Surgical Nursing: Official Journal of the American Society of Plastic and Reconstructive Surgical Nurses, 34, 2.)

20. Health Product InfoWatch - August 2016. Health Canada. Taken 31 October 2017 from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/health-product-infowatch-august-2016.html
21. Djelouah I, Scott C. Adverse incidents with injectable hyaluronic acid dermal fillers. Can Advers Reaction Newsl 2010;20(3):3.

Chapter 7: Discussion and conclusions

AEs associated with the use of aesthetic injectables are underreported in the literature. Therefore, most complication guidelines rely on expert opinion with no direct evidence or very low-quality studies with significant imitations. Moreover, there have been few advancements or changes to expert recommendations in AE action protocols in the last decade, despite a growing number of novice injectors and treatments being performed, and varying product technologies entering the global market. Consequently, there is an increasingly urgent need to re-evaluate currently proposed guidelines in order to provide clinicians with more accurate guidance.

In an early attempt to address this call-to-action, we first graded and summarized evidence-based methods for the prevention, treatment and management of AEs associated with the use of aesthetic injectables. The findings provided a foundational framework for evaluating the current body of evidence. To further assess the quality of these methods, it was determined that prospective studies were required to systematically evaluate outcomes following complication management. Subsequently, a prospective registry capable of evaluating the incidence rates of AEs was developed and validated, thus establishing a real-world timeline between treatment exposure and signs and/or symptoms of AEs.

Future aims should focus on the implementation of the registry into additional clinics, as well as expand reach of service to countries outside of Canada. As the database grows, correlations between risk factors and AEs can be assessed more thoroughly, and AE protocols can be better evaluated and validated.

Appendices

Appendix 1. Models for the prevention, treatment and management of adverse events following the use of aesthetic soft tissue fillers in the face.

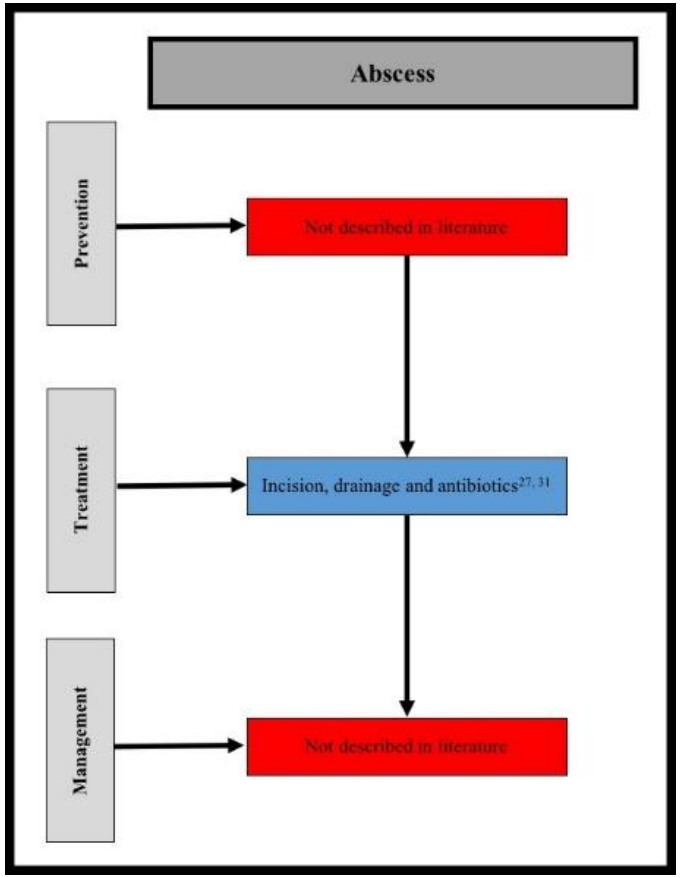


Figure 2a. Models for the prevention, treatment and management of abscesses following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

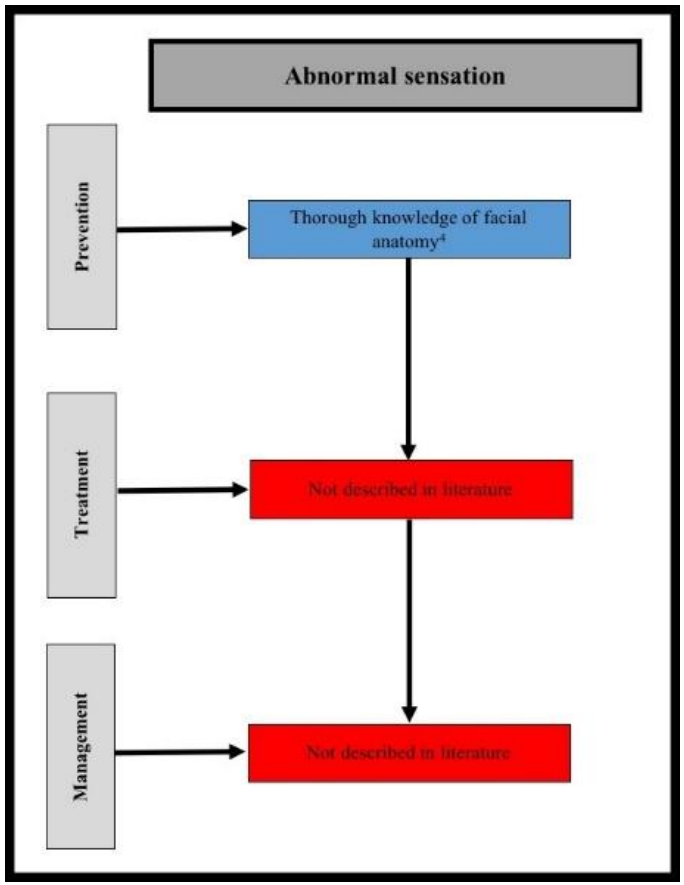


Figure 2b. Models for the prevention, treatment and management of abnormal sensation following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

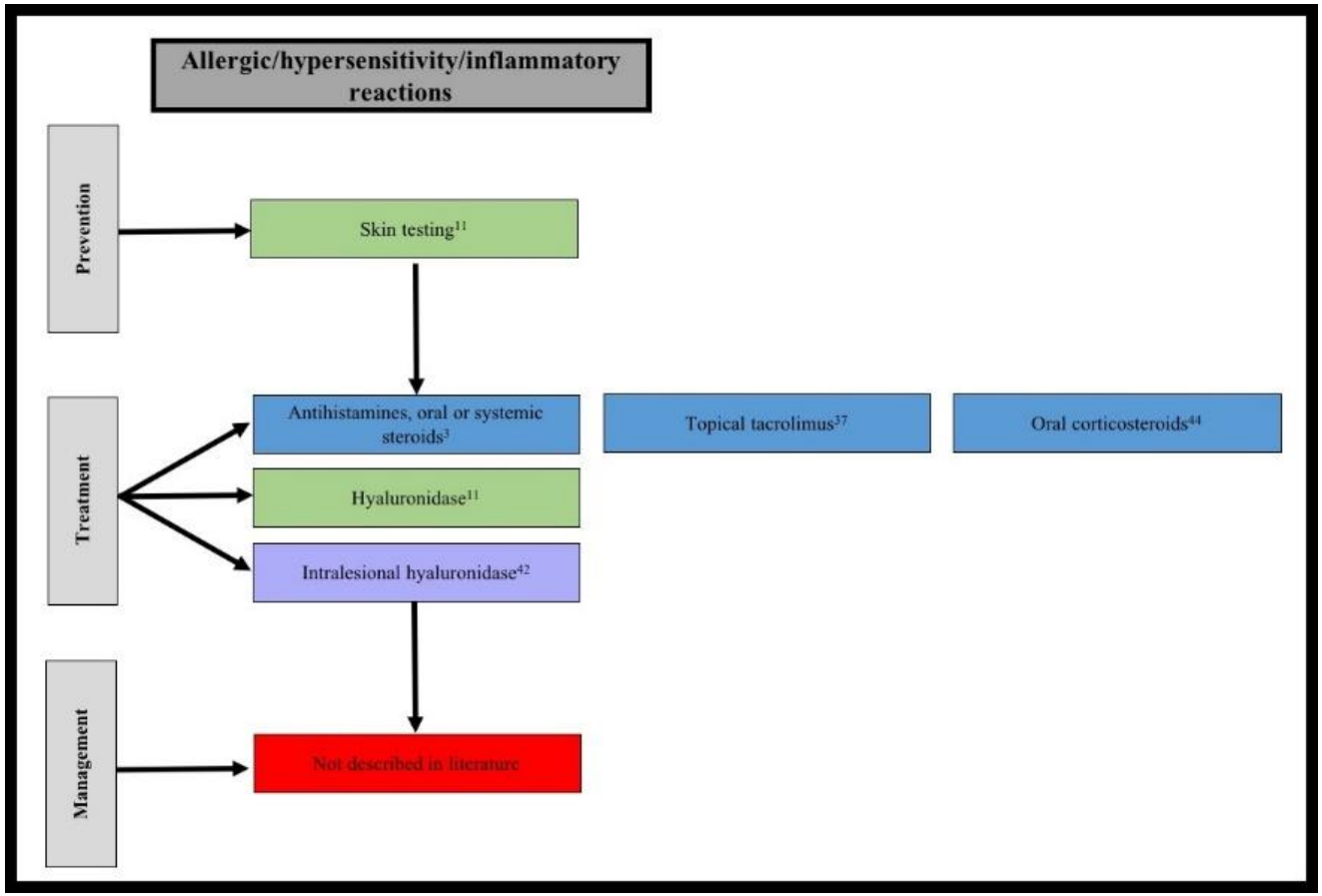


Figure 2c. Models for the prevention, treatment and management of allergic/hypersensitivity/inflammatory reactions following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

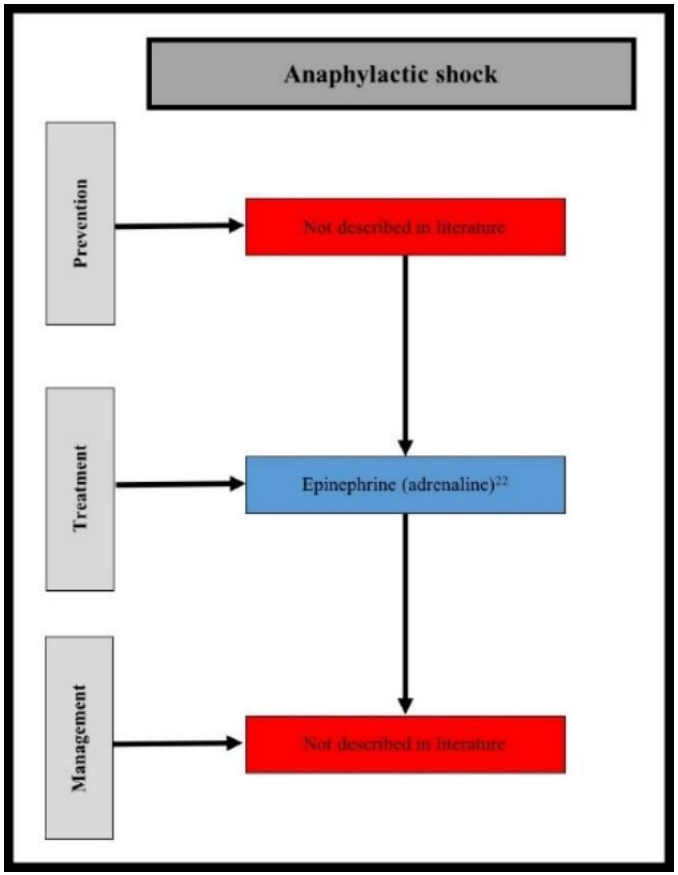


Figure 2d. Models for the prevention, treatment and management of anaphylactic shock following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

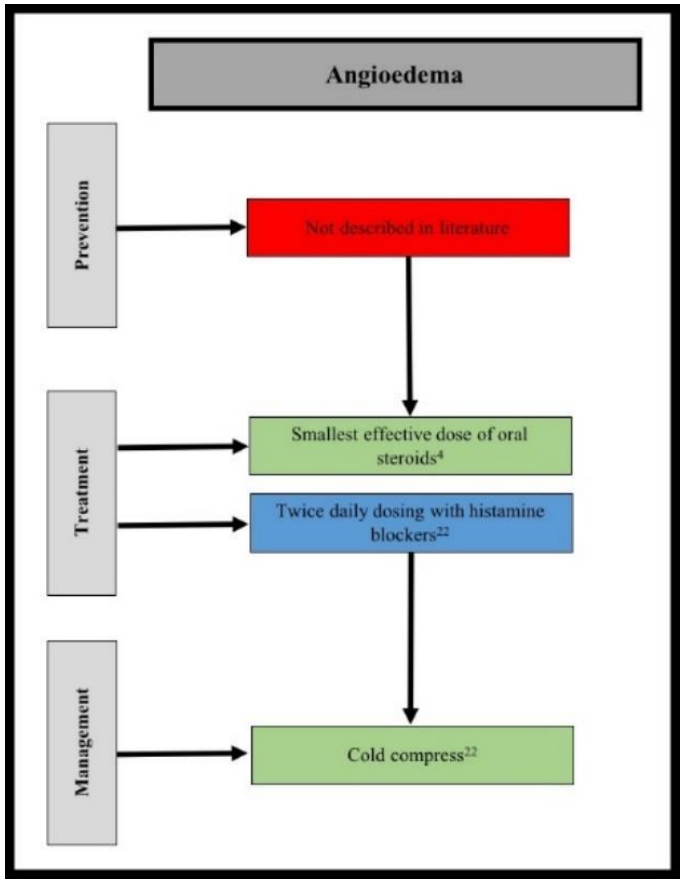


Figure 2e. Models for the prevention, treatment and management of angioedema following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

