Understanding, Avoiding, and Managing Dermal Filler Complications

JOEL L. COHEN, MD*

BACKGROUND Dermal fillers are increasingly being utilized for multiple cosmetic dermatology indications. The appeal of these products can be partly attributed to their strong safety profiles. Nevertheless, complications can sometimes occur.

OBJECTIVE To summarize the complications associated with each available dermal filling agent, strategies to avoid them, and management options if they do arise.

METHODS AND MATERIALS Complications with dermal fillers reported in peer-reviewed publications, prescribing information, and recent presentations at professional meetings were reviewed. Recommendations for avoiding and managing complications are provided, based on the literature review and the author’s experience.

RESULTS Inappropriate placement or superficial placement is one of the most frequent reasons for patient dissatisfaction. Due to the reversibility of hyaluronic acid, complications from these fillers can be easily corrected. Sensitivity to any of the currently approved FDA products is quite rare and can usually be managed with anti-inflammatory agents. Infection is quite uncommon as well and can usually be managed with either antibiotics or antivirals depending on the clinical features. The most concerning complication is cutaneous necrosis, and a protocol to treat the full spectrum of this process is reviewed.

CONCLUSIONS Complications with dermal fillers are infrequent, and strategies to minimize their incidence and impact are easily deployed. Familiarity with each family of soft-tissue augmentation products, potential complications, and their management will optimize the use of these agents.

Over the past several years, a major shift in the use of dermal fillers has occurred in the cosmetic dermatology arena. The use of these products is growing rapidly, due in large part to their effectiveness and versatility, increased public interest, the availability of multiple new options, and a diminishment of the social stigma surrounding their use. Their favorable safety profiles also contribute to the popularity of these products.1,2

However, despite the impressive safety demonstrated with these agents, complications and adverse events can occur. To ensure the best possible outcomes and greatest patient satisfaction, the dermatologist who injects dermal fillers must have proper training in their use and be aware of the types of unwanted effects that can occur and how to treat them. Dermal fillers are commonly categorized by duration of effect: temporary, semipermanent (duration is often longer than 18 months but the exact time frame is unknown), and permanent options (Table 1).

Injection Site Reactions

The most common adverse events associated with fillers are local injection site reactions. In a randomized, double-blind, multicenter comparison of hyaluronic acid (Restylane, Medicis Aesthetics Inc., Scottsdale, AZ) versus collagen (Zyplast, Allergan Inc., Santa Barbara, CA) for the treatment of nasolabial folds in contralateral sides in each patient (n = 138), injection site reactions occurred at 93.5%
(129/138) and 90.6% (125/138) of the hyaluronic acid– and collagen-treated sites, respectively.3 These reactions were predominantly mild or moderate in intensity, lasted less than 7 days, and generally were similar between treatments (Table 2). However, because these adverse events were solicited during the study solely through the use of patient diaries (without corroboration by physician evaluation), the rate of adverse events may be lower in routine clinical practice.

Patients should be informed of the likelihood of injection site reactions, especially in terms of swelling, because most fillers often result in some degree of injection site–related swelling or bruising for 4 to 7 days. Swelling can often be minimized by avoidance of aspirin compounds (provided the patient’s cardiologist or primary physician does not deem them medically necessary [i.e., patients with a history of heart attack, stroke, or blood clot]), nonsteroidal anti-inflammatory drugs, and many vitamin supplements (vitamin E, ginger, ginseng, ginkgo biloba, garlic, kava kava, celery root, fish oils) for 7 to 10 days prior to the procedure.

