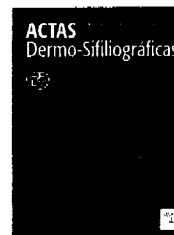




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REVIEW

Dermal Fillers: Types, Indications, and Complications

I. Sánchez-Carpintero,* D. Candelas, and R. Ruiz-Rodríguez

Unidad de Dermatología, Clínica Rúber, Madrid, Spain

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Dermal fillers;
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Hyaluronic acid;
Collagen;
Poly-L-lactic acid;
Calcium
hydroxylapatite

Abstract

There are many types of dermal fillers currently used for cosmetic and medical indications in routine clinical practice. Fillers can be classified as temporary, semipermanent, or permanent depending on the length of time the substance remains in tissue. They can also be classified by the composition of the product. Materials can be based on collagen (bovine, porcine, and human), hyaluronic acid, poly-L-lactic acid, calcium hydroxylapatite, polymethyl methacrylates, and polyacrylamide gels, among others. Temporary fillers are the products most often used for cosmetic purposes, in particular hyaluronic acid. This is due to the ease of application of fillers based on this substance, the good results obtained, and their safety profile. This review presents an overview of the techniques used for the correct placement of dermal fillers and the most common clinical indications for these procedures. It also covers the nature, properties, and mechanisms of action of the principal temporary, semipermanent, and permanent dermal fillers as well as the indications for each type of material. Finally, we describe the most common complications encountered and their treatment.

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PALABRAS CLAVE

Material de relleno;
Rejuvenecimiento;
Ácido hialurónico;
Colágeno;
Ácido poliláctico;
Hidroxiapatita
de calcio

Materiales de relleno: tipos, indicaciones y complicaciones

Resumen

Existen numerosos materiales de relleno utilizados en la práctica clínica diaria con fines cosméticos y médicos. Se pueden clasificar, en función de su duración en el tejido, en temporales, semipermanentes y permanentes. También pueden clasificarse de acuerdo con la composición del relleno: colágeno (bovino, porcino y humano), ácido hialurónico, ácido poliláctico, hidroxiapatita de calcio, polimetilmetacrilatos y geles de poliacrilamida, entre otros. Los rellenos temporales son los más empleados con fines estéticos, especialmente el ácido hialurónico. Este hecho se debe al perfil de seguridad que tienen, a la facilidad en su aplicación y a los buenos resultados encontrados. En esta revisión se exponen las diferentes técnicas descritas para su colocación correcta y las indicaciones

*Corresponding author.

E-mail address: ignacio@ricardoruiz.es (I. Sánchez-Carpintero).

clínicas más frecuentes. También se describe la naturaleza, las propiedades, los mecanismos de acción y las indicaciones de los principales materiales de relleno, tanto temporales como semipermanentes o permanentes. Finalmente se describen las complicaciones más comunes y su tratamiento.

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Introduction

Many types of dermal fillers are currently used in routine clinical practice for cosmetic and medical purposes. The different types of materials on the market and the brand names of some of the most widely used products are shown in Table 1. Not all dermal fillers are approved for cosmetic use. In many cases, European and American regulations differ. The main indication for these products in dermatology is facial rejuvenation. Medical indications, such as for facial lipatrophy, are less common.

Depending on the length of time they remain in tissue, dermal fillers are classified as temporary, semipermanent (when the longevity is at least 18 months), or permanent. They can also be classified by product composition. Primary ingredients include collagen (bovine, porcine, or human),

animal or synthetic hyaluronic acid (HA), poly-L-lactic acid, calcium hydroxylapatite, polymethyl methacrylate, and polyacrylamide gel.^{1,3} The differences between these types of fillers are in their diverse modes of action and the length of time the filler material remains in tissue before it is absorbed. Temporary fillers are the type most often used for cosmetic purposes and there is a logical explanation for this choice. Aging is a dynamic process, making it inadvisable to permanently correct a defect at a specific point in time. The best strategy is to apply fillers as necessary to deal with the signs of aging as they appear. According to data published by the American Society of Aesthetic Plastic Surgery, more than 85% of dermal filler procedures are performed with HA derivatives.⁴ The widespread use of this type of filler is due to its excellent safety profile, ease of application, and the good results achieved.

