Review Article

Aesthetic Surgery Journal
31(1) 110–121

DOI: 10.1177/1090820X10391083
www.aestheticsurgeryjournal.com
SAGE

Etiology, Prevention, and Treatment of Dermal Filler Complications

Steven H. Bailey, MD; Joel L. Cohen, MD; and Jeffrey M. Kenkel, MD

Abstract

The availability of dermal fillers for multiple cosmetic indications has led to a dramatic increase in their application. Although fillers are generally regarded as safe tools for soft tissue augmentation, complications can occur. Therefore, to describe and review the complications associated with the currently-available dermal filling agents, the authors conducted a literature review in peer-reviewed journals and present the reported complication rates. They also describe current strategies to avoid, diagnose, and manage complications if they do occur.

Level of Evidence: 3

Keywords

dermal fillers, soft tissue augmentation, filler complications, filler injection techniques, biofilm prevention

Accepted for publication February 23, 2010.

In recent years, the rate of soft tissue augmentation has exponentially increased for facial rejuvenation. According to statistics published by the American Society for Aesthetic Plastic Surgery, there were over 1.2 million dermal filler injections in 2008, which represents a 200% increase since 1997.[1] It has become a particularly attractive option for patients because the results are easy to appreciate immediately postinjection and have a predictable longevity. Clinicians have embraced injectables because, with proper patient selection and injection technique, most dermal fillers are able to modify the appearance/fullness of the skin and soft tissues while offering an impressive safety profile.[2,3]

Although fillers are generally regarded as safe, unanticipated events and adverse outcomes can occur with these agents.[2-16] To prevent complications and treat potential issues appropriately, it is of the utmost importance that clinicians fully understand the range and types of specific issues that can occur. In this article, we discuss how to avoid, diagnose, and manage complications of soft tissue augmentation agents by outlining key considerations during the preprocedure, intraprocedure, and early and late postprocedure periods.

PREPROCEDURE CONSIDERATIONS

Patient Satisfaction

Soft tissue augmentation is an elective cosmetic procedure, and, as such, the patient's satisfaction is first and foremost. During the initial visit, photographs should be taken to document the patient's appearance prior to the procedure and also to facilitate a clear and frank discussion about the patient's areas of concern. Once the patient's treatment goals have been discussed, the clinician should discuss which filling agents are best suited to the patient's needs, as well as the limitations of dermal filling agents in general. Fillers can treat fill folds, fine wrinkles, and correct contour abnormalities, but these procedures are not meant to replace surgical interventions.[17-20] Patients should be informed about the possibility of swelling and bruising and be advised to avoid these procedures immediately prior to any significant social or professional events. Last, the clinician should discuss the financial commitment that will be involved for a patient to reach his or her intended goal, including an accurate assessment of how many syringes will be needed, in order to establish realistic expectations about the outcome of the procedure.

Dr. Bailey is a Fellow in the Department of Plastic Surgery, and Dr. Kenkel is the Rod J. Rohrich Distinguished Professor in Wound Healing and Plastic Surgery and Vice-Chairman of the Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, Texas. Dr. Cohen is an Associate Clinical Professor in the Department of Dermatology, University of Colorado, Denver, Colorado.

Corresponding Author:
Dr. Jeffrey Kenkel, MD, UT Southwestern Medical Center, Department of Plastic Surgery, 1801 Inwood Road, Dallas, TX 75038, USA.
E-mail: jeffrey.kenkel@utsouthwestern.edu

Skin Testing

Once a filler has been chosen, the reactivity profile should be reviewed. Products that are highly reactive (ie, products containing bovine collagen) require skin testing prior to application. Among the products available in recent years, only Artefill (Suneva Medical, San Diego, California) requires a skin test. To date, no reactions to the product have been documented, but skin testing is required by the Food and Drug Administration (FDA).

Hyaluronic acid (HA) fillers are still the most popular injectable option in the United States.[21-23] There do not appear to be any significant reactions from HA application, whether the formula is bacterial or avian in origin. HA has a low rate of hypersensitivity, ranging from 0.6% to 0.8%.[2] In comparison, bovine collagen's incidence of acute hypersensitivity is 3.5% and delayed hypersensitivity rates range from 3% to 10%.[19,24,25] Reported reactions to HA were most often localized, immediate, and resolved within three weeks, according to data from a European retrospective review of cases between 1997 and 2001.[2,26] Reactions to bovine collagen may be local or systemic.

The skin test for bovine collagen is performed by injecting 0.1 mL of product into the antecubital area and, 30 days later, injecting a separate area (such as the left scalp line). In general, 3.5% of patients will manifest a positive reaction (ie, a local wheal-and-flare reaction) in 48 to 72 hours.[25,27] A negative second skin test lowers the risk of a bovine collagen reaction to less than 0.5%. A single skin test is performed for Artefill, as it also contains bovine collagen. Not all collagen-based fillers require skin testing; some of the newer formulations have lower antigenicity. Human collagen carries a very low risk of reactivity, so Cosmoderm (INAMED Corp, Santa Barbara, California) and Cosmoplast (INAMED) do not require skin testing prior to treatment. Porcine collagen (Evolence, Colbar LifeScience Ltd, Herzliya, Israel) was approved by the FDA in 2008 and offered the advantage of durability as well as the lack of need for skin testing, but has since been removed from the market. A 2007 study by Shoshani et al[28] indicated that the hypersensitivity of Evolence had a calculated risk of 0.58% and was lower than estimated for both bovine and human collagen. Interestingly, the hypersensitivity after injecting Evolence was also lower than what had been observed with nonanimal HA (Restylane; Q-Med, Upssala, Sweden), which had a calculated risk of 0.74%.[28,29]

Prevention of Local Adverse Reactions

Local injection site reactions are the most common adverse event associated with soft tissue augmentation and should be expected to some degree in most patients undergoing these injections. In a large multicenter, randomized, double-blinded comparison study of nasolabial folds comparing collagen and HA, 90.6% and 93.5% of patients (respectively) experienced local injection site reactions.[30] These reactions were less than seven days in duration and ranged from mild to moderate in severity.[30] The frequency with which these events occur necessitates that patients be informed of swelling and/or bruising, which may occur during the seven-day window.

We generally recommend that patients who do not have a history of heart attack, stroke, or blood clot discontinue aspirin five to seven days prior to their procedure. Nonsteroidal anti-inflammatory drug (NSAID) medications and many vitamin/herbal supplements associated with anticoagulation (such as vitamin E, ginseng, ginger, ginko, garlic, kava kava, celery root, and fish oils) are also often discontinued seven to 10 days prior to treatment to reduce the risk of bruising.[31] Some patients are not opposed to being injected while on NSAID medications and accept the increased risk for bruising, for the convenience of continuing their medications.

When assessing patients with cardiovascular stents and/or those who take anticoagulant medication, it is important to consider the timeframe during which the patient will be taking the medication and to assess his or her overall risk of adverse events if the medication is temporarily discontinued.[32] If the medication is prescribed for a limited period of time (ie, anticoagulation for an initial attack of venous thromboembolism), it may be prudent to postpone injection treatment until the medications can be discontinued. However, if the medications are prescribed indefinitely, the risk of eliminating these medications should be evaluated. In general, it is not recommended that patients taking therapeutic anticoagulants such as coumadin or Plavix (sanofi-aventis US, Bridgewater, New Jersey) alter their regimens for these types of procedures, as the risk clearly outweighs the benefit.[33-37] The recent American College of Chest Physicians guidelines recommend continuance of anticoagulation throughout minor dermatological procedures with low risk for bleeding. These patients are at a significantly higher risk of adverse events from thrombosis, which in some cases is as high as 50%.[38] These patients understand that they are at increased risk for bruising while taking anticoagulants, and they accept this risk, considering the risk of serious adverse events and other sequelae with medication termination. We have successfully completed dermal filler treatment in high-risk patients on anticoagulants, often facilitated with local anesthetic containing epinephrine and liberal placement of ice packs.

