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Review Article

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

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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. Non-systematic, 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 evidence-based 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.

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

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).

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
1	Goodman GJ, Magnusson MR, Callan P, et al.	A Consensus on Minimizing the Risk of Hyaluronic Acid Embolic Visual Loss and Suggestions for Immediate Bedside Management.	Aesthet Surg J 40(9):1009-21.	2020	Consensus recommendations	-	-
2	Beleznay K, Carruthers JDA, Humphrey S, Carruthers A, Jones D	Update on Avoiding and Treating Blindness From Fillers: A Recent Review of the World Literature.	Aesthet Surg J 39(6):662-74.	2019	Review	(39)	48 (39)
3	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	-	-
4	Rohrich RJ, Bartlett EL, Dayan E.	Practical Approach and Safety of Hyaluronic Acid Fillers.	Plast Reconstr Surg Glob Open. Jun;7(6):e2172.	2019	Review	-	-
5	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)
6	Heydenrych I, Kapoor KM, De Boulle K, et al.	A 10-point plan for avoiding hyaluronic acid dermal filler-related complications during facial aesthetic procedures and algorithms for management.	Clin Cosmet Investig Dermatol 11:603-11	2018	Guideline	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
7	Vedamurthy M.	Beware What You Inject: Complications of Injectables-Dermal Fillers.	J Cutan Aesthet Surg Apr-Jun;11(2):60-66.	2018	Review	-	-
8	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	-	-
9	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	-	-
10	Delorenzi C.	New high dose pulsed hyaluronidase protocol for hyaluronic acid filler vascular adverse events.	Aesthet Surg J 13:814–25.	2017	Guideline	-	-
11	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)
12	de Maio M, Swift A, Signorini M, Fagien S, Aesthetic Leaders in Facial Aesthetics Consensus C.	Facial Assessment and Injection Guide for Botulinum Toxin and Injectable Hyaluronic Acid Fillers: Focus on the Upper Face.	Plast Reconstr Surg Aug;140(2):265e-76e.	2017	Consensus recommendations	-	-
13	de Maio M, DeBoulle K, Braz A, Rohrich RJ, Alliance for the Future of Aesthetics Consensus C.	Facial Assessment and Injection Guide for Botulinum Toxin and Injectable Hyaluronic Acid Fillers: Focus on the Midface.	Plast Reconstr Surg Oct;140(4):540e-50e.	2017	Consensus recommendations	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
14	Mundada P, Kohler R, Boudabbous S, et al.	Injectable facial fillers: imaging features, complications, and diagnostic pitfalls at MRI and PET CT.	Insights Imaging 8(6):557-572.	2017	Review	-	13
15	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	-	-
16	Abduljabbar MH, Basendwh MA.	Complications of hyaluronic acid fillers and their managements.	J Dermatol Dermatol Surg July;20(2):100-06.	2016	Systematic Review	-	-
17	Buhren BA, Schrumpf H, Hoff NP, Bölke E, Hilton S, Gerber PA.	Hyaluronidase: from clinical applications to molecular and cellular mechanisms.	Eur J Med Res 13;21:5.	2016	Review	-	-
18	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	-	-
19	Ferneini EM, Ferneini AM.	An overview of vascular adverse events associated with facial soft tissue fillers: recognition, prevention, and treatment.	J Oral Maxillofac Surg 74(8):1630–1636.	2016	Review	-	-
20	Fitzgerald R, Bertucci V, Sykes JM, Duplechain JK.	Adverse reactions to injectable fillers.	Facial Plast Surg 32(5):532–555.	2016	Review	-	-
21	Hwang CJ	Periorbital injectables: understanding and avoiding complications.	J Cutan Aesthet Surg 9(2):73–79.	2016	Review	-	-
22	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	-	-

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
23	Signorini M, Liew S, Sundaram H, et al.	Global Aesthetics Consensus Group. Global Aesthetics Consensus: Avoidance and Management of Complications from Hyaluronic Acid Fillers-Evidence- and Opinion-Based Review and Consensus Recommendations.	Plast Reconstr Surg Jun;137(6):961e-71e.	2016	Consensus recommendations	-	-
24	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	-	-
25	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)
26	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	-	-
27	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)
28	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	-	-
29	De Boulle K, Heydenrych I.	Patient factors influencing dermal filler complications: prevention, assessment, and treatment.	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)]
30	Funt D, Pavicic T.	Dermal fillers in aesthetics: an overview of adverse events and treatment approaches.	Plast Surg Nurs 35:13–32.	2015	Review	-	-
31	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	-	-
32	Rzany B, DeLorenzi C.	Understanding, avoiding, and managing severe filler complications.	Plast Reconstr Surg 136(5 Suppl):196S–203S.	2015	Review	-	-
33	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	-	-
34	DeLorenzi C.	Complications of injectable fillers, part 2: Vascular complications.	Aesthet Surg J 34(4):584-600.	2014	Review	-	-
35	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	-	-
36	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	-	-
37	DeLorenzi C.	Complications of injectable fillers, part I.	Aesthet Surg J 33(4):561–575.	2013	Review	-	-
38	Dumitraşcu 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)

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
39	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	-	-
40	Ginat DT, Schatz CJ.	Imaging features of midface injectable fillers and associated complications.	AJNR Am J Neuroradiol. 34(8):1488-95.	2013	Review	-	-
41	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)
42	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)
43	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	-	-
44	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)
45	Bailey SH, Cohen JL, Kenkel JM.	Etiology, prevention and treatment of dermal filler complications.	Aesthet Surg J 31:110–121.	2011	Review	-	-
46	Dayan SH, Arkins JP, Brindise R.	Soft tissue fillers and biofilm.	Facial Plast Surg 27:23–28.	2011	Review	(13)	(40)

Number	Author(s)	Title	Journal/Index	Year	Article Type	Nº Studies [All fillers (Hyaluronic acid)]	Nº Patients [All fillers (Hyaluronic acid)]
47	Funt DK.	Avoiding malar edema during midface/cheek augmentation with dermal fillers.	J Clin Aesthet Dermatol 4(12):32–36.	2011	Review	-	-
48	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)
49	Kim JE, Sykes JM.	Hyaluronic acid fillers: history and overview.	Facial Plast Surg. 27:523–528.	2011	Review	-	-
50	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	-	-
51	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)
52	Lafaille P, Benedetto A.	Fillers: contraindications, side effects and precautions.	J Cutan Aesthet Surg 3(1):16–19.	2010	Review	-	-
53	Rohrich RJ, Monheit G, Nguyen AT, Brown SA, Fagien S.	Soft-tissue filler complications: the important role of biofilms.	Plast Reconstr Surg 125:1250–1256.	2010	Review	-	-
54	Vedamurthy M, Vedamurthy A, Nischal K.	Dermal fillers: do's and dont's.	J Cutan Aesthet Surg 3(1):11–15.	2010	Review	-	-

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.

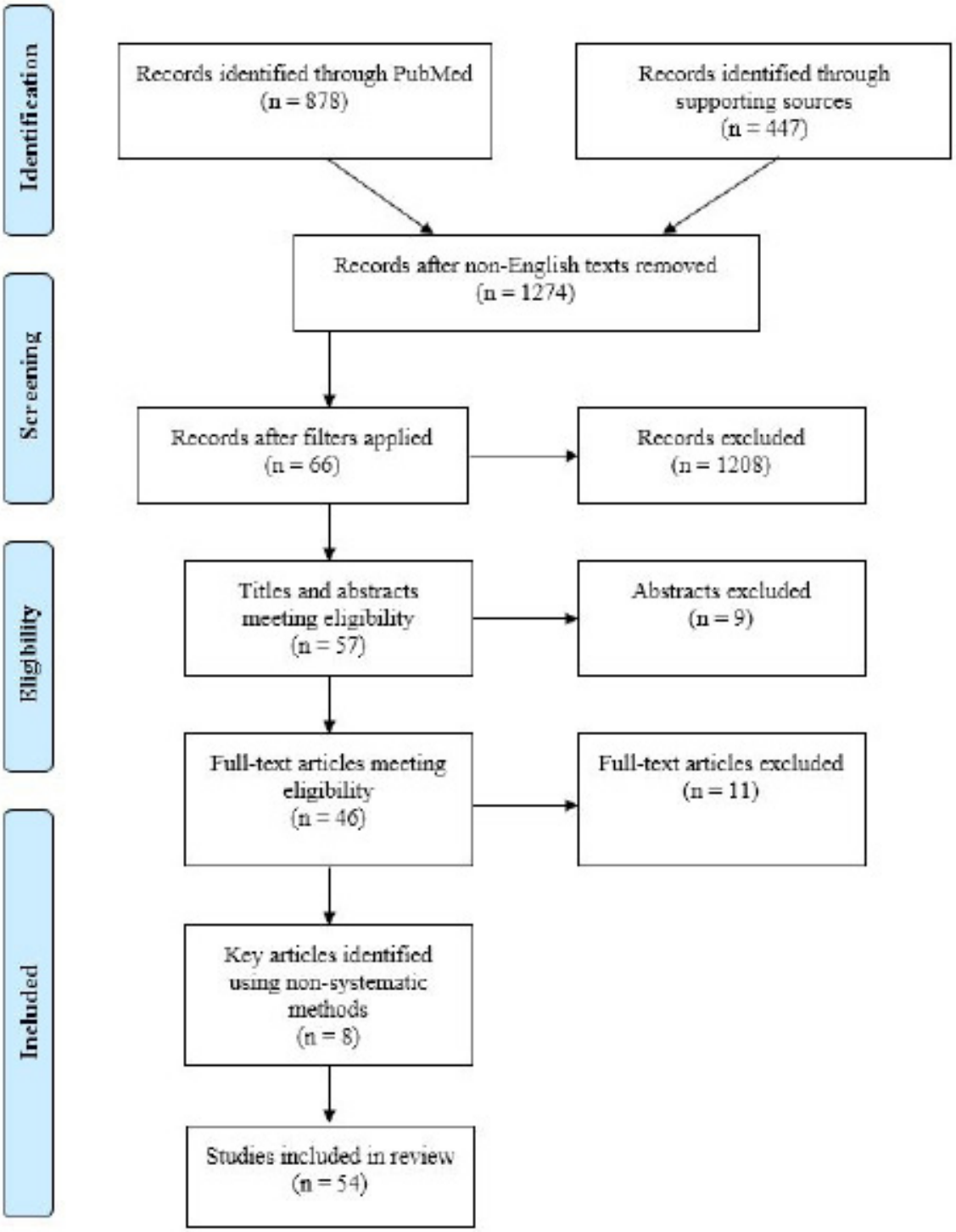

Figure 1: PRISMA flow diagram of the methods applied for assessing publications for inclusion in the present review; Note: **"**Filters applied" included publication year, full text availability and article type. Supporting sources included the reference lists. PRISMA = Preferred Reporting Items for Systematic review and Meta-Analysis.

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%).

Identification Number	Adverse Event	Number of References [N = 54; n (%)]
1	Abscess	5 (9.26)
2	Abnormal sensation (e.g., dysesthesias, paresthesia, anesthesia)	1 (1.85)
3	Allergic/hypersensitivity/inflammatory reactions	6 (11.11)
4	Anaphylactic shock	1 (1.85)
5	Angioedema	3 (5.56)
6	Arterial compromise/occlusion/injection[a]	3 (5.56)
7	Biofilm	13 (24.07)
8	Blindness/Vision loss, disturbances, compromise or impairment[b]	23 (42.59)
9	Bleeding	2 (3.70)
10	Bruising/Ecchymosis	15 (27.78)
11	Contour irregularities[c]	13 (24.07)
12	Dyspigmentation/Hyperpigmentation/Discoloration[d]	3 (5.56)
13	Edema/Swelling	14 (25.93)
14	Erythema	6 (11.11)
15	Foreign body granuloma/Granulomatous reaction	12 (22.22)

16	Hematoma	4 (7.41)
17	Herpetic outbreak	2 (4.35)
18	Hypertrophic scarring	2 (3.70)
19	Infection	18 (33.33)
20	Intra-cranial penetration	1 (1.85)
21	Ischemia/Vascular complications[e]	21 (38.89)
22	Urticaria (hives)	1 (1.85)
23	Migration of filler material	5 (9.26)
24	Necrosis	11 (20.37)
25	Neovascularization	2 (3.70)
26	Nerve palsy	1 (1.85)
27	Nodule	18 (33.33)
28	Pain	2 (3.70)
29	Papules/Papulopustular lesions	2 (3.70)
30	Pruritus	2 (3.70)
31	Scarring	1 (1.85)
32	Stroke	1 (1.85)
33	Telangiectasia (spider veins)	1 (1.85)
34	Tyndall effect	8 (14.81)

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 10/54 (18.52%) articles that referred to "general" or "local" AEs, which presumably refer to the so-called "injection site reactions" that form part of the normal squeal following breaking the dermis with injections (e.g., bleeding, bruising, edema) [45]. 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.

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/hypo-pigmented 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.