### TABLE 1. Common Dermal Fillers

<table>
<thead>
<tr>
<th>Category</th>
<th>Fillers</th>
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<tbody>
<tr>
<td>Temporary</td>
<td>Bovine collagen (Zyderm, Allergan Inc., Santa Barbara, CA; Zyplast, Allergan Inc., Santa Barbara, CA)</td>
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<tr>
<td></td>
<td>Human collagen (CosmoDerm, Allergan Inc, Santa Barbara, CA; CosmoPlast, Allergan Inc., Santa Barbara, CA)</td>
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<tr>
<td></td>
<td>Autologous cultured fibroblasts (Isolagen, Isolagen Technologies, Paramus, NJ)</td>
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<tr>
<td></td>
<td>Cadaveric collagen (Collagenesis, Beverly, MA; Fascian, Fascia Biosystems LLC, Los Angeles, CA; Cymetra, LifeCell Corp., Branchburg, NJ)</td>
</tr>
<tr>
<td></td>
<td>Hyaluronic acid (Restylane, Medicis Aesthetics Inc., Scottsdale, AZ; Hylaform, Allergan Inc., Santa Barbara, CA; Captique, Allergan Inc., Santa Barbara, CA; Juvederm, Allergan Inc., Santa Barbara, CA)</td>
</tr>
<tr>
<td></td>
<td>Calcium hydroxylapatite (Radiesse, BioForm Medical Inc., San Mateo, CA)</td>
</tr>
<tr>
<td>Semipermanent</td>
<td>Poly L-lactide acid (New-Fill/Sculptra (Dermik Laboratories, Berwyn, PA)</td>
</tr>
<tr>
<td>Permanent</td>
<td>Collagen + polymethylmethacrylate (Artecoll/ArteFill, Artes Medical Inc., San Diego, CA)</td>
</tr>
<tr>
<td></td>
<td>Silicone (Adato SIL-OL 5000 [Bausch &amp; Lomb, Rochester, NY], Silikon 1000 [Alcon Laboratories, Fort Worth, TX])</td>
</tr>
<tr>
<td></td>
<td>Soft-form/Gore-Tex (WL Gore &amp; Associates, Flagstaff, AZ)</td>
</tr>
</tbody>
</table>

### TABLE 2. Incidence of Injection Site Reactions Occurring with some Dermal Fillers: Results from a Randomized, Double-Blind Trial (N = 138)*

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Restylane (%)</th>
<th>Zyplast (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>87.0</td>
<td>73.9</td>
</tr>
<tr>
<td>Redness</td>
<td>84.8</td>
<td>84.8</td>
</tr>
<tr>
<td>Tenderness</td>
<td>77.5</td>
<td>64.5</td>
</tr>
<tr>
<td>Pain</td>
<td>57.2</td>
<td>42.0</td>
</tr>
<tr>
<td>Bruising</td>
<td>52.2</td>
<td>48.6</td>
</tr>
<tr>
<td>Itching</td>
<td>30.4</td>
<td>23.9</td>
</tr>
<tr>
<td>Other</td>
<td>24.6</td>
<td>23.9</td>
</tr>
</tbody>
</table>

*Adapted from Narins RS, Brandt F, Leyden J, et al.3 A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds.

### Inappropriate Placement

Inappropriate placement of fillers, including injecting too superficially, can lead to lumps of visible product or bluish bumps under the skin (Tyndall effect) with hyaluronic acid fillers (Figure 1).4 Such reactions can, for the most part, be prevented by use of correct technique. Their occurrence, however, can result in anxiety and dissatisfaction for patients, especially in those who rely on their appearance for their livelihood or who cannot adequately camouflage the reaction.5

Lumps and bumps related to superficial placement can often be treated simply by local massage or by aspiration or incision and drainage.4,5 If the complication is related to a hyaluronic acid product, hyaluronidase is an additional treatment option.5
However, because of the rare risk of sensitivity to the animal-derived hyaluronidase enzyme, a preliminary skin test should be performed prior to its use. For this test, about 3 units can be injected intradermally, and the patient observed for at least 20 minutes or even overnight.6 A local wheal-and-flare reaction indicates a positive reaction. Hyaluronidase is available from the following sources: Amphastar Pharmaceutical (Amphadase; Rancho Cucamonga, CA), Ista Pharmaceuticals Inc. (Vitrase; Irvine, CA), and several compounding pharmacies that provide formulations that may not be as uniform or consistent as the two commercially available brands.

Collagen plus polymethylmethacrylate, which is categorized as a permanent filler due to the Lucite-like polymethylmethacrylate beads in the product, is less forgiving and also can be associated with complications if placed too superficially (Figure 2). Indeed, the most common issues seen with the original formulation of Artecoll (Artes Medical Inc., San Diego, CA) involved superficial placement. There have been reports of long-lasting itching and redness, which can sometimes be treated with topical corticosteroid cream or intradermal corticosteroid injections.7 In addition, excessive superficial placement of the product rarely can lead to hypertrophic scarring of the treated fold(s). This can be softened in some cases with repeated intralesional triamcinolone injections (starting with intralesional triamcinolone 10 mg/ml with subsequent increasing concentrations of 20, 30, and 40 mg/ml progressively if needed at 3- to 4-week intervals) or the use of a pulsed dye laser.