Prevention of Infection

Although the incidence of infection following soft tissue injectables is quite low, there have been reports that reinforce the importance of proper technique.[7] Intuition tells us that when implanting into the body foreign materials that have a certain permanence, sterile techniques should be employed. This has not been the case with dermal filling agents, where the importance of skin preparation is still unrecognized. In many ways, we have taken our knowledge of other subcutaneous injection procedures and applied them to soft tissue fillers, regardless of the fact that filler agents have more significant longevity. To date, there

Table 1. Common Antiseptic Agents

Agent	Use	Mechanism of Action	Speed of Action	Residual Effect
Chlorohexidine swab stick (ChloraPrep; CareFusion, El Paso, TX)	Skin prep	Denaturing proteins; disruption of cell membranes. Not affected by organic material on the skin.	Rapid	Excellent
Chlorhexidine gluconate (2%-4% aqueous)	Surgical scrub, hand wash, and skin prep	Disruption of cell membrane. Not affected by organic material on the skin	Intermediate	Excellent
Chlorxylenol	Surgical scrub, hand wash, and skin prep	Denaturing proteins; inactivates enzymes.	Intermediate	Excellent
Iodophors	Surgical scrub, hand wash, and skin prep	Substitutes Iodine. Organic material on the skin affects efficiency of antisepsis	Intermediate	Minimal
Alcohol	Surgical scrub, hand wash, and skin prep	Denaturing proteins. No data on whether organic matter on the skin affects efficiency of antisepsis	Rapid	None
Tinture of iodine (2%)	Skin prep	Denaturing proteins; substitution by free iodine. No data on whether organic material affects efficiency of antisepsis.	Rapid	Minimal

have been no data with specific, universal guidelines on the appropriate method of preparing the skin. Until adequate data are available, it is useful to consider prior publications regarding clinical experiences with central lines and other implantable devices.

It has been shown that skin preparation is critical in preventing superficial soft tissue infections.[39] Each of the commercially available skin preparation solutions has properties that make it a good antibacterial compound, and each has differences that make it unique (Table 1). According to Calfee et al's comparison[39] of 10% povidone-iodine, 70% isopropyl alcohol, tincture of iodine, and povidone-iodine with 70% ethyl alcohol, there was no difference in the rate of contaminated blood cultures. Considering the low cost, convenience, and tolerability, the authors recommended 70% isopropyl alcohol for skin prep prior to obtaining blood cultures. Since that report, chlorhexidine-based antiseptic agents have become more prevalent because they offer the quick-acting ability of alcohol with much longer durability and higher efficacy.[40,41]

The current guidelines for the prevention of intravascular catheter-related infections recommend application of maximal sterile barrier precautions during central venous catheter (CVC) insertion and a 2% chlorhexidine preparation for skin antisepsis.[42] Some injectors employ alcohol, as well as either chlorhexidine or chlorxylenol, to prepare the skin prior to treatment with dermal filler agents. It is important to note that chlorhexidine should be avoided in the periocular area due to potential risk of keratitis and possible ocular injury.

Once the skin has been prepared, all other forms of contamination must be avoided. Theoretically, fillers can be contaminated in four ways: (1) during manufacture, (2) during reconstitution, (3) during dilution with lidocaine, or (4) by surface bacteria during injection, by injection into an active soft tissue infection, or by topical contamination immediately postprocedure via needle puncture sites (when a patient applies topical ointment or makeup with unclean fingertips).

Prevention of biofilm formation is the next frontier in the management of infections related to implantable devices. Biofilms likely play a role in many delayed-onset skin reactions. A biofilm is composed of a glue-like matrix secreted by bacteria that becomes a nidus in which many types of bacteria thrive. The problem with a biofilm is that it can form on any surface, from teeth to rocks to implants. These infections are difficult to treat because they can require, on average, approximately 32 times the amount of antibiotic required to kill free-floating bacteria.[43]

Needle size is another important consideration for many reasons. Needle size can affect pain, the size of the skin puncture, and the risk of trauma to adjacent structures or vessels. The ideal needle choice is the smallest needle that still allows for accurate injection of the filler. Smaller needles may possibly reduce tissue damage and also leave smaller conduits in the skin that may reduce the risk of infection. In general, for less viscous fillers, a 30-gauge (or, off-label, a 32-gauge) needle is employed, whereas more viscous fillers may require a 27-gauge needle (eg, calcium hydroxylapatite) or even a 25-gauge needle (eg, poly-L-lactate) to avoid clumping or clogging.[44,45] Needle size is dependent on the viscosity of the tissues and whether the formula is diluted.

Considering the recommendations for short-term and long-term catheters, as well as the information known about biofilms and possible means of contamination, clinicians treating patients with dermal fillers should adhere to the following procedures: (1) thorough handwashing, (2) advising patients to remove all makeup and other potential contaminants on the skin and to delay reapplication for a minimum of four hours posttreatment, (3) cleansing the skin with an antimicrobial preparation prior to injection, (4) taking sterile precautions during reconstitution/dilution, (5) avoiding injection during active soft tissue infection,

and (6) selecting the smallest sized needle possible during injection.

INTRAPROCEDURE CONSIDERATIONS

Following initial evaluation, the next key step to optimizing results and decreasing the likelihood of adverse events is proper placement of the product. Appropriate placement is multifaceted and encompasses thorough knowledge of the anatomical planes (superficial, deep dermal, subcutaneous, preperiosteal), understanding of techniques for individual filler agents, and familiarity with specific techniques for each area of the face.

Product Placement

Superficial placement of dermal fillers is a common error and is associated with a range of complications, from obviously visible product (Figure 1) to inflammatory nodule formation (Figure 2) and even hypertrophic scarring.[12,16,46-49] These complications are avoidable when the practitioner recognizes the visual clues that indicate appropriate depth, but determining this during injection can be difficult. Arlette and Trotter[50] found, in a study assessing the difference in perceived versus actual depth of placement of HA fillers, that injectors were actually at a different dermal level (deeper) than they believed themselves to be.

The visual cues are simple and come primarily from assessing the color and shape of the needle, as well as the response of the skin and subcutaneous tissues. In the superficial (intradermal) plane, the gray of the needle can be seen, and the skin blanches.[48,51,52] Although this plane is too superficial for most filler indications, it is necessary to deposit appropriate filler superficially for acne scars and fine lines. Injection of a thin-particle, superficial filler such as Cosmoderm and Zyderm (Allergan, Irvine, California) may be useful in these situations. For most other indications, fillers should be placed in the deep dermal or superficial subdermal regions.

Key visual cues to confirm placement in deep dermal or superficial subdermal level are as follows: (1) the gray of the needle is not visible, (2) the shape of the needle is apparent, and (3) the injector is able to press down the fat by pointing the tip of the needle down.[48,51,52] It is important to understand, again, that most injectors are actually deeper than they believe. Dermal filling agents should not be placed intramuscularly due to the risk of causing lumps and nodules from uncontrolled displacement of the filler during routine muscle movement.[48,51,52] This was the likely etiology of nodularities when early advocates of calcium hydroxylapatite were placing this filler into the lip body.