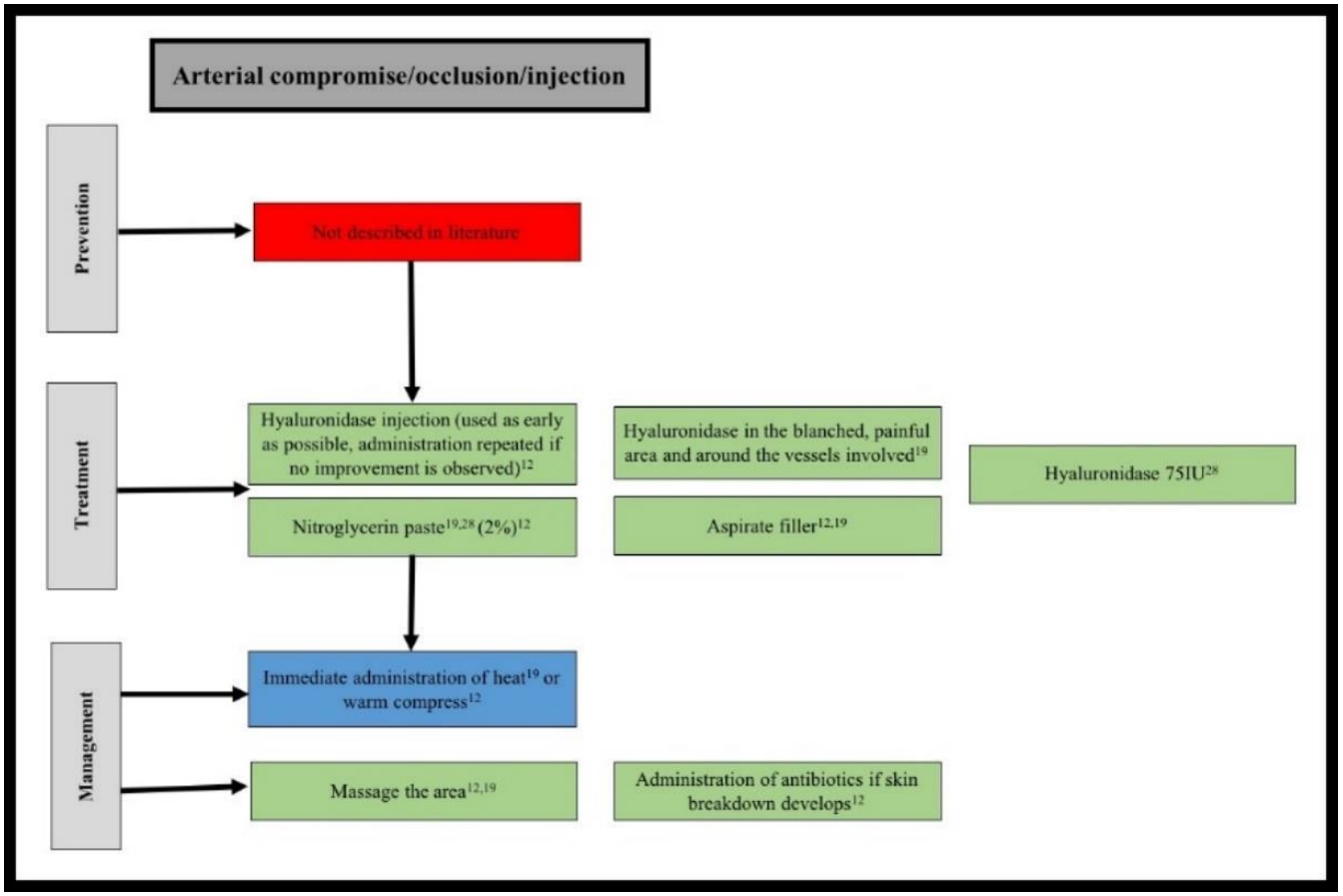


Figure 2f. Models for the prevention, treatment and management of arterial compromise/occlusion/injection following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

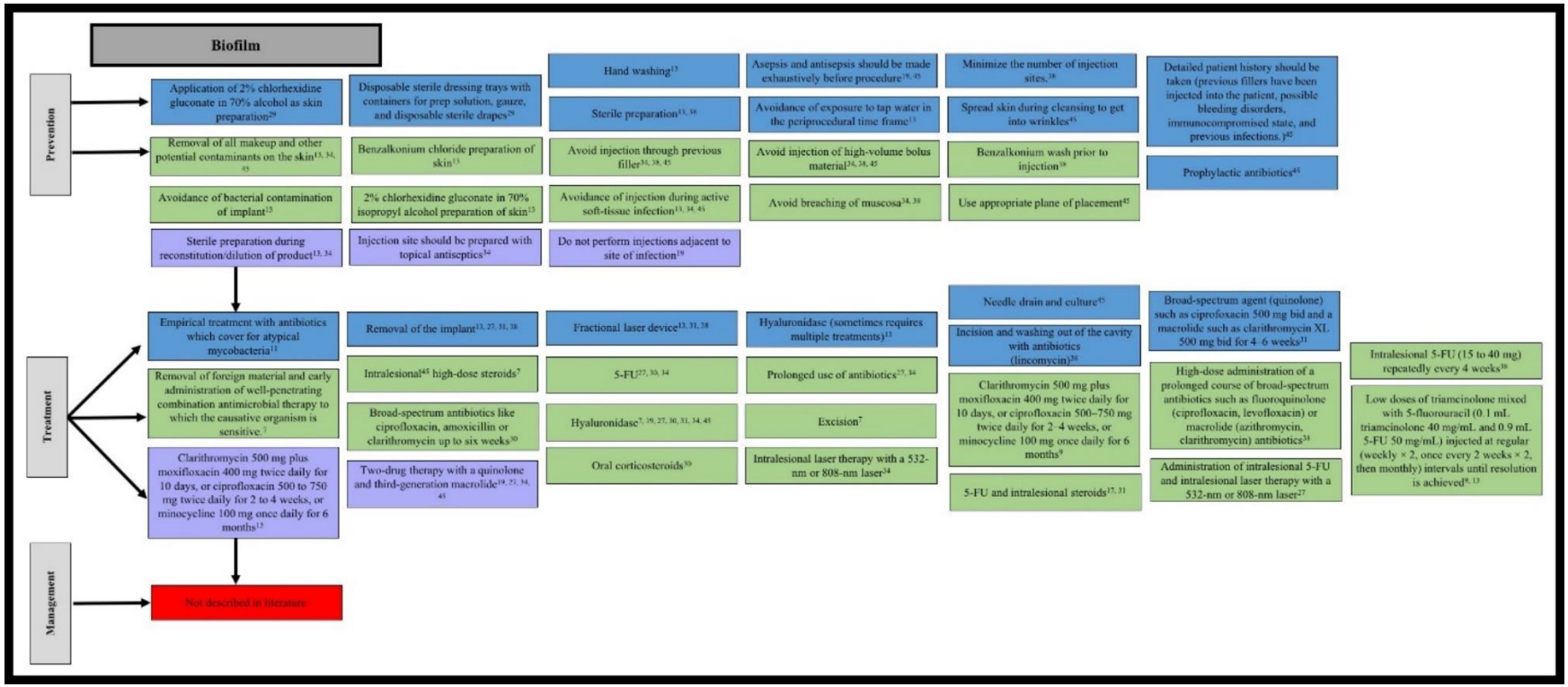


Figure 2g. Models for the prevention, treatment and management of biofilms following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

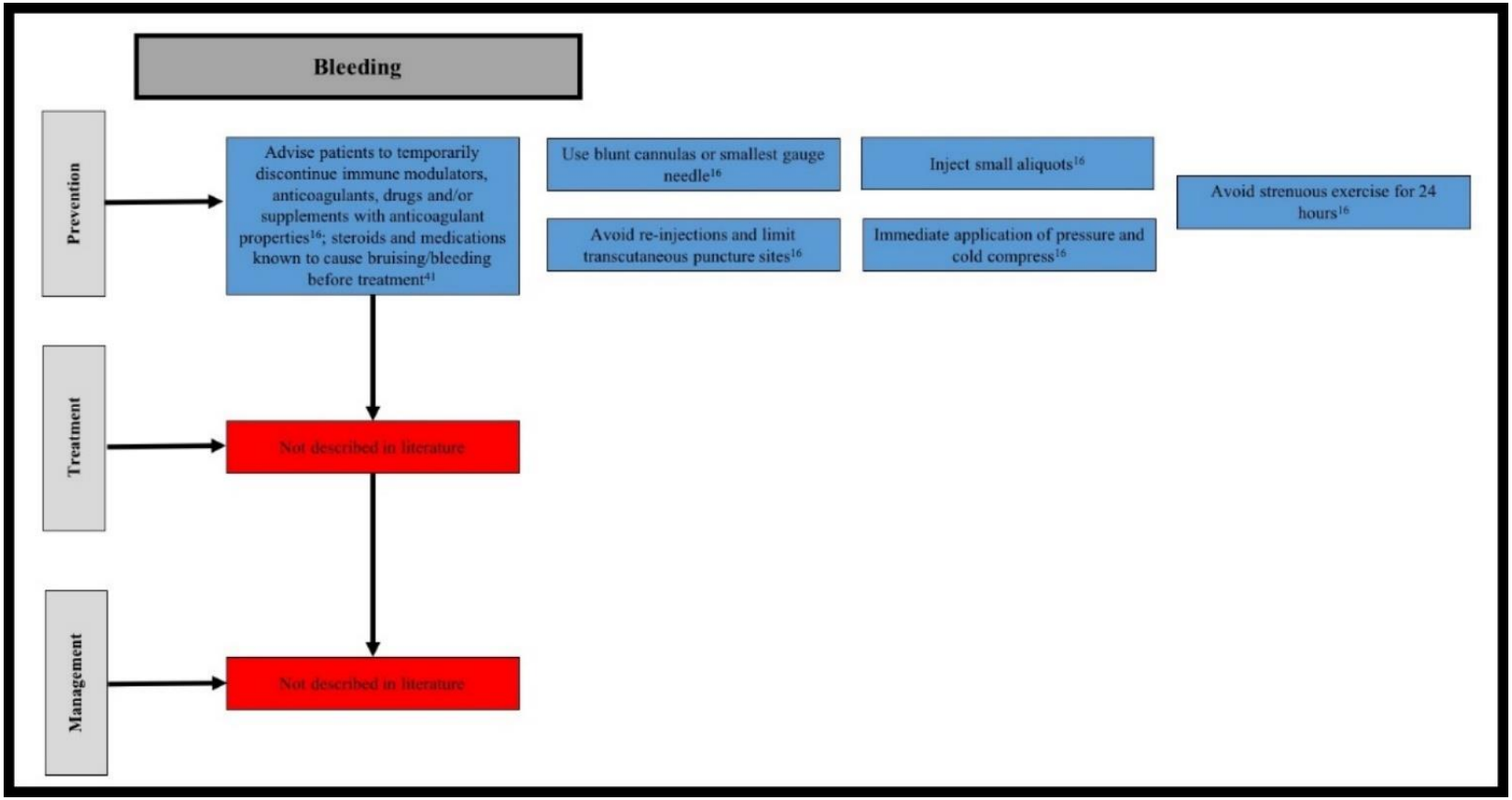


Figure 2h. Models for the prevention, treatment and management of bleeding following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

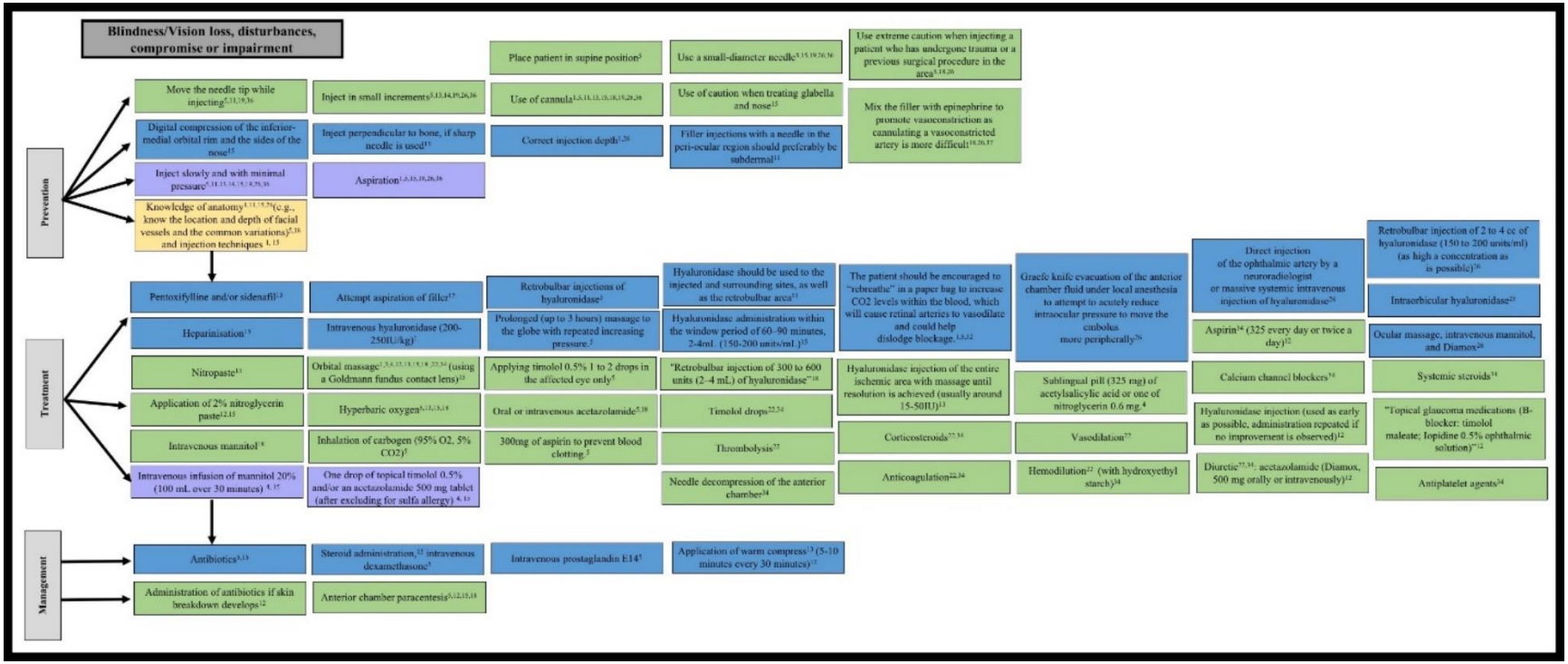


Figure 2i. Models for the prevention, treatment and management of blindness/vision loss, disturbances, compromise or impairment following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