If calcium hydroxylapatite (Radiesse, BioForm Medical Inc., San Mateo, CA) is placed too superficially (i.e., in the mid or superficial dermis), white nodules may become visible. These can usually be treated by puncturing the nodules with a No. 11 blade or needle and then expressing the contents.8 Similarly, due to the thin skin in the tear trough, injection of calcium hydroxylapatite too superficially in this area can result in visibility of the filler. Thus, tear trough injections are considered advanced techniques and should be performed only by those experienced with using fillers in this area. Migration of product nodules superficially in the lips can occur despite proper placement of calcium hydroxylapatite to deeper lip levels; this may be due to the “pumping” action of the orbicularis oris muscle with routine use (such as speaking or chewing). For this reason, use of Radiesse in the lips is no longer recommended; however, if a patient presents with these lip nodules, opening up the site(s) with a needle and expressing or even removing them surgically is usually curative.8
Product Sensitivity

Given that all fillers (with the exception of autologous fat) are composed of foreign-body material, varying degrees of immune system reactivity can occur.9 Severe reactions are rare but can have important aesthetic implications. In addition to product-specific sensitivity reactions, the introduction of a foreign substance other than the filler (e.g., residual lipstick incompletely removed from the patient’s lips prior to a filling procedure) could cause a reaction or an unwanted visible mark. Therefore, makeup in the area of treatment must be removed preprocedure.

Collagens

Given its animal source, bovine collagen can be immunogenic, and the incidence of granulomatous foreign-body reactions reaches 1.3% in some series.10 Prior to bovine collagen injection, two skin tests are recommended to test for sensitivity: the first is usually placed in the left antecubital area, and the second is often placed in noncentral facial skin such as at the left scalp line. Approximately 3.5% of patients will have a positive first reaction; 70% of these reactions will manifest in 48 to 72 hours.11 A negative second test lowers the risk for reaction to less than 0.5%.

A possible reaction with human collagen has been documented in a report on two patients, one of whom had previously tested negative to a bovine collagen skin test at both 72 hours and 30 days.12 Human collagen (1 mL) was subsequently administered into the nasolabial folds of that patient. Seventy-two hours later, the patient complained of an erythematous, indurated, and burning reaction of the face. She was treated with the topical calcineurin inhibitor 0.1% tacrolimus ointment (Protopic, Astellas Pharma US Inc., Deerfield, IL) twice daily, and symptoms resolved slowly over the next 3 weeks. In the second patient, bovine collagen had previously been injected with no reports of any apparent sensitivity. Human collagen (1 mL) was injected peri- orally, and 5 days later a second 1-mL syringe was administered. The patient reported red lumps at the injection site 10 days after the first injection, with examination revealing palpable, perioral erythematous and nonerythematous subcutaneous lumps. This patient also was treated with 0.1% tacrolimus ointment, and lesions resolved within 6 weeks.

HA Products

Hypersensitivity also has been very rarely reported with hyaluronic acid products. One rare but dramatic type of reaction was an angioedema-type hypersensitivity following injection with a nonanimal-stabilized hyaluronic acid gel into the upper lip.13 In this case, a female patient was treated with hyaluronic acid (Restylane) in the lips. One hour postprocedure, the woman returned to the office and was found to have angioedema-type swelling of the upper lip (see Figure 2); she denied difficulty breathing. It is still possible that this reaction was due to another procedure performed at the same session, such as a very rare sensitivity to the lidocaine of the nerve block or to botulinum neurotoxin type A administered the same day. The patient was treated with 8 mg of dexamethasone sodium phosphate intramuscularly and was observed for about 2 hours. Stabilization of swelling occurred, and she was treated with a 6-day prednisone taper. Edema resolved 5 days postprocedure.

Persistent nodules, in the form of granulomatous foreign-body reactions, also have been very rarely reported with hyaluronic acid products. In a case reported by Fernández-Aceñero and colleagues,10 a 48-year-old female received a hyaluronic acid agent in the lips for the purposes of augmentation. This patient developed discrete nodules initially associated with eczematous changes in the overlying skin in her upper lip 6 weeks postinjection. Histologic analysis showed the presence of a sharply demarcated nodule in the subcutaneous fat that corresponded to a granulomatous foreign-body reaction, with multinucleated cells surrounding a blue amorphous material with the tinctorial features of hyaluronic acid. The patient was lost to follow-up.
A more recent article by Brody documents the use of hyaluronidase to treat a hyaluronic acid–related granulomatous foreign-body reaction. A “true hypersensitivity and granulomatous reaction” persisted in a patient for 5 months; treatment with cortisone injections and topical tacrolimus application were of little help. The patient was subsequently treated with 15 U of hyaluronidase injected into the nodule, and within 24 hours it disappeared; the reaction did not recur.