Occasionally, fillers are placed to augment the soft tissues. These are placed at the preperiosteal level. The appropriate technique for finding the preperiosteal plane involves inserting the needle down through the skin and subcutaneous tissues until the periosteum can be palpated with the tip of the needle. This step should be performed carefully, as the periosteum can be disrupted, leading to subperiosteal hemorrhage and pain.[53] Repetitive contact with the periosteum will result in dulling of the needle, necessitating replacement more often during treatment. Once the periosteum is reached, the needle should be pulled back slightly to prevent placement of the product directly on the bone, deeper than the overlying musculature.[48,53]

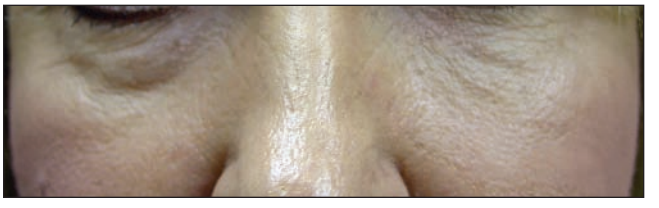

Figure 1. A nodule of filler product is visible under this patient's right eye, resulting from superficial placement of a large volume of Restylane, and superficial small linear threads of filler are apparent at the left lower lid.

Figure 2. A granulomatous-appearing nodule is clinically apparent on the dorsum of the hand two months after Restylane injection.

Manifestation of Superficial Filler Placement

Superficial placement of dermal fillers is an avoidable complication. Manifestation of this is variable and dependent on the individual qualities of the injected product and the anatomic region of injection.[6] Caution must be taken when applying any filler superficially. Areas such as the tear trough pose a higher risk for product visibility and should be injected only by those with considerable experience with the product.[6,46,52,54,55]

Hyaluronic Acid

HA should be injected into either the deep dermis or the subdermal plane. Superficial placement of this clear gel can potentially result in the appearance of small lumps and bumps.[12] These bumps present relatively quickly and can appear blue. This bluish-gray appearance occurs because light of differing wavelengths is scattered differentially based on the substances it encounters (in this case, the gel within the dermis). This is known as the Tyndall effect.[56,57]

Superficial placement of HA can be treated in several different ways. If caught early, the gel can be massaged to distribute the filler more evenly. If this fails, incision and drainage with an 18-gauge needle or number-11 blade may facilitate expulsion of the product from the dermis.[12,58] Hyaluronidase (an enzyme that breaks down HA fillers) has also been reported to be helpful.[58] The hyaluronidase (commercially available in various proprietary formulations) is often diluted prior to injection; 75 units of hyaluronidase can be mixed in 1.5 mL of 1% lidocaine (with or without epinephrine if trying to dissolve a nodule). Brody's report[58] of HA nodule treatment with 15 units of hyaluronidase indicated complete resolution in 24 hours, without recurrence.

Most hyaluronidase preparations are animal based (except Hylenex [Baxter Healthcare, Deerfield, Illinois], which is not currently on the market at the time of press) and may cause sensitivity.[58] For an appropriate skin test, an injection of three units should be placed intradermally and the patient should be monitored for approximately 20 minutes (although, in rare cases, observation will extend overnight).[46] A positive reaction is noted when a wheal or flare occurs at the tested site.[52] The reaction occurs from sensitivity to either the animal protein or the ingredient thimerisol. Patients with bee sting allergies may be highly sensitive to hyaluronidase. Bee venom contains hyaluronidase and may be responsible for a cross-reaction to injectable hyaluronidase.

Calcium Hydroxylapatite

Calcium hydroxylapatite (CaHA) is ideally placed in the deep dermis or, preferably, subdermally. When placed too superficially, visible white nodules may be seen. These nodules can be treated by puncture with a number-11 blade or needle, which will express the contents. Areas such as this require advanced techniques[56] with deeper placement, and injections should be performed only by those clinicians who have filler experience in this area and a detailed understanding of the region's anatomy.

Product migration may occur when the injectable is placed too superficially or in more mobile anatomic areas. This complication has been associated with injection of CaHA in the lip, even when placed within the muscular body. While speaking or eating, the superficial and deep muscular portions of the orbicularis oris act as a pump, which causes coalescence of the product and nodule formation.[6] Treatment options for this complication include intralesional steroid injections or even injection of dilute saline followed by massage, which may help to mechanically break up the product. Alternatively, the site can be opened with a needle or number-11 blade for manual expression of the product. Surgical removal, although rarely required, is also an option.[6,59]

Polymethylmethacrylate

Polymethylmethacrylate (PMMA), a permanent filler agent, is now available for use in the United States as Artefill. The European product is marketed by the same manufacturer as Artecoll. Although similarities exist between these two products, there are some distinct differences. Artefill is derived from a closed US bovine herd, is more consistent in particle size, and has a larger particle size. The larger particle size confers a lower risk of immunogenicity and digestion by macrophages. PMMA fillers are optimally placed in the deep dermis or, preferably, the subdermis. Superficial placement may be associated with pruritis, redness, and (rarely) hypertrophic scarring.[49] Localized itching and redness can sometimes be treated with topical steroids or intralesional corticosteroids. Hypertrophic scarring can be softened with a pulsed dye laser or topical or intralesional steroids.[46]

Following the various treatment algorithms listed above will usually reverse or greatly improve imperfections caused by superficial placement of various products.

Injection Patterns and Injection Technique

Selection of appropriate injection techniques for each patient helps ensure successful outcomes and limits the risk of contour irregularities. Several patterns have been described for appropriate placement of various fillers: fanning, serial puncture, cross-hatching, and linear threading. The choice of pattern is usually predicated on the site to be injected and the agent being employed. Proper pattern selection will help the injector more uniformly treat the desired area.

The glabella, philtral columns, fine rhytides, and even the nasolabial folds lend themselves well to either the serial puncture or linear threading techniques. Serial puncture is performed by making multiple injections sequentially along the wrinkle or crease. Care should be taken to keep the injection sites close together, so that the injected material can merge into a smooth, continuous line that ultimately lifts the wrinkle or fold. Pulling the skin away slightly while injecting can help develop and smooth the contiguous effect. If postinjection gaps occur, molding and massage can help blend the material into a smooth layer. Regardless of injection technique, it is important to palpate and massage the treated site, working out any irregularities.

The vermiliocutaneous border and nasolabial folds are ideal sites for linear threading. The correct technique involves inserting the full length of the needle into the middle of the wrinkle or fold to create a channel and then filling the channel with the product. The filler can be injected while the needle is advanced in an antegrade fashion or as the needle is withdrawn in a retrograde fashion (Figures 3 and 4). Retrograde injection seems to be the more common pattern, but both techniques can lead to excellent results in the hands of skilled injectors. In highly vascular areas such as the glabellar crease, a retrograde injection is the safest technique, decreasing the likelihood of an intra-arterial injection. The vermillion border is an excellent location for an antegrade approach because the potential space along the white roll allows for the product to flow along the border quite easily.