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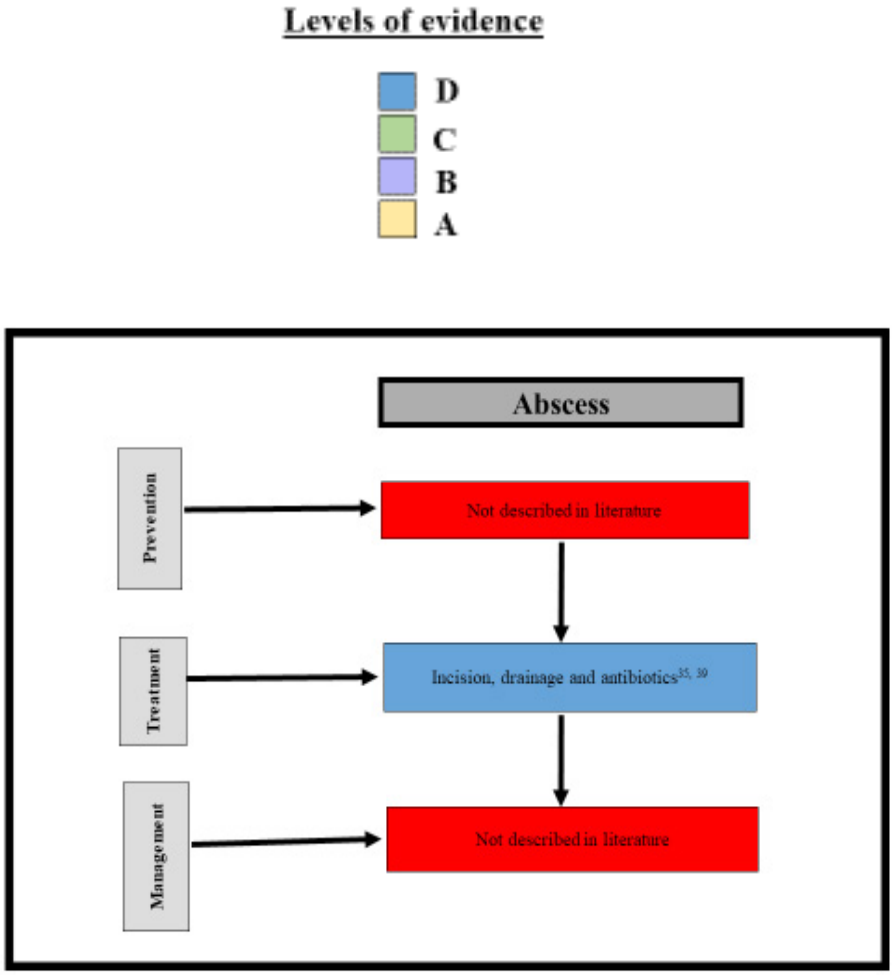
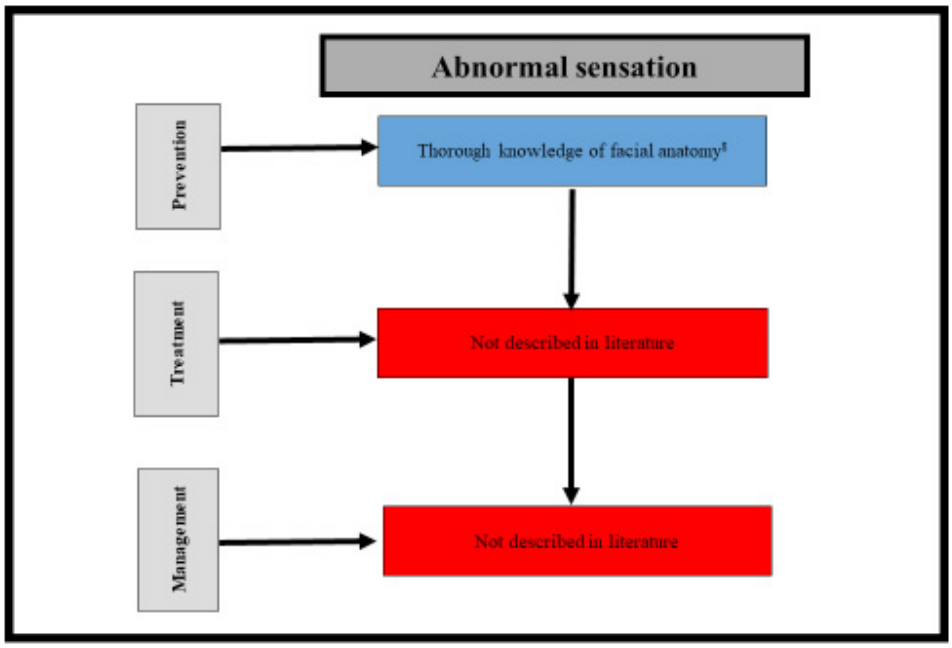
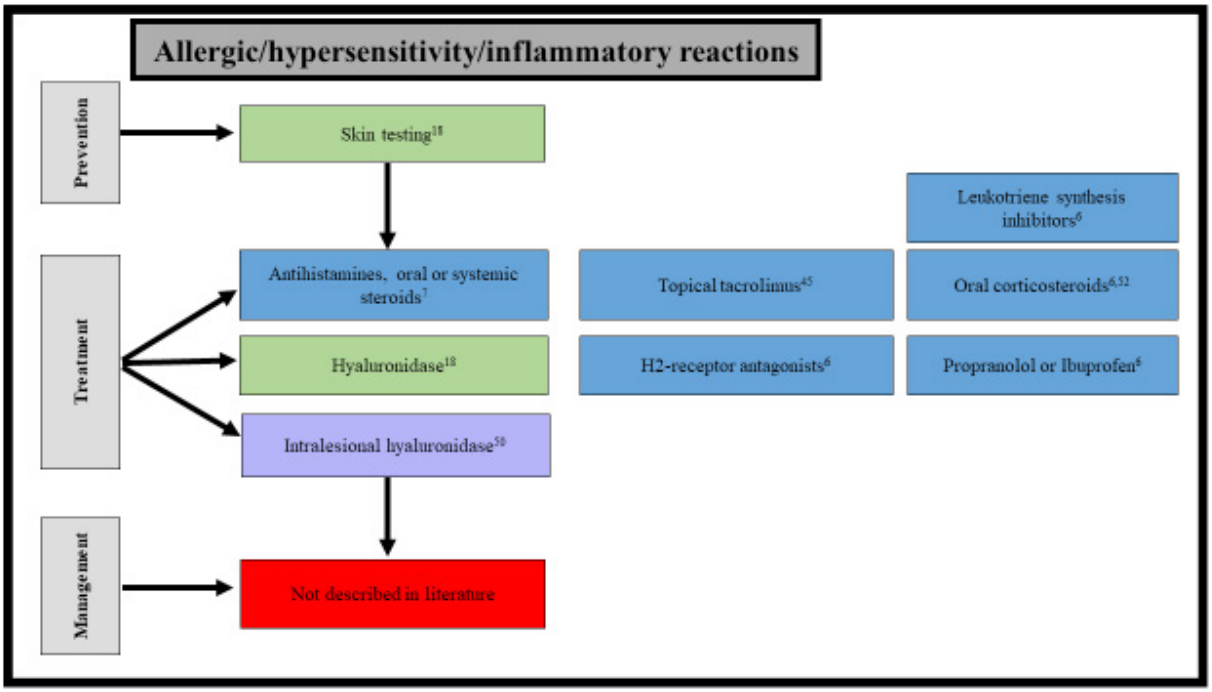
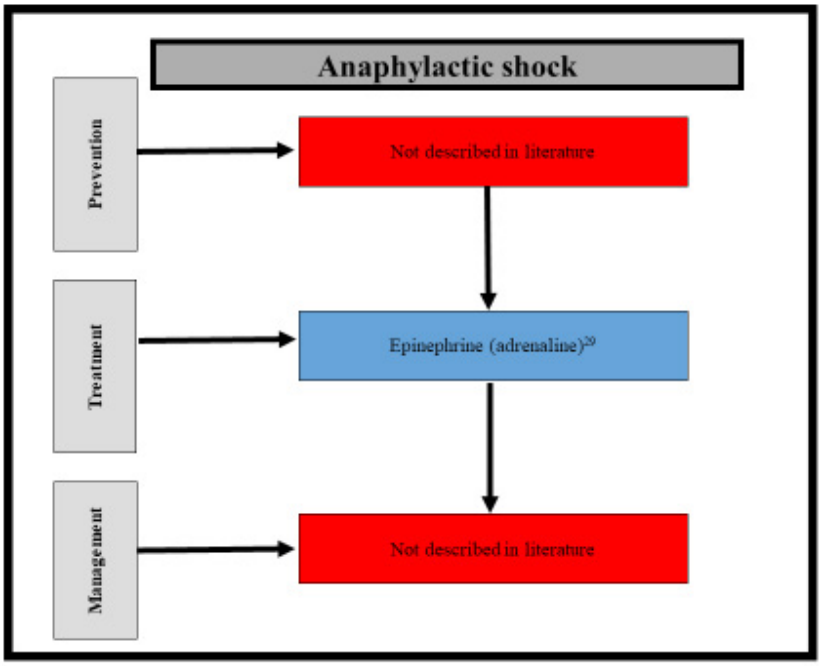
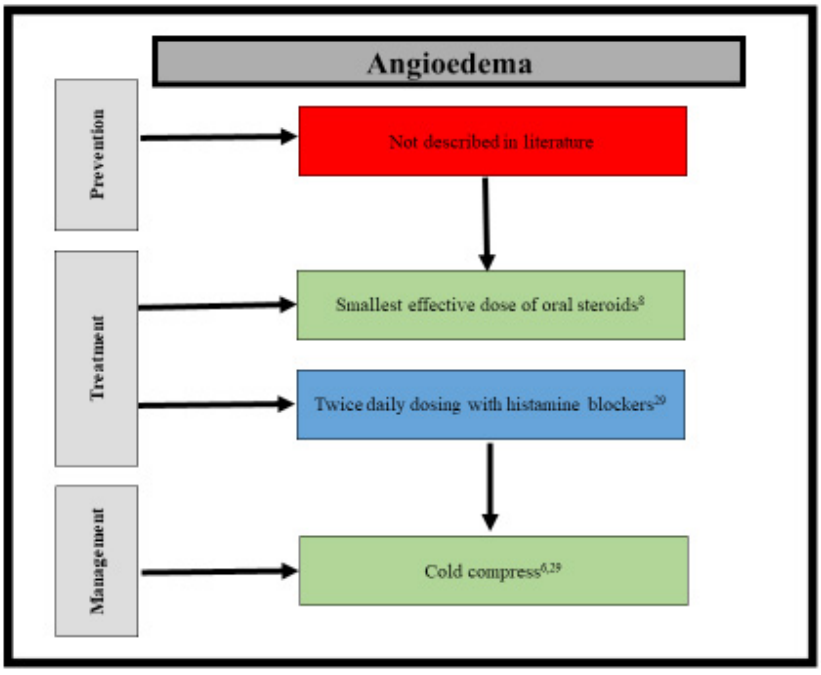
Figure 2: Models for the prevention, treatment and management of adverse events following the use of aesthetic soft tissue fillers in the face; Note: If a recommendation was supported by various levels of evidence between publications, it was categorized based on the highest level of evidence. Reference numbers in Figure 2 correspond to the article identification numbers listed in Table 2 and not those disclosed at the end of the manuscript.

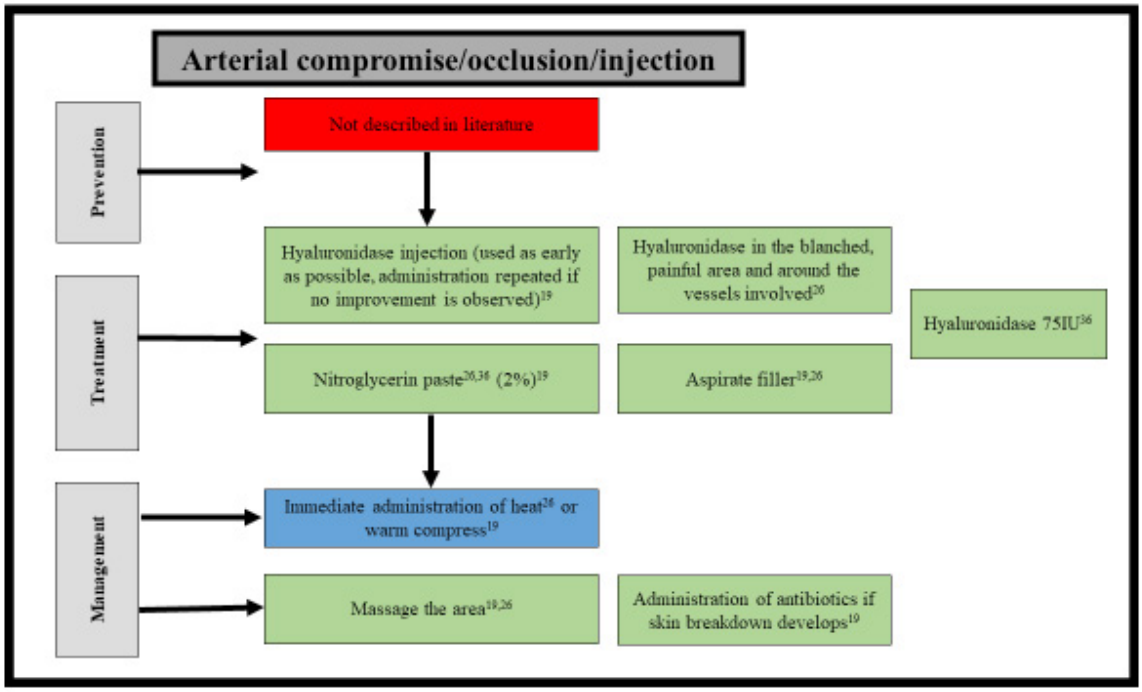


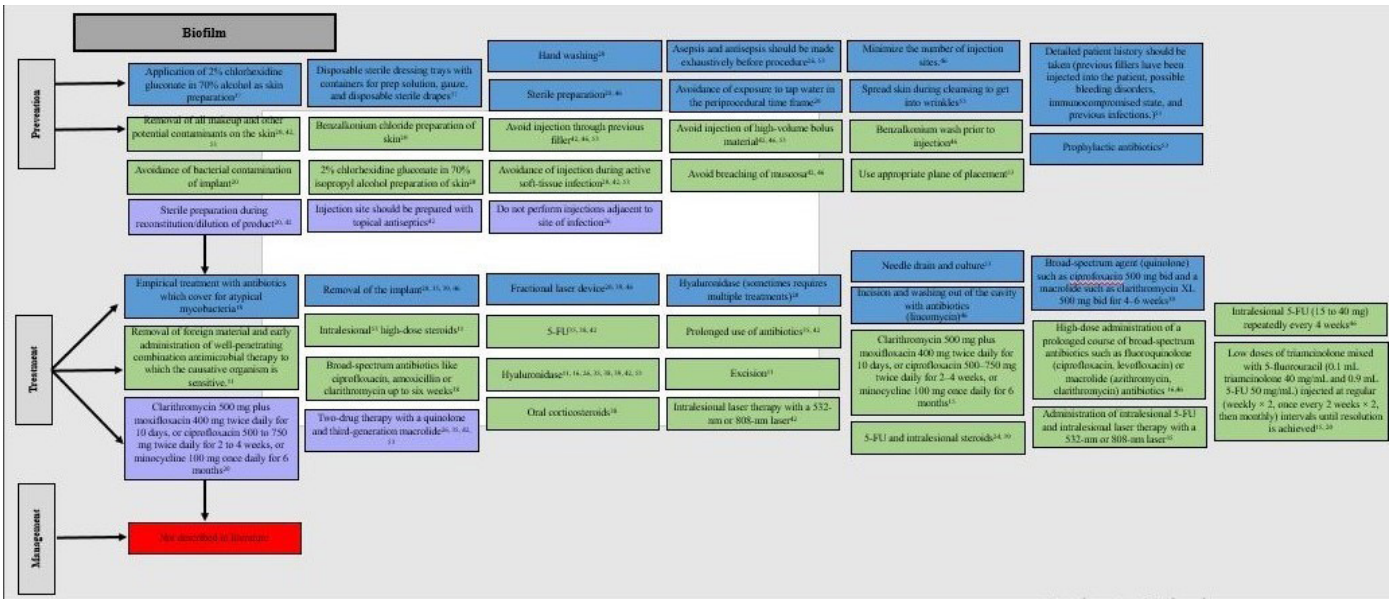

Abnormal sensation
Prevention
Thorough knowledge of facial anatomy[8]
Treatment
Not described in literature
Management
Not described in literature

