

Patient factors influencing dermal filler complications: prevention, assessment, and treatment

Koenraad De Boulle¹
Izolda Heydenrych²

On behalf of the Consensus Group

¹Aalst Dermatology Group, Aalst, Belgium; ²Cape Town Cosmetic Dermatology Centre, Century City, South Africa



Correspondence: Koenraad De Boulle
Aalst Dermatology Group,
Leopoldlaan, 43, 9300 Aalst, Belgium
Tel +32 53 781 899
Email koen@doctordeboulle.be

Abstract: While rare, complications do occur with the esthetic use of dermal fillers. Careful attention to patient factors and technique can do much to avoid these complications, and a well-informed practitioner can mitigate problems when they do occur. Since cosmetic surgery is usually an elective process, requested by the patient, clinical trials are complex to organize and run. For this reason, an international group of practicing physicians in the field of esthetics came together to share knowledge and to try and produce some informed guidance for their colleagues, considering the literature and also pooling their own extensive clinical experience. This manuscript aims to summarize the crucial aspects of patient selection, including absolute contraindications as well as situations that warrant caution, and also covers important considerations for the pre- and posttreatment periods as well as during the procedure itself. Guidance is given on both immediate and long-term management of adverse reactions. The majority of complications are related to accepting patients inappropriate for treatment or issues of sterility, placement, volume, and injection technique. It is clear that esthetic practitioners need an in-depth knowledge of all aspects of treatment with dermal fillers to achieve optimal outcomes for their patients.

Keywords: dermal fillers, complications, prevention, assessment, treatment, patient factors

Introduction

A wide range of dermal fillers is now available for use in facial esthetics.¹ All are potentially capable of causing complications,^{2,3} but fortunately, serious occurrences are rare, although probably underreported. Careful attention to patient selection, education, and injection technique can minimize the incidence of complications, and an understanding of the early signs of complications and their proactive management can decrease their impact.

Selecting appropriate patients, or perhaps more importantly, not treating inappropriate patients, is the first and a crucial step in avoiding complications with dermal fillers. This review considers the factors that should be borne in mind when assessing a patient for suitability for dermal filler treatment. It aims to give the practitioner an overview of contraindications, preventative measures, recognition of events, and appropriate treatment options. There remains, however, no consensus on the best treatment for adverse reactions, and each treatment option with its advantages and disadvantages should be carefully considered and discussed with the patient.⁴

Cosmetic surgery is usually an elective process, requested by the patient. As such, clinical trials are complex to organize and conduct. For this reason, an international group of practicing physicians in the field of cosmetic surgery came together to share

knowledge and to try and summarize what is published and produce some informed guidance for their colleagues. This manuscript is the result of preparation, study, and discussion among the group and is based on the literature as well as the group's clinical experience. The authors acknowledge that this guidance is based on the collective experience of the group at the time of writing, but it is not definitive, and there is a paucity of previously published data in many areas.

Methods

The first author regularly receives queries and referrals relating to complications with dermal fillers, with an increasing proportion originating from outside the major EU countries. A round table meeting was convened with interested physicians from some of these countries to discuss adverse events associated with dermal filler treatments and the training requirements for injectors.

Patient selection emerged as a core topic of concern, and in the light of the lack of information, the delegates wished to collate their experience in avoiding complications. Subsequently, the authors developed this consensus paper based on those discussions and a review of the current literature.

PubMed and Ovid Medline databases were searched using terms of "complications" OR "soft filler complications" OR "injectable complications" AND "dermal fillers". Papers from 2005 were selected (although older papers may be referred to in discussions where relevant). References cited in selected articles were also reviewed to identify additional relevant reports.

Because of the nature of esthetic procedures, where patients are not referred, but elect to have treatment by the practitioner of their own choosing, it is challenging to devise meaningful clinical trials. Some authors have conducted prospective trials, but these are the minority of studies and are often not randomized or controlled. Therefore, our knowledge base comprises case reports and summaries of individual practitioner's experience. This underlines the need to gather consensus views from experienced injectors who have treated many patients.

Pre-procedure considerations

Patients' expectations must be managed, so they do not envisage an unrealistic outcome, and they must be made aware of the limitations and risks of dermal fillers. The treatment of inadequately informed patients can be fraught with problems and may cause dissatisfaction.⁵ Caution should be exercised when confronting an individual who exhibits signs

of an underlying mental disturbance or dysmorphic tendency.

Well-focused pretreatment photographs should be taken, not only for assessment of treatment effects and any adverse effects but also for medicolegal purposes.^{5,6}

The patient's medical history and subsequent evaluation must be comprehensive, and patients should be advised to include cosmetic treatments when giving their history. de Bree et al⁷ reported on a patient who received polyacrylamide gel and developed a paranasal granuloma. The authors emphasized that the patient did not disclose her cosmetic treatment history, which confounded the diagnosis.

The suitability of different fillers needs to be discussed, and the patient given an indication of the likely value that can be obtained from treatment.^{2,6} Soft tissue augmentation is an elective procedure, and not all those seeking treatment may be suitable candidates on medical grounds. It is important to avoid treating patients who have preexisting conditions that clearly mandate against the use of dermal fillers (Table 1). This is a crucial and often neglected area of esthetic practice. Other patients may be somewhat dubious candidates, where treatment must be at the discretion of the physician whose informed judgment is paramount.

A convenient way of considering patient-related factors is as skin-related or systemic factors. A clear link needs to be made between the two to ensure that the patients are forthcoming about all conditions or treatments, even if they believe them to be completely unrelated.