Table 1 Types of Dermal Fillers and Some of the Commercially Available Products of Each Type

Material	Brand Name	Duration and Biodegradability
Autologous fat		Temporary and biodegradable
Hyaluronic acid	<i>Restylane</i> ®, <i>Restylane Perlane</i> ®, <i>Restylane Lipp</i> ®, <i>Restylane Touch</i> ®, <i>Restylane Vital</i> ® <i>Macrolane</i> ® 20, 30 <i>Juvederm Ultra 1, 2, 3</i> ®, <i>Juvederm Voluma</i> ® <i>Hylaform</i> ®, <i>Hylaform Plus</i> ®, <i>Hylaform Finesline</i> ® Others: <i>Rofilan Forte</i> ®, <i>Matridur</i> ®, <i>Puragen</i> ®, <i>Glytone</i> ®, <i>Isogel</i> ®, <i>Prevelle</i> ®, etc	Temporary and biodegradable
Collagen	<i>Zyplast</i> ®/ <i>Zyderm</i> ® (bovine) <i>Cosmoderm</i> ®/ <i>Cosmoplast</i> ® (human) <i>Evolence</i> ®, <i>Permacol</i> ®, <i>Fibroquel</i> ® (porcine)	Temporary and biodegradable
Calcium hydroxylapatite	<i>Radiesse</i> ®	Semipermanent and biodegradable
Poly-L-lactic acid	<i>Sculptra</i> ®/ <i>New Fill</i> ®	Semipermanent and biodegradable
β-tricalcium phosphate with hyaluronic acid	<i>Atlean</i> ®	Semipermanent and biodegradable
Polyacrylamide gel	<i>Aquamid</i> ® <i>Bio-Alcamid</i> ®	Permanent and not biodegradable
Polymethyl methacrylate	<i>Arteplast</i> ®, <i>Artecoll</i> ®, <i>Artefill</i> ® <i>Dermalive</i> ®/ <i>Dermadeep</i> ®	Semipermanent and not biodegradable
Dimethylsiloxane polymers	Silicone	Permanent and not biodegradable

The first section of this review is a description of the techniques used to inject dermal fillers. We then go on to discuss the most common indications for these materials and their less common uses. The following section describes the principal temporary, semipermanent, and permanent dermal fillers, with a review of the nature, properties, mode of action, and indications of each one. A number of dermal fillers only recently launched on the market are also included. Finally, we describe the most common complications and their treatment.

Injection Techniques for Dermal Fillers

Pretreatment Preparation and General Recommendations

Pretreatment preparation is important to minimize risks and unwanted side effects. Patients must be properly informed to ensure that their expectations are realistic. Written informed consent must always be obtained, and pretreatment photographs should be obtained when possible. A complete medical history is always necessary and should cover allergic or hypersensitivity reactions to any substance, including anesthetics. Dermal fillers are contraindicated during pregnancy and breastfeeding and are not recommended in immunocompromised individuals, patients with autoimmune diseases or receiving certain drugs, such as interferon.⁵ Patients should be instructed not to take any medication that might increase the risk of bleeding during the 10 to 14 days prior to treatment. Nonsteroidal anti-inflammatory drugs and vitamin complexes containing vitamin E should also be avoided.⁶ Permanent and semi-permanent fillers should not be used in individuals with a history of keloid or hypertrophic scars. A skin allergy test prior to treatment is only necessary when bovine collagen fillers are used. Particular attention must be paid to avoiding overcorrection. The strategy of many authors is to carry out an initial treatment session followed by a second visit a few weeks later to refine the results and achieve the desired final outcome. Topical anesthetics or a nerve block will be used depending on the patient's pain threshold. Some dermal fillers contain lidocaine, which helps the patient to tolerate the injections.

Injection Techniques

A certain amount of practice and experience is required to inject dermal fillers. It is essential to choose the filling agent best suited to each patient and anatomical site, and to determine the appropriate amount of filler to be injected. Another crucial aspect in achieving a good outcome with dermal fillers is the depth at which the material is implanted. Most dermal fillers are injected into the deep dermis or the fatty tissue.⁷ A number of different injection techniques have been described.⁸

Linear Threading or Tunneling

In the linear threading technique the needle is introduced along the length of the fold or line and a thread of filler is

then gradually deposited as the needle is withdrawn. This technique is mainly used to correct isolated rhytides or folds, such as the nasolabial fold.

Serial Puncture

Serial puncture involves multiple injections along the wrinkle or fold. These must be placed close enough together to prevent irregularities, and massaging the area will help to distribute the product evenly.