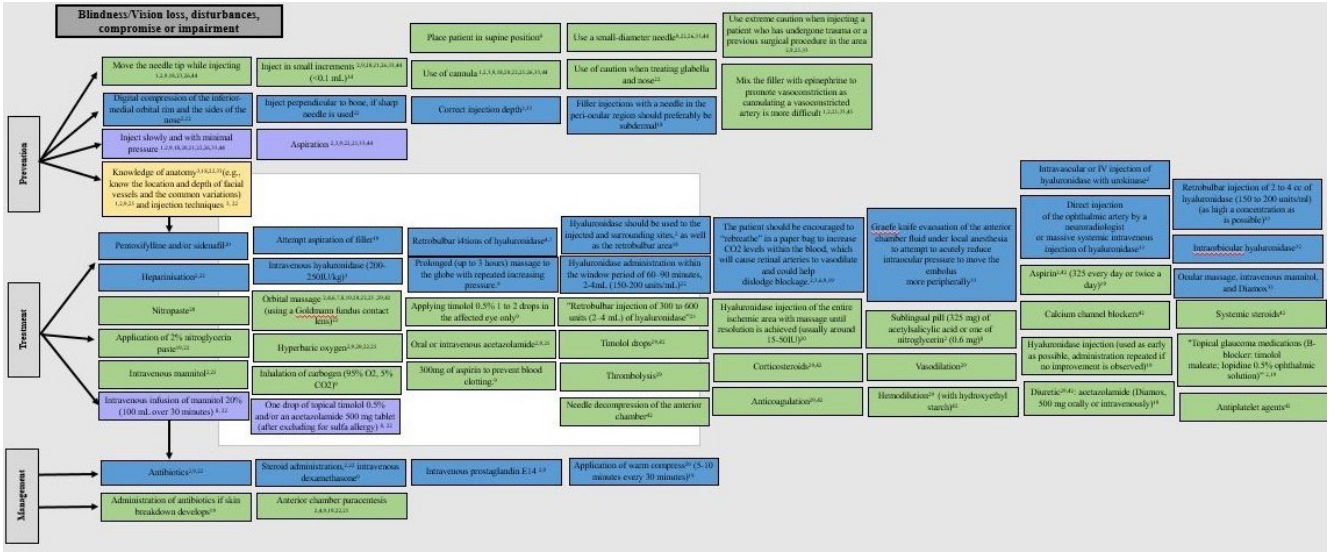

Allergic/hypersensitivity/inflammatory reactions
Prevention
Skin testing[18]
Treatment
Antihistamines, oral or systemic steroids[7]
Hyaluronidase[18]
Intralesional hyaluronidase[50]
Topical tacrolimus[45]
H2-receptor antagonists[6]
Leukotriene synthesis inhibitors[6]
Oral corticosteroids[6,52]
Propranolol or Ibuprofen[6]
Management
Not described in literature

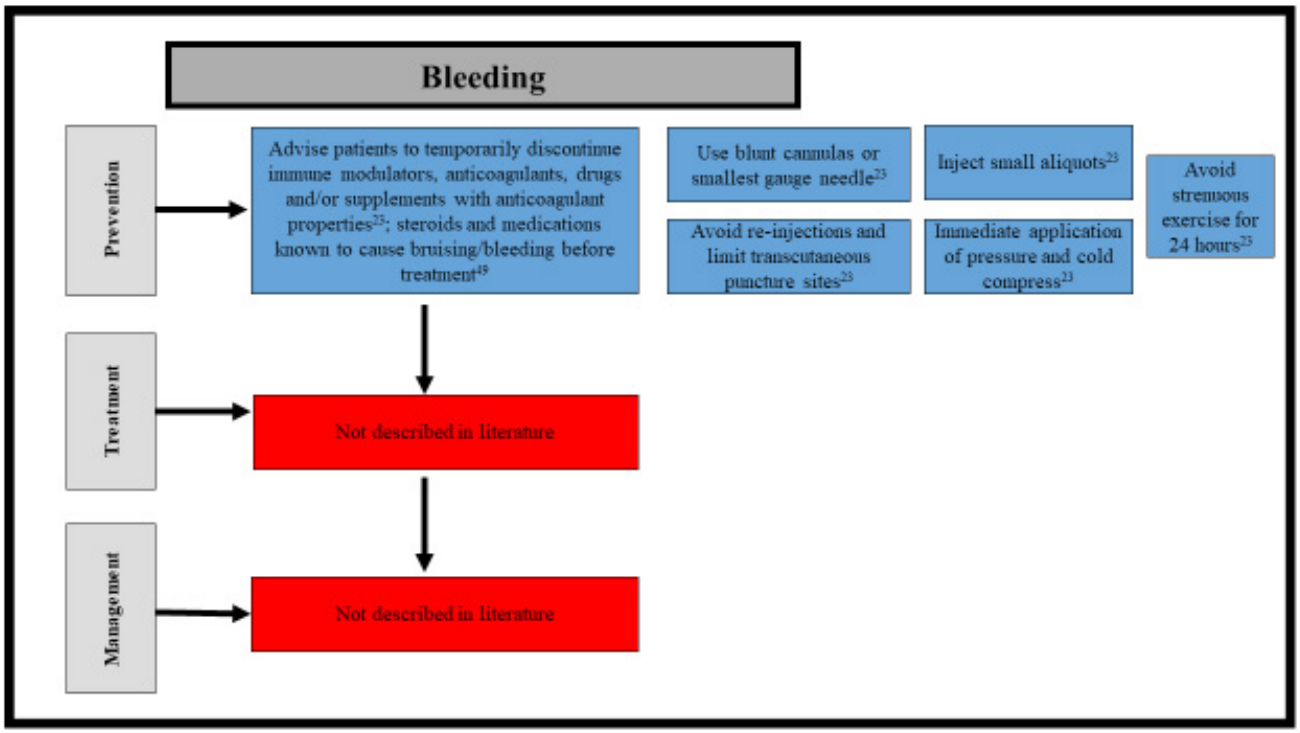

Anaphylactic shock
Prevention
Not described in literature
Treatment
Epinephrine (adrenaline)[29]
Management
Not described in literature

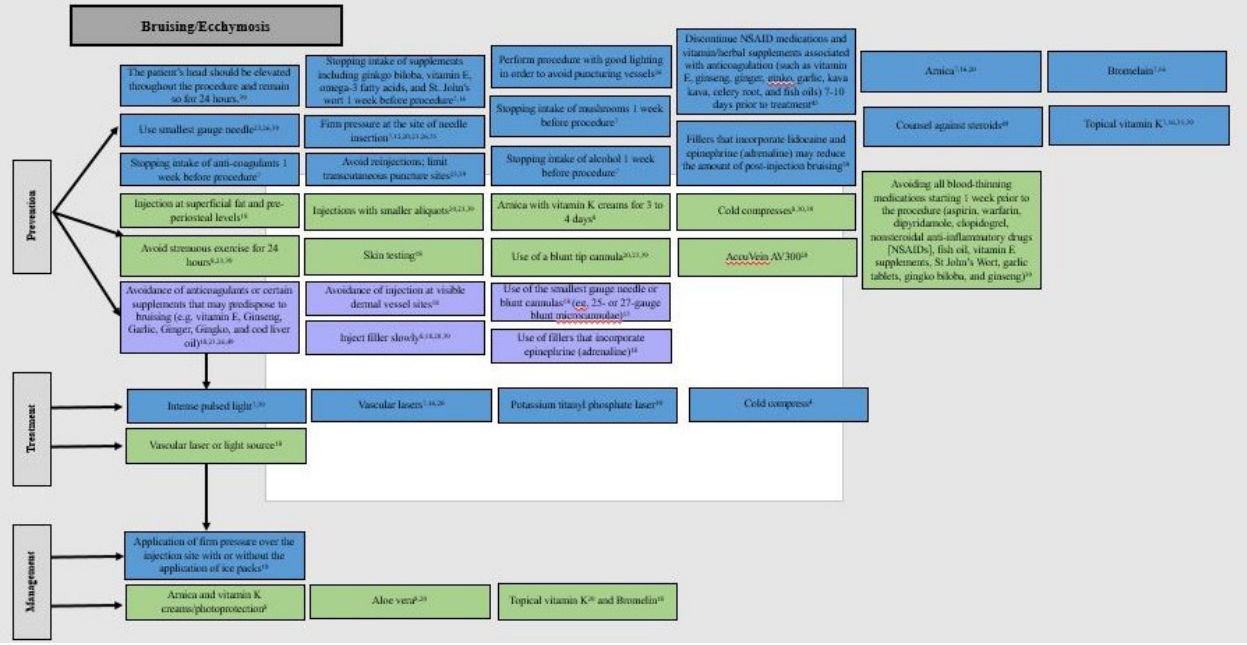

Angioedema
Prevention
Not described in literature
Treatment
Smallest effective dose of oral steroids[8]
Twice daily dosing with histamine blockers[29]
Management
Cold compress[6,29]

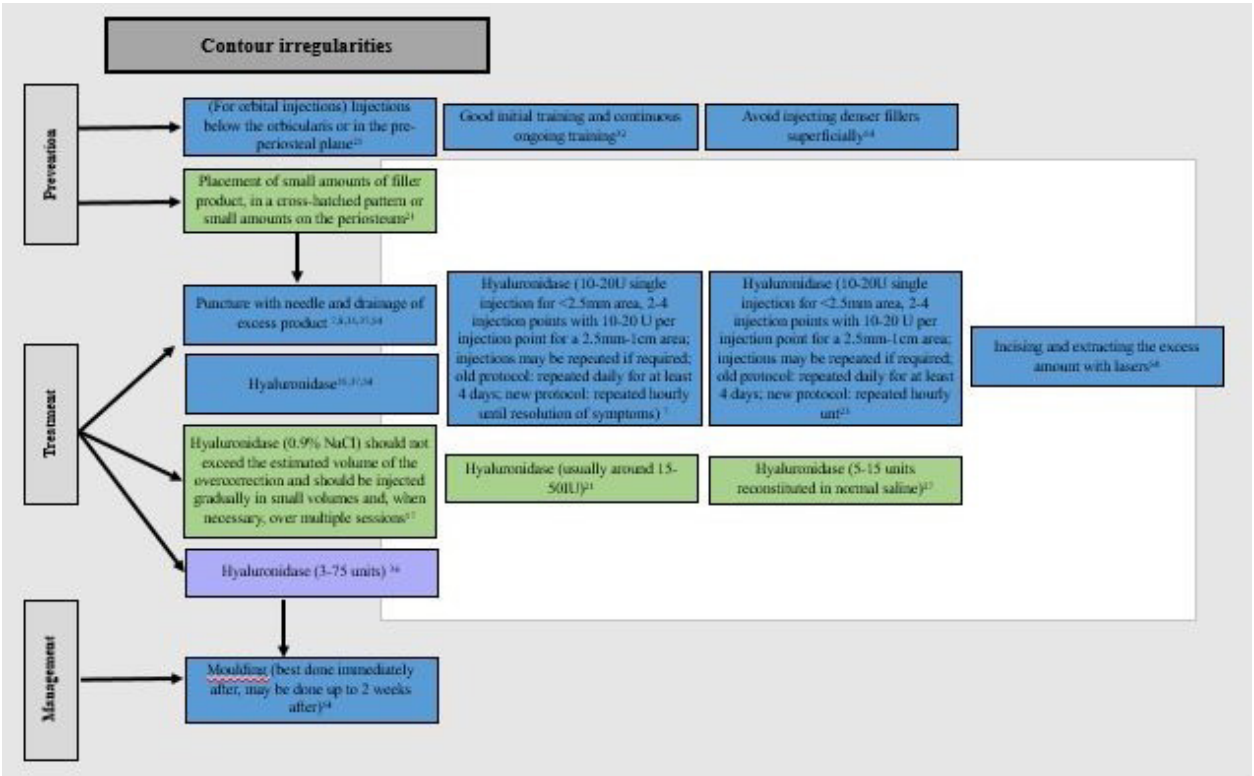

Arterial compromise/occlusion/injection
Prevention
Not described in literature
Treatment
Hyaluronidase injection (used as early as possible, administration repeated if no improvement is observed)[19]
Hyaluronidase in the blanched, painful area and around the vessels involved[26]
Hyaluronidase 75IU[36]
Nitroglycerin paste[26,36] (2%)[19]
Aspirate filler[19,26]
Management
Immediate administration of heat[26] or warm compress[19]
Massage the area[19,26]
Administration of antibiotics if skin breakdown develops[19]