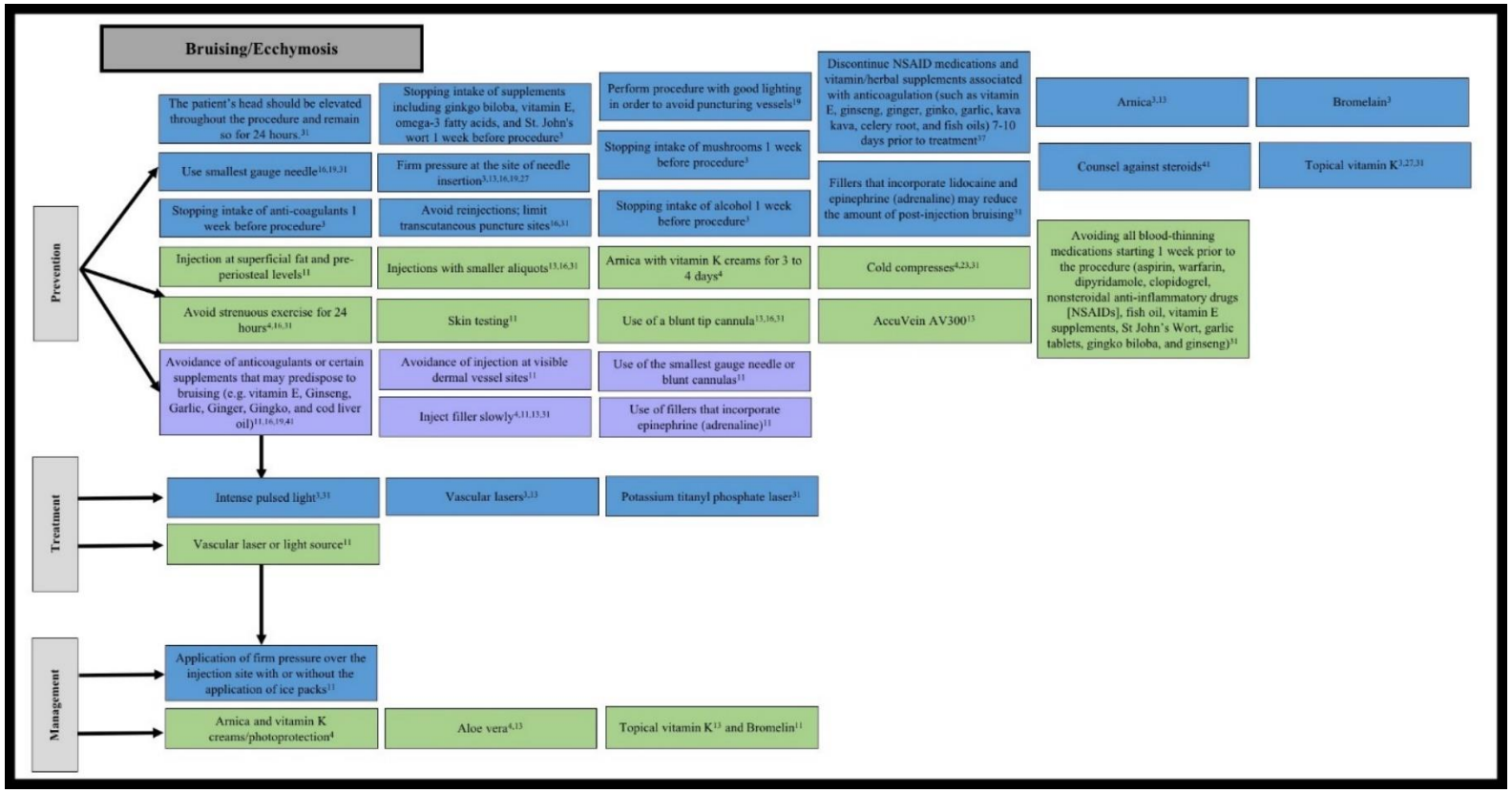


Figure 2j. Models for the prevention, treatment and management of bruising/ecchymosis following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

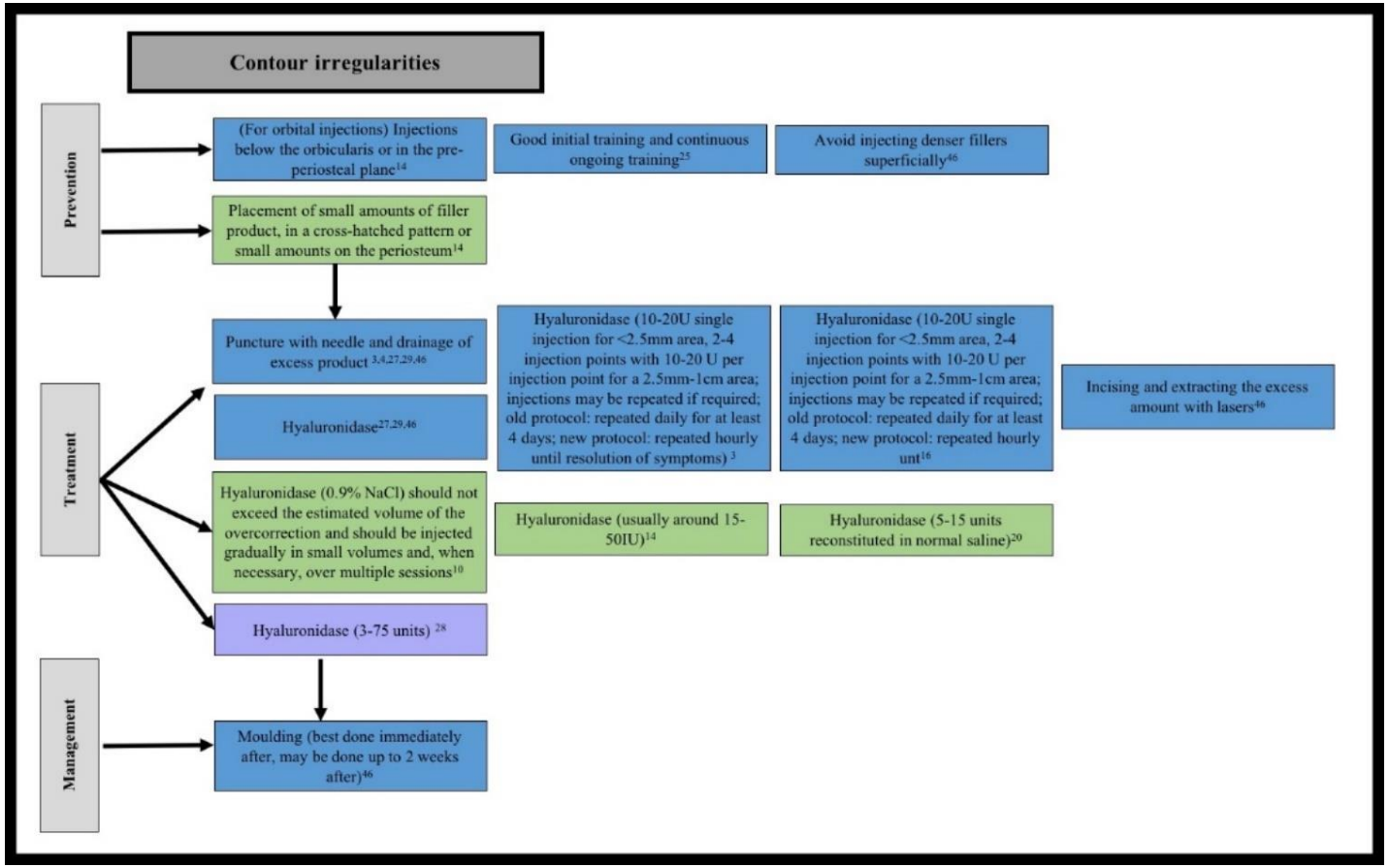


Figure 2k. Models for the prevention, treatment and management of contour irregularities following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

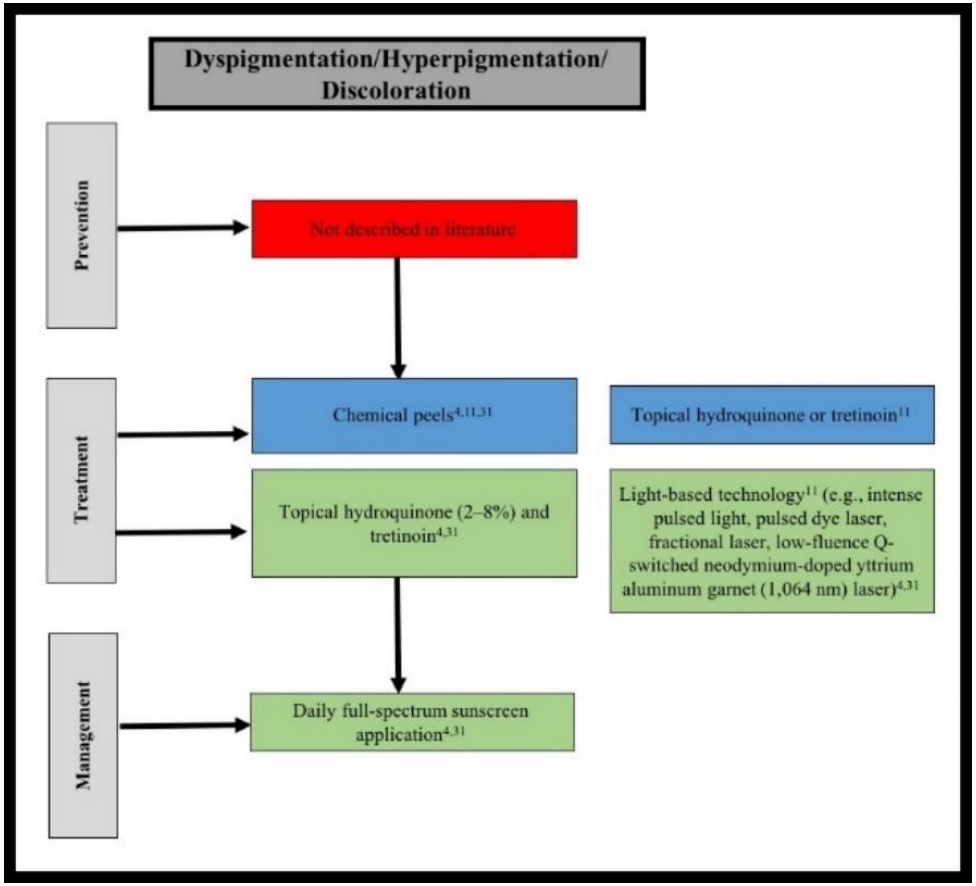


Figure 2l. Models for the prevention, treatment and management of dyspigmentation/hyperpigmentation/discoloration following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

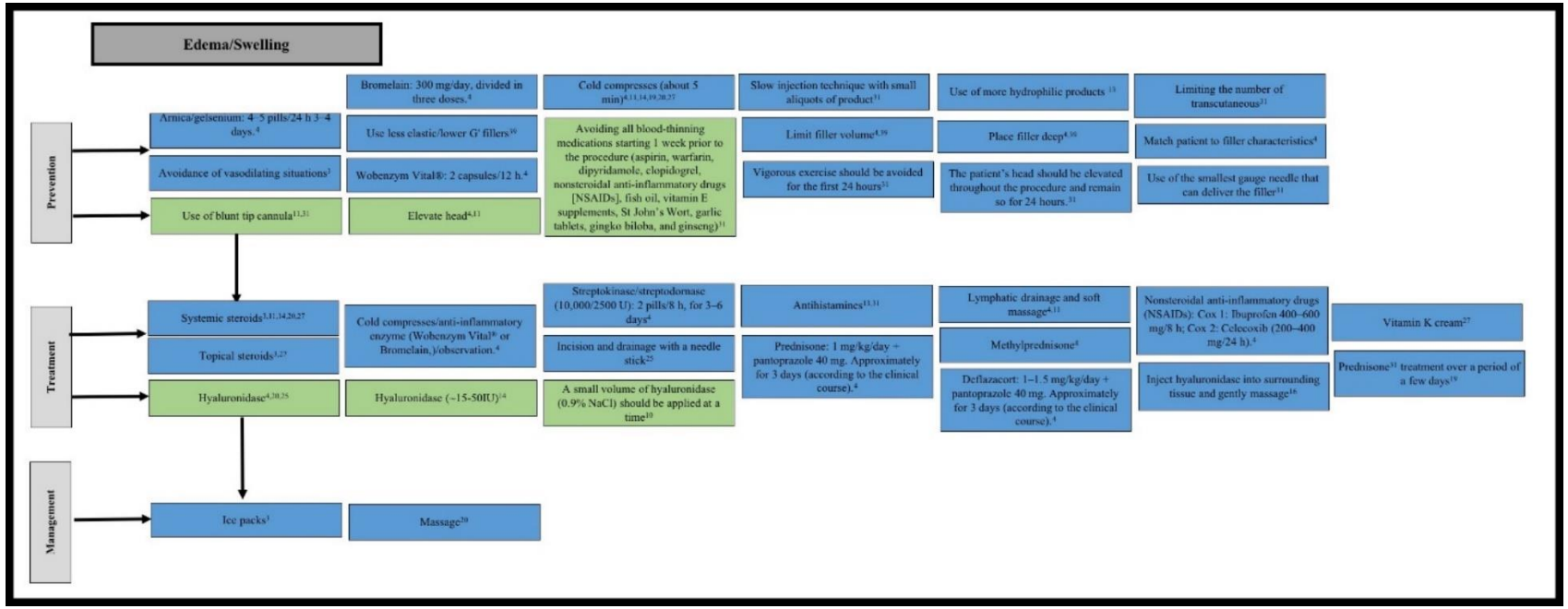


Figure 2m. Models for the prevention, treatment and management of edema/swelling following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

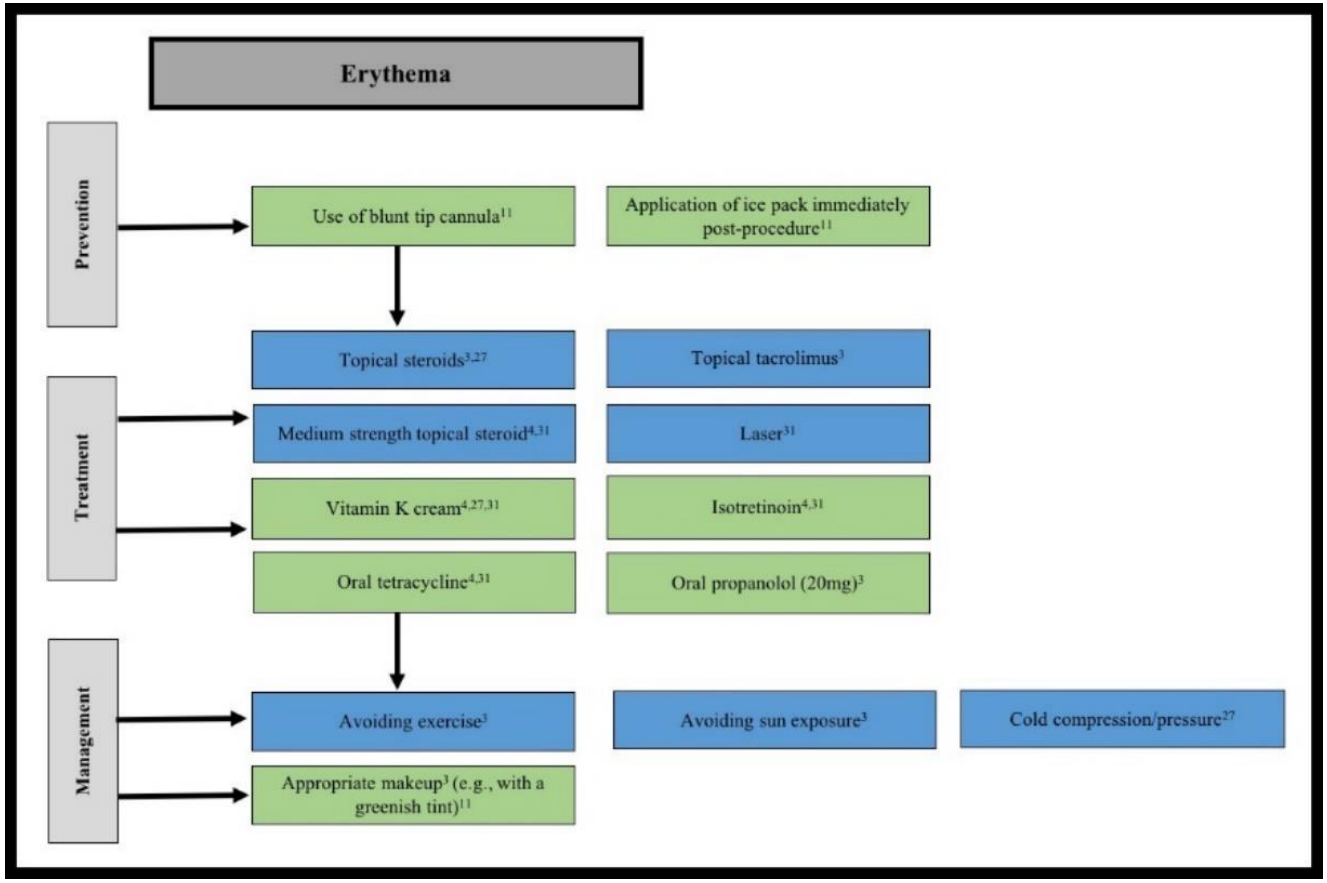


Figure 2n. Models for the prevention, treatment and management of erythema following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