For larger areas such as the cheek or even marionette lines, cross-hatching can be a very effective tool. Some

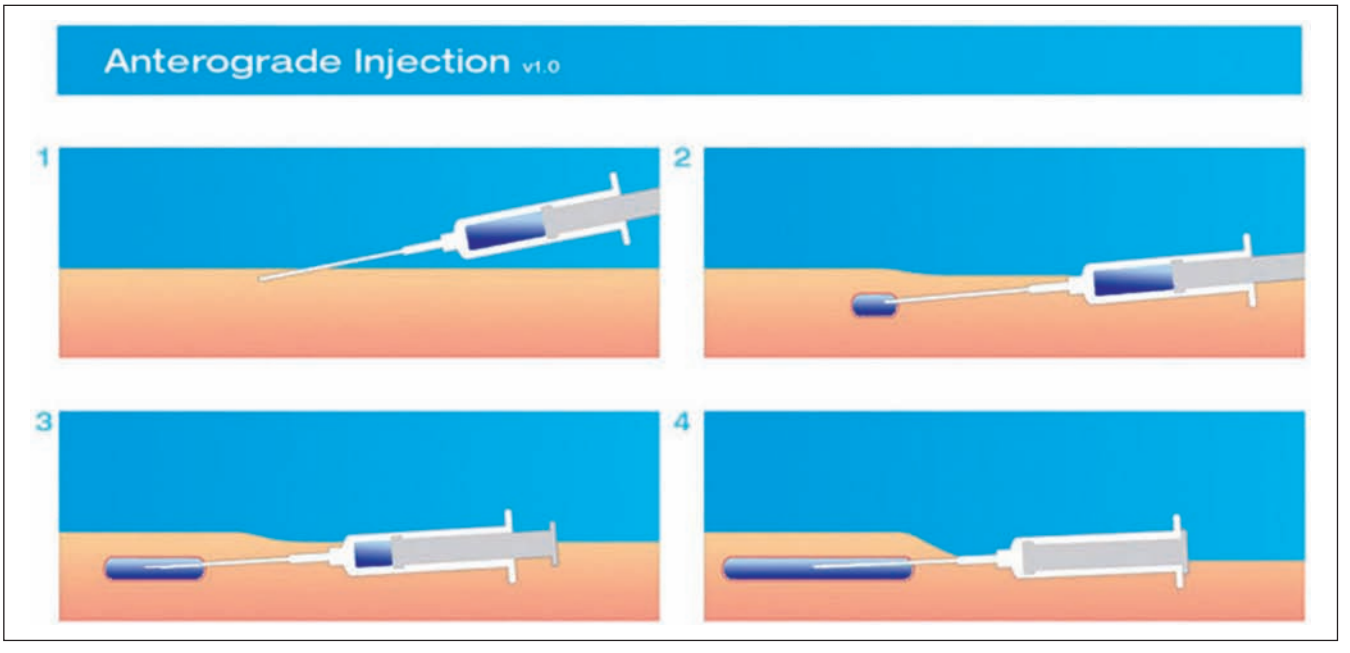

Figure 3. Anterograde injection technique. Modified from images by Medical Education Advocates; reprinted with permission.

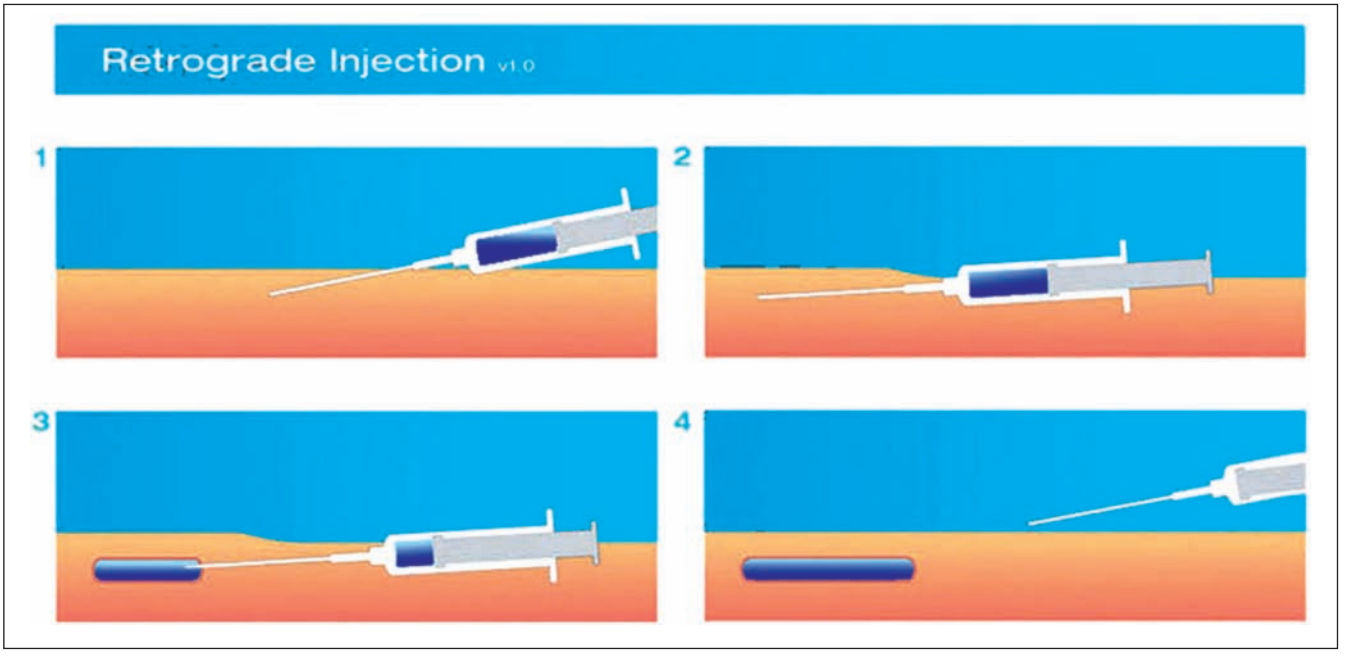

Figure 4. Retrograde injection technique. Modified from images by Medical Education Advocates; reprinted with permission.

injectors find it useful to mark the area to be treated, to create a road map of the treatment area. Cross-hatching entails making a series of linear threading injections evenly spaced in a progressive grid to ensure that the space is evenly filled. Once an area is filled, gentle massage allows for blending and smoothing of the region. It is not unusual for injectors to apply this technique at several different levels to help fill and lift the area of treatment.

Last, fanning is performed by inserting the needle in a similar fashion to linear threading, but before the needle is completely withdrawn, it is advanced in a different direction (clockwise or counterclockwise), ensuring that the filler does not clump at the base,[51,53,60,61] thereby also allowing the injector to fill a peripheral area from the same injection site (Figure 5).

As mentioned previously, proper injection technique helps ensure a successful outcome. Glogau and Kane[62]