Radial Fanning

In the radial fanning technique, threads of filler are deposited using the tunneling technique. However, before the needle is completely withdrawn, it is reinserted in a radial pattern and another thread is deposited along the new axis. This is repeated as necessary until the desired effect is achieved. This technique is used to augment volume in the malar region.

Crosshatching

Crosshatching is another variation on the tunneling technique. Several parallel lines of filler are created across the treatment area followed by a second set of parallel threads perpendicular to the first set forming a grid pattern. This technique is used to correct marionette lines and the prejowl sulcus.

Indications for Dermal Fillers

The main indication for the use of dermal fillers is facial rejuvenation. Their use, often in combination with botulinum toxin injections, produces very satisfactory results with a very low incidence of side effects.⁹ Ideal subjects are patients with early signs of aging.

The nasolabial fold becomes accentuated with age, forming an increasingly pronounced furrow. In this area, dermal fillers should be injected deeply (Figure 1). The techniques most often used are tunneling and serial puncture. The injection is usually made parallel and medial to the fold, with the initial insertion point at the lower end. The desired effect can usually be achieved with 0.5 to 2 mL of filler per side.^{7,10}

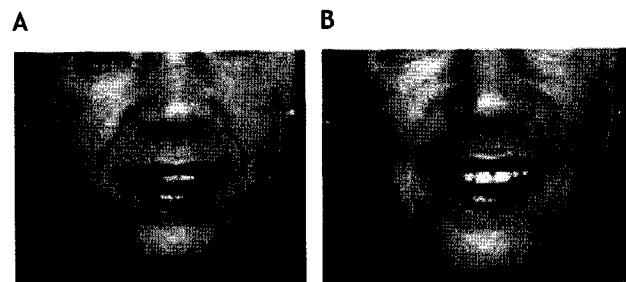


Figure 1 Patient treated with hyaluronic acid filler in the nasolabial folds before (A) and after (B) treatment. (Image supplied by Q-Med, Spain, S.L.).

Dermal fillers are also used to correct volume deficiencies and improve facial contours.⁸ Another area that can be improved is the tear trough located below the lower eyelid in the transition area between the eye and the malar region.¹¹ This deformity usually develops late in life as a result of herniation of the infraorbital fat pillows and flattening or sagging of malar fat. The loss of natural convexity between the lower eyelid and the malar region gives rise to a tired look and a more aged appearance, with the formation of a depression and an unsightly shadow. Tunneling and serial puncture are the preferred techniques for correcting tear trough deformity. Permanent fillers are not usually recommended for this purpose because poor technique can easily give rise to surface irregularities in this area. The initial insertion point is lateral and the needle is introduced in a medial direction. Filler should not be deposited closer than 2 to 4 mm from the nasal wall to avoid creating the appearance of a broad nose. To avoid eye damage, the injection should be made below the infraorbital rim. Filler is injected supraperiosteally, and a volume of 0.5 to 1 mL per side is usually sufficient. To augment the volume of the malar region and create a more convex appearance, the radial fanning technique is generally used to deposit 1 to 2 mL of filler in the subperiosteal plane. The injection is made a few millimeters from the lateral superior aspect of the malar eminence.

Considerable improvement can also be achieved in the perioral region, in particular in the lips, marionette lines, and prejowl sulcus (Figure 2).⁸ In young patients, increased volume in the central part of the lips is all that is needed. The filler is injected into the lip mucosa along the transition line between mucosal tissue and skin. The outline of the cupid's bow can also be improved. Temporary fillers are usually used for this purpose (Figure 3). The injection techniques used are tunneling and serial puncture. The filler should be injected into the submucosa above the orbicularis oris muscle. If the patient wishes to enhance the transition between the mucosa and the skin, the needle should be introduced into the space between the vermilion and white parts of the lip to deposit the filler. When the needle is correctly positioned, filler can be injected without resistance and elevation of the edge of the lip is immediately apparent. The overall appearance of the lips can be enhanced by shaping the philtral columns through injection of filler into the mid dermis starting from the base of the columns. In older patients, the entire length of the lip must be

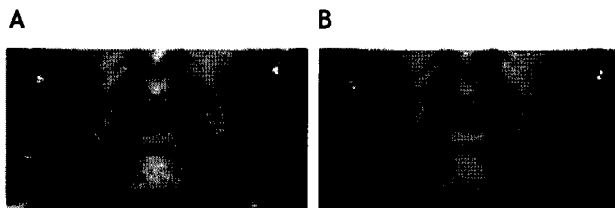


Figure 2 Patient treated with hyaluronic acid in the perioral region before (A) and after (B) treatment. (Image supplied by Q-Med, Spain, S.L.).