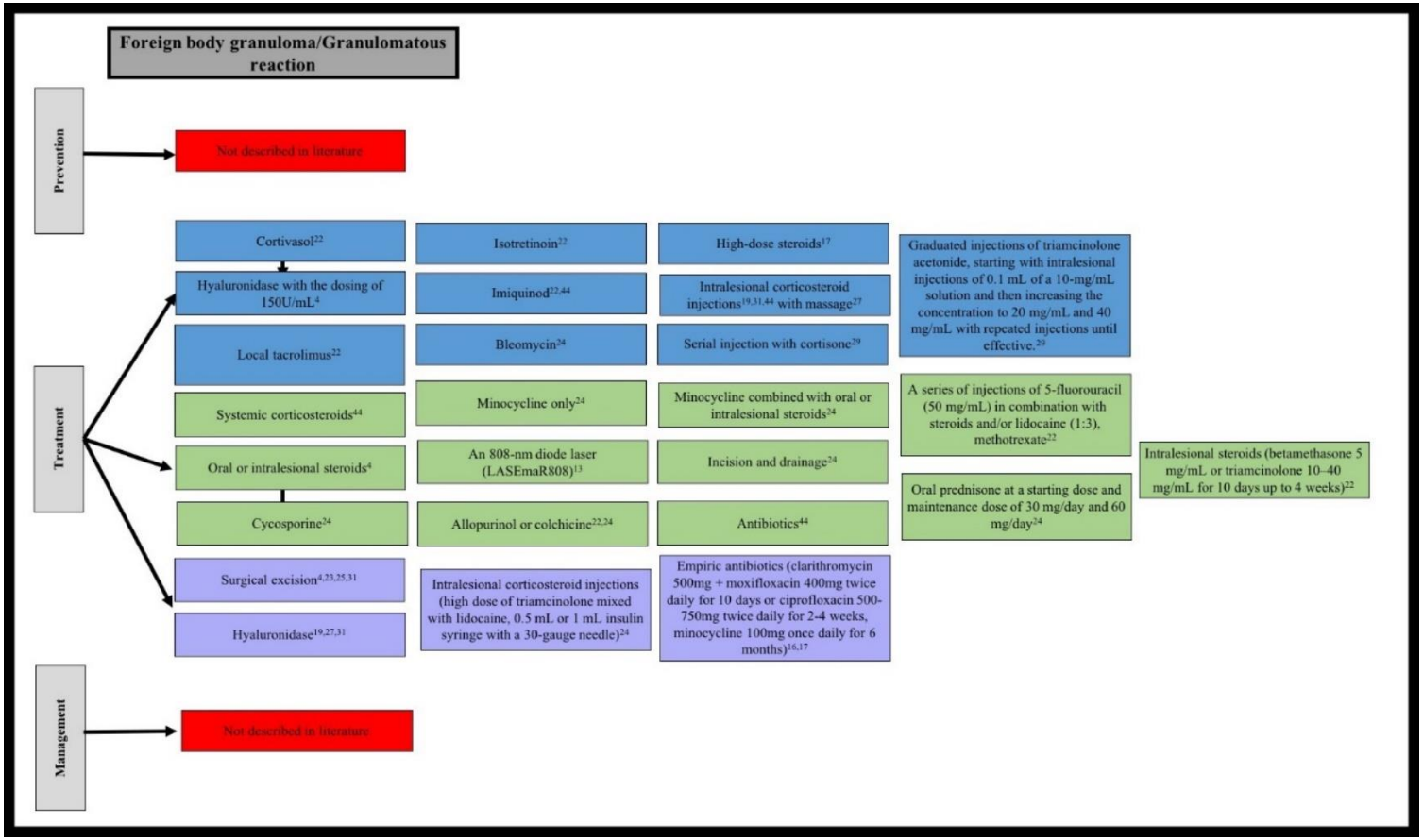


Figure 2o. Models for the prevention, treatment and management of foreign body granuloma following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

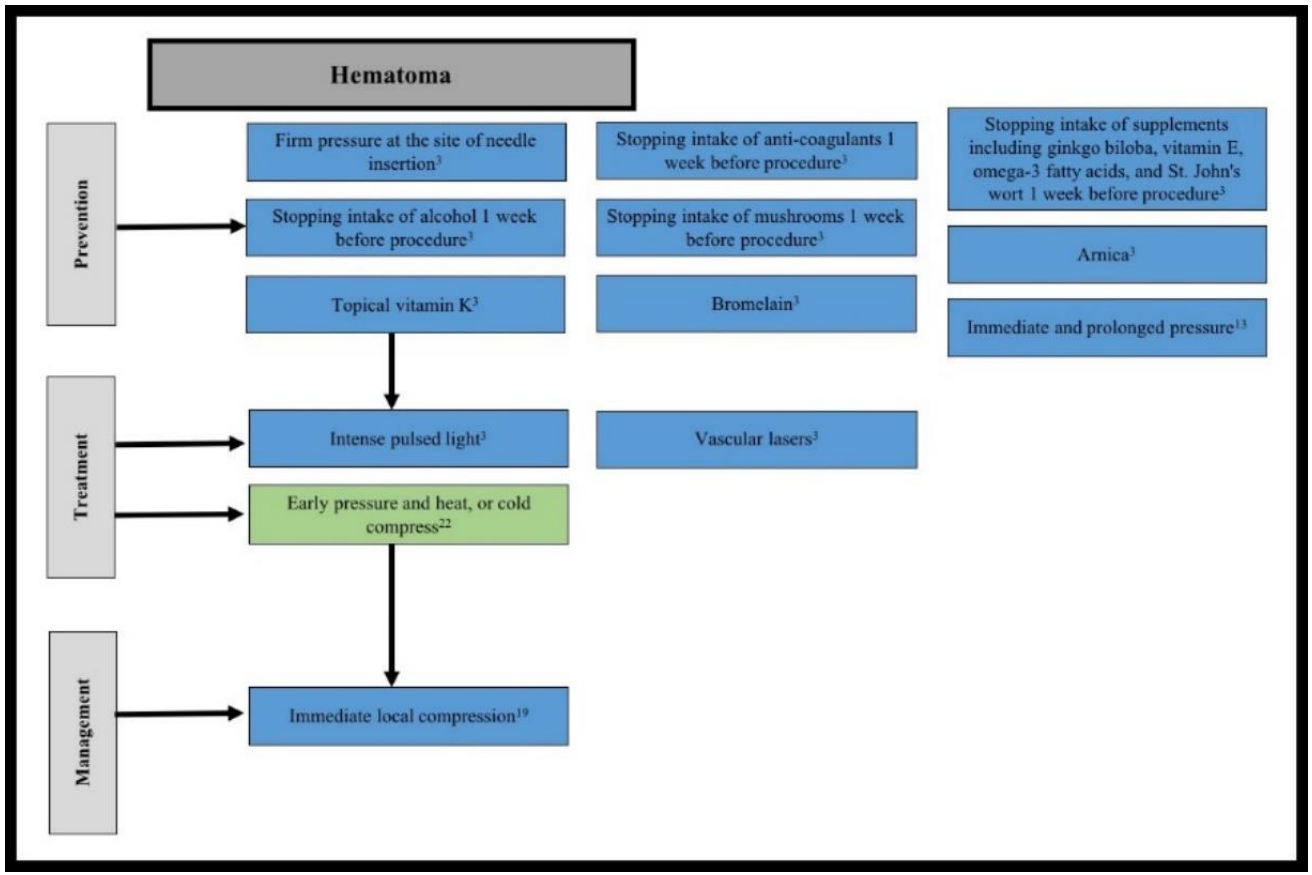


Figure 2p. Models for the prevention, treatment and management of hematoma following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

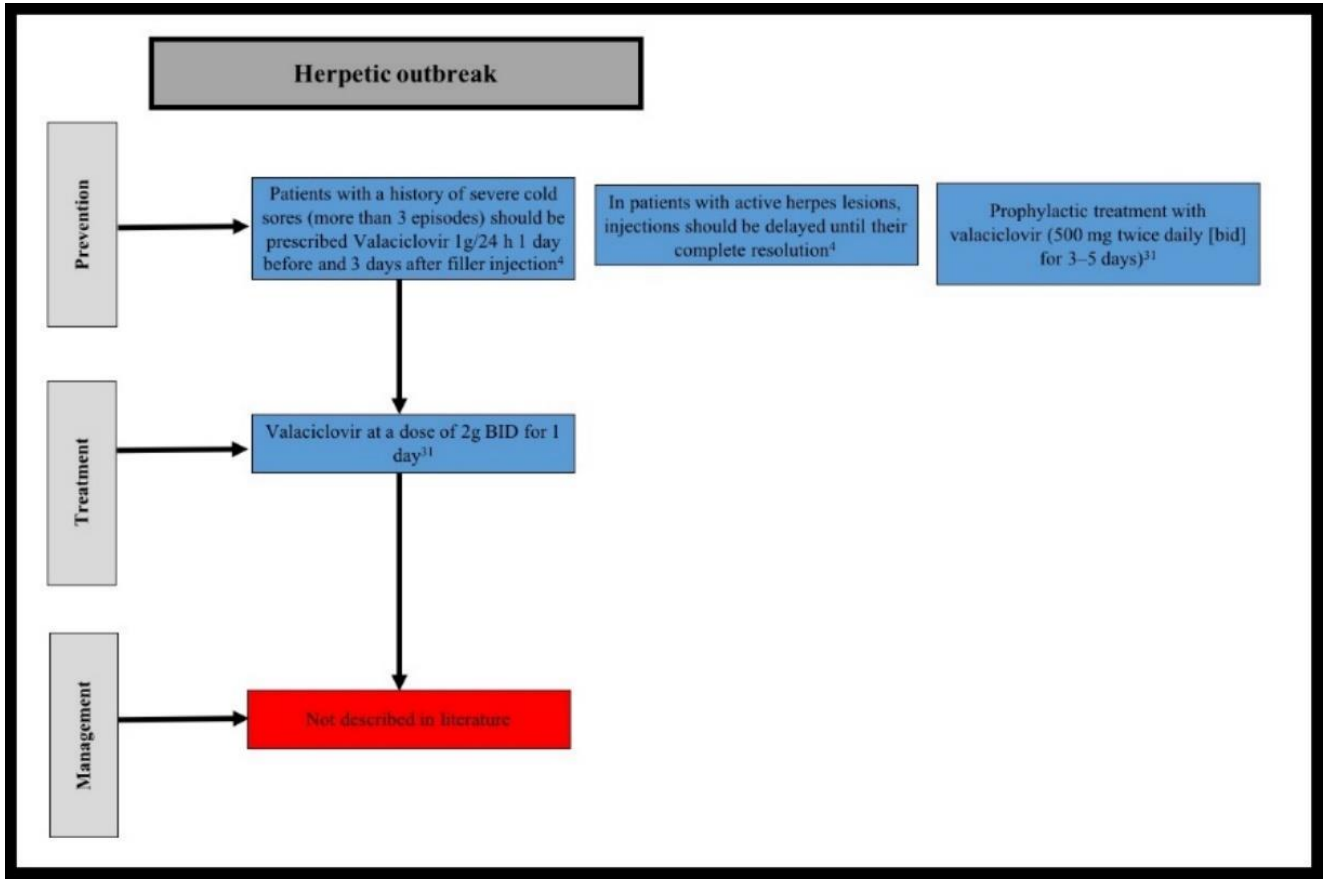


Figure 2q. Models for the prevention, treatment and management of herpetic outbreak following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

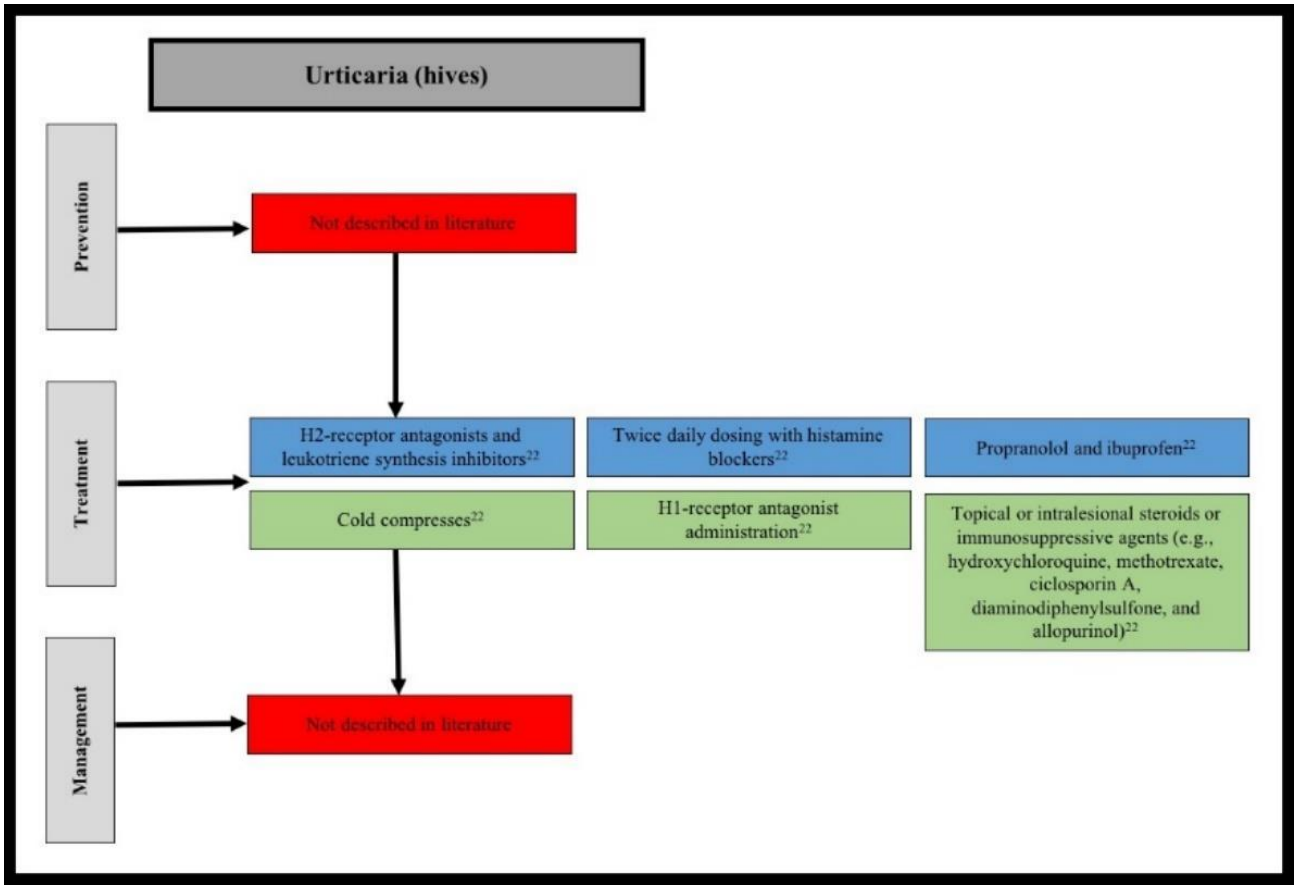


Figure 2r. Models for the prevention, treatment and management of urticaria (hives) following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