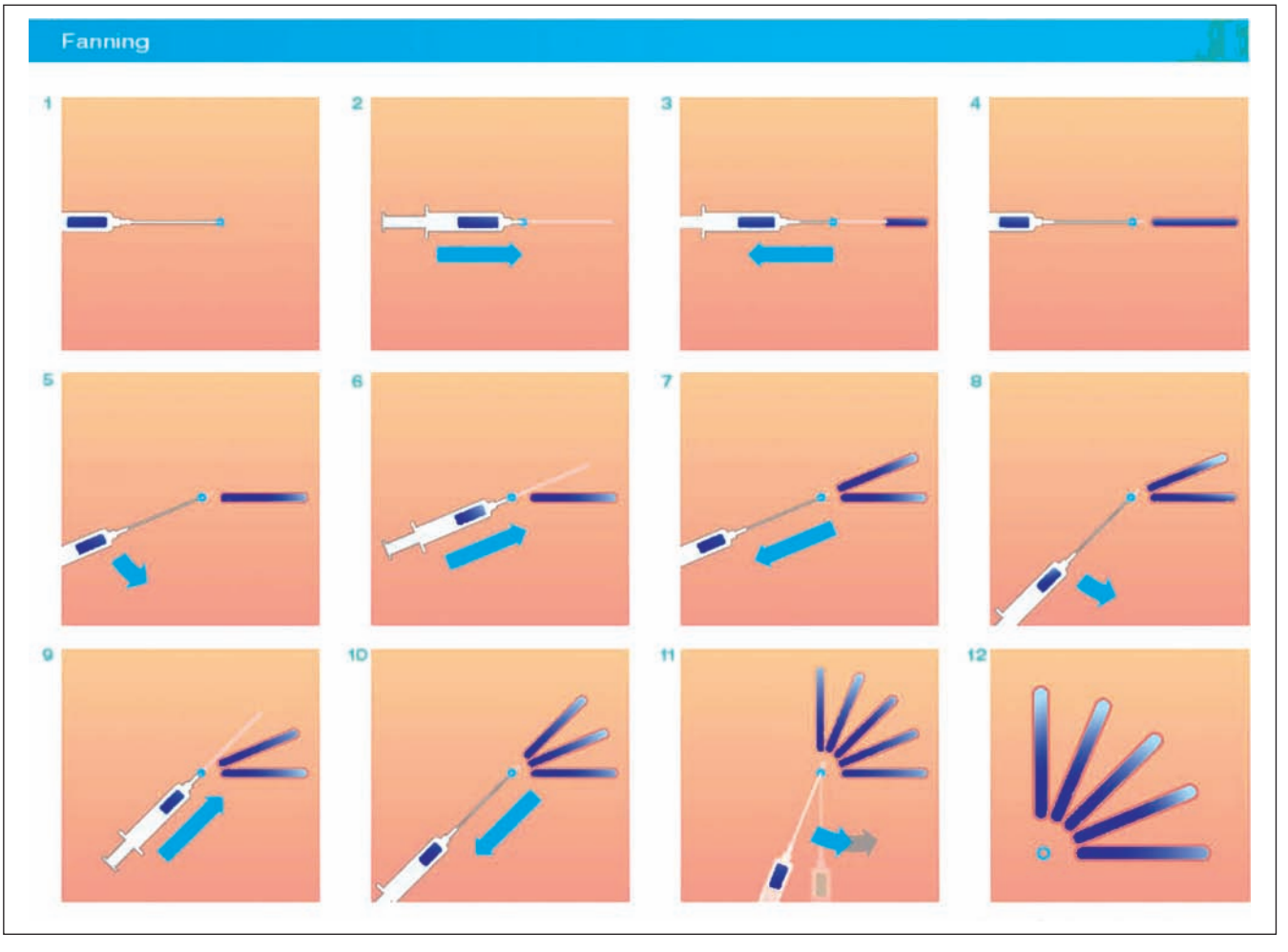

Figure 5. Fanning injection technique. Note that as the needle is withdrawn and the direction is changed, the needle remains in the skin. Modified from images by Medical Education Advocates; reprinted with permission.

found in a randomized, prospective, blinded, controlled study of 283 patients that injection techniques can contribute to the occurrence of local adverse events. The elements that were found to be associated with an increased risk of adverse events included injection techniques that increased the dissection of the subepidermal plane (ie, a fan-like injection pattern), rapid injection, rapid flow rates, and higher volumes. Interestingly, injection techniques that increased epidermal damage and/or subcutaneous contact (ie, multiple punctures or subcutaneous injection) had no effect on adverse events.[62] Clinicians should keep these aspects in mind, especially when treating patients at risk for adverse events.

Special Considerations

Certain section of the face, such as the periocular and tear trough regions, can be particularly challenging to augment. The skin in these areas is quite thin and can be unforgiving. Without stringent adherence to proper technique, serious adverse events can occur in these regions. For example, the periorbital region is surrounded by several major facial vessels and careless injection in this area without aspiration could result in visual impairment or even blindness.[63] Furthermore, injection above the bony border of the orbit can result in a postseptal injection and possible injury to the globe. Once globe injury or blindness occurs, there are very few options available to reverse the effects. Therefore, it is incumbent on the clinician to be aware of these possible complications and take every precaution to avoid them.

EARLY POSTPROCEDURE CONSIDERATIONS

Allergic and Other Hypersensitivity Reactions

Fillers, with the exception of autologous fat and autologous collagen, are generally composed of foreign material. As such, they can theoretically trigger varying degrees of

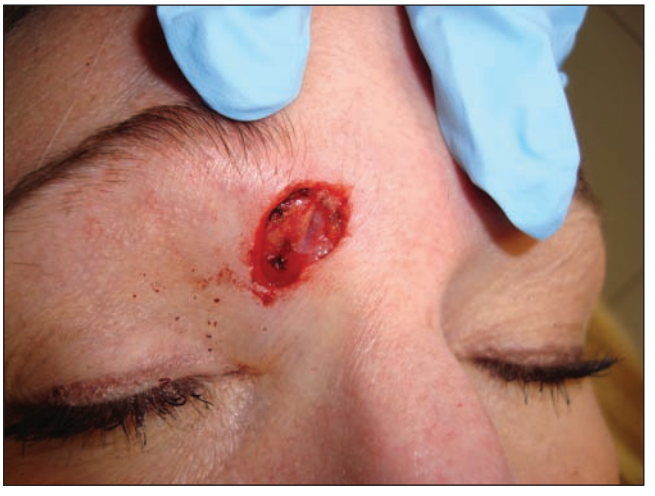

Figure 6. This patient's supratrochlear artery was visible after Mohs surgical removal of a basal cell carcinoma. Note the superficial location of the supratrochlear artery and the small caliber of this vessel. These vessels should be avoided during soft tissue augmentation, as compromise can lead to glabellar necrosis.

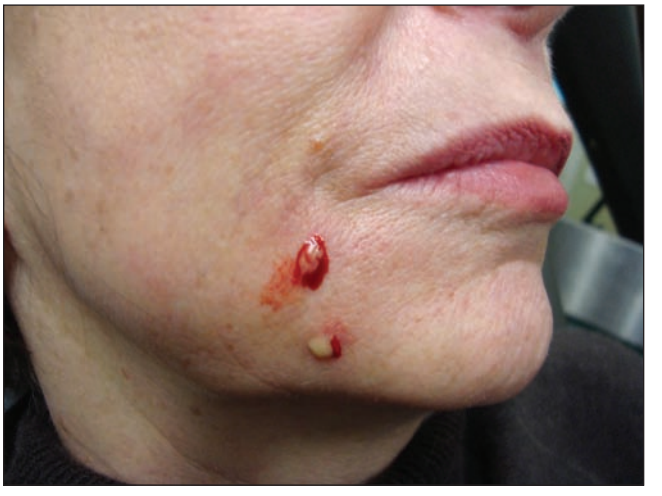

Figure 7. This patient had "sterile abscesses" (two negative cultures) that developed a few weeks postinjection with hyaluronic acid. The patient responded to a combination of oral clarithromycin, local hyaluronidase injections, and intralesional steroids over two months. This case may represent a biofilm reaction, which can be quite difficult to culture.

immune activity. These reactions can range from mild irritation and redness to anaphylaxis.[2,3,5,6,9,11,13,15,49,54,64] Despite adequate skin testing and the selection of fillers with a low reactivity profile, reactions can still occur, however rare they may be. Stolman[65] and Nijhawan et al[66] reported rare cases of allergic reactions to human collagen products consisting of erythema, induration, burning, and nonerythematous subcutaneous lumps. Both patients in the Stolman case report had previous exposure to bovine collagen, either through previous treatment or through skin testing, without any report of sensitivity. Fortunately, a localized allergic reaction to either bovine collagen or the extremely rare reaction to human collagen generally does not produce long-term morbidity. Specifically, these reactions can often be treated by topical tacrolimus, intralesional steroids, systemic steroids, or antihistamines.[65]

A rare case of angioedema-type hypersensitivity has been reported after Restylane injection in the lips. This reaction occurred one hour postprocedure without airway compromise. The patient was treated with 8 mg of dexamethasone intramuscularly and observed. Stabilization of swelling occurred after two hours and the patient was treated with a six-day prednisone taper. The patient's edema resolved five days postprocedure.[10]