Firstly, contraindications detailed in the instructions for use of the chosen filler should be closely adhered to. These mainly refer to the product constituents or excipients; patients with multiple or severe allergies and those with a history of anaphylaxis should not be treated.

Similarly, where data are available on a particular product or technique, the physician should take care not to extrapolate the results or assume that they are transferrable. This includes results obtained only in one area of the anatomy.⁸

Prospective patients with abnormally thin skin or skin atrophy, such as seen in corticosteroid-induced atrophy of the skin due to long-term topical or peroral steroid use, or with conditions such as anetoderma, vermiculate atrophoderma, or rheumatoid arthritis-associated skin thinning of the dorsum of the hands, are not suitable candidates for superficial or medium-depth placement of certain fillers. Very thin skin on the eyelids and in cheeks that have many fine wrinkles is also a contraindication for certain fillers.⁹

Infections in, or adjacent to, the region to be treated can be exacerbated and cause complications, since the infecting

Table 1 Conditions contraindicating or warranting caution in the use of dermal fillers

Condition	Examples or comment	CI	PD	NAC
Active skin infection	Impetigo, herpes simplex, massive demodex folliculorum, pityrosporum, <i>Propionibacterium acnes</i> , viral warts	X		
Inflammatory conditions of the skin	Atopic patients, allergic contact dermatitis, “status cosmeticus” or sensitive skin syndrome, seborrheic dermatitis, active lichen planus, active acne rosacea		X	
Other inflammatory diseases	Pyoderma Osteoarthritis		X	
Active localized infection	Ear, nose, or throat infections, dental abscess, periodontitis	X		
Active generalized infection	Gastroenteritis, urinary bladder infection	X		
Noninfectious gastrointestinal conditions	Crohn’s disease, ulcerative colitis		X	
Allergy/hypersensitivity	Hypersensitivity to filler components including lidocaine, chronic urticaria, and Quincke’s edema	X		
Active psoriasis arthropatic	If condition is more arthropatic: caution warranted If condition is more psoriatic than arthropatic: treatment is possible		X	X
Systemic infections: viral	HIV		X	
Conditions potentially causing a Koebner response	Lichen planus, lichen nitidus, or lichen sclerosus, psoriasis, viral warts		X	
Active collagenoses	Mixed connective tissue disease Active morphea, active systemic lupus	X		
Other collagenoses	Marfan syndrome, Ehlers–Danlos syndrome Stabilized morphea		X	X
Immune compromise	Graft versus host disease	X		
Immune compromise	Bullous diseases		X	
Autoimmune conditions	Active Hashimoto’s disease Mixed connective tissue disease	X		
Autoimmune conditions	Dermatomyositis/polymyositis, lupus erythematosus, rheumatoid arthritis		X	
Transplant patients	Heart, kidney, liver, bone marrow transplant: beware of increased risk of infections		X	
Immunosuppressive therapy			X	
Thyroid dysfunction	Not a contraindication to treatment, but physician needs to be aware that eyelid swelling is common (unrelated and unprovoked by filler use)		X	
Metabolic disorders	Diabetes, porphyria			X
Catabolic status		X		
Cachexic state	Does not contraindicate treatment, but product may be more visible in patients who lack subcutaneous fat and have thin tissue coverage		X	
Conditions affecting skin pigmentation	Melasma and post-inflammatory hyperpigmentation		X	
Skin pigmentation/depigmentation	Fitzpatrick Types 5 and 6 skin, vitiligo, and albinism			X
Systemic infections: bacterial	Tuberculosis	X		
Active anticoagulant medication	Thrombolytics	X		
Hemostatic or coagulation disorders	Hemophilia, hemoglobin pathology, thalassemia	X		
Cutaneous collagenoses	Chronic discoid lupus erythematosus, active but not end-stage scleroderma		X	
Food intolerance			X	
Bariatric gastric sleeve surgery	Potentially reduced time of esthetic effect			X

Abbreviations: CI, contraindicated; PD, treat at physician’s discretion; NAC, no apparent contraindication.

organism may populate the site of filler use. Thus, any patient with an ongoing skin infection in the area intended to be treated or in the close vicinity of it should not be treated.¹⁰ These conditions include the following: viral infections such as herpes simplex virus (HSV) and perioral human papilloma virus (HPV); mollusca contagiosa; bacterial infections with streptococci or staphylococci, such as impetigo; yeast infections; and extensive

pityrosporum folliculitis. The presence of excessive amounts of *Propionibacterium acnes* or parasitic mite infections, such as massive demodex folliculorum infestation, also makes the patient an unsuitable candidate for treatment.

Active inflammatory dermatitis, including atopic dermatitis, allergic contact dermatitis, “status cosmeticus”, or seborrheic dermatitis, also cautions against treatment, and

physicians must make a judgment based on the severity of the condition and its proximity to the treatment area.

When active HSV is evident, treatment should be deferred, and a prophylactic agent (acyclovir, valaciclovir, or famciclovir) prescribed to prevent reactivation and spread of HSV because of injection trauma. When treating the perioral area and lips, prophylactic prescribing to patients with known history of HSV episodes should be considered to prevent virus reactivation.^{2,11}

Patients may attend for treatment of one facial area while harboring an infectious condition in another (eg, active folliculitis with pustules), assuming that the infected area will not affect their treatment. There is little guidance, and to our knowledge, there are no published studies assessing the possible sequelae of treating individuals with active infection, regardless of distance from the treated area.