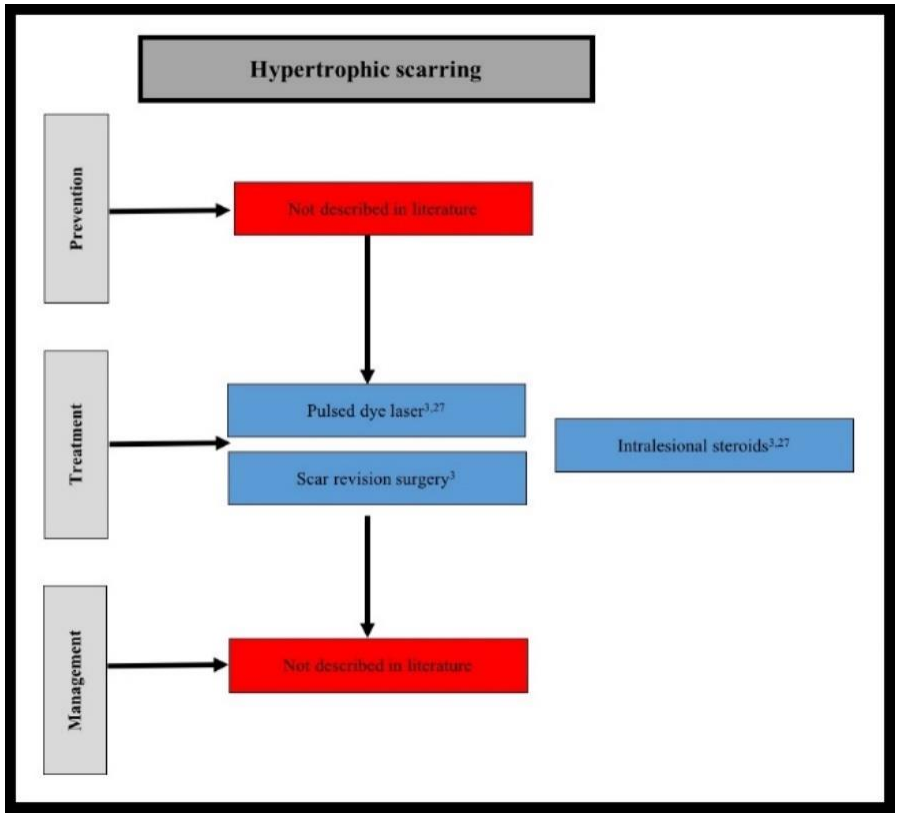


Figure 2s. Models for the prevention, treatment and management of hypertrophic scaring following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

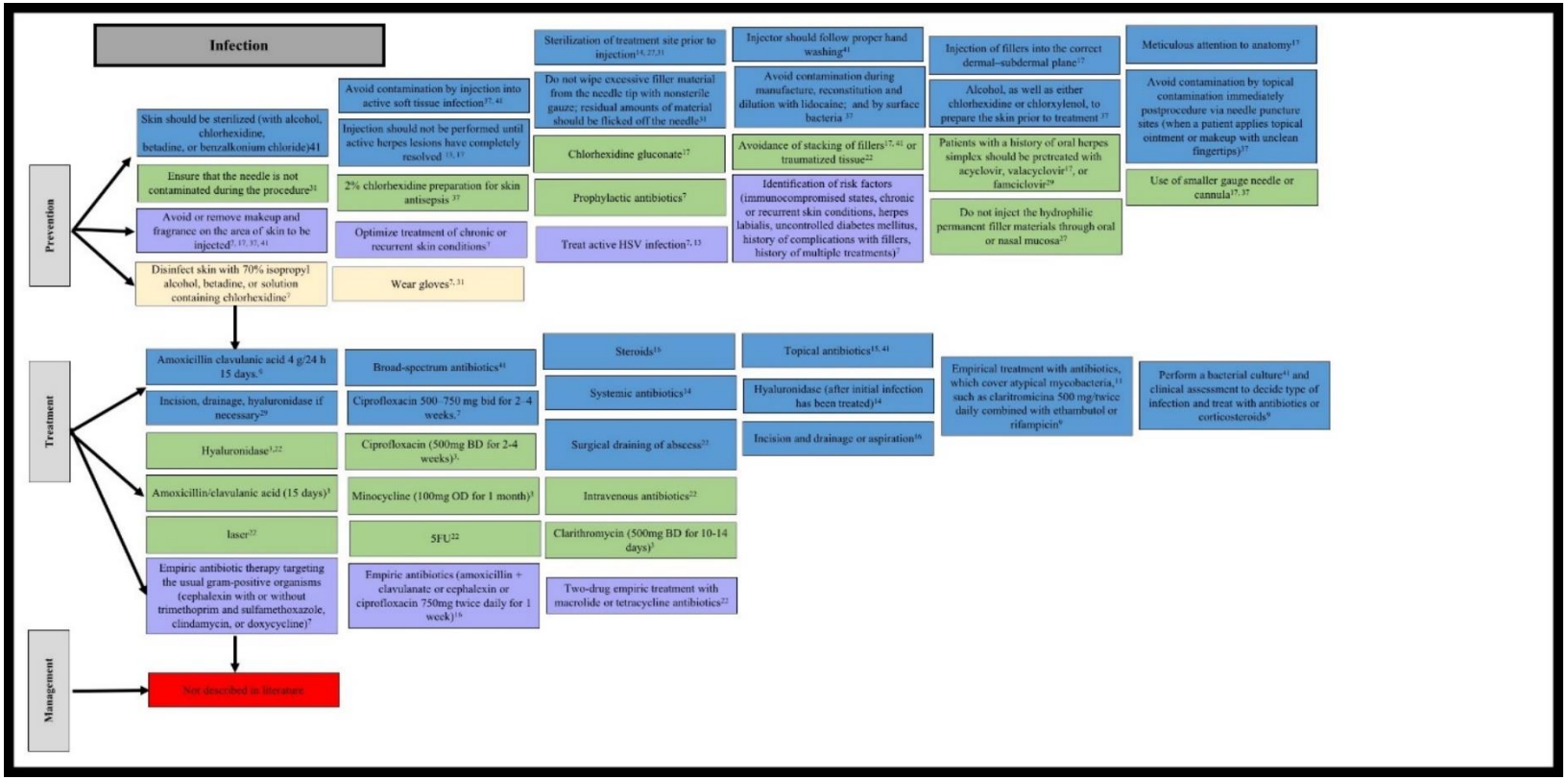


Figure 2t. Models for the prevention, treatment and management of <u>infection</u> following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

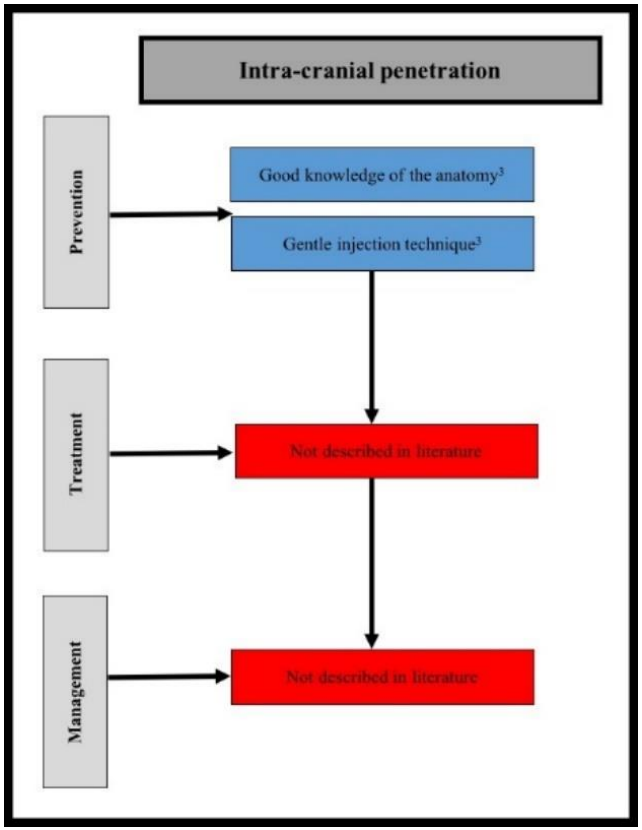


Figure 2u. Models for the prevention, treatment and management of intracranial penetration following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

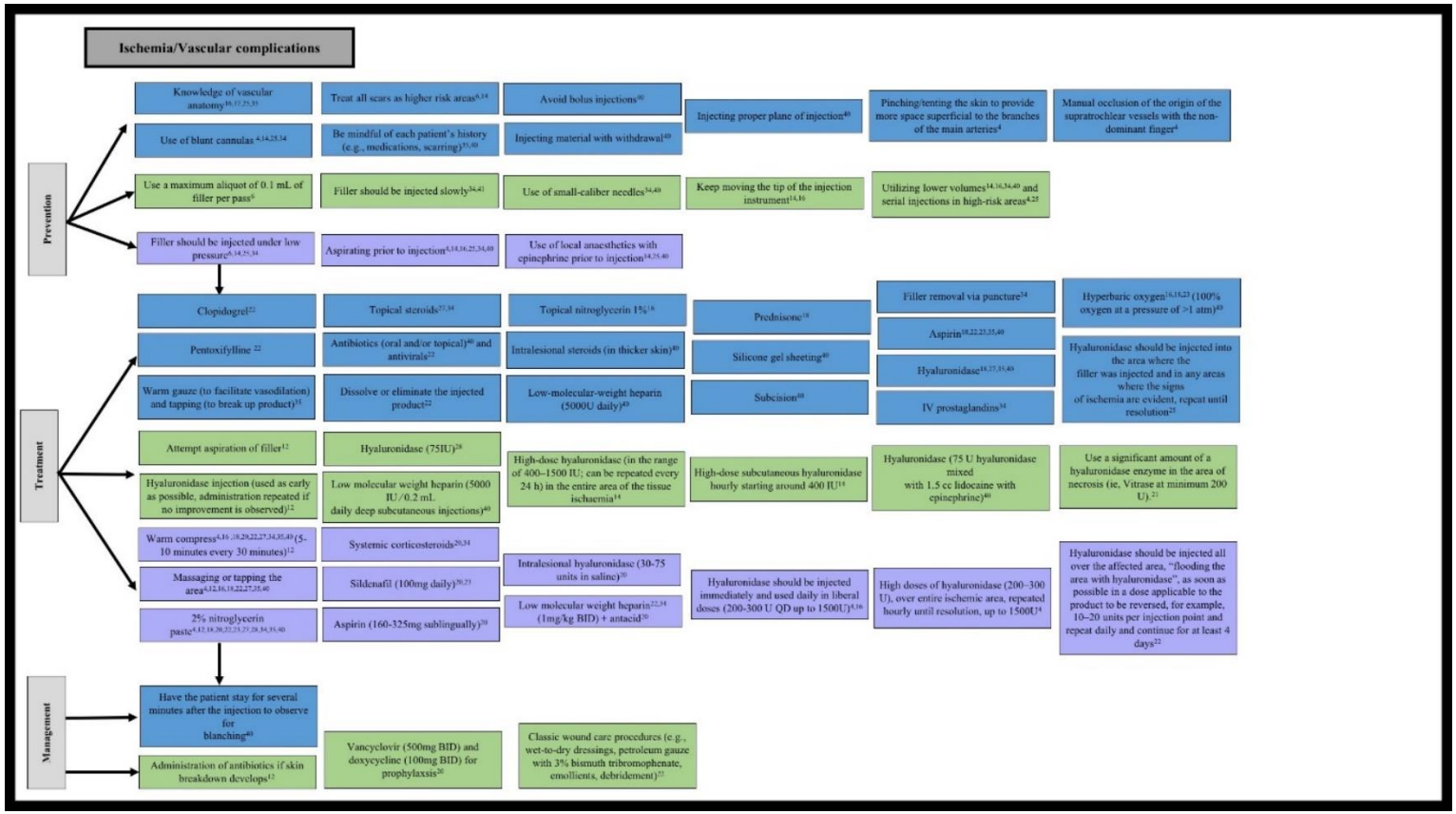


Figure 2v. Models for the prevention, treatment and management of ischemia/vascular complications following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

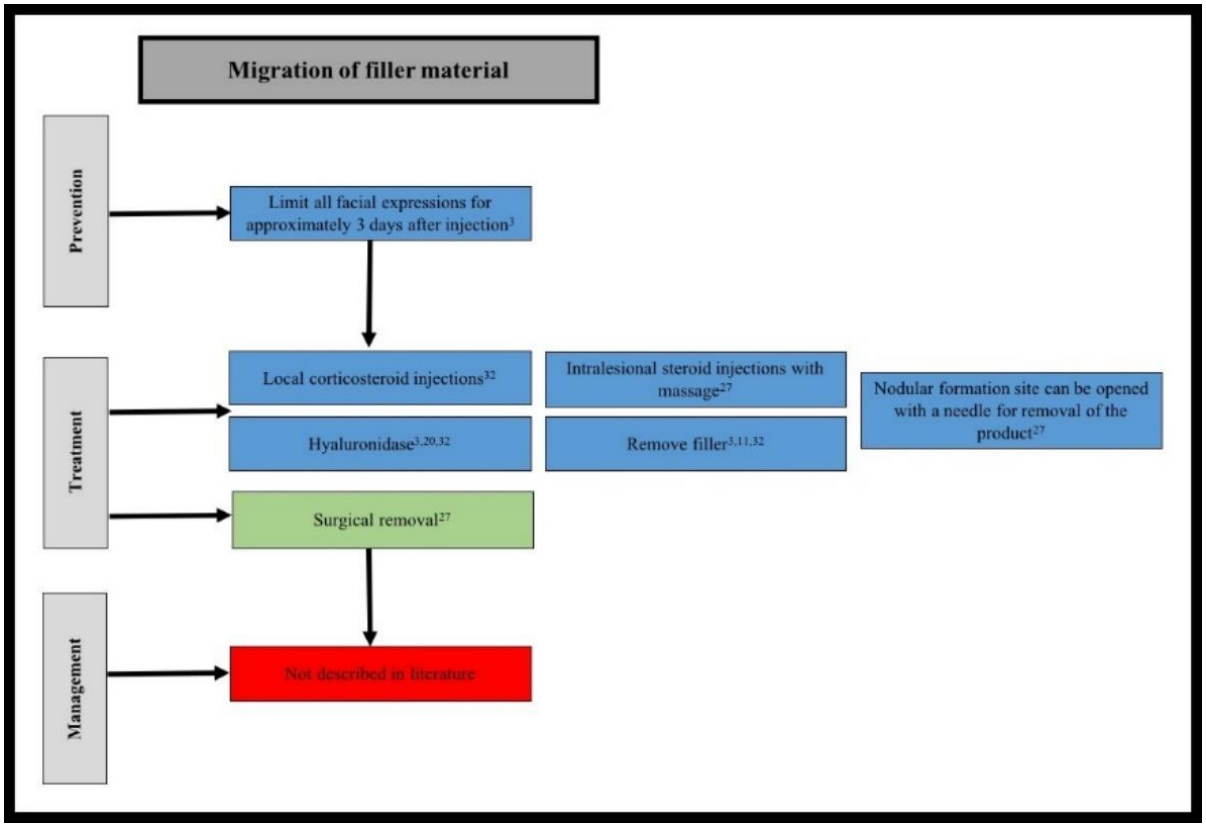


Figure 2w. Models for the prevention, treatment and management of migration of filler material following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