Skin Necrosis

Skin or injection site necrosis is fortunately a rare occurrence. With proper education and technique, this is largely an avoidable complication. Vascular embarrassment occurs by external compression of the blood supply by the product or occlusion of the vessel via direct injection of the product into the blood vessel. The glabellar region is considered a high-risk area because the vessels are of a small caliber (Figure 6) and do not have a good source of collateral circulation. The risk of skin necrosis can be reduced by (1) aspirating prior to injection, (2) utilizing lower volumes and serial injections in high-risk areas, (3) injecting in a more superficial plane (utilizing filler agents that can be placed more superficially, such as CosmoDerm), (4) treating one side at a time, (5) pinching/tenting the skin to provide more space superficial to the branches of the main arteries, and (6) manual occlusion of the origin of the supratrochlear vessels with the nondominant finger.[4,63] Other injectors prefer an HA-based product (including but not limited to a low-concentration HA product such as Prevelle Silk [Mentor Corp., Santa Barbara, California], which can usually be placed more superficially) in higher risk areas so that hyaluronidase dissolution of product would then be an option in the case of vascular compromise.

It is imperative that any injector of filler products be familiar with the signs of skin necrosis and the appropriate therapy, as time before and type of treatment help determine outcomes following this potentially devastating complication. The goal of the urgent therapy is to promote increased blood flow to the affected area. This may be accomplished by applying warm gauze, tapping the area to facilitate vasodilatation, and applying nitroglycerin paste (in the office and at home by the patient) to further promote vasodilatation.[67] Hyaluronidase injection has been suggested in cases of impending necrosis after HA injection and there are cases documenting improvement from careful injection along the distribution of the underlying vessel, seemingly through decompression of the vessel.[4,67] For extreme and severe cases of unresponsive necrosis, there is a case report demonstrating a good

response to local subcutaneous injections of low molecular weight heparin.[68]

LATE POSTPROCEDURE CONSIDERATIONS

Nodule Formation and Granulomatous Reactions

Delayed-onset nodule formation and granulomatous reactions have been reported following placement of several injectables. "Delayed" responses, for the sake of this discussion, are those that occur after six weeks. Although the presentation can often be the same as early onset reactions, the mechanism behind the reaction is different. The sections below describe late reactions that occur with HA fillers, poly-L-lactic acid (PLLA) fillers, CaHA fillers, and PMMA fillers.

Hyaluronic Acid

Nodule formation following injection of HA fillers is most commonly due to superficial placement of the product. Granulomatous reactions/inflammatory nodules are of a different nature and have been reported in the literature as persistent nodules and delayed-onset "angry red bumps." The etiology of these sometimes tender, erythematous nodules has been attributed to possible allergic reaction, foreign body reaction, infection, and sterile abscess (Figure 7). Recently, there has been a great deal of discussion on the role of biofilms in the presentation of late-onset nodule formation.[12,69-72] These lesions are more resistant to treatment. Case reports describe some that fail to improve with standard measures such as topical, oral, and injectable steroids. Some reports of these reactions to HA indicate that injecting the enzyme hyaluronidase may be a therapeutic option for granulomatous lesions that are otherwise refractory to steroid injection.[58] Brody[58] reported successful treatment of refractory HA-induced nodules with 15 units of hyaluronidase injected directly into the lesion, with complete resolution in 24 hours. The management of delayed-onset "angry red bumps" with empiric antibiotics such as clarithromycin has been well documented, along with incision and drainage treatment followed by close observation.[12]

Poly-L-Lactic Acid

Nodule formation with PLLA fillers was quite common initially, with an incidence of between 31% and 52% in early European studies in patients with HIV-related lipodystrophy. Lower incidences of these nodules were reported by several US authors and ranged between 6% and 13%.[15,46,73] Pursuant to the high rate of nodule formation, treatment protocols changed. These modifications include injecting in a deeper plane as previously discussed (provided that the filler is not placed into the muscle), reconstitution with higher volumes (ie, 5 mL or more of sterile water and 1 mL of lidocaine added prior to injection), and longer reconstitution times (ideally eight hours or more prior to injection).[74] Lam et al[45] and others[73] have more recently recommended dilution with a volume of 5 to 10 mL of sterile water and 1 to 2 mL of 1% lidocaine with epinephrine. We advocate that the reconstitution timeframe should not be less than 12 hours, with an ideal time of 24 hours to ensure complete reconstitution.[45] Butterwick and Lowe[75] promoted diluting the filler with 5 mL or more of sterile water and an additional 1 mL of lidocaine prior to injection, as well as extending the reconstitution time to at least overnight for all facial applications. Furthermore, upon review of the literature, they suggested specifically that appropriate injection technique (ie, injection in the subcutaneous plane, even distribution of the product, and no more than 0.1-0.2 mL of product per pass of the needle) and posttreatment massage are helpful in reducing nodule formation.[45,74,76-80] There are reports of nodule treatment with intralesional steroids in combination with topical 5% imiquimod cream or 5-fluorouracil, topical 5% imiquimod cream alone, 5-fluorouracil alone, and surgical excision, but only surgical excision has been noted to yield a satisfactory result.[5]

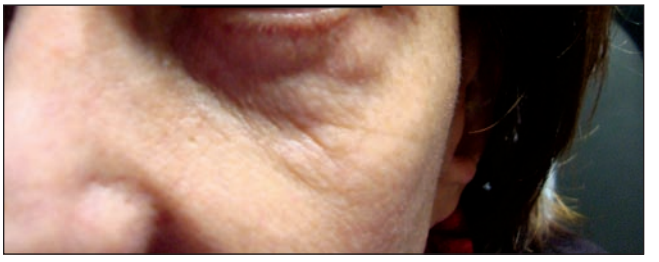

Figure 8. This patient developed infraorbital nodules 2.5 years after treatment with Sculptra (Sanofi-Aventis US, Bridgewater, New Jersey) by a nurse injector.

Calcium Hydroxylapatite

Nodule formation following CaHA injection has also been reported. Although the injection to the lips has never been an approved indication for this product, in the early part of this decade, some US injectors were performing lip and perioral augmentation with a nodule formation incidence of 20% or higher. As a result, its use in the perioral region has been abandoned by most injectors today. The product is injected safely and effectively in many other areas such as the nasolabial folds, oral commissures, and cheeks. If nodules do occur in these areas, they appear as small lumps close to the site of injection. There have been reports of nodules appearing up to 2 cm distal to the site of injection (Figure 8). These lesions can be treated with steroid injection or surgical excision.[59] Theoretic concerns of bone stimulation following injection of CaHA have been raised,[81] but to date, no studies have shown this theory to be true. Although it is still only conjecture, it is recommended that care be taken to avoid contact with the bone when injecting in the preperiosteal plane.[6]

Polymethylmethacrylate

Delayed granuloma formation has been associated with the PMMA filler Artecoll. The rate is quite low (0.01%) but can be troublesome because of its delayed appearance, often six to 24 months after injection.[49,82] Treatment gener-

ally involves repeated intralesional steroid injection at increasing concentrations over a three- to four-week interval.[46] It is important to distinguish this type of nodule formation versus superficial beading and ridging that represents a hypertrophic scar due to superficial placement of PMMA as the latter may eventually require therapies, including laser or excision.[61]

CONCLUSIONS

Soft tissue augmentation with filler agents is in higher demand due in large part to increased public exposure to these products and increasing confidence that these agents provide a safe and consistent means of facial rejuvenation. Despite the impressive safety profile of these products, complications do occur. It is important for the injector to be knowledgeable about regional anatomy and select the product most likely to address the patient's concerns. The injector must be conversant about each product, the best injection techniques specific to that product, and the potential risks so that the patient can be properly informed. If a complication does occur, thorough understanding of the diagnosis and treatment algorithms will help the injector safely navigate through these circumstances to minimize long-term sequelae. This article outlined key methods to help clinicians at all levels understand fillers and their complications in a way that will allow them to successfully avoid, accurately diagnose, and efficiently manage potential adverse events.