Patients with infections such as sinusitis, periodontal disease, ear, nose, or throat infections, or dental abscesses should not be treated until the condition has resolved.¹² Increasingly, clinical evidence is emerging indicating that these infections might subsequently invade implanted filler areas, inducing biofilm reactions. Later, transition from infection to an established hypersensitivity, via toll-like receptors, is possible, since these molecules have been shown to be involved in the development of many pathological conditions, including infectious diseases, tissue damage, and autoimmune and neurodegenerative diseases.¹³

Dermal filler treatment can also aggravate more generalized skin conditions or connective tissue disease, or might not be suitable in some of these conditions. Examples include prominent scars, hypertrophic scarring and keloid, bullous diseases, pyoderma, cutaneous collagenoses (chronic discoid lupus erythematosus or lupus erythematosus, active but not end-stage scleroderma), Marfan syndrome, Ehlers–Danlos syndrome, mixed connective tissue disease, conditions that cause Koebner response such as lichen planus (and related conditions), and active psoriasis. Uncontrolled immune deficiencies, such as graft versus host disease, chronic urticaria, and Quincke's edema, may also be adversely affected by dermal filler injection, or conversely might affect the behavior of the filler in the tissue.

Dermal fillers are not contraindicated in patients in whom wound healing is normal, even though they may have an underlying systemic disease. No association has been established between use of fillers and autoimmune conditions. Thus, patients with HIV, rheumatoid arthritis, diabetes, or scleroderma who have normal wound healing may be treated.^{9,10} Conditions such as tuberculosis, Wegener's

granulomatosis, transplant patients, patients with inflammatory bowel disease (Crohn's disease or ulcerative colitis), substantial food intolerance, repetitive urinary infections or impaired renal or hepatic function, thyroid dysfunction, and cachectic or catabolic status need careful consideration on a case-by-case basis.

Disorders of hemostasis or coagulation, for example, coagulopathies, protein C deficiency, hemophilia, and hemoglobin disorders such as thalassemia, need a careful assessment, and an accurate clinical picture of their severity and management must be obtained.

Immune depression or suppression is not necessarily a contraindication to any type of filler,⁹ although poly-L-lactic acid should be avoided.¹⁰ Clinical experience suggests hyaluronic acid fillers to be safe in patients with porphyria (Meissner, personal communication).

A full medical treatment history is essential, and although there are no defined interactions, certain immunosuppressive agents and steroids should flag up the need to understand the patient's medical history more clearly. Even agents that interfere with cytochrome P450 should be considered as signals to proceed with caution.

Patients should be advised to stop anti-inflammatory and antiplatelet agents a week prior to treatment (if medically appropriate) to minimize bruising, and they may benefit from a list of foodstuffs, herbal supplements, and over-the-counter medications to avoid.^{14–16}

Although there is weak evidence that antiplatelet therapy may be continued safely in the perioperative period,¹⁷ there are few publications addressing the issue systematically, and esthetic practitioners are warned to be mindful of the bleeding risk that applies to individual patients.¹⁸ Patients with cardiovascular stents or taking anticoagulants in the long term need careful consideration, and the risks must be explained.⁶

Although the most commonly used hyaluronic acid-based products have a favorable safety profile, adverse events can and do occur. Mild and self-limiting complications are relatively common. Edema and bruising are more or less inevitable, and these mild events resolve quickly.^{2,6,12} Although bruising tends to occur more extensively with certain injection techniques, such as fast injection, aggressive fanning, high-volume filler deposits, or large bolus injections (more than 0.5 mL per bolus), all sensible precautions should be taken with any injection technique.^{19,20}

Timing of other cosmetic procedures

Botulinum toxin treatment should be planned 2 weeks prior to filler. Using botulinum toxin first can help in assessment

of the need for treatment of residual issues such as static lines and deep folds that can be treated with hyaluronic acid fillers.²¹ From a safety perspective, however, the treatments may be given on the same day.

Microdermabrasion, chemical peels, and intense pulsed light (IPL) should ideally be carried out 1–2 weeks pre- or posttreatment and fractional resurfacing 3–4 weeks distant to allow erythema to diminish and the skin barrier to reestablish. One small pilot study, however, compared injection of hyaluronic acid-based filler immediately followed by laser, radiofrequency (RF), or pulsed light treatments (IPL) to injection of filler alone. The results suggested that laser, RF, and IPL may be safely administered immediately after hyaluronic acid gel implantation. Data suggest that deeper filling immediately before laser therapy, when the concomitant swelling may facilitate the effect of the laser, may be acceptable.⁹ Using biodegradable or temporary fillers over permanent fillers has always been a heavily debated subject. Lemperle et al stated that temporary fillers may be injected on top of a permanent filler or can be used preceding the permanent filler with no interference between the two and that fear of a second filler inducing granuloma formation remains hypothetical.⁹ The present authors, however, would strongly discourage this practice, as it is generally accepted that the formerly called “permanent” fillers (now referred to as late or minimally biodegradable fillers) are associated with substantially more frequent and late-occurring side effects, sometimes occurring years after implantation.

When one type of filler is used on top of, or around, the other, and a side effect emerges, it is impossible to determine the causal agent without biopsy, specific pathology staining, and examination of the sample. Moreover, the duration, prognosis, and eventual treatment options of the side effects may be completely different for the two types of filler. Caution is also needed – albeit to a lesser extent – when injecting over surgically inserted solid implants (eg, expanded polytetrafluoroethylene or polylactic acid plates and screws).

To avoid possible infection or hypersensitivity, treatment should not be undertaken in the immediate period following other routine medical procedures (including vaccination).¹² Dental procedures should be performed at least 2 weeks pre- or posttreatment to minimize the risk of hematogenous bacterial spread and potential development of biofilm. Chlorhexidine mouthwash prior to perioral injections (lips, borderline mucosal, or oral cavity approach of injection) will reduce oral bacterial flora for 8 hours, also minimizing the risk of contamination when lip licking.²²

Patients should understand the need to take precautions and be scrupulously clean after treatment, such as avoiding touching and keeping hair away from the treated area for several hours. Patients should not use cosmetics (especially lipstick post-lip enhancement) for 24 hours and use new containers of lotions and new/clean brushes, sponges, etc.^{15,23} The patient should be willing and able to attend a consultation 2–4 weeks after any procedure and should report any concerns or signs of problems as soon as possible.