Hyaluronic acid products also have been associated with delayed erythema and painful, swollen lumps; bumps without pain or tenderness also have been reported. Based on the collective experience of several well-known aesthetic physicians, an algorithm was designed to help manage these inflammatory nodules, which were informally characterized as delayed-onset “angry red bumps.” This algorithm is shown in Figure 3.

Poly-l-lactic Acid

Product-related injection site nodules have been more commonly seen with poly-l-lactic acid, particularly in the human immunodeficiency virus (HIV)-infected population. In clinical studies, such subcutaneous papules were confined to the injection site and defined as “lesions of 5 mm or less, typically palpable, asymptomatic, and nonvisible.” These nodules were seen in 52% (26/50) and 31% (9/29) of patients in two separate European HIV-related lipoatrophy studies, each with a 2-year follow-up period. In the first study (the only one for which onset data are available), nodule onset occurred at an average of 7 months posttreatment (range, 0.3–25 months). Lower incidences of poly-l-lactic acid nodules were seen in two American HIV-related lipoatrophy studies and in an immunocompetent patient study with 1-year follow-up periods. In the American HIV-related lipoatrophy studies, nodules occurred in 6% (6/99) of patients in the first study and in 13% (13/99) of patients in the second study. In a recently presented 13-month study comparing poly-l-lactic acid with collagen for the correction of nasolabial fold wrinkles in 233 non–HIV-infected patients, nodules <5 mm in diameter occurred in 8.6% (10/116) of patients receiving poly-l-lactic acid and 3.4% (4/117) of those receiving collagen; application site nodules (>5 mm diameter) occurred in 6.9% (8/116) of subjects receiving poly-l-lactic acid and 6.0% (7/117) of subjects receiving collagen. No histologic data are available, and none of the studies reported any treatment information. However, in one of the European 2-year follow-up studies, the subcutaneous papules resolved spontaneously over the course of the study in 23% (6/26) of the patients.

European reports that the occurrence of these types of nodularities was quite common initially elicited a degree of skepticism and, at the very least, caution regarding injecting this substance. It is believed that modifications to the initial European injection protocol and technique help minimize the occurrence of the subcutaneous papules seen subsequent to poly-l-lactic acid administration. First, the product should
be constituted at a higher volume than done initially in Europe—specifically, mixed with $\geq 5$ ml sterile water, with 1 ml lidocaine later added prior to injection. Longer reconstitution times are also recommended, with reconstitution ideally occurring $\geq 8$ hours prior to injection. Injections should be made into the high fat, definitely not the mid dermis; care should also be taken not to inject the precipitate at the end of the syringe.

One article reported three cases in which more serious complications of foreign-body induced nodularities—giant cell granulomatous reactions—occurred after skin augmentation with poly-l-lactic acid; these reactions were attributed to the aberrant reactivity of the recipient to the material.9 Treatment in two cases, one with intrallesional steroid therapy plus topical 5% imiquimod cream and one with imiquimod cream, achieved no visible clinical improvement. The latter case was then treated with intrallesional steroid injections; results with this regimen were not reported. Treatment in the third case involved excision of the largest nodules, with a “satisfactory” result. The physicians recommend that, if feasible, surgical excision is the best option for this type of reaction; however, this would result in at least some degree of clinical scarring and, in some cases, deformity. While some US physicians report success with this product using the modifications mentioned previously, many physicians are still concerned because this product has received approval from the US Food and Drug Administration (FDA) only for HIV-related lipoatrophy. Thus, it has been most studied in relation to this condition, in which a fully intact immune system is lacking. At present, the risk of immune response to poly-l-lactic acid among immunocompetent patients is still an unresolved concern of several key opinion leaders.16 There have also been reports of subcutaneous nodules at the infraorbital skin after the use of this product.17 It is possible that this superficial placement in the infraorbital hollow results from injectors not realizing the change in thickness of the skin between the cheek and the lower lid.