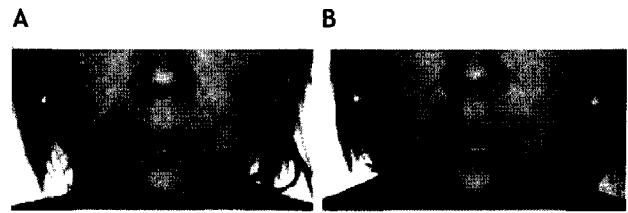


Figure 3 Patient treated with hyaluronic acid in the lips before (A) and after (B) treatment. (Image supplied by Q-Med, Spain, S.L.).

treated and the correction of vertical lip lines should also be considered. Since these lines are superficial, collagen filler is the recommended treatment. Another treatment option is to increase the volume of filler at the edge of the lips. Since this is where the vertical lines originate, they are reduced or become less visible when the lip is expanded.

Another indication for dermal fillers is the treatment of marionette lines, the folds that extend downwards from the corners of the mouth and give rise to an aged appearance and an unhappy expression. The injection techniques usually used in this case are tunneling and serial puncture. If the area is affected by an overall loss of volume, the crosshatching technique may also be used. Finally, the contour of the jaw line can become deformed over time as a result of bone resorption and sagging skin, giving rise to a shadow called the prejowl sulcus between the lower jaw and the chin. This area is often treated at the same time as the marionette lines. Dermal fillers can improve this defect, giving the patient a younger appearance by restoring the transition between the chin and the posterior jaw line. Between these 2 areas some 2 to 3 mL is normally injected.⁸

Nose remodeling with dermal fillers is a very attractive alternative to conventional surgery. The tip, bridge and root of the nose can all be projected or raised. Temporary fillers are normally used for this purpose. To prevent lateral spread of filler, the skin should be pinched during the procedure. The injections should be deep, and small volumes (0.5 to 1 mL) are usually sufficient to achieve the desired effect.¹²

The glabellar region is usually treated with a combination of filler and botulinum toxin.³ Once paralysis has been achieved, dermal filler can be used to correct persistent depressions. The use of fillers that must be injected into the deep dermis is not advisable in this area because of the possibility of serious complications, including cutaneous necrosis. Consequently, some authors recommend the exclusive use of fillers that are injected very superficially in this area.⁶

Dermal fillers can also be used in the periorcular region. Before any decision is made concerning the areas to be treated, an initial evaluation of the patient is essential. Candidate areas include the lower eyelids, the infraorbital groove, the upper eyelids, the brow, and the transition area between the glabellar region and the root of the nose. Some authors recommend the exclusive use of temporary fillers (such as HA) and, within this

group, the products with greater viscosity are preferred as this property facilitates better control of the dose and placement of the filler, and the incidence of inflammation and edema associated with treatment is lower.¹³ The filler should be injected deeply. The most common complications are overcorrection and the appearance of lumps, bruises, and localized edema. Only experienced practitioners should undertake this procedure because this is one of the most complicated and delicate treatment areas. Isolated cases of blindness following treatment have been reported, probably caused by poor technique.¹⁴ The likelihood of such a complication can be minimized by administering nerve block anesthesia with epinephrine, which produces vasoconstriction. The recommended technique is to use 30-gauge needles to slowly inject small amounts of filler.

Less Common Indications for Dermal Fillers

Scarring

Although, no studies in the literature have demonstrated any long-term benefits associated with the treatment of scars with dermal fillers, the injection of HA can improve the patient's appearance, especially in the case of atrophic acne scars. Small amounts of filler should be injected over a number of sessions.³ Good long-term results have also been reported with poly-L-lactic acid,¹⁵ and porcine collagen has also been used.¹⁶

Chin Shaping in Patients With Implants

In patients with chin implants, contouring with HA can improve the transition between the implant and the adjacent soft tissue. To obtain the best results, these treatments are usually combined with botulinum toxin treatment.³

Earlobe Treatment

With age, the earlobes tend to sag and create folds, and the injection of fillers such as HA can improve their appearance. The effects of treatment last longer in the earlobes than elsewhere, probably because it is metabolically inactive tissue that moves very little.³