Proactive prevention recommendations

Injectors need to have a thorough knowledge of facial anatomy and the potential danger areas, especially the distribution of the facial arteries and nerves.³ However, textbook anatomy is representative of the general population, and subtle individual variations are relatively common,^{24,25} warranting continuous caution upon injecting fillers and awareness of the possibility of perforating, lacerating, or compromising vessels. Patients with a history of dental or facial surgery may have areas of unusual vascular distribution because of aberrant neovascularization after the trauma of a procedure in combination with a decrease in tissue laxity.²⁶ It is of paramount importance that any material placed under the skin is injected under sterile conditions using aseptic technique. The patient's skin should be cleaned, degreased, and disinfected. There are no universally recommended topical antiseptics, but chlorhexidine, cloxylenol, iodophors, alcohol, and iodine may all be appropriate.^{6,15,23} Rarely, a patient may experience an allergic reaction to cleansers and topical anesthetic agents, and physicians need to recognize the signs and immediately remove the product responsible from the skin. Patients may also be allergic to the lidocaine mixed in the syringe of the filler.¹⁰

The injector should wash his/her hands thoroughly, remove watches and rings, and wear surgical gloves (although not necessarily sterile).¹⁵ Areas of irritation or inflammation should not be injected, needles or cannulas must be sterile and changed frequently during the procedure, excess filler on the syringe needle should only be removed with sterile gauze,^{6,15} and aseptic technique followed throughout the procedure. Treatment areas should not be reinjected within 2 weeks of the initial procedure. Even with perfect tissue integration, a certain level of edema and extravasation of blood can be present in the early postinjection phase, creating an ideal environment for bacteria to proliferate upon repeated injection.

Before injecting, aspiration should be performed as a prophylactic measure,⁶ particularly in highly vascularized

areas, and a new needle without filler used prior to deep bolus injections. Blood on aspiration indicates that the needle is in a blood vessel and the injection point should be altered. Injection must be performed slowly and with caution, allowing time to assess and react to any untoward response, changes in skin color, or disproportionate pain.^{6,27,28}

Filler should be injected slowly with a low flow rate in small quantities at multiple points and overfilling avoided.²⁰ Small-bore needles are recommended by some to slow the injection rate²⁷ and blunt needles/cannulas in high-risk regions to reduce vessel injury.^{29,30} Avoiding anesthesia with epinephrine (adrenalin) close to a vascular bundle to prevent vasospasm and tenting the skin to avoid the vascular supply are also appropriate recommendations.¹⁶

To prevent the technique-related problems of irregularities, lumps, or beading, injection technique and depth should be appropriate for the area being injected and the area massaged after injection.²⁸ Accidental intramuscular injection of synthetic fillers other than hyaluronic acid and collagen should be avoided, since muscle contraction can dislocate the filler and create unwanted lumps.⁹

Recognition and treatment recommendations – early events

Vascular occlusion

Vascular occlusion can occur if a filler is injected into a blood vessel or when sufficient quantity is injected near the vessel to cause a compression blockage.^{14,31,32} The two types are arterial (generally an acute onset – during injection) and venous (generally a delayed onset – often when the patient has left the clinic), although the two are not mutually exclusive.^{6,26}

Arterial occlusion is the more serious complication and can potentially be very damaging, leading to ischemia, tissue degradation, and necrosis. In rare cases, it can even cause visual impairment or blindness if it affects the retinal artery. The underlying mechanism is related to retrograde embolization from peripheral vessels into the ophthalmic arterial system.^{33–35} This makes it vital for the clinician to be aware of the early warning signs to facilitate quick diagnosis and an immediate, aggressive response.^{3,27}

The two primary diagnostic symptoms of vascular occlusion are pain and changes in skin color. Immediate, severe, and disproportionate pain and acute onset of color changes – blanching (or white spots/blotches) – are an indication of arterial occlusion.²⁷ Venous occlusion may be associated with less severe, dull, or delayed pain; in some cases, there may be no pain (this is rare in the case of arterial occlusion). Skin color changes may be immediate or up to 3–4 hours

later, and red/bluish coloration is indicative of venous occlusion.²⁷ Other secondary (and later stage) diagnostic symptoms are blisters and pustules, tissue necrosis (which generally develops a few days after the initial complication), and scarring, which is the end stage of the necrosis and healing process.

When vascular occlusion is suspected, it is vital that the injection is stopped immediately and treatment is rapidly instigated. The goal is to promote blood flow to the affected area, which may be achieved by applying a warm compress, massaging or tapping the area, and applying 2% nitroglycerin paste to promote vasodilatation.^{6,27,28,36} Attempts should be made to dissolve or eliminate the injected product. In the case of hyaluronic acid-based fillers, hyaluronidase should be injected all over the affected area, “flooding the area with hyaluronidase”, as soon as possible in a dose applicable to the product to be reversed, for example, 10–20 units per injection point.^{26,32} If a hydroxyapatite filler has been used, saline could be injected. Hyaluronidase has been suggested as a treatment for all cases of vascular compromise, regardless of filler employed, since it can reduce edema and potentially decrease vessel-occluding pressure.^{3,37} It is important to be aware that hyaluronidase has been associated with rare immediate and delayed reactions, and prescribing guidelines should be closely followed.^{38,39}

It may be possible to use ultrasound or MRI to assess the location and amount of filler, and Doppler; arteriography or phlebography may help in assessing vascular damage and aid treatment planning.