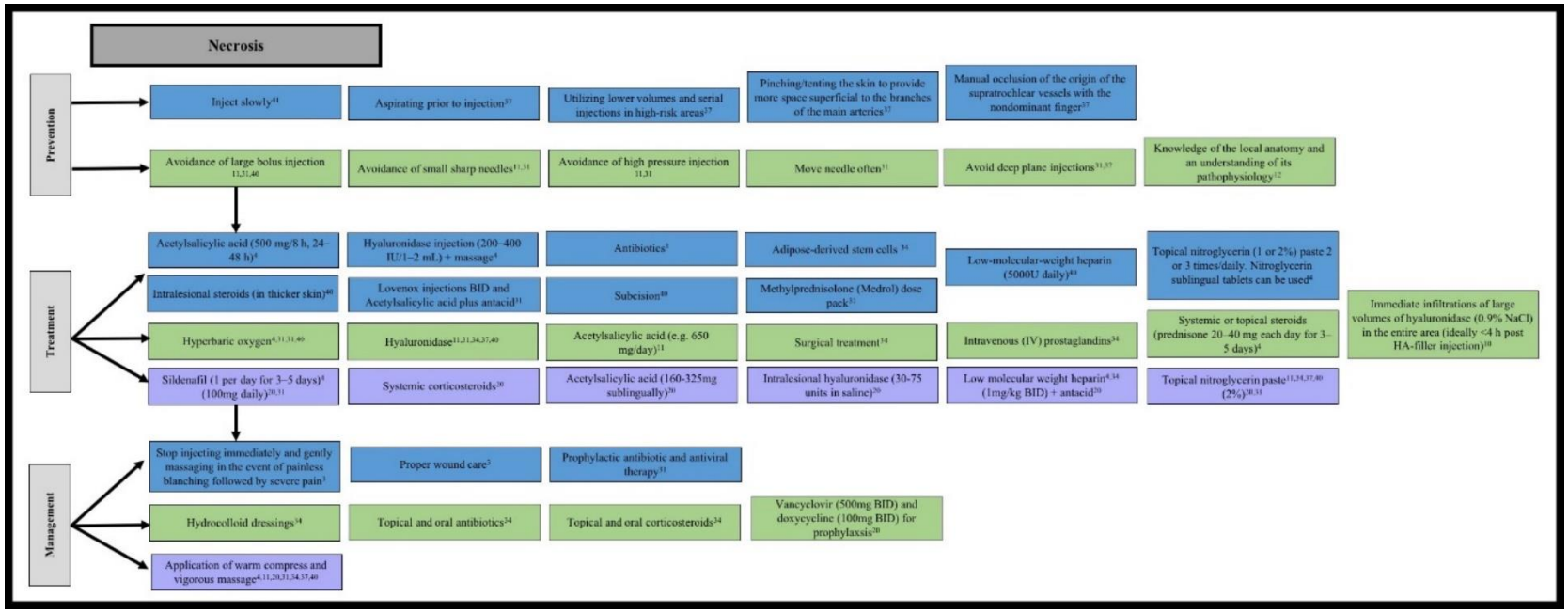


Figure 2x. Models for the prevention, treatment and management of necrosis following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

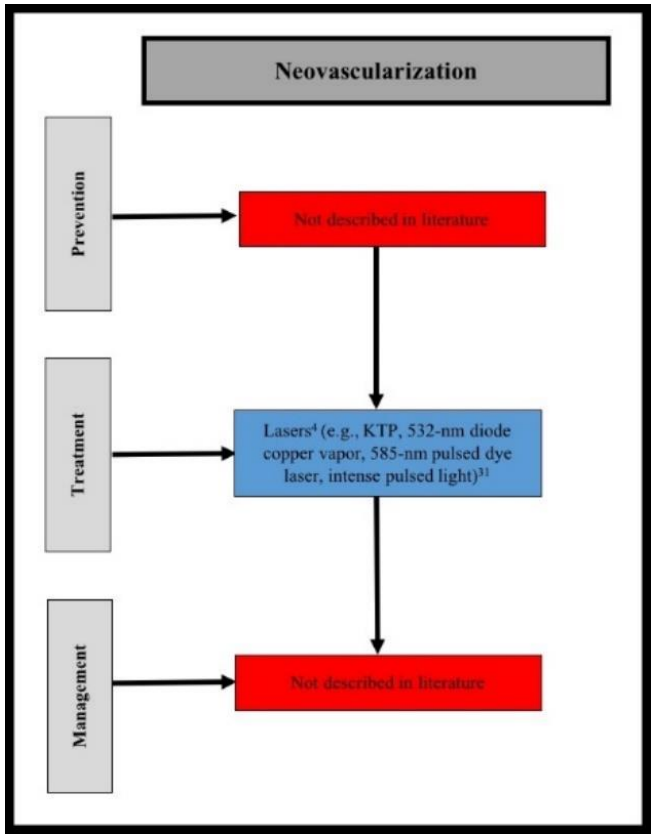


Figure 2y. Models for the prevention, treatment and management of neovascularization following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

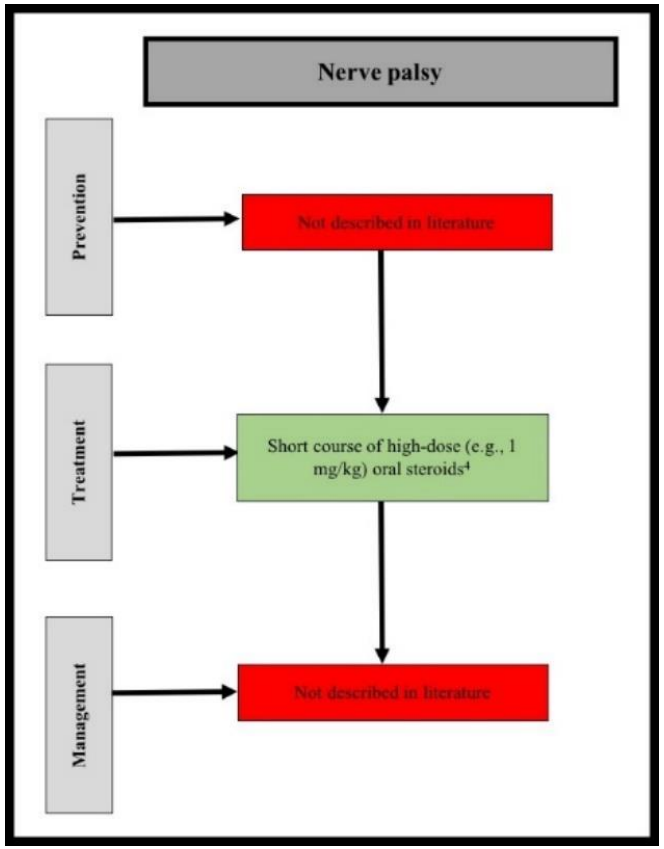


Figure 2z. Models for the prevention, treatment and management of nerve palsy following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

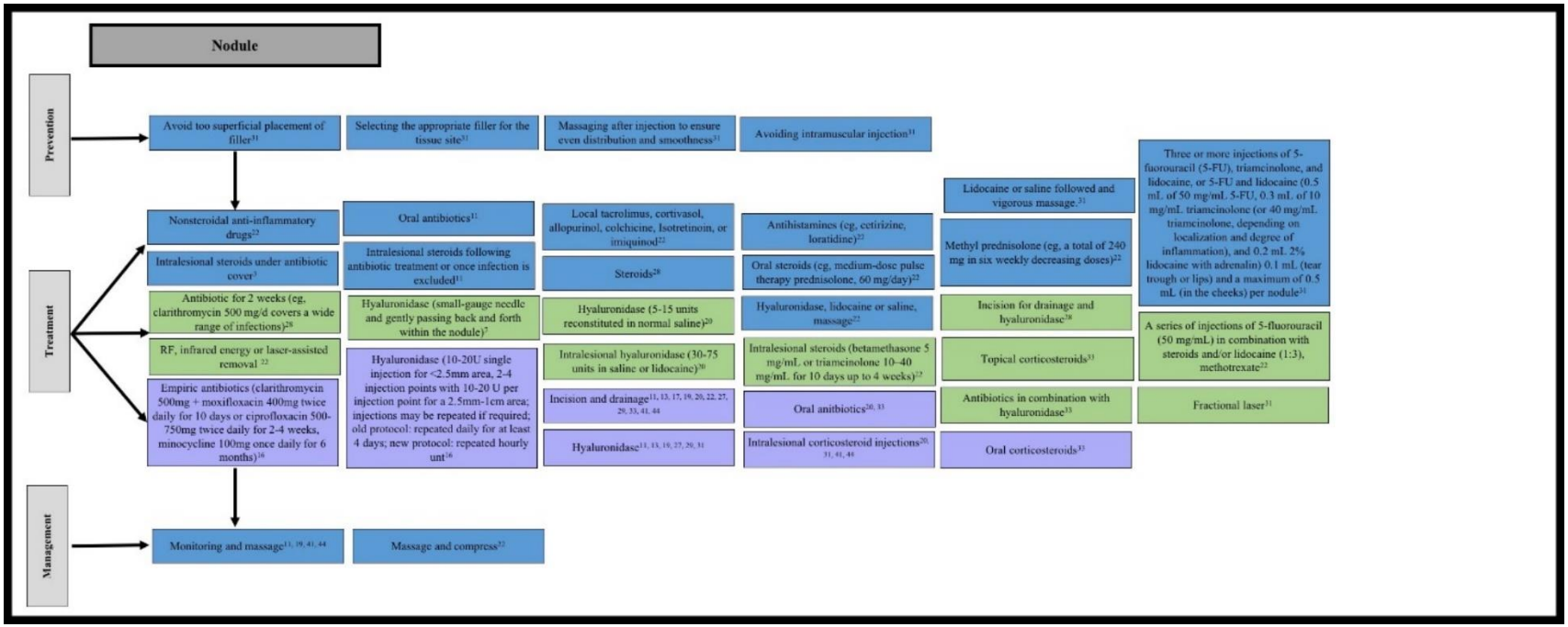


Figure 2zi. Models for the prevention, treatment and management of nodule following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

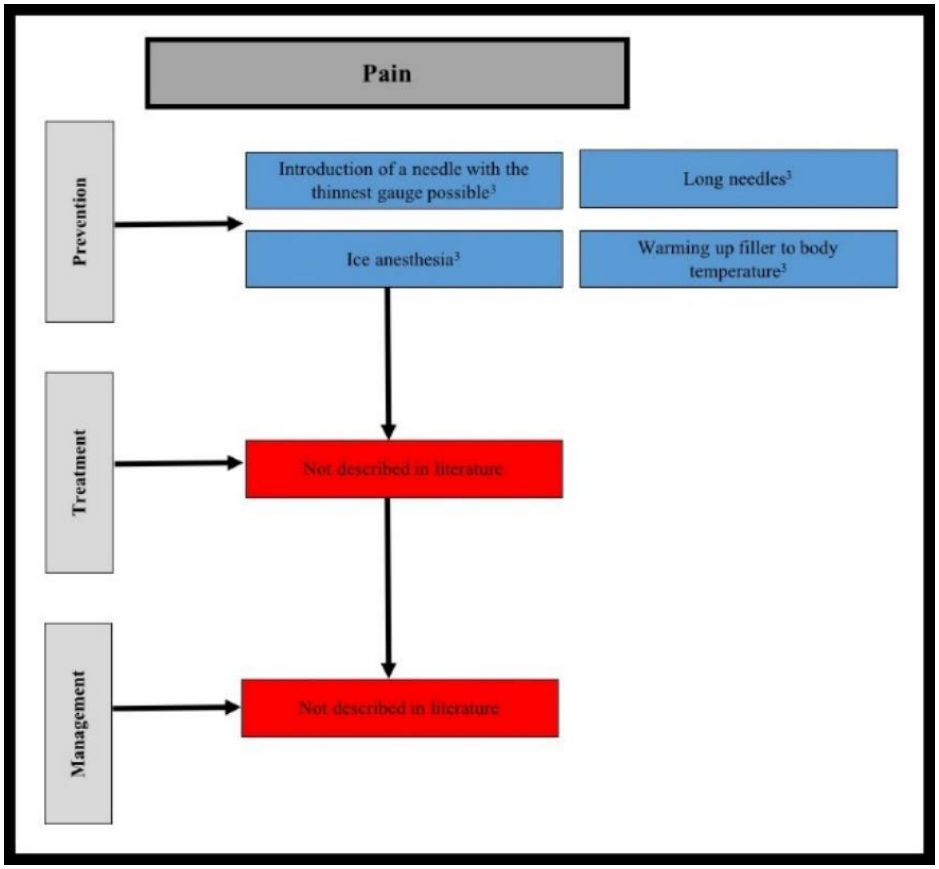


Figure 2zii. Models for the prevention, treatment and management of pain following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

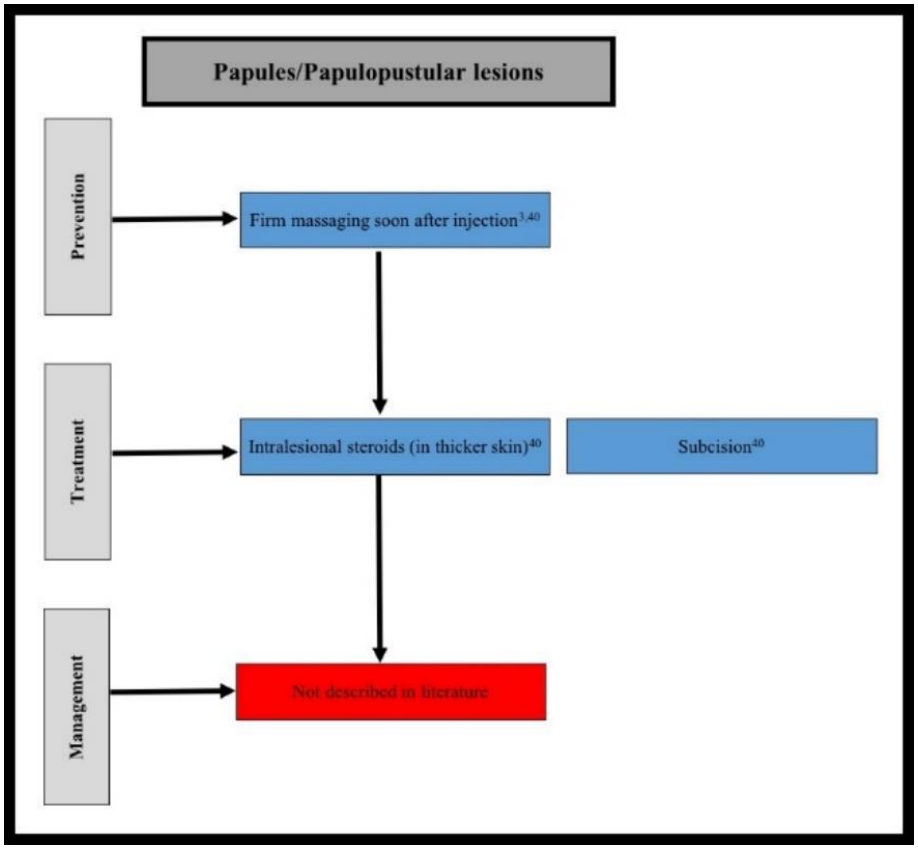


Figure 2ziii. Models for the prevention, treatment and management of papules/papulopustular lesions following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