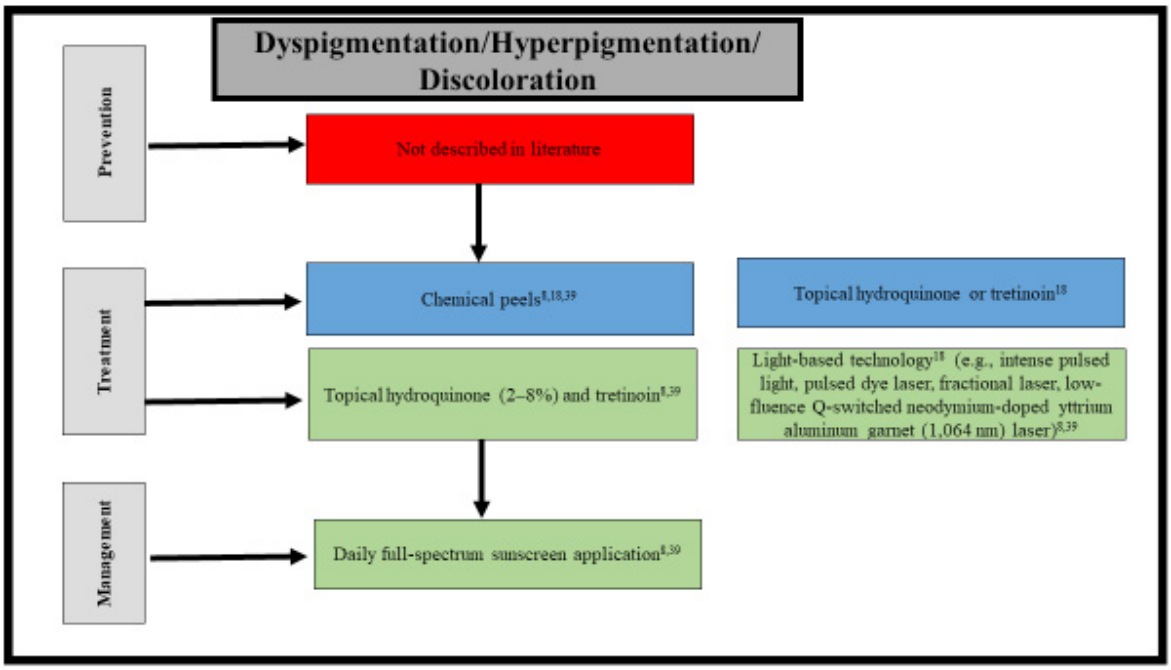

Biofilm
Prevention
Application of 2% chlorhexidine gluconate in 70% alcohol as skin preparation[37]
Disposable sterile dressing trays with containers for prep solution, gauze, and disposable sterile drapes[37]
Hand washing[28]
Asepsis and antisepsis should be made exhaustively before procedure[26, 33]
Minimize the number of injection sites.[36]
Detailed patient history should be taken (previous fillers have been injected into the patient, possible bleeding disorders, immunocompromised state, and previous infections.)[33]
Removal of all makeup and other potential contaminants on the skin[26, 42, 43]
Benzalkonium chloride preparation of skin[26]
Sterile preparation[26, 46]
Avoidance of exposure to tap water in the periprocedural time frame[26]
Spread skin during cleansing to get into wrinkles[33]
Avoid injection through previous filler[42, 46, 53]
Avoid injection of high-volume bolus material[42, 46, 53]
Benzalkonium wash prior to injection[44]
Prophylactic antibiotics[53]
Avoidance of bacterial contamination of implant[20]
2% chlorhexidine gluconate in 70% isopropyl alcohol preparation of skin[26]
Avoidance of injection during active soft-tissue infection[26, 42, 53]
Avoid breaching of mucosa[42, 46]
Use appropriate plane of placement[53]
Sterile preparation during reconstitution/dilution of product[20, 42]
Injection site should be prepared with topical antiseptics[42]
Do not perform injections adjacent to site of infection[26]
Treatment
Empirical treatment with antibiotics which cover for atypical mycobacteria[16]
Removal of the implant[20, 33, 39, 46]
Fractional laser device[20, 38, 46]
Hyaluronidase (sometimes requires multiple treatments)[38]
Needle drain and culture[53]
Broad-spectrum agent (quinolone) such as ciprofloxacin 500 mg bid and a macrolide such as clarithromycin XL 500 mg bid for 4–6 weeks[39]
Intralesional 5-FU (15 to 40 mg) repeatedly every 4 weeks[46]
Removal of foreign material and early administration of well-penetrating combination antimicrobial therapy to which the causative organism is sensitive.[53]
Intralesional[53] high-dose steroids[53]
5-FU[33, 38, 42]
Prolonged use of antibiotics[33, 42]
Incision and washing out of the cavity with antibiotics (lincomycin)[46]
High-dose administration of a prolonged course of broad-spectrum antibiotics such as fluoroquinolone (ciprofloxacin, levofloxacin) or macrolide (azithromycin, clarithromycin) antibiotics[38,46]
Low doses of triamcinolone mixed with 5-fluorouracil (0.1 mL triamcinolone 40 mg/mL and 0.9 mL 5-FU 50 mg/mL) injected at regular (weekly × 2, once every 2 weeks × 2, then monthly) intervals until resolution is achieved[33, 39]
Clarithromycin 500 mg plus moxifloxacin 400 mg twice daily for 10 days, or ciprofloxacin 500 to 750 mg twice daily for 2 to 4 weeks, or minocycline 100 mg once daily for 6 months[20]
Broad-spectrum antibiotics like ciprofloxacin, amoxicillin or clarithromycin up to six weeks[38]
Hyaluronidase[33, 38, 39, 38, 38, 42, 53]
Excision[53]
Clarithromycin 500 mg plus moxifloxacin 400 mg twice daily for 10 days, or ciprofloxacin 500–750 mg twice daily for 2–4 weeks, or minocycline 100 mg once daily for 6 months[53]
Administration of intralesional 5-FU and intralesional laser therapy with a 532-nm or 808-nm laser[39]
Two-drug therapy with a quinolone and third-generation macrolide[20, 39, 42, 53]
Oral corticosteroids[38]
Intralesional laser therapy with a 532-nm or 808-nm laser[42]
5-FU and intralesional steroids[34, 39]
Management
Not described in literature

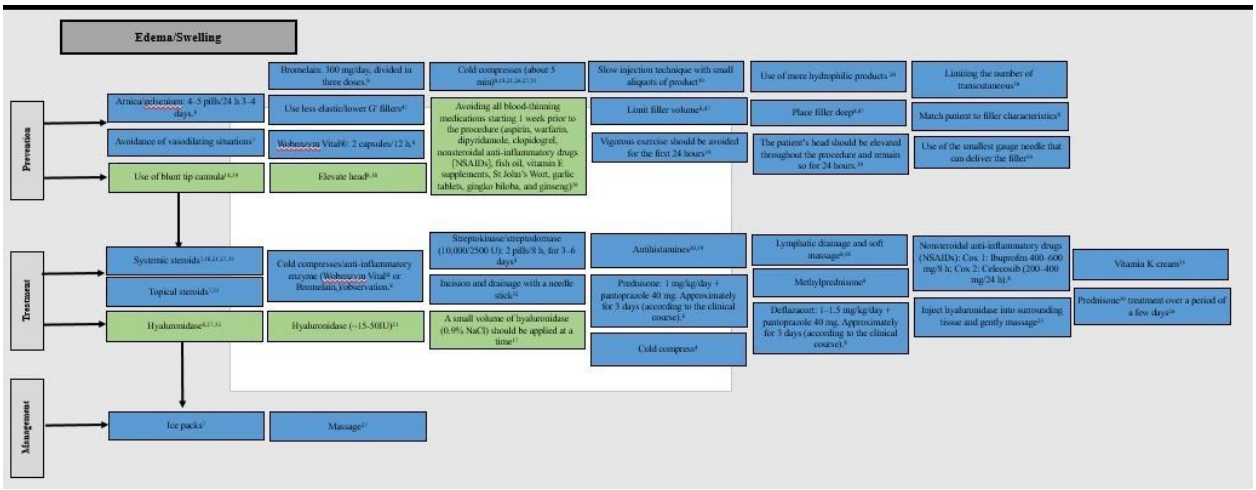

Blindness/Vision loss, disturbances, compromise or impairment
Prevention
Move the needle tip while injecting
Digital compression of the inferior-medial orbital rim and the sides of the nose
Inject slowly and with minimal pressure
Knowledge of anatomy (e.g., know the location and depth of facial vessels and the common variations) and injection techniques
Inject in small increments (<0.1 mL)
Inject perpendicular to bone, if sharp needle is used
Aspiration
Place patient in supine position
Use of cannula
Correct injection depth
Use a small-diameter needle
Use of caution when treating glabella and nose
Filler injections with a needle in the peri-ocular region should preferably be subdermal
Use extreme caution when injecting a patient who has undergone trauma or a previous surgical procedure in the area
Mix the filler with epinephrine to promote vasoconstriction as cannulating a vasoconstricted artery is more difficult
Treatment
Pentoxifylline and/or sildenafil
Heparinisation
Nitropaste
Application of 2% nitroglycerin paste
Intravenous mannitol
Intravenous infusion of mannitol 20% (100 mL over 30 minutes)
Attempt aspiration of filler
Intravenous hyaluronidase (200-250IU/kg)
Orbital massage (using a Goldmann fundus contact lens)
Hyperbaric oxygen
Inhalation of carbogen (95% O2, 5% CO2)
One drop of topical timolol 0.5% and/or an acetazolamide 500 mg tablet (after excluding for sulfa allergy)
Retrobulbar infiltrations of hyaluronidase
Prolonged (up to 3 hours) massage to the globe with repeated increasing pressure
Applying timolol 0.5% 1 to 2 drops in the affected eye only
Oral or intravenous acetazolamide
300mg of aspirin to prevent blood clotting
Hyaluronidase should be used to the injected and surrounding sites, as well as the retrobulbar area
Hyaluronidase administration within the window period of 60–90 minutes, 2-4mL (150-200 units/mL)
"Retrobulbar injection of 300 to 600 units (2–4 mL) of hyaluronidase"
Timolol drops
Thrombolysis
Needle decompression of the anterior chamber
The patient should be encouraged to "rebreathe" in a paper bag to increase CO2 levels within the blood, which will cause retinal arteries to vasodilate and could help dislodge blockage
Hyaluronidase injection of the entire ischemic area with massage until resolution is achieved (usually around 15-50IU)
Corticosteroids
Anticoagulation
Graefe knife evacuation of the anterior chamber fluid under local anesthesia to attempt to acutely reduce intraocular pressure to move the embolus more peripherally
Sublingual pill (325 mg) of acetylsalicylic acid or one of nitroglycerin (0.6 mg)
Vasodilation
Hemodilution (with hydroxyethyl starch)
Intravascular or IV injection of hyaluronidase with urokinase
Direct injection of the ophthalmic artery by a neuroradiologist or massive systemic intravenous injection of hyaluronidase
Aspirin (325 every day or twice a day)
Calcium channel blockers
Hyaluronidase injection (used as early as possible, administration repeated if no improvement is observed)
Diuretic; acetazolamide (Diamox, 500 mg orally or intravenously)
Retrobulbar injection of 2 to 4 cc of hyaluronidase (150 to 200 units/ml) (as high a concentration as is possible)
Intracebular hyaluronidase
Ocular massage, intravenous mannitol, and Diamox
Systemic steroids
*Topical glaucoma medications (B-blocker: timolol maleate; lopidine 0.5% ophthalmic solution)
Antiplatelet agents
Management
Antibiotics
Administration of antibiotics if skin breakdown develops
Steroid administration intravenous dexamethasone
Anterior chamber paracentesis
Intravenous prostaglandin E1
Application of warm compress (5-10 minutes every 30 minutes)

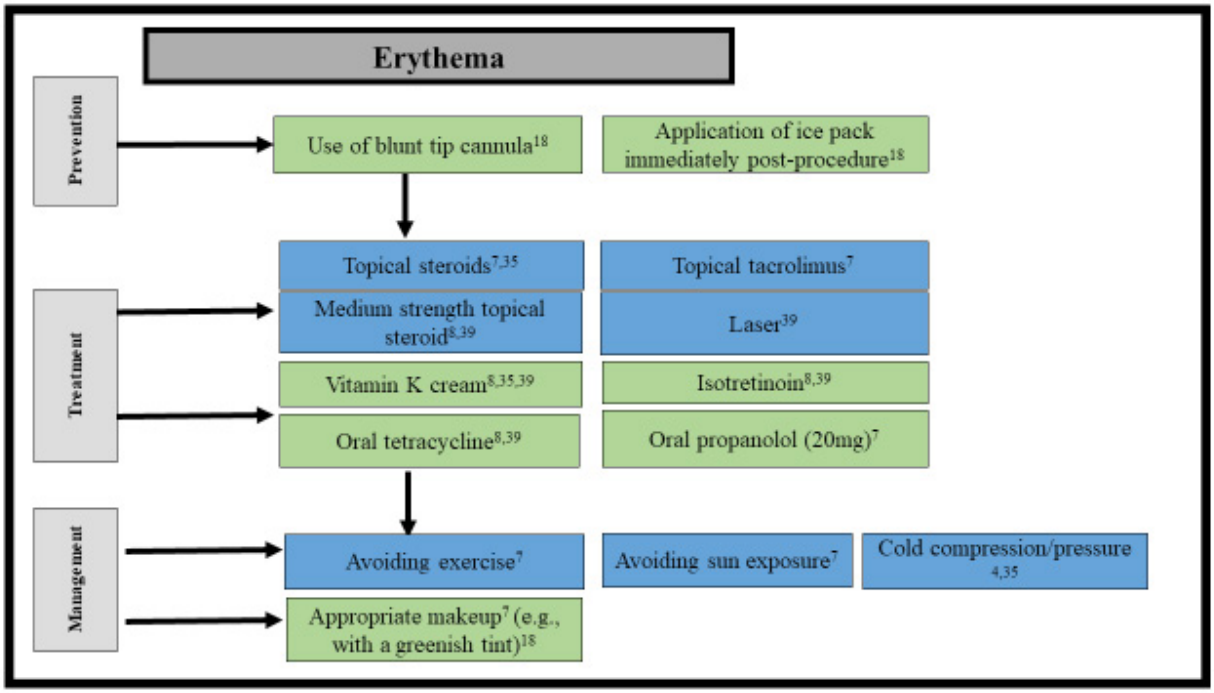

Bleeding
Prevention
Advise patients to temporarily discontinue immune modulators, anticoagulants, drugs and/or supplements with anticoagulant properties; steroids and medications known to cause bruising/bleeding before treatment
Use blunt cannulas or smallest gauge needle
Inject small aliquots
Avoid strenuous exercise for 24 hours
Avoid re-injections and limit transcutaneous puncture sites
Immediate application of pressure and cold compress
Treatment
Not described in literature
Management
Not described in literature

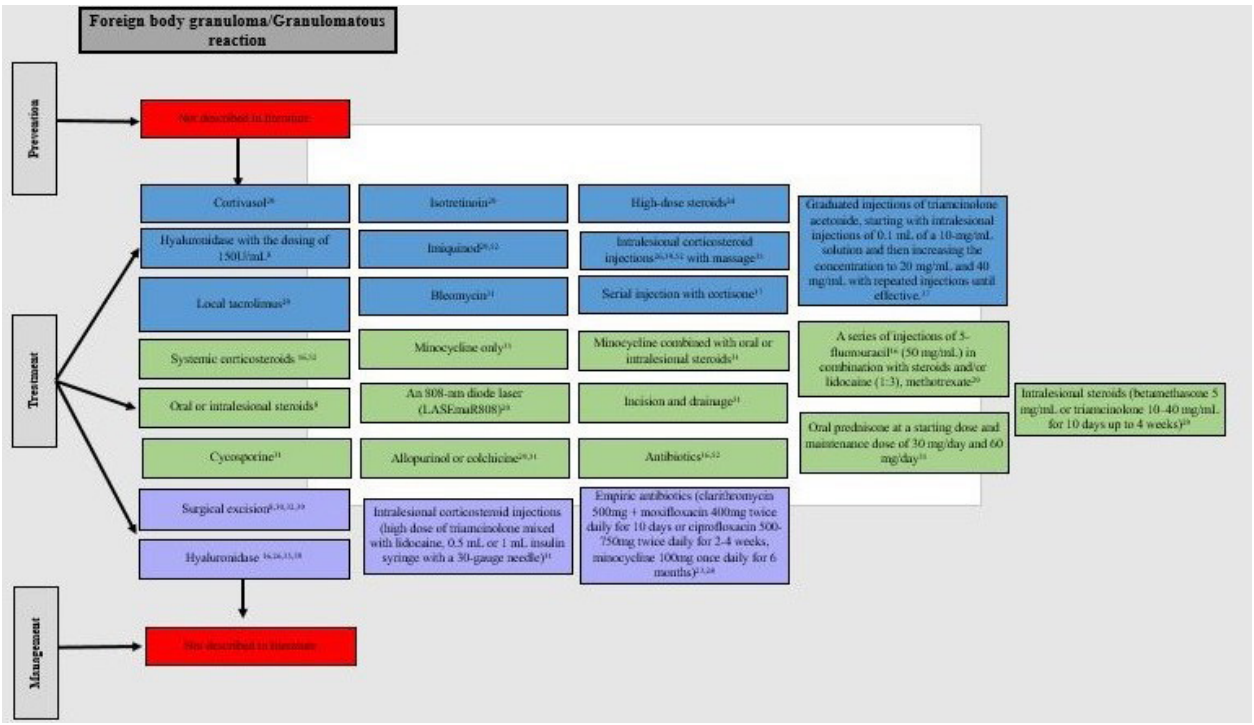

Bruising/Ecchymosis
Prevention
The patient's head should be elevated throughout the procedure and remain so for 24 hours.[39]
Stopping intake of supplements including ginkgo biloba, vitamin E, omega-3 fatty acids, and St. John's wort 1 week before procedure[7,16]
Perform procedure with good lighting in order to avoid puncturing vessels[16]
Discontinue NSAID medications and vitamin/herbal supplements associated with anticoagulation (such as vitamin E, ginseng, ginger, arnica, garlic, kava kava, celery root, and fish oils) 7-10 days prior to treatment[6]
Arnica[7,14,20]
Bromelain[7,14]
Use smallest gauge needle[13,16,19]
Firm pressure at the site of needle insertion[7,12,20,23,26,35]
Stopping intake of mushrooms 1 week before procedure[3]
Counsel against steroids[48]
Topical vitamin K[7,30,33,39]
Stopping intake of anti-coagulants 1 week before procedure[7]
Avoid reinjections; limit transcutaneous puncture sites[13,19]
Stopping intake of alcohol 1 week before procedure[7]
Fillers that incorporate lidocaine and epinephrine (adrenaline) may reduce the amount of post-injection bruising[18]
Injection at superficial fat and pre-periosteal levels[18]
Injections with smaller aliquots[24,23,39]
Arnica with vitamin K creams for 3 to 4 days[8]
Cold compresses[8,39,18]
Avoiding all blood-thinning medications starting 1 week prior to the procedure (aspirin, warfarin, dipyridamole, clopidogrel, nonsteroidal anti-inflammatory drugs [NSAIDs], fish oil, vitamin E supplements, St John's Wort, garlic tablets, gingko biloba, and ginseng)[39]
Avoid strenuous exercise for 24 hours[8,23,39]
Skin testing[26]
Use of a blunt tip cannula[20,23,39]
AccuVein AV300[18]
Avoidance of anticoagulants or certain supplements that may predispose to bruising (e.g. vitamin E, Ginseng, Garlic, Ginger, Gingko, and cod liver oil)[18,23,26,49]
Avoidance of injection at visible dermal vessel sites[16]
Use of the smallest gauge needle or blunt cannulas[18] (eg. 25- or 27-gauge blunt microcannulae)[23]
Inject filler slowly[8,18,28,39]
Use of fillers that incorporate epinephrine (adrenaline)[18]
Treatment
Intense pulsed light[3,39]
Vascular lasers[7,16,28]
Potassium titanyl phosphate laser[16]
Cold compress[8]
Vascular laser or light source[18]
Management
Application of firm pressure over the injection site with or without the application of ice packs[18]
Arnica and vitamin K creams/photoprotection[8]
Aloe vera[8,28]
Topical vitamin K[28] and Bromelin[16]