Hyaluronidase (or alternative) injections should be repeated on a daily basis where appropriate and continued for at least 4 days or as long as there are signs of ischemia.²⁷ However, some evidence suggests that after day 1, any additional effect is minimal.²⁶

An anticoagulant, such as low-molecular weight heparin, aspirin, clopidogrel, or pentoxifylline, could also be prescribed to increase blood flow to the wound. Other authors have suggested the use of sildenafil to dilate compromised vasculature.³

Antibiotics (oral and/or topical) and antivirals are recommended to reduce infection in the case of pustule/blister formation. In severe cases, hyperbaric oxygen could be used to aid survival of compromised tissue.

Classic wound care procedures (wet-to-dry dressings, petroleum gauze with 3% bismuth tribromophenate, emollients, debridement, etc) should be followed, and the patient assessed for scar evaluation and management. Surgery and reconstruction may be indicated at a later date.¹⁶

In cases of visual impairment, the individual should undergo an urgent ophthalmologic consultation.³³ Orbital pain and visual disturbance may be managed with additional ocular massage, timolol maleate eye drops, diuretics, corticosteroids, hemodilution, vasodilation, anticoagulation, or thrombolysis as required under expert guidance.³⁷

Allergic/hypersensitivity reactions

Hypersensitivity and allergic reactions such as angioedema can occur when the injected dermal filler (or an agent used in gel production or injection procedure) triggers an immune response.^{6,9,14} This can be a type I hypersensitivity reaction, which typically has an early onset (within minutes to hours of injection), or a type IV reaction, which has a delayed onset (1–3 days up to several weeks after injection).³¹ Although not demanding the urgent attention that vascular occlusion requires, it can be a problem that causes considerable patient distress.²

The primary diagnostic symptoms of hypersensitivity reactions may include edema (either localized around injection sites or more generalized), erythema, pruritus, pain or tenderness (related to pressure effects), rash, and induration.^{2,14} Delayed reactions may also present with various types of skin lesions⁴⁰ including painful erythematous nodules.³¹

Once a hypersensitivity reaction is suspected, the time of onset should be established, the patient's medical history re-reviewed, and a full medical examination undertaken. In cases of diagnostic uncertainty, special investigations include blood tests such as markers for inflammation (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) and acute-phase reactants. The latter appear to be the most sensitive markers for the presence of autoimmune/inflammatory syndrome induced by adjuvants (ASIA) related to dermal filler use. A biopsy (if a previously used product is of unknown type), MRI, or ultrasound (high frequency) should be considered.

A study of responses to a wide range of dermal fillers demonstrated that calcium hydroxyapatite, methacrylate, acrylamides, and silicone produced notable chronic activation of the immune system (mediated by macrophages and polymorphonuclear leukocytes). By contrast, hyaluronic acid elicited little immune response.⁴¹ The plasma levels of myeloperoxidase and the chitin-like proteins chitotriosidase and YKL-40 may be important markers indicative of immune response activation in certain cases.

Hypersensitivity reactions can be severe, and occasionally, anaphylactic shock has been reported.¹⁴ Generalized edema is suggestive of anaphylaxis; vital signs should be checked

to differentiate between anaphylaxis and angioedema, as the latter or localized urticaria do not cause alteration in vital signs. However, even progressing angioedema can become a medical emergency due to airway obstruction. Any systemic manifestations should be considered as impending anaphylaxis and treated as such. Resuscitation equipment should be available at the clinic or nearby. Epinephrine (adrenalin) should be administered immediately, intravenous access obtained, and fluid resuscitation considered. Hospital admission may be advisable for severe cases, as late-phase reactions may occur up to 36 hours after the initial event. It remains important that the “triggering” substance is removed if at all possible, and hyaluronidase may be used where appropriate.

Additional vasopressor agents should be considered (dopamine, norepinephrine, and glucagon) if the above measures are insufficient to maintain perfusion. H1-receptor antagonists (in combination with cimetidine) could be used for histamine-induced hypotension, oral corticosteroids administered to prevent late-phase reactions, and inhaled bronchodilators given if respiratory symptoms are noted.

Localized angioedema and urticaria should be managed by cold compresses and H1-receptor antagonist administration to reduce pruritus.² The value of additional H2-receptor antagonists and leukotriene synthesis inhibitors should be considered. Twice daily dosing with histamine blockers may be required for the symptomatic management of histamine release. It is not uncommon for higher than normal doses to be required. Propranolol and ibuprofen have both been advocated in reducing persistent erythema.

Additional treatment options include topical or intral-lesional steroids, or immunosuppressive agents (under specialist supervision). These include hydroxychloroquine, methotrexate, ciclosporin A, diaminodiphenylsulfone, and allopurinol.^{2,42}

Recognition and treatment recommendations – delayed events

Infection

Any procedure that breaks the surface of the skin carries with it a risk of infection, and injecting dermal fillers is no exception. Treatment-related infections are generally bacterial (but can be fungal or viral). They can be broadly categorized as acute infections, which appear as acute inflammation or abscesses at the site of injection (typically due to common pathogens present on the skin such as *Staphylococcus aureus* or *Streptococcus pyogenes*), or delayed-onset, chronic infections, which generally develop 2 or more weeks

after injection. Delayed-onset infections tend to affect a more generalized area and may involve an atypical organism (such as *Mycobacteria* or *Escherichia coli*). Insidious late infection or biofilm can also occur.^{31,43} These are challenging for both diagnosis and treatment and can cause a chronic inflammatory response.