Hand Rejuvenation

Hands can also be improved with dermal fillers, although this application is not very widespread. Stabilized HA fillers are a good choice.¹⁷ Other fillers that have been used in the hand include calcium hydroxylapatite¹⁸ and bovine collagen.¹⁹

Temporary Dermal Fillers

Autologous Fat

Subcutaneous fat is distributed across independent

compartments separated by fibrous septa. In the youthful face, the transition between these subcutaneous fat compartments is subtle, but aging gives rise to abrupt changes of contour between these spaces, whether due to loss of volume or fat misplacement. One example is orbital fat, which tends to herniate and create bags around the eyes. The use of the patient's own fat as a filler is a safe and natural method. One drawback of this technique is that it must be performed in an operating theater environment with local anesthesia and sedation; specific instruments and materials are also required. Fat is extracted from areas such as the thighs or abdomen using special cannulas. The harvested fat is then purified by centrifugation. Using a different type of cannula, the processed fat is then injected into the treatment areas depending on the needs of the patient (forehead, brow, cheeks, suborbital region, perioral areas, jaw line, etc). Fat is injected at different depths (subdermal, intramuscular, and subperiosteal) and in different quantities depending on the patient and the anatomical area treated.^{20,21} The longevity of injected autologous fat ranges from 8 months to several years.

Hyaluronic Acid

Under normal circumstances, HA is present in the human body as a component of the extracellular matrix. It is a polysaccharide (a glycosaminoglycan disaccharide composed of an alternating and repeating unit of D-glucuronic acid and N-acetyl-D-glucosamine) with hydrophilic properties (a very high affinity for attracting and binding water molecules).²² Owing to their hydrophilic properties, HA filler materials can achieve substantial soft tissue augmentation after injection. The initial filling effect is directly related to the volume of the exogenous HA injected, but it has been shown that HA also has an indirect effect in that, once deposited in the dermis, it activates the dermal fibroblasts.²³ HA is a temporary injectable filler. However, unlike collagen fillers, which only remain in tissue for a few weeks or months, HA can last for as long as 6 to 9 months or sometimes longer, depending on the type of HA filler used. When an appropriate volume is correctly placed, this material cannot be detected either visually or by palpation.

Most of the HA products on the market are synthetic, sourced from stabilized nonanimal HA. This makes pretreatment skin testing unnecessary since there is no possibility of an allergic reaction. To further its longevity in tissue, the HA is manipulated using a process called crosslinking that involves the use of substances such as divinyl sulfone, 1,2,7,8-diepoxyoctane, and butanediol-diglycidyl-ether. The differences between the types of HA on the market are due in part to the degree of crosslinking and the agent used in this process. Crosslinking modifies the solubility of HA, and the degree of crosslinking is directly related to the viscosity of the gel. Any allergic reaction produced by such products is thought to be caused by the agent used in the crosslinking process.²⁴

The main indications for some of the HA products most commonly used in clinical practice are listed below. There

are so many such products on the market that it would be impossible to mention all of them in this review.

Restylane

Restylane® (Sub-Q, Uppsala, Sweden) was the first HA product sold in the United States. The gel has a particle size of 400 µm. The areas that respond best to treatment with this product are the nasolabial folds, the lips, and the oral commissures. It can also be used for cheek augmentation and to improve deformities of the chin and prejowl sulcus. It is not generally recommended for the treatment of fine lines.

Perlane® or Restylane Perlane®

Perlane® (Sub-Q, Uppsala, Sweden), like Restylane®, is a stabilized HA of nonanimal origin. It has a larger particle size (1000 µm) and is used to treat moderate to severe rhytides and folds. The product contains 0.3% lidocaine.

Juvederm®

The chief advantage of Juvederm® (Allergan Inc, Santa Barbara, CA, USA) over Restylane® is that it is softer and produces fewer lumps in the skin when injected close to the surface. Juvederm is very useful for correcting slight or moderate nasolabial folds in patients with fine skin. It is also used for lip enhancement and to treat minor defects in facial contours. In general, this product is less well known than Restylane®.

Restylane Lipp®

Restylane Lipp® (Sub-Q, Uppsala, Sweden) is a compact and cohesive HA gel specifically designed for lip augmentation. The gel must be homogeneously distributed. Care should be taken not to inject excessive volume since the material cannot be effectively massaged or redistributed. The tunneling technique is usually used to inject this product, whose effect lasts about 12 months.