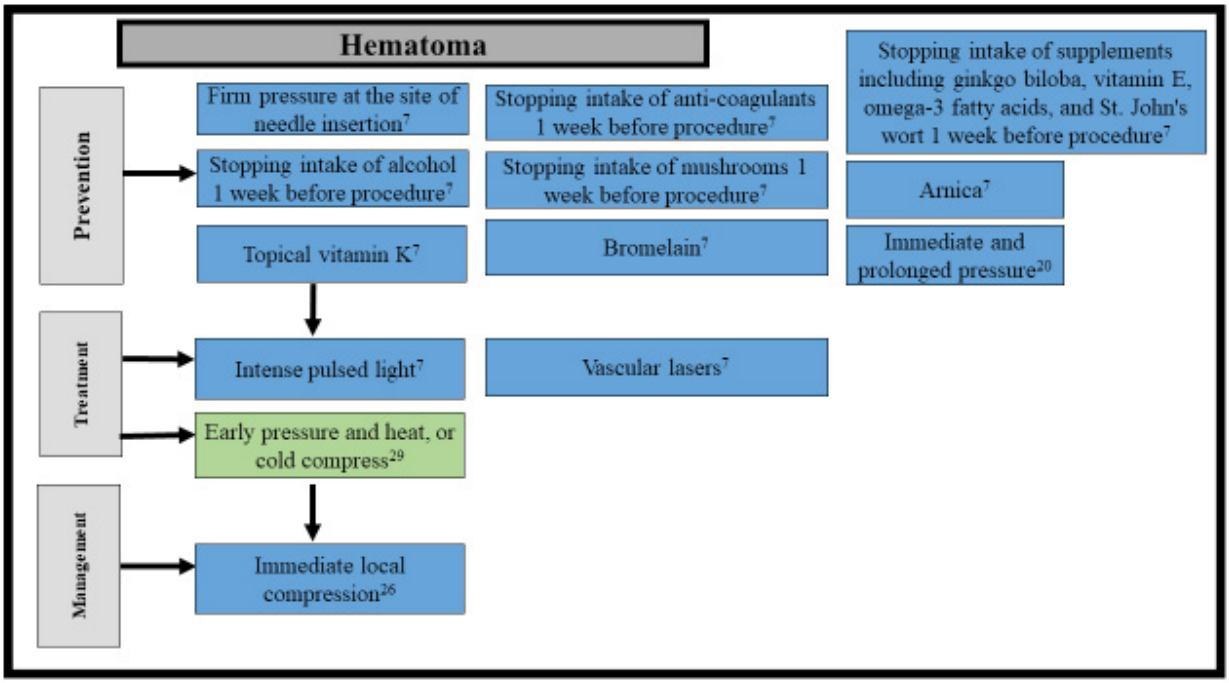

Contour irregularities
Prevention
(For orbital injections) Injections below the orbicularis or in the pre-periosteal plane[23]
Good initial training and continuous ongoing training[7,2]
Avoid injecting denser fillers superficially[2,4]
Placement of small amounts of filler product, in a cross-hatched pattern or small amounts on the periosteum[21]
Treatment
Puncture with needle and drainage of excess product [7,8,16,37,2,4]
Hyaluronidase[16,37,24]
Hyaluronidase (10-20U single injection for <2.5mm area, 2-4 injection points with 10-20 U per injection point for a 2.5mm-1cm area; injections may be repeated if required; old protocol: repeated daily for at least 4 days; new protocol: repeated hourly until resolution of symptoms) [7]
Hyaluronidase (10-20U single injection for <2.5mm area, 2-4 injection points with 10-20 U per injection point for a 2.5mm-1cm area; injections may be repeated if required; old protocol: repeated daily for at least 4 days; new protocol: repeated hourly until[2,3]
Incising and extracting the excess amount with lasers[2,8]
Hyaluronidase (0.9% NaCl) should not exceed the estimated volume of the overcorrection and should be injected gradually in small volumes and, when necessary, over multiple sessions[2,3]
Hyaluronidase (usually around 15-50IU)[21]
Hyaluronidase (5-15 units reconstituted in normal saline)[37]
Hyaluronidase (3-75 units) [16]
Management
Moulding (best done immediately after, may be done up to 2 weeks after)[2,4]

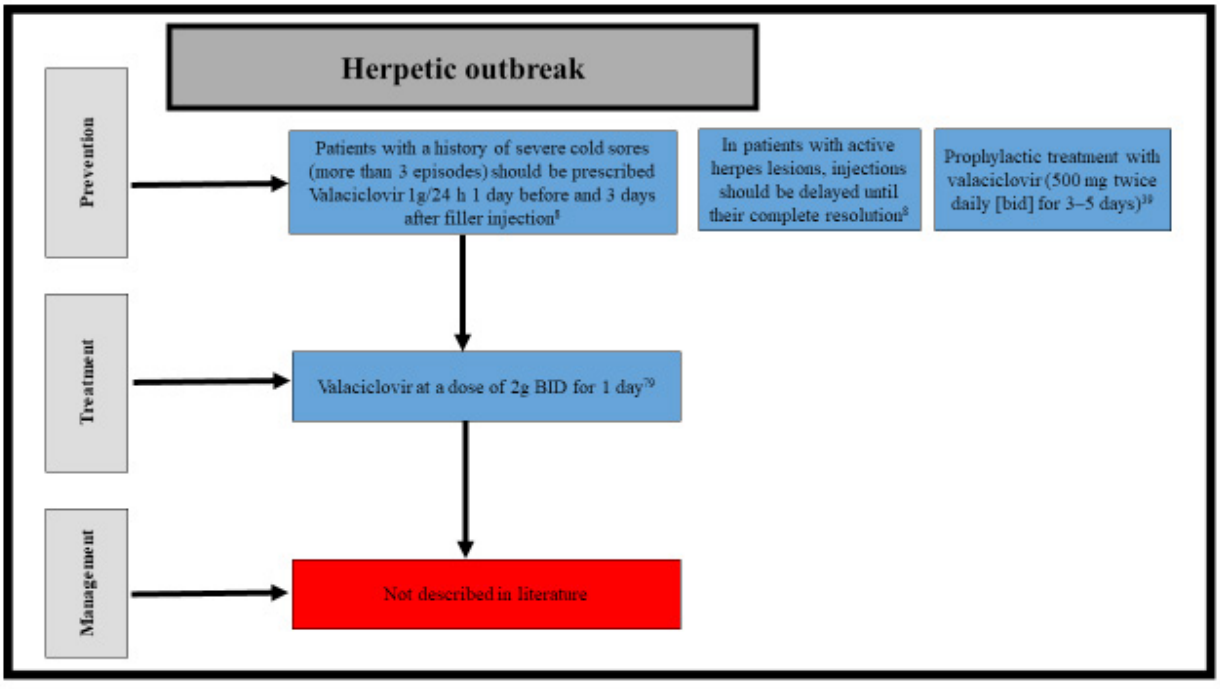

Dyspigmentation/Hyperpigmentation/ Discoloration
Prevention
Not described in literature
Treatment
Chemical peels[8,18,39]
Topical hydroquinone or tretinoin[18]
Topical hydroquinone (2–8%) and tretinoin[8,39]
Light-based technology[18] (e.g., intense pulsed light, pulsed dye laser, fractional laser, low-fluence Q-switched neodymium-doped yttrium aluminum garnet (1,064 nm) laser)[8,39]
Management
Daily full-spectrum sunscreen application[8,39]

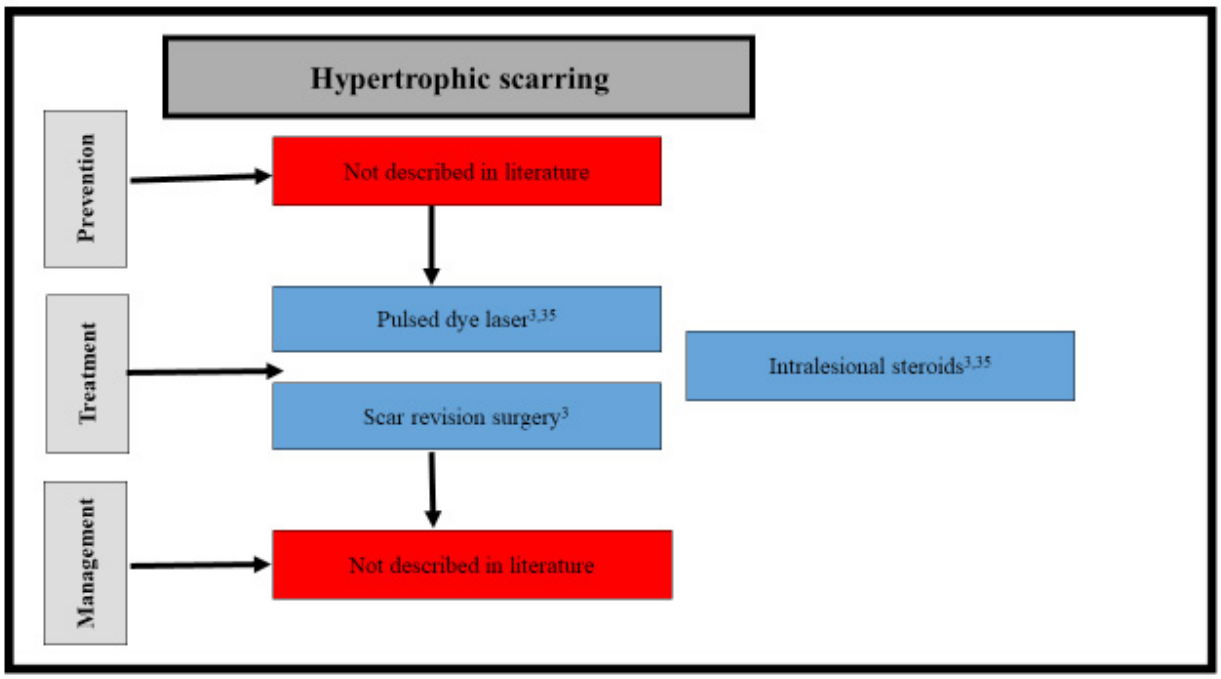

Edema/Swelling
Prevention
Arnica/selenium: 4–5 pills/24 h 3–4 days.[8]
Avoidance of vasodilating situations[7]
Use of blunt tip cannula[5,19]
Bromelain: 300 mg/day, divided in three doses.[8]
Use less elastic/lower G' fillers[47]
Wobenzym Vital®: 2 capsules/12 h.[8]
Elevate head[9,10]
Cold compresses (about 5 min)[8,18,21,26,27,31]
Avoiding all blood-thinning medications starting 1 week prior to the procedure (aspirin, warfarin, dipyridamole, clopidogrel, nonsteroidal anti-inflammatory drugs [NSAIDs], fish oil, vitamin E supplements, St John's Wort, garlic tablets, gingko biloba, and ginseng)[48]
Slow injection technique with small aliquots of product[10]
Limit filler volume[4,47]
Vigorous exercise should be avoided for the first 24 hours[10]
Use of more hydrophilic products [10]
Place filler deep[9,47]
The patient's head should be elevated throughout the procedure and remain so for 24 hours.[10]
Limiting the number of transcutaneous[10]
Match patient to filler characteristics[47]
Use of the smallest gauge needle that can deliver the filler[10]
Treatment
Systemic steroids[7–10,21,27,31]
Topical steroids[7,31]
Hyaluronidase[8,27,31]
Cold compresses/anti-inflammatory enzyme (Wobenzym Vital® or Bromelain)/observation.[8]
Hyaluronidase (~15-50IU)[31]
Streptokinase/streptodornase (10,000/2500 U): 2 pills/8 h, for 3–6 days[8]
Incision and drainage with a needle stick[10]
A small volume of hyaluronidase (0.9% NaCl) should be applied at a time[11]
Antihistamines[26,10]
Prednisone: 1 mg/kg/day + pantoprazole 40 mg. Approximately for 3 days (according to the clinical course).[8]
Cold compress[8]
Lymphatic drainage and soft massage[8,10]
Methylprednisone[8]
Deflazacort: 1–1.5 mg/kg/day + pantoprazole 40 mg. Approximately for 3 days (according to the clinical course).[8]
Nonsteroidal anti-inflammatory drugs (NSAIDs): Cox 1: Ibuprofen 400–600 mg/8 h; Cox 2: Celecoxib (200–400 mg/24 h).[8]
Inject hyaluronidase into surrounding tissue and gently massage[10]
Vitamin K cream[10]
Prednisone[10] treatment over a period of a few days[10]
Management
Ice packs[7]
Massage[10]