The primary diagnostic symptoms of infection are erythema, warmth, tenderness, pain, swelling (usually at or close to site of injection), local signs of abscess (pustules, nodules, areas of fluctuation, crusts), and systemic fever. It is prudent to be highly suspicious of any area near the site of injection exhibiting local symptoms. Differentiation between infection and hypersensitivity is important during diagnosis, as the use of steroids should be avoided in infection. Important differentiating factors which indicate infection are skin temperature, pain (absent, more diffuse, or less intense in cases of hypersensitivity), fever or signs of an abscess, and the absence of pruritus.

The time of injection in relation to time of onset, blood tests, or infective markers (such as CRP, ESR, and procalcitonin) may be diagnostically useful, and purulent material may be cultured to determine the type of pathogen and the most appropriate antibiotic.

Acute, mild infections can be treated with oral antibiotics.⁴³ Empiric treatment should begin with macrolide or tetracycline antibiotics, which may have some anti-inflammatory and immunomodulatory effects.^{14,27} Two-drug therapy should be considered to broaden the spectrum of cover. Hyaluronidase has been shown to help break down the matrix, decreasing any associated biofilm mass,⁴⁴ and other options are prolonged or intravenous antibiotics, intralesional 5-fluorouracil, or laser^{45,46} and surgical drainage of any abscess. Examples of antibiotic courses that are typically prescribed to treat complicated infections are as follows:

- Ciprofloxacin 500–750 mg bid for 2–4 weeks
- Clarithromycin 500 mg + moxifloxacin 400 mg bid for 10 days
- Vancomycin IM 600–1,000 mg five times every second day, followed by 300–500 mg od for 10 days
- A quinolone at 500 mg bid for up to 50 days
- Minocycline 100 mg od for 6 months
- Cephalexin, dicloxacillin, or nafcillin
- Topical antibiotics – fucidic acid.

Nodule formulation and granulomatous reactions

Nodules and lumps are common complications resulting from the use of dermal fillers. Careful assessment is required

to establish their etiology and confirm the diagnosis. They may be inflammatory or non-inflammatory in nature and related or unrelated to infection. Historically, nodules tend to be described as granulomata without the histopathological evidence.

Early-onset nodules – occurring within 4 weeks – tend to be painless and non-inflammatory, and are most likely the result of suboptimal techniques such as excess filler use, superficial placement, and incorrect product for the indication.^{1,9,15,27} These early-onset nodules tend to occur in areas of thin soft tissue coverage. Early red, painful, and tender nodules usually signal a concomitant infection.

Delayed-onset nodules (after 4 weeks and up to a year or longer) are more likely to be inflammatory (immune responses to the filler material) and/or infection related (including biofilm) but may just be persistent non-inflammatory nodules.^{2,27,31,47,48} If nodules are biofilm related, a culture test will frequently be negative. It is therefore important to use polymerase chain reaction or fluorescence in situ hybridization tests for delayed-onset nodule complications where biofilm involvement is suspected.³¹ Delayed-onset nodules may also result from the incorrect use of fibroblast stimulatory fillers (eg, polylactic acid, calcium hydroxyapatite) in areas where skin is thin or mobile.

Foreign body granulomas may form as the body's immune system responds to a foreign body that cannot be broken down by the usual mechanisms. They can develop several months, or even years, after injection and present as red, firm papules, nodules, or plaques. Diagnosis of nodules and lumps is further complicated by the fact that clinicians are sometimes faced with patients with unknown or incomplete medical and cosmetic treatment history.

The therapeutic approach will be determined by the type of lumping/nodule diagnosed. Early-onset nodules should be treated by massage, application of a compress, and puncturing of the nodule if appropriate. If a hematoma is present, early pressure and heat, and then cold compress should be applied.²⁷ For both early- and late-onset nodules, disruption with hyaluronidase, lidocaine, or saline followed by massage can be effective. If the nodule is infection related and there is fluctuance or impending signs of erosion, incision and drainage should be performed with culture and antibiotic cover continued for up to 4–6 weeks.²⁷ Hypersensitivity-related nodules may be treated with antihistamines (eg, cetirizine, loratidine), oral steroids (eg, medium-dose pulse therapy prednisolone, 60 mg/day), methyl prednisolone (eg, a total of 240 mg in six weekly decreasing doses), and/or nonsteroidal anti-inflammatory drugs² once infection has been ruled out.

RF or infrared energy may also be a useful adjunctive treatment option in some areas.⁴⁷

For late-onset nodules or granulomas, intralesional steroids (betamethasone 5 mg/mL or triamcinolone 10–40 mg/mL for 10 days up to 4 weeks) can be considered, although care needs to be taken to avoid skin atrophy.^{2,4}

For persistent cases, additional measures can include a series of injections of 5-fluorouracil (50 mg/mL) in combination with steroids and/or lidocaine (1:3), methotrexate, local tacrolimus,^{2,4,49} cortivasol, allopurinol, colchicine, isotretinoin, imiquinod,⁴⁹ laser-assisted removal,⁴⁵ or ultimately excision by surgery as a last resort.¹²

Summary and conclusion

The wide range of dermal fillers available for use in facial esthetics makes it essential to have a thorough knowledge of the relevant product characteristics. Clinicians must have a sound understanding of facial anatomy and be suitably trained and experienced to ensure correct product selection, preparation, and injection technique. Appropriate patient selection is vital, and the importance of fully investigating the patient's previous medical injection history prior to treatment should not be underestimated.