Disclosures

The authors declared no conflicts of interest with respect to the authorship and publication of this article.

Funding

The authors received no financial support for the research and authorship of this article.

REFERENCES

1. American Society for Aesthetic Plastic Surgery 2008 Cosmetic Surgery National Data Bank statistics. Available at: *http://www.surgery.org/sites/default/files/2008stats.pdf*
2. Andre P. Evaluation of the safety of a non-animal stabilized hyaluronic acid (NASHA—Q-Medical, Sweden) in European countries: a retrospective study from 1997 to 2001. *J Eur Acad Dermatol Venereol* 2004;18:422-425.
3. Godin MS, Majmundar MV, Chrzanowski DS, Dodson KM. Use of Radiesse in combination with Restylane for facial augmentation. *Arch Facial Plast Surg* 2006;8:92-97.
4. Glaich AS, Cohen JL, Goldberg LH. Injection necrosis of the glabella: protocol for prevention and treatment after use of dermal fillers. *Dermatol Surg* 2006;32:276-281.
5. Beljaards ROBC, De Roos K-P, Bruins FG. NewFill for skin augmentation: a new filler or failure? *Dermatol Surg* 2005;31:772-777.
6. Berlin A, Cohen JL, Goldberg DJ. Calcium hydroxylapatite for facial rejuvenation. *Semin Cutan Med Surg* 2006;25:132-137.
7. Brian R, Toy PJF. Outbreak of mycobacterium abscessus infection after soft tissue augmentation. *Dermatol Surg* 2003;29:971-973.
8. Inoue K, Sato K, Matsumoto D, Gonda K, Yoshimura K. Arterial embolization and skin necrosis of the nasal ala following injection of dermal fillers. *Plast Reconstr Surg* 2008;121:127e-128e.
9. Jham BC, Nikitakis NG, Scheper MA, Papadimitriou JC, Levy BA, Rivera H. Granulomatous foreign-body reaction involving oral and perioral tissues after injection of biomaterials: a series of 7 cases and review of the literature. *J Oral Maxillofac Surg* 2009;67:280-285.
10. Leonhardt JMM, Lawrence NM, Narins RSM. Angioedema acute hypersensitivity reaction to injectable hyaluronic acid. *Dermatol Surg* 2005;31:577-579.
11. Fernández-Aceñero MJ, Zamora E, Borbujo J. Granulomatous foreign body reaction against hyaluronic acid: report of a case after lip augmentation. *Dermatol Surg* 2003;29:1225-1226.
12. Narins RSM, Jewell MM, Rubin MM, Cohen JM, Strobos JM. Clinical conference: management of rare events following dermal fillers-focal necrosis and angry red bumps. *Dermatol Surg* 2006;32:426-434.
13. Parada MB, Michalany NS, Hassun KM, Bagatin E, Talarico S. A histologic study of adverse effects of different cosmetic skin fillers. *Skinmed* 2005;4:345-349.
14. 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.
15. Stewart DB, Morganroth GS, Mooney MA, Cohen J, Levin PS, Gladstone HB. Management of visible granulomas following periorbital injection of poly-L-lactic acid. *Ophthal Plast Reconstr Surg* 2007;23:298-301.
16. Zielke H, Wölber L, Wiest L, Rzany B. Risk profiles of different injectable fillers: results from the injectable filler safety study (IFS Study). *Dermatol Surg* 2008;34:326-335.
17. Eppley BL, Dadvand B. Injectable soft-tissue fillers: clinical overview. *Plast Reconstr Surg* 2006;118:98e-106e.
18. Johl SS, Burgett RA. Dermal filler agents: a practical review. *Curr Opin Ophthalmol* 2006;17:471-479.
19. Murray CA, Zloty D, Warshawski L. The evolution of soft tissue fillers in clinical practice. *Dermatol Clin* 2005;23:343-363.
20. Rohrich RJ, Rios JL, Fagien S. Role of new fillers in facial rejuvenation: a cautious outlook. *Plast Reconstr Surg* 2003;112:1899-1902.
21. Beasley KL, Weiss MA, Weiss RA. Hyaluronic acid fillers: a comprehensive review. *Facial Plast Surg* 2009;25:86-94.
22. Bogdan Allemann I, Baumann L. Hyaluronic acid gel (Juvederm) preparations in the treatment of facial wrinkles and folds. *Clin Interv Aging* 2008;3:629-634.
23. Cosmetic Surgery National Data Bank Statistics. 2007. Available at: *http://www.cosmeticplasticsurgerystatistics.com/statistics.html#*