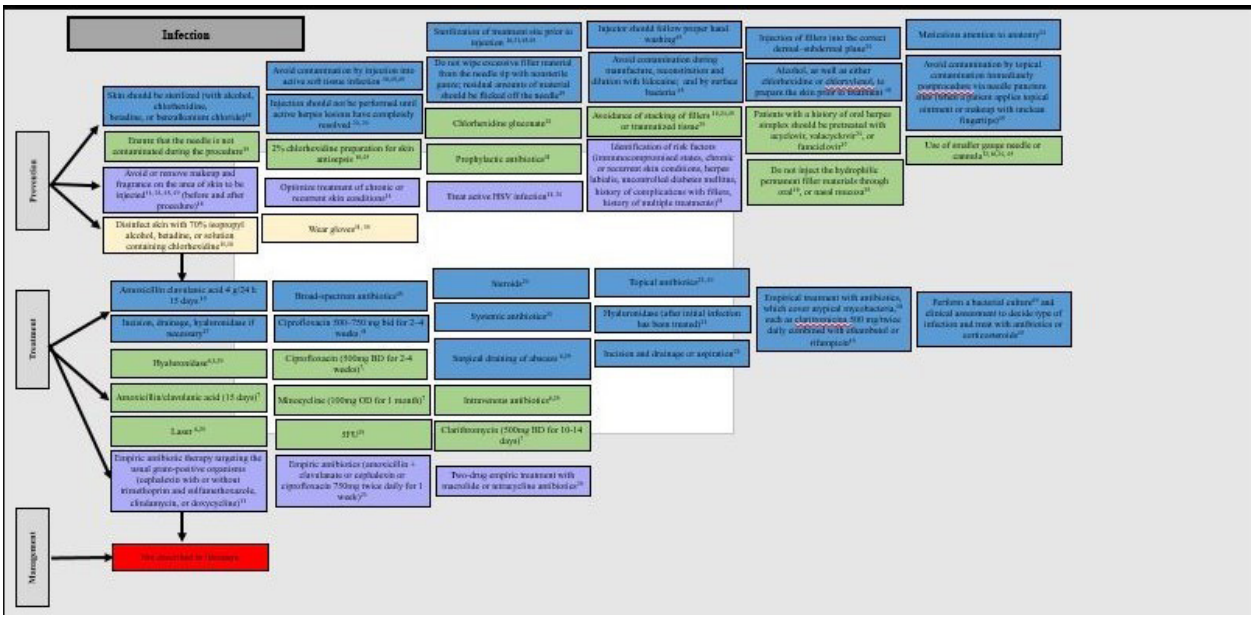

Erythema
Prevention
Use of blunt tip cannula[18]
Application of ice pack immediately post-procedure[18]
Treatment
Topical steroids[7,35]
Topical tacrolimus[7]
Medium strength topical steroid[8,39]
Laser[39]
Vitamin K cream[8,35,39]
Isotretinoin[8,39]
Oral tetracycline[8,39]
Oral propanolol (20mg)[7]
Management
Avoiding exercise[7]
Avoiding sun exposure[7]
Cold compression/pressure[4,35]
Appropriate makeup[7] (e.g., with a greenish tint)[18]

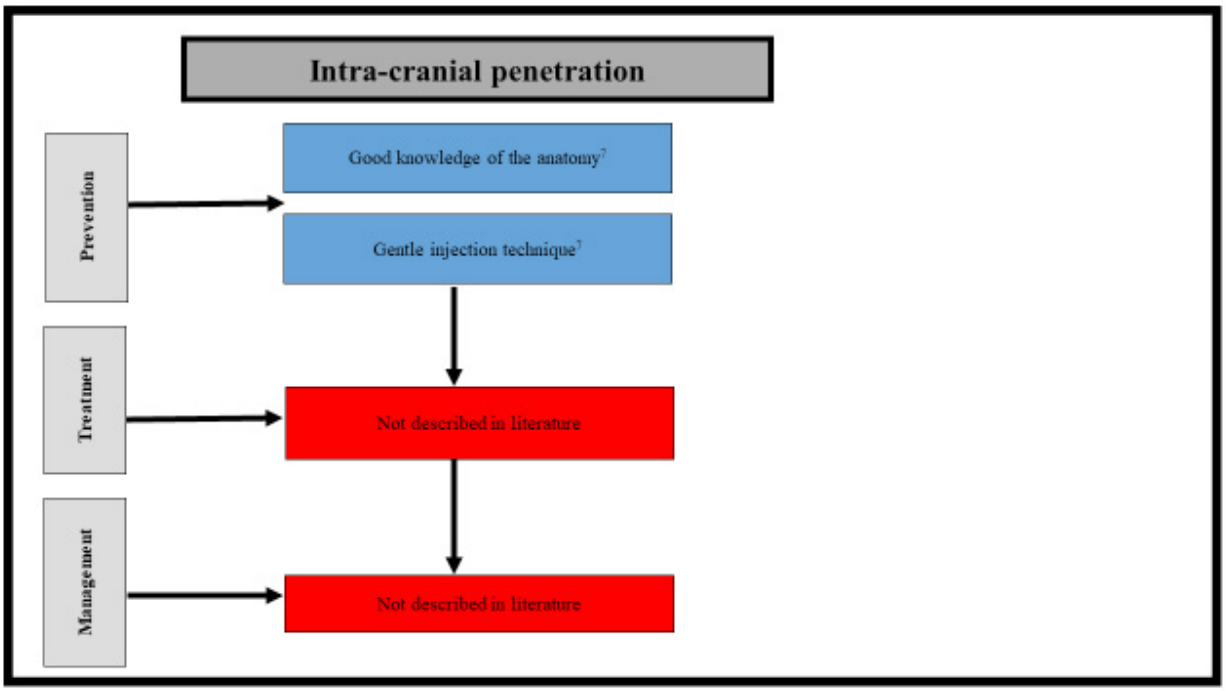

Foreign body granuloma/Granulomatous reaction
Prevention
Not described in literature
Treatment
Cortivasol[36]
Isotretinoin[36]
High-dose steroids[24]
Graduated injections of triamcinolone acetonide, starting with intralesional injections of 0.1 mL of a 10-mg/mL solution and then increasing the concentration to 20 mg/mL and 40 mg/mL with repeated injections until effective.[37]
Hyaluronidase with the dosing of 150IU/mL[5]
Imiquimod[36,52]
Intralesional corticosteroid injections[36,54,55] with massage[55]
Local tacrolimus[29]
Bleomycin[31]
Serial injection with cortisone[31]
Systemic corticosteroids[36,52]
Minocycline only[53]
Minocycline combined with oral or intralesional steroids[31]
A series of injections of 5-fluorouracil[46] (50 mg/mL) in combination with steroids and/or lidocaine (1:3), methotrexate[20]
Intralesional steroids (betamethasone 5 mg/mL or triamcinolone 10–40 mg/mL for 10 days up to 4 weeks)[20]
Oral or intralesional steroids[8]
An 808-nm diode laser (LASEmaR808)[23]
Incision and drainage[31]
Oral prednisone at a starting dose and maintenance dose of 30 mg/day and 60 mg/day[31]
Cyclosporine[31]
Allopurinol or colchicine[20,31]
Antibiotics[16,52]
Surgical excision[8,39,52,39]
Intralesional corticosteroid injections (high dose of triamcinolone mixed with lidocaine, 0.5 mL or 1 mL insulin syringe with a 30-gauge needle)[41]
Empiric antibiotics (clarithromycin 500mg + moxifloxacin 400mg twice daily for 10 days or ciprofloxacin 500-750mg twice daily for 2-4 weeks, minocycline 100mg once daily for 6 months)[3,28]
Hyaluronidase[16,26,33,38]
Management
Not described in literature

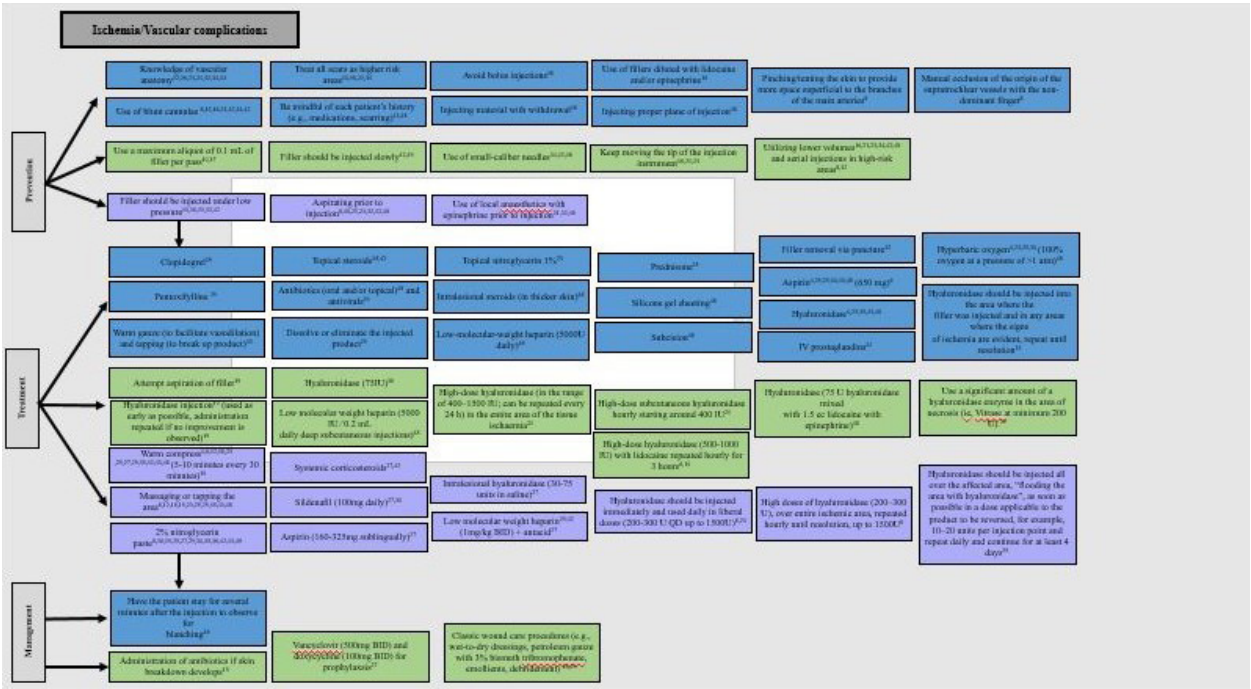

Hematoma
Prevention
Firm pressure at the site of needle insertion[7]
Stopping intake of anti-coagulants 1 week before procedure[7]
Stopping intake of supplements including ginkgo biloba, vitamin E, omega-3 fatty acids, and St. John's wort 1 week before procedure[7]
Stopping intake of alcohol 1 week before procedure[7]
Stopping intake of mushrooms 1 week before procedure[7]
Arnica[7]
Topical vitamin K[7]
Bromelain[7]
Immediate and prolonged pressure[20]
Treatment
Intense pulsed light[7]
Vascular lasers[7]
Early pressure and heat, or cold compress[29]
Management
Immediate local compression[26]

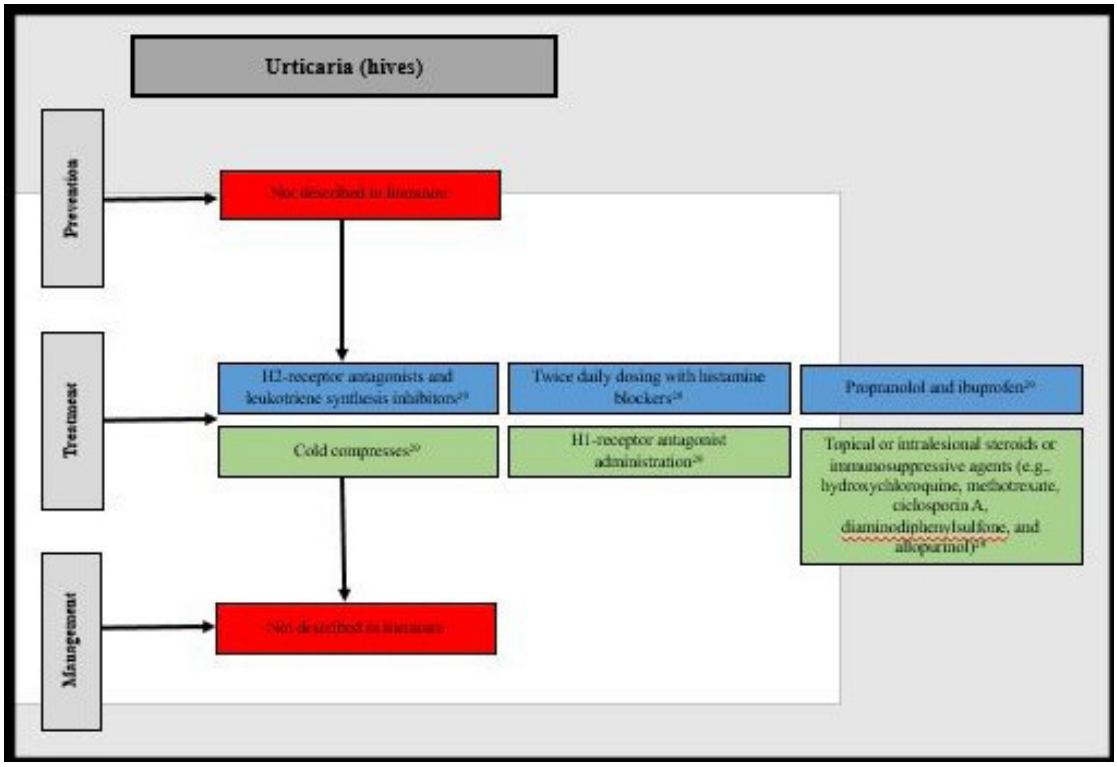

Herpetic outbreak
Prevention
Patients with a history of severe cold sores (more than 3 episodes) should be prescribed Valaciclovir 1g/24 h 1 day before and 3 days after filler injection[8]
In patients with active herpes lesions, injections should be delayed until their complete resolution[8]
Prophylactic treatment with valaciclovir (500 mg twice daily [bid] for 3–5 days)[39]
Treatment
Valaciclovir at a dose of 2g BID for 1 day[79]
Management
Not described in literature

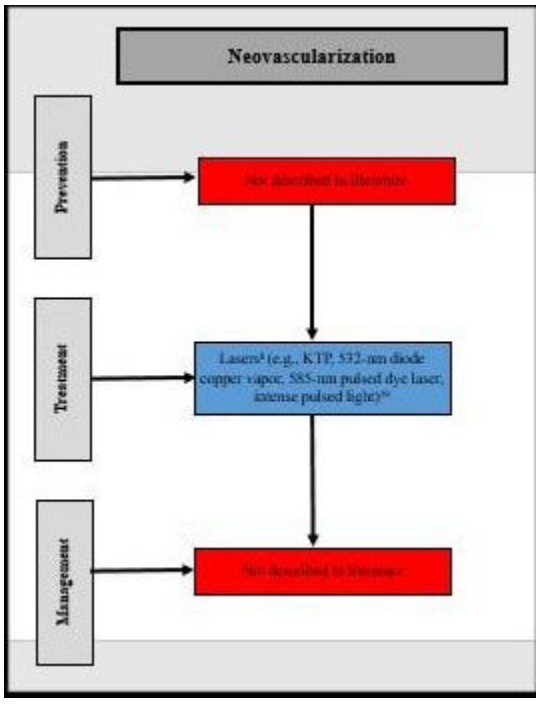

Hypertrophic scarring
Prevention
Not described in literature
Treatment
Pulsed dye laser3,35
Intralesional steroids3,35
Scar revision surgery3
Management
Not described in literature