The majority of complications are related to sterility, placement, volume, and injection technique. Small, slow, deep injection with massage should be considered at every procedure to introduce the product gently and evenly. Clinicians should be fully aware of the signs and symptoms related to complications and be prepared with agents readily available in the office to enable them to act swiftly and proactively.

Adverse events and the treatment options are not discrete. A broad knowledge and in-depth investigations are important for satisfactory management and outcome. Equally, collecting and sharing adverse reactions is important to improve our knowledge and to the development of consistent, effective protocols. Finally, clinicians should always consider seeking advice from a trusted colleague.

Acknowledgments

The manuscript development was supported by an unrestricted educational grant from Allergan Inc. The authors would also like to acknowledge the International consensus group: Radina Denkova, Bulgaria; Renata Handlova, Czech Republic; Dimitrios Sykianakis, Greece; Eyal Kramer, Israel; Greta Valanciene, Lithuania; Sylwia Lipko-Godlewska, Poland; Madalina Ciupan, Viviana Iordache, Romania; Ekaterian Gutop, Elena Razumovskaya, Olga Zabnenkova,

Russia; Marshall Murdoch, Albertus Niemann, Daniel Nortje, Martina van der Mescht, South Africa; Tunc Tiryaki, Gun Ersu, Ulvi Guner, Alpalan Topcu, Serhan Tuncer, Turkey; Oleksandr Turkevych, Ukraine.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Requena L, Requena C, Christensen L, Zimmermann US, Kutzner H, Cerroni L. Adverse reactions to injectable soft tissue fillers. *J Am Acad Dermatol*. 2010;64:1–34.
2. De Boule K. Management of complications after implantation of fillers. *J Cosmet Dermatol*. 2004;3:2–15.
3. Funt D, Pavicic T. Dermal fillers in aesthetics: an overview of adverse events and treatment approaches. *Clin Cosmet Invest Dermatol*. 2013;6:295–316.
4. Sperling B, Bachmann F, Hartmann V, Erdmann R, Wiest L, Rzany B. The current state of treatment of adverse reactions to injectable fillers. *Dermatol Surg*. 2010;36:1895–1904.
5. Vedamurthy M, Vedamurthy A, Nischal KC. Dermal fillers: do's and don'ts. *J Cutan Aesthet Surg*. 2010;3:11–15.
6. Bailey SH, Cohen JL, Kenkel JM. Etiology, prevention and treatment of dermal filler complications. *Aesthetic Surg J*. 2011;31:110–121.
7. de Bree R, Middelweerd MJ, van der Waal I. Severe granulomatous inflammatory response induced by injection of polyacrylamide gel into the facial tissue. *Arch Facial Plast Surg*. 2004;6(3):204–206.
8. Micheels P, Sarazin D, Besses S, Sundaram H, Flynn TC. A blanching technique for intradermal injection of the hyaluronic acid Belotero. *Plast Reconstruct Surg*. 2013;132(4 Suppl 2):59S–68S.
9. Lemperle G, Rullan PP, Gautier-Hazan N. Avoiding and treating dermal filler complications. *Plast Reconstr Surg*. 2006;118(3 Suppl):92S–107S.
10. Lafaille P, Benedetto A. Fillers: contraindications, side effects and precautions. *J Cutan Aesthet Surg*. 2010;3:16–19.
11. Narins RS, Jewell M, Rubin M, Cohen J, Strosob J. Clinical conference: management of rare events following dermal fillers – focal necrosis and angry red bumps. *Dermatol Surg*. 2006;32:426–434.
12. Narins RS, Coleman WP, Glogau RG. Recommendations and treatment options for nodules and other filler complications. *Dermatol Surg*. 2009;35:1667–1671.
13. Chen K, Huang J, Gong W, Iribarren P, Dunlop NM, Wang JM. Toll-like receptors in inflammation, infection and cancer. *Int Immunopharmacol*. 2007;7(10):1271–1285.
14. Lowe NJ, Maxwell CA, Patnaik R. Adverse reactions to dermal fillers: review. *Dermatol Surg*. 2005;31:1616–1625.
15. Alam M, Gladstone H, Kramer EM, et al; American Society for Dermatologic Surgery. ASDS guidelines of care: injectable fillers. *Dermatol Surg*. 2008;34:S115–S148.
16. Levy LL, Emer JJ. Complications of minimally invasive cosmetic procedures: prevention and management. *J Cutan Aesthet Surg*. 2012;5:121–132.
17. Kraft CT, Bellile E, Baker SR, Kim JC, Moyer JS. Anticoagulant complications in facial plastic and reconstructive surgery. *JAMA Facial Plast Surg*. 2014. Epub ahead of print.
18. Brown DG, Wilkerson EC, Love WE. A review of traditional and novel oral anticoagulant and antiplatelet therapy for dermatologists and dermatologic surgeons. *J Am Acad Dermatol*. 2014;72(3):524–534.
19. Gladstone HB, Cohen JL. Adverse events when injecting facial fillers. *Semin Cutan Med Surg*. 2007;26(1):34–39.
20. Glogau RG, Kane MA. Effect of injection techniques on the rate of local adverse events in patients implanted with non-animal hyaluronic acid gel fillers. *Dermatol Surg*. 2008;34:S105–S109.