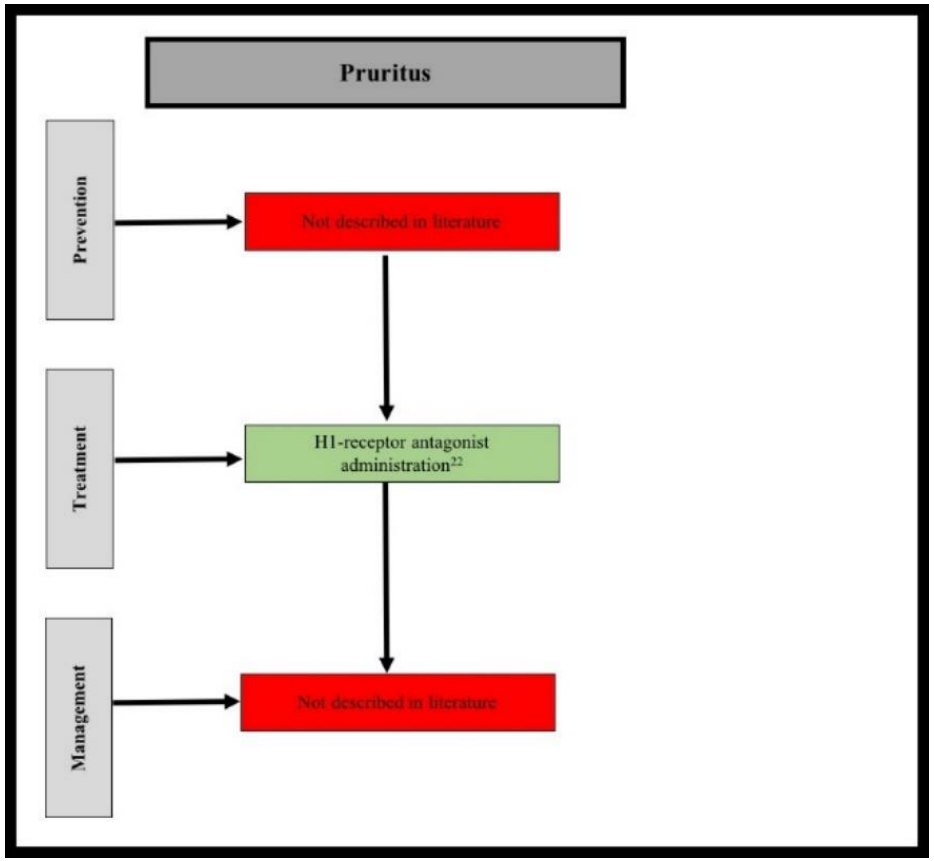


Figure 2ziv. Models for the prevention, treatment and management of pruritus following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

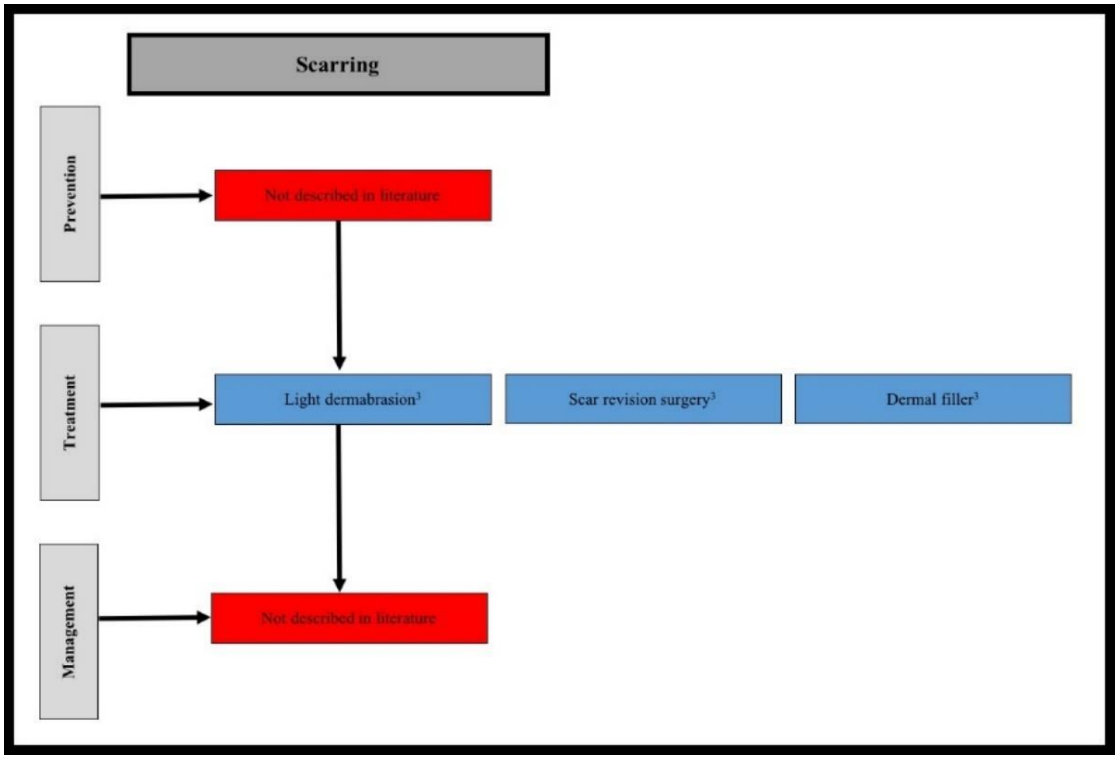


Figure 2zv. Models for the prevention, treatment and management of scarring following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

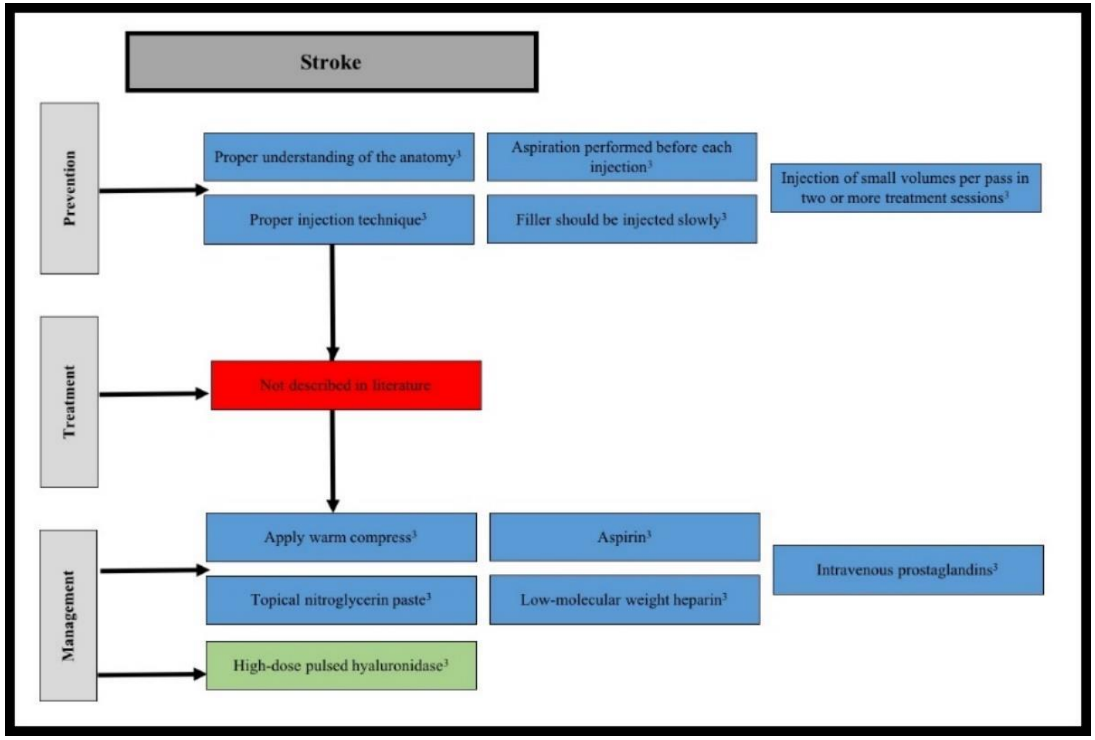


Figure 2zvi. Models for the prevention, treatment and management of stroke following the use of aesthetic soft tissue fillers in the face.

Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

Appendix 2. Site screening questionnaire used for recruiting sites for participation in the GRACE Portal.

Site Screening Questionnaire

We would like to assess your interest in participating as an investigator in the GRACE (Global Registry of Adverse Clinical Events) Study, an observational trial of adverse events following face and/or neck injectable treatments. We request that this questionnaire be completed by the physician or a delegated team member.

Please return completed questionnaires to Ms. Kaitlyn Enright at: kenright@vicpark.com.

Call 514-248-7033 for any further information regarding this trial or the current application.

Part 1: Physician Contact Details			
First Name:		Last Name:	
Institution Name:		Institution Type:	☐ Private clinic ☐ Academic ☐ Hospital
Street Address:			
Province:		Postal Code:	
Email:		Telephone:	

Part 2. Clinic Demographics	
Amount of patients treated with facial and/or neck aesthetic injections *per year*:	
The number of years the physician has been performing aesthetic injections:	
Amount of personnel performing injections at site:	
Type of injectors at site (select all that apply and specify amount):	☐ Plastic Surgeon(s): #_____ ☐ Dermatologist(s): #_____ ☐ Aesthetic Physician(s): #_____ ☐ Nurse(s): #_____
Are source documents at site currently computerized or paper based?	☐ Mostly computerized ☐ Mostly paper based

Do you have a research coordinator? If yes, please list contact details: Name: _____ Phone: _____ Email: _____	☐ Yes ☐ No
Number of staff members available for data entry:	
What is your level of interest in participating?	☐ Very interested ☐ Interested ☐ Not interested ☐ Do not have the time/resources
Is the physician and team members familiar with Good Clinical Practice Guidelines for conducting clinical trials?	☐ Yes ☐ No
How many research studies are ongoing at your site?	
If there are ongoing studies at your site, how many study patients do you currently oversee?	
Will the physician or a delegated staff member be available for resolution of issues pertaining to the study?	☐ Yes ☐ No
Will the physician be available for regulatory matters and essential document signatures?	☐ Yes ☐ No
Will there be any sub-investigators at your site? If so, please list names and degrees: 1._____ 2._____ 3._____ 4._____	☐ Yes ☐ No
Has your site ever been audited by Health Canada, the US FDA or another regulatory agency? If yes, describe results/findings.	☐ Yes ☐ No

Part 3. Subject Recruitment

Based on the following criteria, please indicate approximately how many patients you could enroll into the registry *per year:* <u>Inclusion (requires both):</u> 1. Patient treated with a Galderma injectable product (e.g., Restylane, Emervel); and 2. Patient presents with an adverse event following aesthetic injection(s) in the face and/or neck.	

Part 4. Co-authorship and Publications	
Are you willing to be a co-author on any publication(s) that may arise from this research?	☐ Yes ☐ No

Please note the following:

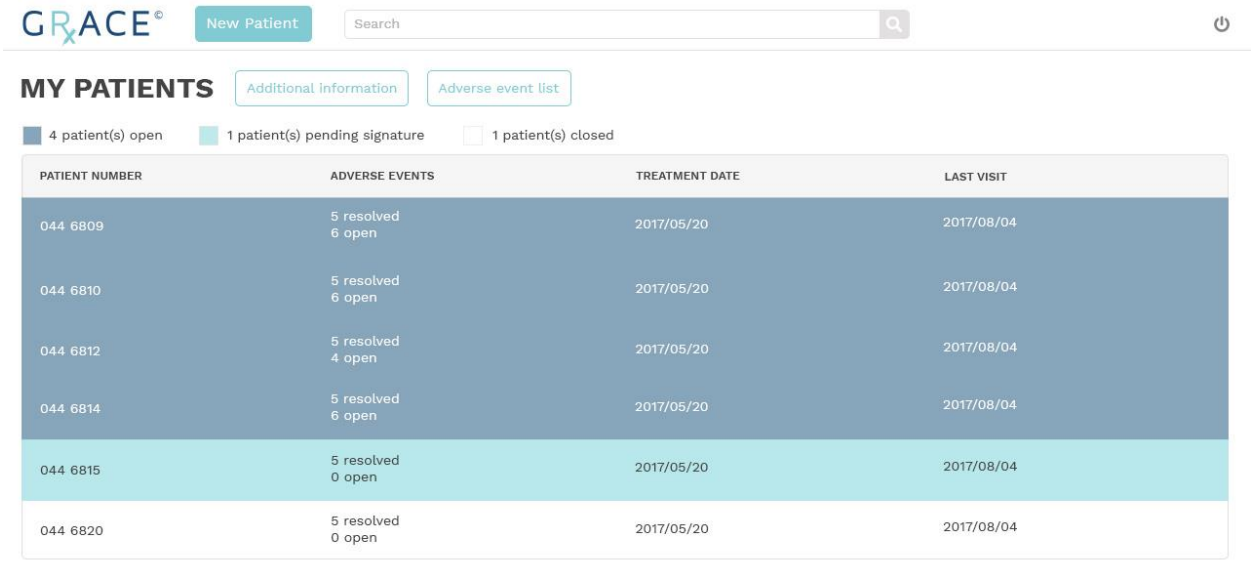
- Patient treatment and management will not be affected by participation in this study. All assessments including follow up will be as per routine care, at the discretion of the attending physician.
- Selected sites <u>MUST AGREE</u> to open access and *mandatory* periodic random chart review.

Please attach a copy of the physician's CV and medical license when returning the duly-filled questionnaire.