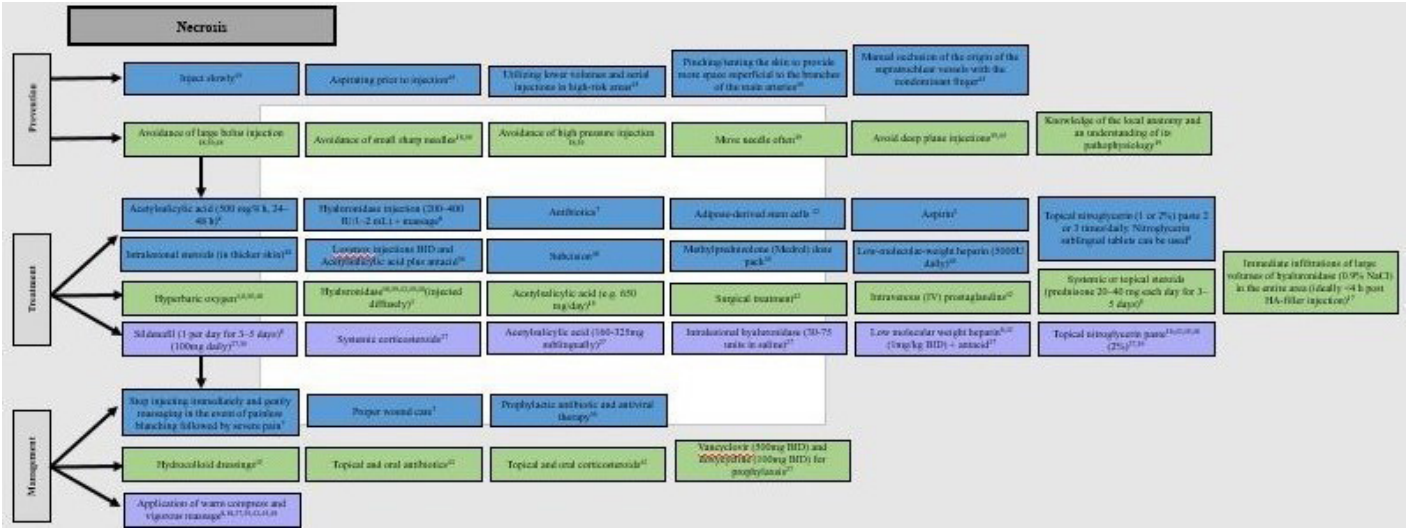

Infection
Prevention
Treatment
Management

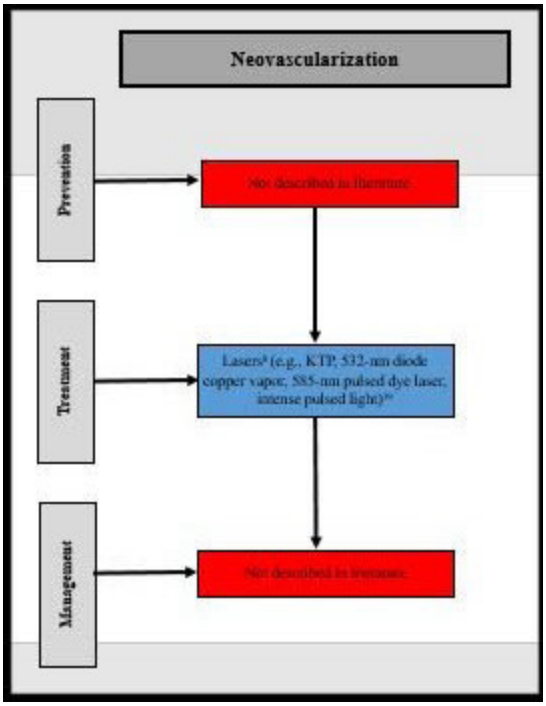

Intra-cranial penetration
Prevention
Good knowledge of the anatomy[7]
Gentle injection technique[7]
Treatment
Not described in literature
Management
Not described in literature

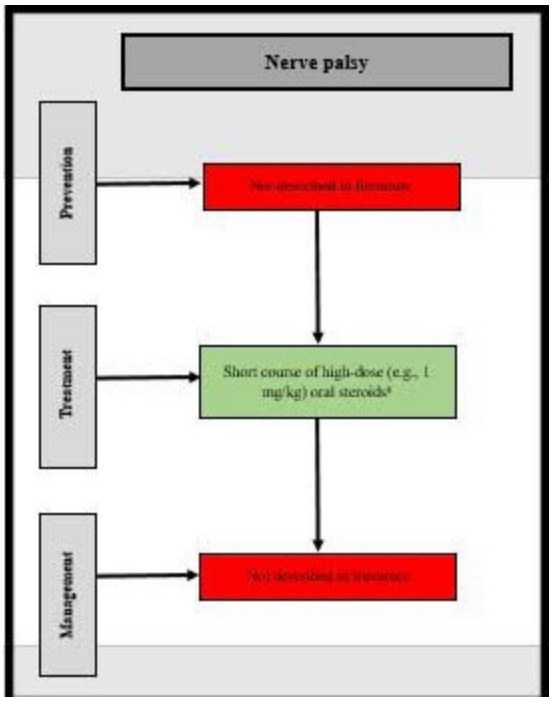

Ischemia/Vascular complications
Prevention
Treatment
Management

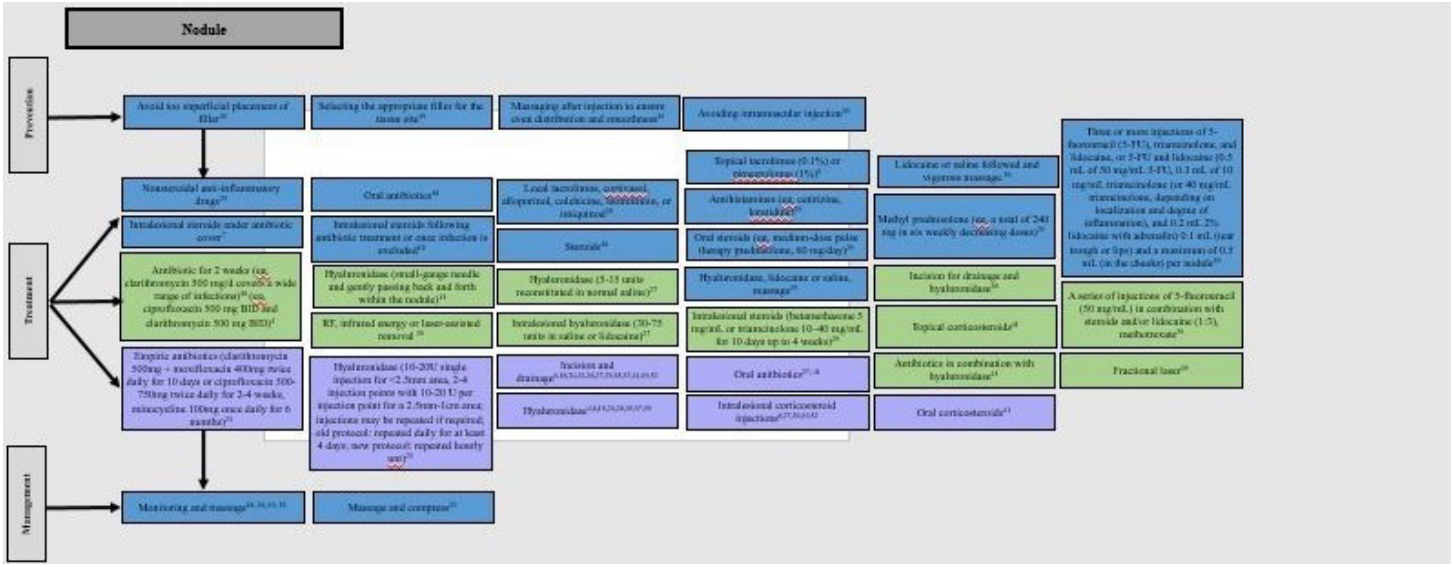

Urticaria (hives)
Prevention
Not described in literature
Treatment
H2-receptor antagonists and leukotriene synthesis inhibitors[19]
Twice daily dosing with histamine blockers[18]
Propranolol and ibuprofen[20]
Cold compresses[20]
H1-receptor antagonist administration[20]
Topical or intralesional steroids or immunosuppressive agents (e.g., hydroxychloroquine, methotrexate, ciclosporin A, diaminodiphenylsulfone, and allopurinol)[18]
Management
Not described in literature

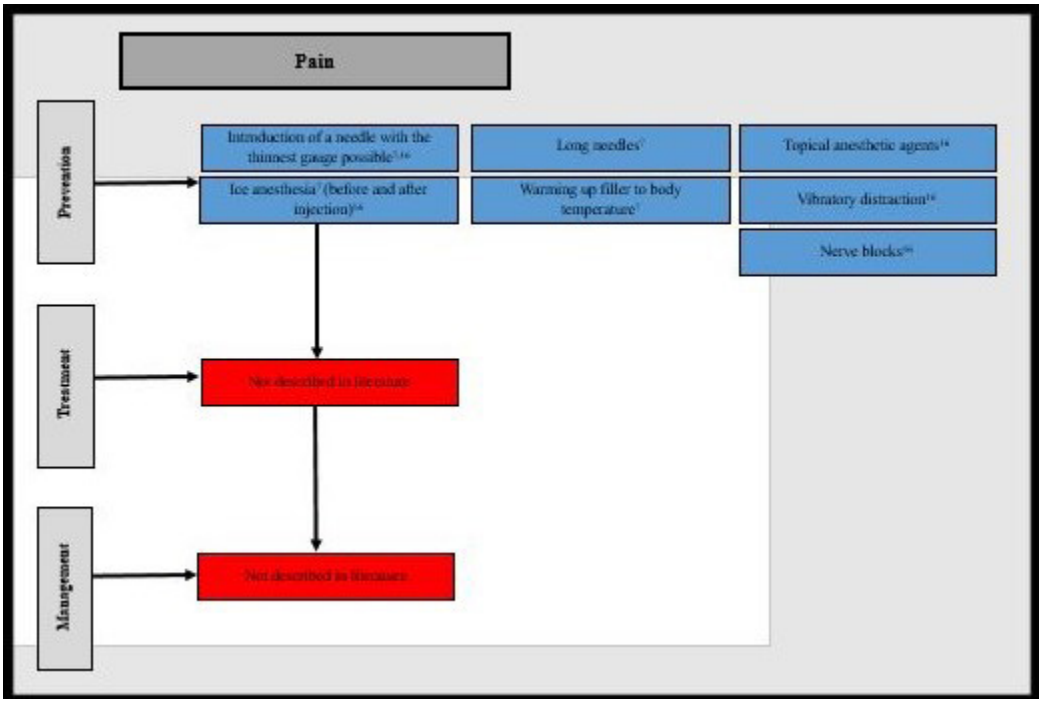

Neovascularization
Prevention
Not described in literature
Treatment
Lasers[3] (e.g., KTP, 532-nm diode copper vapor, 585-nm pulsed dye laser, intense pulsed light)[20]
Management
Not described in literature

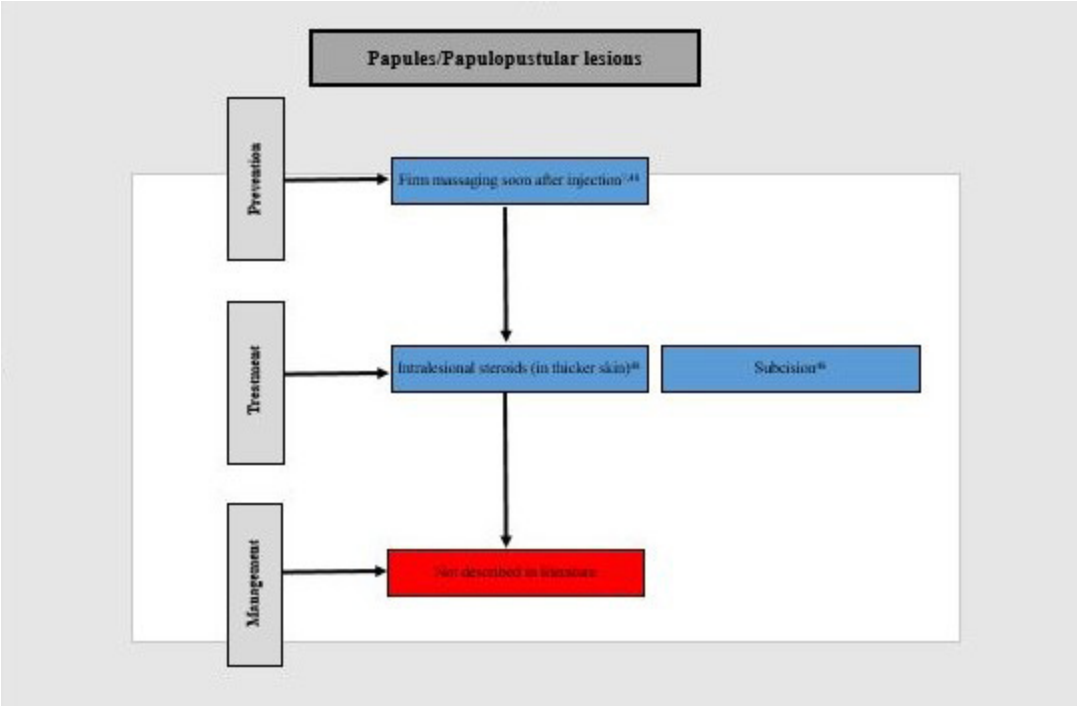

Necrosis
Prevention
Treatment
Management
Inject slowly
Aspirating prior to injection
Utilizing lower volumes and serial injections in high-risk areas
Pinching/tenting the skin to provide more space superficial to the branches of the main arteries
Manual occlusion of the origin of the supratrochlear vessels with the nondominant finger
Avoidance of large bolus injection
Avoidance of small sharp needles
Avoidance of high pressure injection
More needle often
Avoid deep plane injections
Knowledge of the local anatomy and an understanding of its pathophysiology
Acetylsalicylic acid (500 mg/8 h, 24–48 h)
Hyaluronidase injection (200–400 IU/1–2 mL) + massage
Antibiotics
Adipose-derived stem cells
Aspirin
Topical nitroglycerin (1 or 2%) paste 2 or 3 times daily. Nitroglycerin sublingual tablets can be used
Intralesional steroids (in thicker skin)
Lidocaine injections BID and Acetylsalicylic acid plus antacid
Nifedipine
Methylprednisolone (Medrol) dose pack
Low-molecular-weight heparin (5000U daily)
Systemic or topical steroids (prednisone 20–40 mg each day for 3–5 days)
Immediate infiltrations of large volumes of hyaluronidase (0.9% NaCl) in the entire area (ideally <4 h post HA-filler injection)
Hyperbaric oxygen
Hyaluronidase (injected diffusely)
Acetylsalicylic acid (e.g. 650 mg/day)
Surgical treatment
Intravenous (IV) prostaglandins
Sildenafil (1 pur day for 3–5 days) (100mg daily)
Systemic corticosteroids
Acetylsalicylic acid (160-325mg sublingually)
Intralesional hyaluronidase (30-75 units in saline)
Low molecular weight heparin (1mg/kg BID) + antacid
Topical nitroglycerin paste (2%)
Stop injecting immediately and gently massaging in the event of painless blanching followed by severe pain
Proper wound care
Prophylactic antibiotic and antiviral therapy
Hydrocolloid dressings
Topical and oral antibiotics
Topical and oral corticosteroids
Vancyclovir (500mg BID) and acyclovir (800mg BID) for prophylaxis
Application of warm compress and vigorous massage