21. Carruthers J, Glogau R, Blitzer A; Facial Aesthetics Consensus Group Faculty. Advances in facial rejuvenation: botulinum toxin type A, hyaluronic acid dermal fillers, and combination therapies – consensus recommendations. *Plast Reconstr Surg*. 2008;121:5–30.
22. Hermesch CB, Hilton TJ, Biesbrock AR, et al. Perioperative use of 0.12% chlorhexidine gluconate for the prevention of alveolar osteitis: efficacy and risk factor analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;85:381–387.
23. Baima J, Isaac Z. Clean versus sterile technique for common joint infections: a review from the psychiatry perspective. *Curr Rev Musculoskeletal Med*. 2008;1:88–91.
24. Kim YS, Choi DY, Gil YC, Hu KS, Tansatit T, Kim HJ. The anatomical origin and course of the angular artery regarding its clinical implications. *Dermatol Surg*. 2014;40(10):1070–1076.
25. Yang HM, Lee JG, Hu KS, et al. New anatomical insights on the course and branching patterns of the facial artery: clinical implications of injectable treatments to the nasolabial fold and nasojugal groove. *Plast Reconstr Surg*. 2014;133(5):1077–1082.
26. Kim DW, Yoon ES, Ji YH, Park SH, Lee BI, Dhong ES. Vascular complications of hyaluronic acid fillers and the role of hyaluronidase in management. *J Plast Reconstr Aesthet Surg*. 2011;64:1590–1595.
27. Sclafani AP, Fagien S. Treatment of injectable soft tissue filler complications. *Dermatol Surg*. 2009;35:1672–1680.
28. Cohen JL. Understanding, avoiding and managing dermal filler complications. *Dermatol Surg*. 2008;34(Suppl 1):S92–S99.
29. Zeichner JA, Cohen JL. Using blunt-tipped cannulas in specific regions for soft-tissue augmentation. *J Drugs Dermatol*. 2012;11:40–41.
30. Cassuto D. Blunt-tipped microcannulas for filler injection: an ethical duty? *J Drugs Dermatol*. 2012;11:S42.
31. Dayan SH, Arkins JP, Brindise R. Soft tissue fillers and biofilm. *Fac Plast Surg*. 2011;27:23–28.
32. Hirsch RJ, Cohen JL, Carruthers JD. Successful management of an unusual presentation of impending necrosis following a hyaluronic acid injection embolus and a proposed algorithm for management with hyaluronidase. *Dermatol Surg*. 2007;33:357–360.
33. Peter S, Mennel S. Retinal branch artery occlusion following injection of hyaluronic acid (Restylane). *Clin Experiment Ophthalmol*. 2006;34(4):363–364.
34. Hwang YH, Hwang JH, Kim JS. Branch retinal artery occlusion after periocular dermal filler injection. *Retin Case Brief Rep*. 2008;2:338–341.
35. Lazzeri D, Agostini T, Figus M, Nardi M, Pantaloni M, Lazzeri S. Blindness following cosmetic injections of the face. *Plas Reconstruct Surg*. 2012;129:995–1012.
36. Kleidman K, Cohen JL, Marmor E. Nitroglycerin: a review of its use in the treatment of vascular occlusion after soft tissue augmentation. *Dermatol Surg*. 2012;38:1889–1897.
37. Ozturk CN, Li Y, Tung R, Parker L, Piliang MP, Zins JE. Complications following injection of soft tissue fillers. *Aesth Surg J*. 2013;33:862–877.
38. Brody HM. Relevance of cosmeceuticals to the dermatologic surgeon. *Dermatol Surg*. 2005;31:796–798.
39. Feighery C, McCoy EP, Johnson PB, Armstrong DKB. Delayed hypersensitivity to hyaluronidase (Hyalase™) used during cataract surgery. *Contact Dermatitis*. 2007;57:343.
40. Reidl MA, Casillas AM. Adverse drug reactions: types and treatment options. *Am Fam Physician*. 2003;68:1781–1790.
41. Sánchez O, Rodríguez-Sureda V, Domínguez C, et al. Study of biomaterial-induced macrophage activation, cell-mediated immune response and molecular oxidative damage in patients with dermal bioimplants. *Immunology*. 2012;217(1):44–53.
42. Moody BR, Sengelmann RD. Topical tacrolimus in the treatment of bovine collagen hypersensitivity. *Dermatol Surg*. 2001;27:789–791.
43. Christensen LH. Host tissue interaction, fate, and risks of degradable and non-degradable gel fillers. *Dermatol Surg*. 2009;35:1612–1619.
44. Pecharki D, Petersen FC, Scheie AA. Role of hyaluronidase in *Streptococcus lintermedius* biofilm. *Microbiology*. 2008;154:932–938.
45. Nyhlen A, Ljungberg B, Nilsson-Ehle I, Odenholt I. Bactericidal effect of combinations of antibiotic and antineoplastic agents against *Staphylococcus aureus* and *Escherichia coli*. *Chemotherapy*. 2002;48:71–77.
46. Cassuto D, Marangoni O, De Santis G, Christensen L. Advanced laser techniques for filler-induced complications. *Dermatol Surg*. 2009;35:1689–1695.
47. Cassuto D, Sundaram H. A problem-oriented approach to nodular complications from hyaluronic acid and calcium hydroxyapatite fillers: classification and recommendations for treatment. *Plast Reconstr Surg*. 2013;132:48S–58S.
48. 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*. 2013;14:401–411.
49. Lemperle G, Gauthier-Hazan N. Foreign body granulomas after all injectable fillers: part 2. Treatment options. *Plast Reconstr Surg*. 2009;123:1864–1873.

Clinical, Cosmetic and Investigational Dermatology

Publish your work in this journal

Clinical, Cosmetic and Investigational Dermatology is an international, peer-reviewed, open access, online journal that focuses on the latest clinical and experimental research in all aspects of skin disease and cosmetic interventions. All areas of dermatology will be covered; contributions will be welcomed from all clinicians and

basic science researchers globally. This journal is indexed on CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/clinical-cosmetic-and-investigational-dermatology-journal>

Dovepress