**Bovine Collagen Plus Polymethylmethacrylate**

Bovine collagen plus polymethylmethacrylate (Artecoll, ArteFill [Artes Medical Inc.]) also can be associated with product sensitivity in the form of delayed granulomas, although the rate is low: from 1995 to 2000, these complications occurred in just 0.01% (15/200,000) of patients.7 Granulomas in those receiving bovine collagen plus polymethylmethacrylate have generally occurred 6 to 24 months posttreatment. Histologically, these enlarging granulomas, which often appear after the second or third implantation of product, show a wide distance between microspheres filled with macrophages, giant cells, fibroblasts, and broad bands of collagen fibers. The specific cause of these reactions is unknown; however, half of the patients experiencing them reported an associated severe infection (influenza) or some type of facial injury. Treatment can include intralesional injections of corticosteroids (triamcinolone up to 20 mg/ml or betamethasone up to 5 mg/ml, which are injected directly into the nodule, progressing to higher concentrations if needed at 3- to 4-week intervals). It is important to note that the new product ArteFill is not the same as the Artecoll that has been reported on. ArteFill is derived from a closed US bovine herd and is said to have much more consistency in polymethylmethacrylate particle size, so there is believed to be significantly less risk of ingestion of smaller particles of product by macrophages and thus a very low risk of immunogenicity.

**Infection**

Two infectious disease issues have been associated with dermal fillers. It is possible that fillers may trigger recurrent herpetic lesions;4 thus, in patients with a history of herpes outbreaks, prophylactic antiviral treatment is often recommended for lip augmentation. In patients with active herpes lesions, injections should obviously not be performed until the lesions have completely resolved.

Infection or contamination is another issue that could potentially occur with the use of soft tissue augmentation agents, especially with non–FDA-
approved products as recently reported by Toy and Frank. Specifically, in 2002, there was an outbreak of *Mycobacterium abscessus* infection in New York City following soft tissue augmentation with an unapproved hyaluronic acid product called Hyacell; the procedure was performed illicitly by a woman posing as a physician. Two individuals were known to be affected, and both developed tender, subcutaneous nodules. Hyacell contains hyaluronic acid, zinc, selenium, vanadium, and unspecified “embryonic extracts.” As a non–FDA-approved product, it was illegally brought into the United States from South America. Empiric treatment with clarithromycin and prednisone resulted in the clearance of lesions in both patients.

Clearly, infections can also potentially occur after using licensed products by experienced aesthetic physicians. To hopefully help minimize the risk of infection, clean preparation of the skin is recommended (such as using alcohol or an agent like chlorhexidine) in the area of treatment prior to filler placement. If an infection is suspected at some point, it is best to culture the exudate and initiate empiric treatment with an antibiotic such as clarithromycin until the more specific culture results become available. Of note, in the infraorbital area, it is recommended to avoid chlorhexidine due to the potential of contact with the eye resulting in a keratitis.

**Necrosis**

Injection necrosis is a rare but important complication associated with dermal fillers (Figure 4). Necrosis can be attributed to one of two factors: an interruption of vascular supply due to compression or frank obstruction of vessels by direct injection of the material into a vessel itself. The glabella is the injection site commonly believed to be at greater risk, as small-caliber vessels branch from the supratrochlear arteries to supply this watershed region with minimal collateral circulation.

According to a recent treatment algorithm, a number of precautions can be taken to avoid necrosis. In the glabella, these precautions include injecting superficially and medially, aspirating before injecting, and using low volumes of product in two or more treatment sessions (or treating only one side each session) instead of using a high volume in one session. Using only products that are placed superficially, such as CosmoDerm (Allergan Inc.), should also be considered. If impending necrosis is suspected, treatment options include immediately applying warm gauze and tapping the area to theoretically facilitate vasodilation and blood flow. The application of nitroglycerin paste (in office and at home by the patient) to further promote vasodilation is also believed to be of potential benefit. For cases in which a hyaluronic acid filler is used, there has recently been a report of a case of impending necrosis where hyaluronidase was successfully used along the distribution of the underlying vessel and the adjacent patchy violaceous skin to remove some of the product and seemingly decompress the vessel. For more severe or unresponsive cases of necrosis, Schanz and colleagues described their success using deep subcutaneous injections of low-molecular-weight heparin into the affected area.

**Conclusion**

The use of dermal fillers for cosmetic dermatology indications is increasing rapidly, due in large part to enhanced public interest in these products, decreased
social stigma, and a larger range of effective options available for a number of cosmetic enhancements. In addition, the proven safety of these products also has been a factor in their increased utilization. Although rare, complications do occur. Therefore, an awareness of the potential complications associated with each product, as well as how best to avoid or manage them if they do occur, can help maximize success with these important therapeutic tools.

References


Address correspondence and reprint requests to: Joel L. Cohen, MD, AboutSkin Dermatology, 499 E. Hampden Avenue, Suite 450, Englewood, CO 80113, or e-mail: jcohenderm@yahoo.com