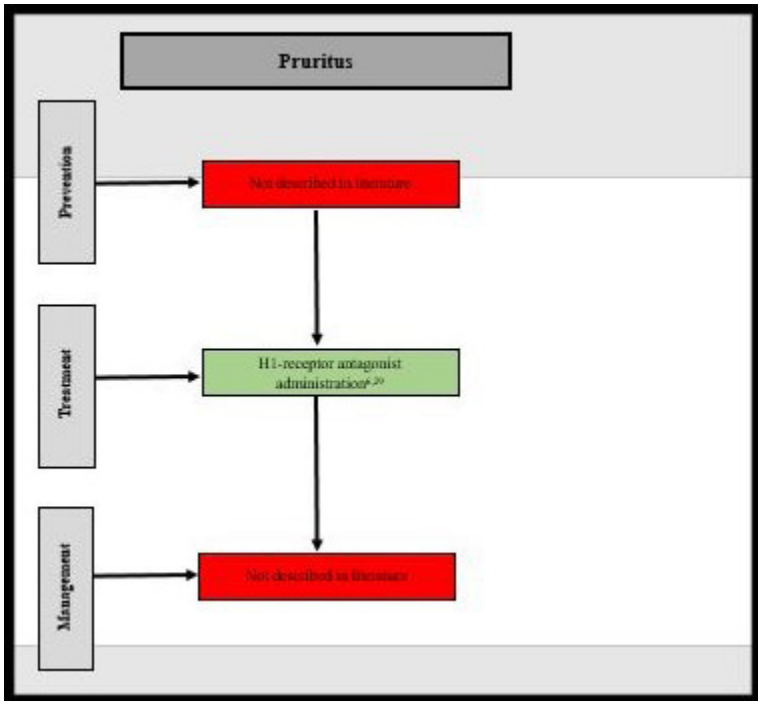

Neovascularization
Prevention
Not described in literature
Treatment
Lasers (e.g., KTP, 532-nm diode copper vapor, 585-nm pulsed dye laser, intense pulsed light)
Management
Not described in literature

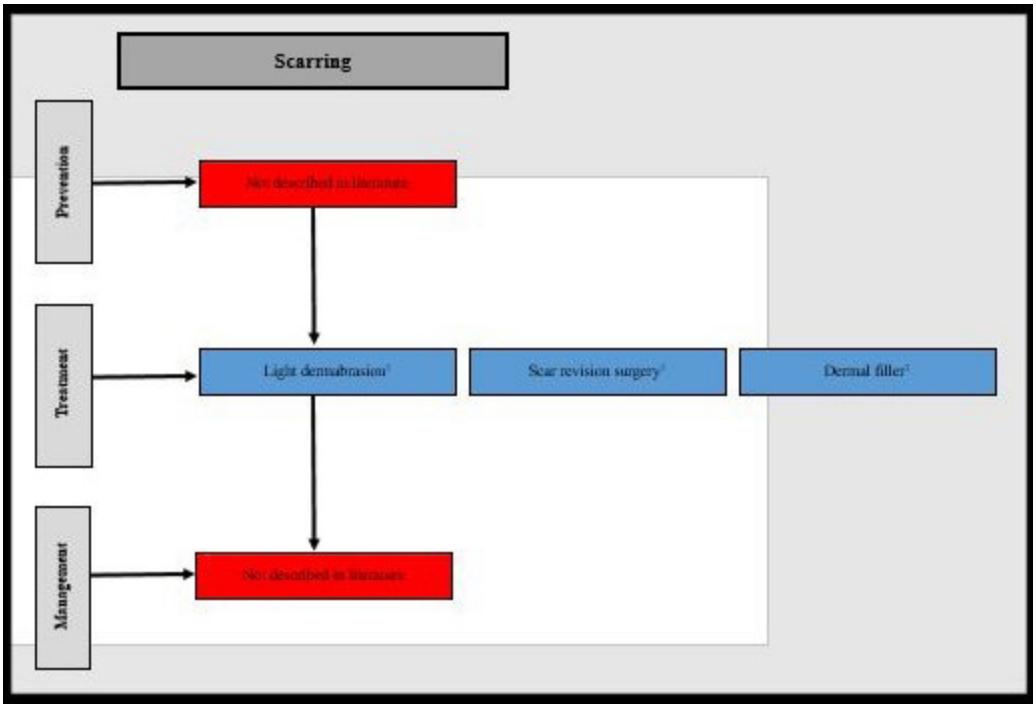

Nerve palsy
Prevention
Not described in literature
Treatment
Short course of high-dose (e.g., 1 mg/kg) oral steroids
Management
Not described in literature

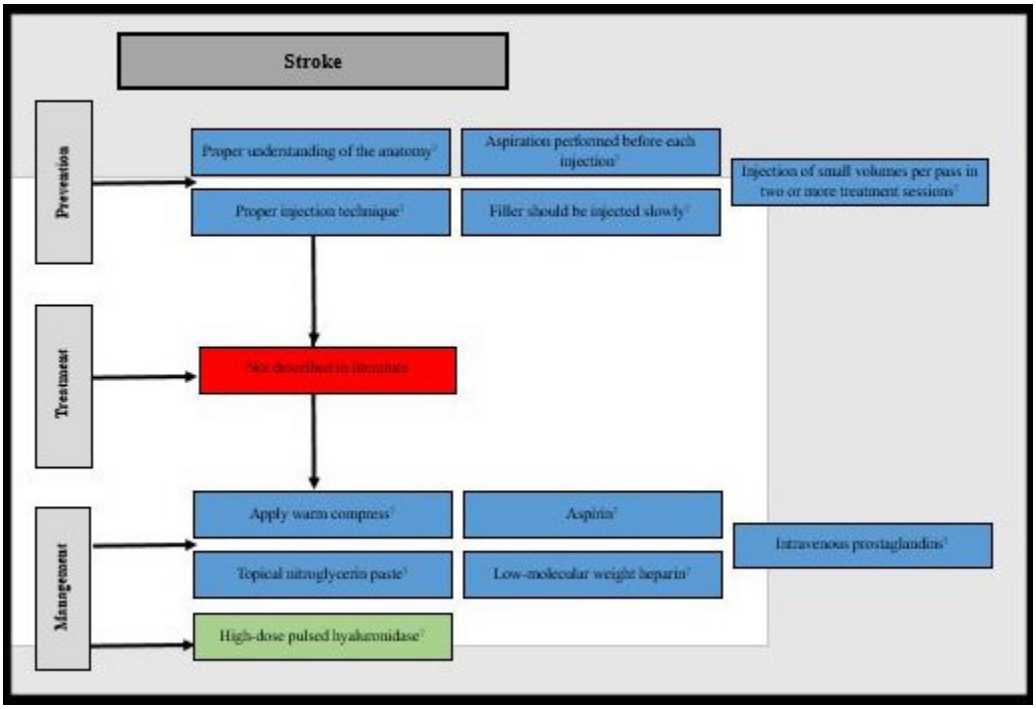

Nodule
Prevention
Treatment
Management
Nonsteroidal anti-inflammatory drugs
Intralesional steroids under antibiotic cover
Oral antibiotics
Intralesional steroids following antibiotic treatment or once infection is excluded
Hyaluronidase (small-gauge needle and gently passing back and forth within the nodule)
RF, infrared energy or laser-assisted removal
Topical tacrolimus (0.1%) or pimecrolimus (1%)
Antihistamines (eg, cetirizine, loratadine)
Oral steroids (eg, medium-dose pulse therapy prednisone, 80 mg/day)
Hyaluronidase, lidocaine or saline, massage
Intralesional steroids (betamethasone 5 mg/mL or triamcinolone 10–40 mg/mL for 10 days up to 4 weeks)
Oral antibiotics
Intralesional corticosteroid injections
Lidocaine or saline followed and vigorous massage
Methyl prednisolone (eg, a total of 240 mg in six weekly decreasing doses)
Incision for drainage and hyaluronidase
Topical corticosteroids
Antibiotics in combination with hyaluronidase
Oral corticosteroids
Three or more injections of 5-fluorouracil (5-FU), triamcinolone, and lidocaine, or 5-FU and lidocaine (0.5 mL of 50 mg/mL 5-FU, 0.3 mL of 10 mg/mL triamcinolone (or 40 mg/mL triamcinolone, depending on localization and degree of inflammation), and 0.2 mL 2% lidocaine with adrenalin) 0.1 mL (rear trough or lips) and a maximum of 0.3 mL (in the cheeks) per nodule
A series of injections of 5-fluorouracil (50 mg/mL) in combination with steroids and/or lidocaine (1:3), methotrexate
Fractional laser
Monitoring and massage
Massage and compress

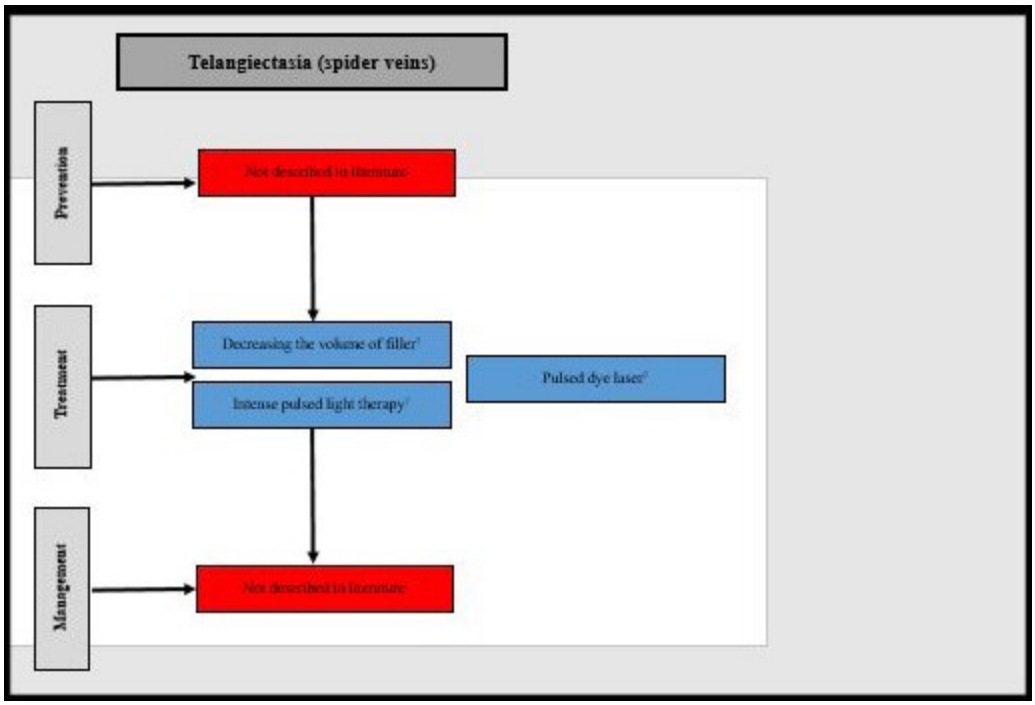

Pain
Prevention
Introduction of a needle with the thinnest gauge possible
Long needles
Topical anesthetic agents
Ice anesthesia (before and after injection)
Warming up filler to body temperature
Vibratory distraction
Nerve blocks
Treatment
Not described in literature
Management
Not described in literature

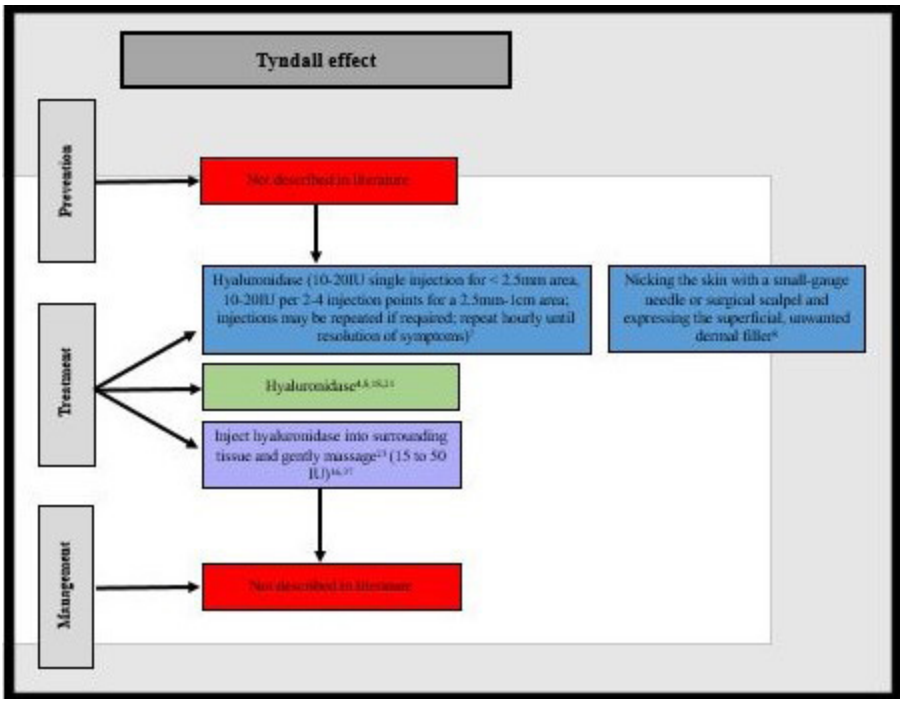

Papules/Papulopustular lesions
Prevention
Firm massaging soon after injection
Treatment
Intralesional steroids (in thicker skin)
Subcision
Management
Not described in literature


Pruritus
Prevention
Not described in literature
Treatment
H1-receptor antagonist administration[39]
Management
Not described in literature


Scarring
Prevention
Not described in literature
Treatment
Light dermabrasion[3]
Scar revision surgery[3]
Dermal filler[3]
Management
Not described in literature


Stroke
Prevention
Proper understanding of the anatomy
Aspiration performed before each injection
Injection of small volumes per pass in two or more treatment sessions
Proper injection technique
Filler should be injected slowly
Treatment
Not described in literature
Management
Apply warm compress
Aspirin
Intravenous prostaglandins
Topical nitroglycerin paste
Low-molecular weight heparin
High-dose pulsed hyaluronidase


Telangiectasia (spider veins)
Prevention
Not described in literature
Treatment
Decreasing the volume of filler
Pulsed dye laser
Intense pulsed light therapy
Management
Not described in literature


Tyndall effect
Prevention
Not described in literature
Treatment
Hyaluronidase (10-20IU single injection for < 2.5mm area; 10-20IU per 2-4 injection points for a 2.5mm-1cm area; injections may be repeated if required; repeat hourly until resolution of symptoms)
Nicking the skin with a small-gauge needle or surgical scalpel and expressing the superficial, unwanted dermal filler
Hyaluronidase
Inject hyaluronidase into surrounding tissue and gently massage (15 to 50 IU)
Management
Not described in literature