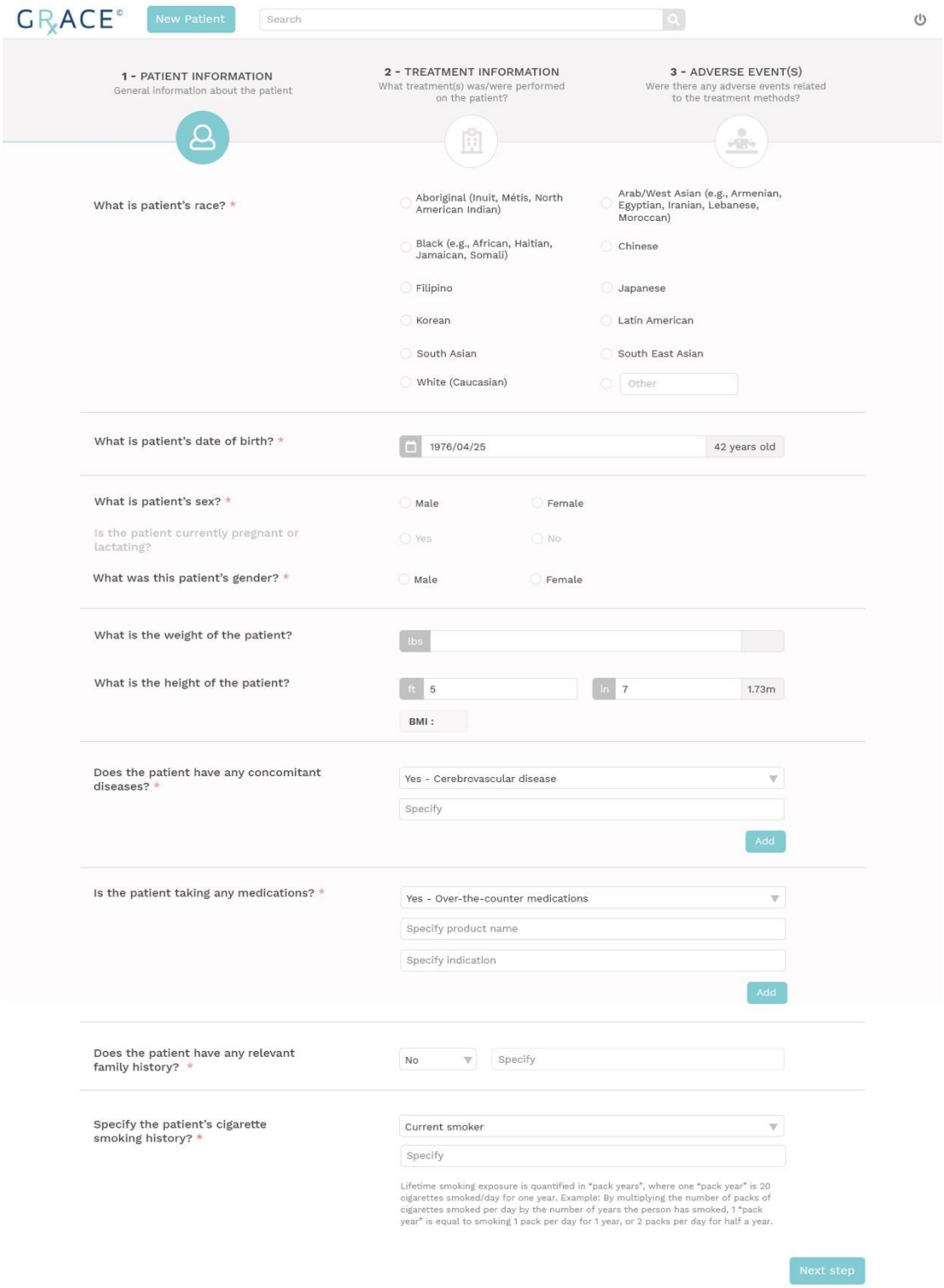
Thank you for taking the time to complete this questionnaire.

Kaitlyn M. Enright
C.514-248-7033

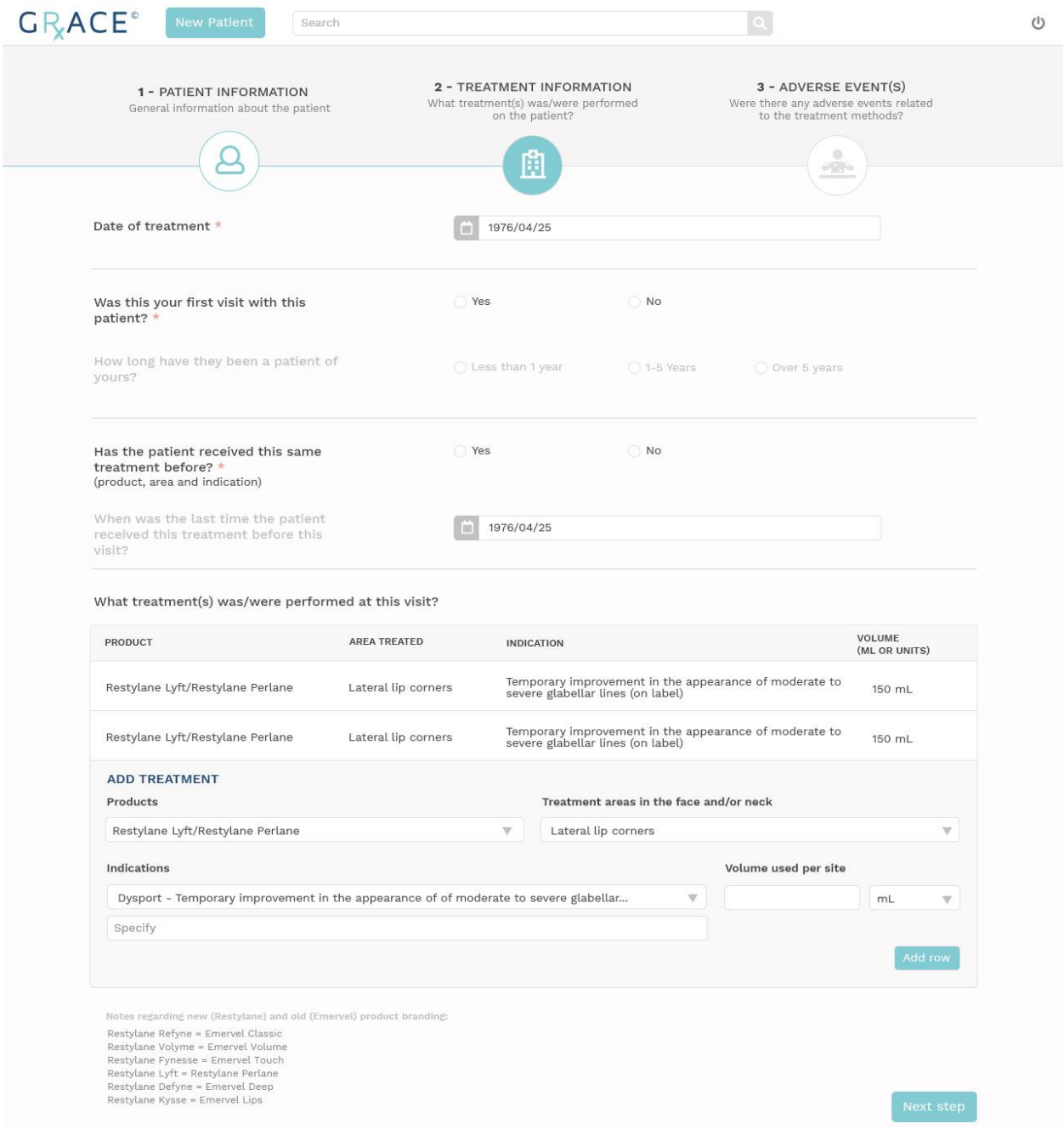
Appendix 3. Example Electronic Clinical Report Forms (eCRFS) of the GRACE Portal.



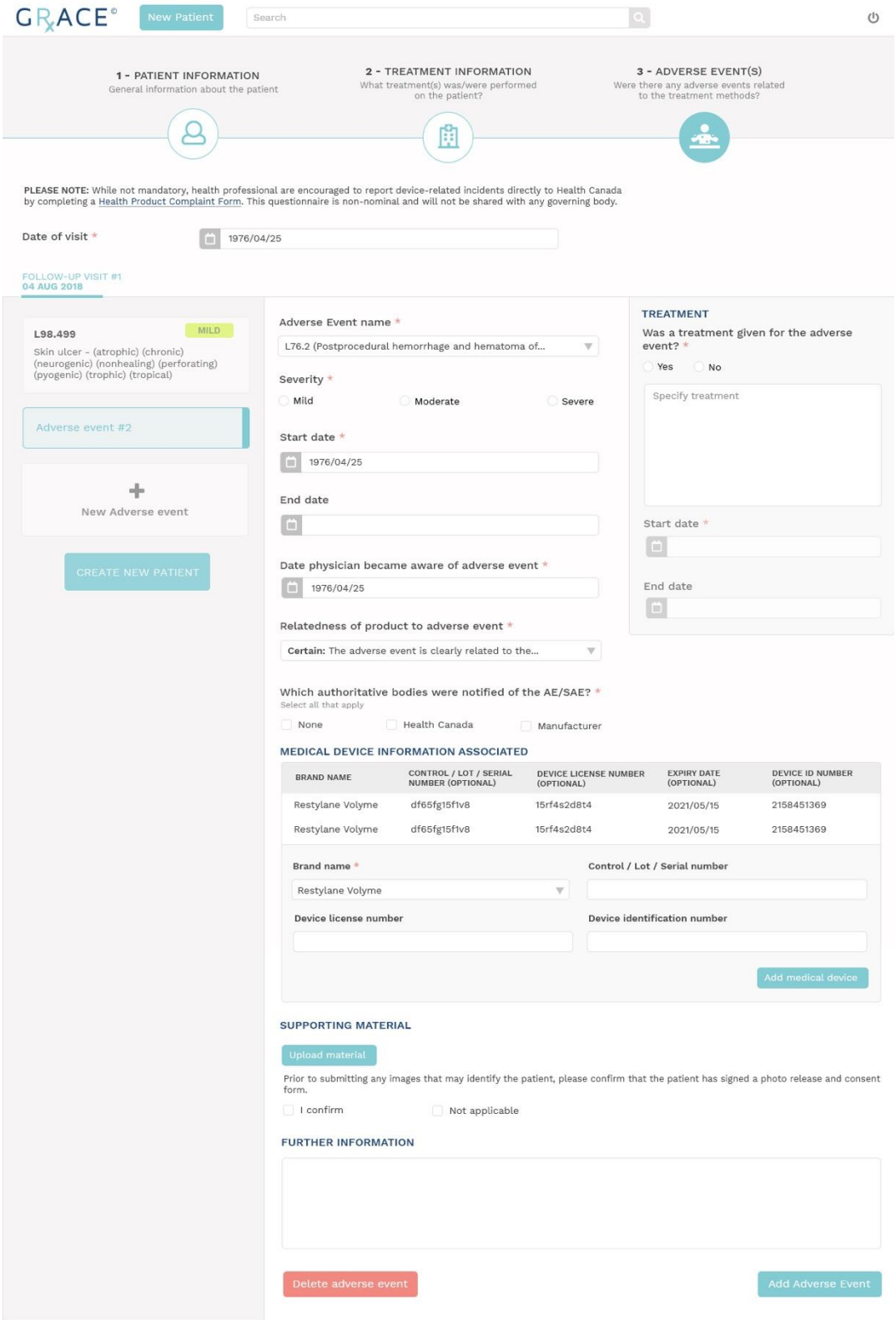
eCRF Page 1: Patient List (example).



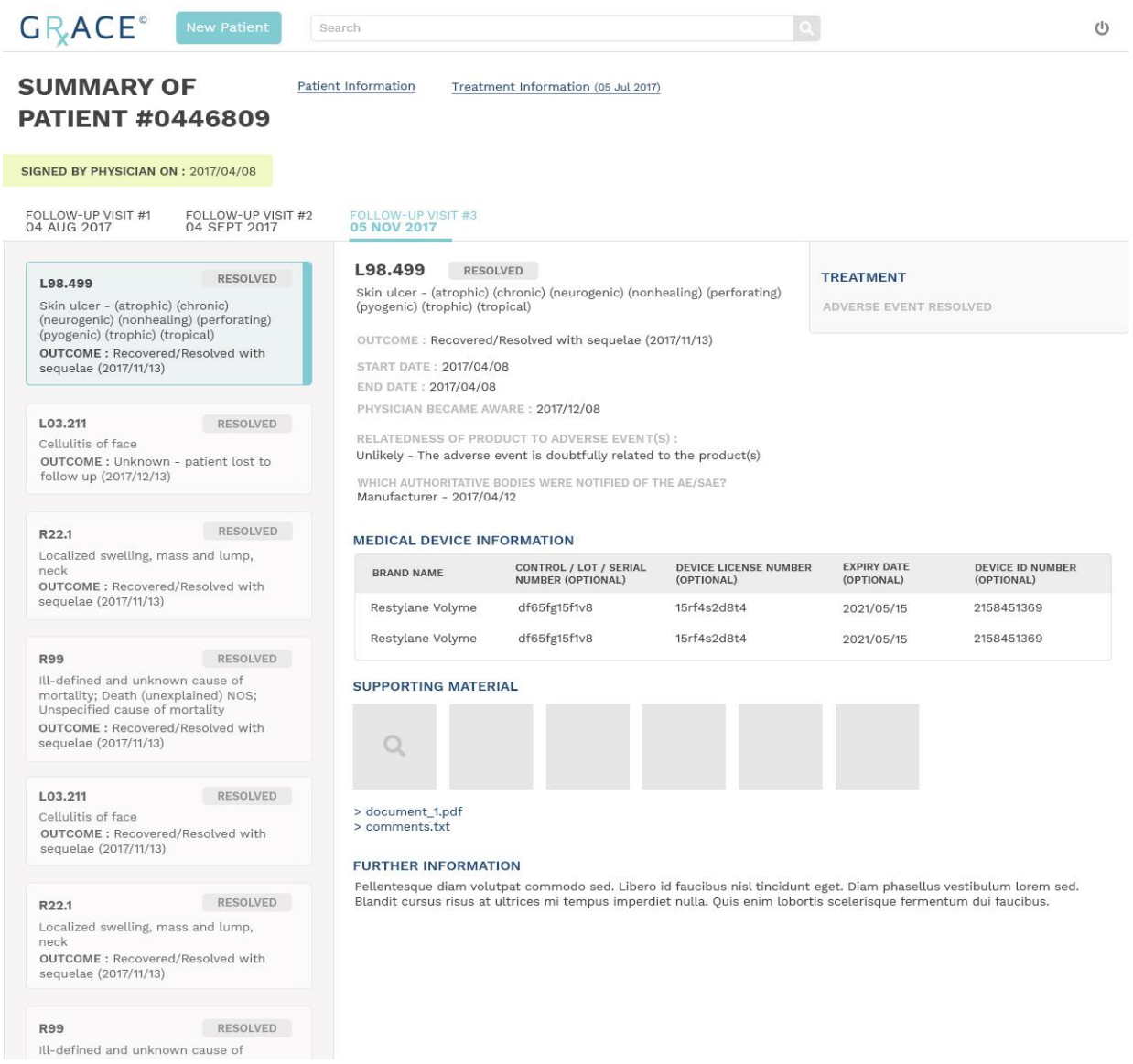
eCRF Page 2: Patient Information (example).



eCRF Page 3: Treatment information (example).



eCRF Page 4: Adverse event information (example).



eCRF Page 5: Patient summary (example).