24. Owens JM. Soft tissue implants and fillers. *Otolaryngol Clin North Am* 2005;38:361-369.
25. Cockerham K, Hsu VJ. Collagen-based dermal fillers: past, present, future. *Facial Plast Surg* 2009;25:106-113.
26. Friedman PM, Mafong EA, Kauvar AN, Geronemus RG. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. *Dermatol Surg* 2002;28:491-494.
27. Klein AW. Skin filling: collagen and other injectables of the skin. *Dermatol Clin* 2001;19:491-508.
28. Shoshani D, Markovitz E, Cohen Y, Heremans A, Goldlust A. Skin test hypersensitivity study of a cross-linked, porcine collagen implant for aesthetic surgery. *Dermatol Surg* 2007;33(suppl 2):S152-S158.
29. Narins RS, Brandt FS, Lorenc ZP, Maas CS, Monheit GD, Smith SR. Twelve-month persistency of a novel ribose-cross-linked collagen dermal filler. *Dermatol Surg* 2008;34(suppl 1):S31-S39.
30. Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M, Smith S. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg* 2003;29:588-595.
31. Dinehart SM, Henry L. Dietary supplements: altered coagulation and effects on bruising. *Dermatol Surg* 2005;31:819-826, discussion 826.
32. Khalifeh MR, Redett RJ. The management of patients on anticoagulants prior to cutaneous surgery: case report of a thromboembolic complication, review of the literature, and evidence-based recommendations. *Plast Reconstr Surg* 2006;118:110e-117e.
33. Ong AT, Hoye A, Aoki J, et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J Am Coll Cardiol* 2005;45:947-953.
34. Silber S, Albertsson P, Aviles FF, et al; Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology [see comment]. *Eur Heart J* 2005;26:804-847.
35. King SB III, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 writing group to review new evidence and update the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention, writing on behalf of the 2005 writing committee [erratum appears in *Circulation* 2008;117:e161]. *Circulation* 2008;117:261-295.
36. Stone GW, Aronow HD. Long-term care after percutaneous coronary intervention: focus on the role of antiplatelet therapy. *Mayo Clin Proc* 2006;81:641-652.
37. Zimarino M, Renda G, De Caterina R. Optimal duration of antiplatelet therapy in recipients of coronary drug-eluting stents. *Drugs* 2005;65:725-732.
38. Douketis JD, Berger PB, Dunn AS, et al; American College of Chest Physicians. The perioperative management of antithrombotic therapy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:299S-339S.
39. Calfee DP, Farr BM. Comparison of four antiseptic preparations for skin in the prevention of contamination of percutaneously drawn blood cultures: a randomized trial. *J Clin Microbiol* 2002;40:1660-1665.
40. Reichel M, Heisig P, Kohlmann T, Kampf G. Alcohols for skin antisepsis at clinically relevant skin sites. *Antimicrob Agents Chemother* 2009;53:4778-4782.
41. Soothill JS, Bravery K, Ho A, Macqueen S, Collins J, Lock P. A fall in bloodstream infections followed a change to 2% chlorhexidine in 70% isopropanol for catheter connection antisepsis: a pediatric single center before/after study on a hemopoietic stem cell transplant ward. *Am J Infect Control* 2009;37:626-630.
42. Donald LM, Naomi POG. Guidelines for the prevention of intravascular catheter-related infections: recommendations relevant to interventional radiology. *J Vasc Interv Radiol* 2003;14:S355-S358.
43. Moskowitz SM, Foster JM, Emerson J, Burns JL. Clinically feasible biofilm susceptibility assay for isolates of Pseudomonas aeruginosa from patients with cystic fibrosis. *J Clin Microbiol* 2004;42:1915-1922.
44. Alam M, Yoo SS. Technique for calcium hydroxylapatite injection for correction of nasolabial fold depressions. *J Am Acad Dermatol* 2007;56:285-289.
45. Lam SM, Azizzadeh B, Graivier M. Injectable poly-L-lactic acid (Sculptra): technical considerations in soft-tissue contouring. *Plast Reconstr Surg* 2006;118:55S-63S.
46. Cohen JL. Understanding, avoiding, and managing dermal filler complications. *Dermatol Surg* 2008;34(suppl 1):S92-S99.
47. Donald WB, Murad A, John YSK. Injectable fillers for facial rejuvenation: a review. *J Plast Reconstr Aesthetic Surg* 2009;62:11-18.
48. Lemperle G, Rullan PP, Gauthier-Hazan N. Avoiding and treating dermal filler complications. *Plast Reconstr Surg* 2006;118:92S-107S.
49. Lemperle G, Romano JJ, Busso M. Soft tissue augmentation with Artecoll: 10-year history, indications, techniques, and complications. *Dermatol Surg* 2003;29:573-587.
50. Arlette JP, Trotter MJ. Anatomic location of hyaluronic acid filler material injected into nasolabial fold: a histologic study. *Dermatol Surg* 2008;34(suppl):S56-S62.
51. Buck DW II, Alam M, Kim JY. Injectable fillers for facial rejuvenation: a review. *J Plast Reconstr Aesthetic Surg* 2009;62:11-18.
52. Narins RS, Bowman PH. Injectable skin fillers. *Clin Plast Surg* 2005;32:151-162.
53. Werschler WMP. Advanced injection techniques of poly-L-lactic acid: a case-based presentation. *Dermatol Ther* 2007;20(suppl):S16-S19.
54. Kusin S, Lippitz J. Skin fillers. *Dis Mon* 2009;55:236-256.
55. Nicolau PJ. Long-lasting and permanent fillers: biomaterial influence over host tissue response. *Plast Reconstr Surg* 2007;119:2271-2286.
56. Hirsch RJ, Carruthers JD, Carruthers A. Infraorbital hollow treatment by dermal fillers. *Dermatol Surg* 2007;33:1116-1119.

57. Hirsch RJ, Narurkar V, Carruthers J. Management of injected hyaluronic acid induced Tyndall effects. *Lasers Surg Med* 2006;38:202-204.
58. Brody HJ. Use of hyaluronidase in the treatment of granulomatous hyaluronic acid reactions or unwanted hyaluronic acid misplacement [erratum appears in *Dermatol Surg* 2008;34:135]. *Dermatol Surg* 2005;31:893-897.
59. Beer KR. Radiesse nodule of the lips from a distant injection site: report of a case and consideration of etiology and management. *J Drugs Dermatol* 2007;6:846-847.
60. Rohrich RJ, Ghavami A, Crosby MA. The role of hyaluronic acid fillers (Restylane) in facial cosmetic surgery: review and technical considerations. *Plast Reconstr Surg* 2007;120:41S-54S.
61. Carruthers JD, Carruthers A. Facial sculpting and tissue augmentation. *Dermatol Surg* 2005;31:1604-1612.
62. Glogau RG, Kane MA. Effect of injection techniques on the rate of local adverse events in patients implanted with nonanimal hyaluronic acid gel dermal fillers. *Dermatol Surg* 2008;34(suppl 1):S105-S109.
63. Cohen JL, Brown MR. Anatomic considerations for soft tissue augmentation of the face. *J Drugs Dermatol* 2009;8:13-16.
64. Broder KW, Cohen SR. ArteFill: a permanent skin filler. *Expert Rev Med Devices* 2006;3:281-289.
65. Stolman LP. Human collagen reactions. *Dermatol Surg* 2005;31:1634.
66. Nijhawan RI, Cohen JL, Kaufman J. Persistent erythema after human collagen injections. *Cosmetic Dermatol* 2008;21:90-94.
67. 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.
68. Schanz S. Arterial embolization caused by injection of hyaluronic acid (Restylane). *Br J Dermatol* 2002;146:928-929.
69. Lemperle G, Gauthier-Hazan N, Wolters M, Eisemann-Klein M, Zimmermann U, Duffy DM. Foreign body granulomas after all injectable dermal fillers: Part 1. Possible causes. *Plast Reconstr Surg* 2009;123:1842-1863.
70. Bentkover SH. The biology of facial fillers. *Facial Plast Surg* 2009;25:73-85.
71. Christensen L, Breiting V, Janssen M, Vuust J, Hogdall E. Adverse reactions to injectable soft tissue permanent fillers. *Aesthetic Plast Surg* 2005;29:34-48.
72. Christensen L. Normal and pathologic tissue reactions to soft tissue gel fillers. *Dermatol Surg* 2007;33(suppl 2):S168-S175.
73. Hamilton DG, Gauthier N, Robertson BF. Late-onset, recurrent facial nodules associated with injection of poly-L-lactic acid. *Dermatol Surg* 2008;34:123-126, discussion 126.
74. Woerle B, Hanke CW, Sattler G. Poly-L-lactic acid: a temporary filler for soft tissue augmentation. *J Drugs Dermatol* 2004;3:385-389.
75. Butterwick K, Lowe NJ. Injectable poly-L-lactic acid for cosmetic enhancement: learning from the European experience. *J Am Acad Dermatol* 2009;61:281-293.
76. Burgess CM, Quiroga RM. Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy. *J Am Acad Dermatol* 2005;52:233-239.
77. Lowe NJ, Maxwell CA, Patnaik R. Adverse reactions to dermal fillers: review. *Dermatol Surg* 2005;31:1616-1625.
78. Vleggaar D. Soft-tissue augmentation and the role of poly-L-lactic acid. *Plast Reconstr Surg* 2006;118:46S-54S.
79. Borelli C, Kunte C, Weisenseel P, Thoma-Greber E, Korting HC, Konz B. Deep subcutaneous application of poly-L-lactic acid as a filler for facial lipoatrophy in HIV-infected patients. *Skin Pharmacol Physiol* 2005;18:273-278.
80. Salles AG, Lotierzo PH, Gimenez R, Camargo CP, Ferreira MC. Evaluation of the poly-L-lactic acid implant for treatment of the nasolabial fold: 3-year follow-up evaluation. *Aesthetic Plast Surg* 2008;32:753-756.
81. Holzapfel AM, Mangat DS, Barron DS. Soft-tissue augmentation with calcium hydroxylapatite: histological analysis. *Arch Facial Plast Surg* 2008;10:335-338.
82. Alcalay J, Alkalay R, Gat A, Yorav S. Late-onset granulomatous reaction to Artecoll. *Dermatol Surg* 2003;29:859-862.