Other HA products on the market include Hylaform® (Allergan Inc, Santa Barbara, California, USA), Rofilan Hylan Gelv® (Rofil Medical International, Breda, Netherlands), AchHyal® (Tedec-Meiji Farma S.A. Madrid, Spain), Matridur® (Biopolymer, Siershahn, Germany), Hyal System® (Merz Pharma GmbH, Frankfurt, Germany), Puragen® (Mentor Corp, Santa Barbara, California, USA), and Restylane Vital® and Vital Light® (Sub-Q, Uppsala, Sweden), among others (Table 1).

Depending on the anatomical region and defect to be treated, it may be more appropriate to use one type of HA or another. For example, the following can be used in the nasolabial folds: Juvederm Ultra® or Ultra Plus®, Restylane®, Perlane®, and other HA products. The treatment of facial lines is generally more complex, and Juvederm Ultra® may be more useful in such cases. When the problem to be treated requires a more substantial increase in volume, such as very flat cheeks or the prejowl sulcus, an HA product with a harder gel, such as Restylane®, Perlane®, or Juvederm Ultraplus®,

is recommended. For areas that require remodeling with large volumes, Juvederm Voluma® may a better choice. In general, the different types of HA can also be used in patients with high phototypes (IV-V), since no complications have been reported in such cases.²⁵

Collagen Fillers

Collagen makes up 70% to 80% of the dermis. With age, dermal collagen is lost and becomes fragmented, as the transformation from new and complete collagen (type I) to fibrotic collagen (type III) gives rise to the appearance of rhytides and folds. Collagen fillers can be bovine, human or porcine in origin. One of the advantages of collagen fillers over HA is that they are less viscous and can be more useful for the correction of fine lines and wrinkles because they are less likely to produce irregularities when injected superficially.

Bovine Collagen

The 2 bovine collagen products most used are Zyderm® and Zyplast® (Allergan Inc, Santa Barbara, California, USA). Bovine collagen, a temporary and biodegradable filler, was the first collagen to be sold as a filler. Pretreatment skin testing is necessary. Some authors even recommend administering 2 skin tests separated by an interval of 2 to 4 weeks.²⁶ The incidence of local hypersensitivity reactions in patients tested prior to treatment is estimated to be between 3% and 5%. Zyderm® is indicated for superficial rhytides and Zyplast® for deeper rhytides or defects. Zyplast® should never be used in the glabellar region because cases of local cutaneous necrosis caused by intra-arterial injection of the product have been reported.²⁷ A shorter duration of effect in the treatment of nasolabial folds than that obtained with HA fillers has been reported.²⁸ These products remain in tissue between 2 and 6 months.

Human Collagen

Human collagen is produced from human dermal fibroblast cell lines using bioengineering techniques. No pretreatment skin test is required. The two most frequently used dermal filling products are Cosmoderm® and Cosmoplast® (Allergan Inc, Santa Barbara, USA). Both products are biodegradable and therefore temporary and have a duration of effect from 3 to 7 months.²⁹ Cosmoderm® is indicated for superficial and Cosmoplast® for deep rhytides or defects,¹ and both contain the anesthetic agent lidocaine. Collagen can also be obtained from the tissue of human cadavers.⁶ Products that contain collagen of human origin include Fascian® (Fascia Biosystems LLC, Los Angeles, CA, USA) and Cymetra® (LifeCell Corp, Branchburg, NJ, USA).

Porcine Collagen

Porcine collagen is also temporary and biodegradable and has a duration in tissue of around 12 months. A number of products on the market contain porcine collagen, including Evolence® and Evolence Breeze® (ColBar LifeScience,

Herzliya, Israel). The porcine collagen in these products is crosslinked using natural sugar, a technology called Glymatrix®. Collagen extracted from porcine tendons is broken down using enzymes and the crosslinking is then reconstituted using the Glymatrix® system. Since this proprietary technology does not involve the use of chemical crosslinking agents, it eliminates all potentially antigenic compounds that might induce allergic reactions. No pretreatment skin test is required. The particles are incorporated into the recipient tissue and neovascularization occurs. The product is broken down over time by enzymatic mechanisms. Another advantage of this type of filler is the low incidence of edema and hematomas following injection because of the hemostatic properties of collagen.³⁰ Other porcine collagen products on the market include Fibroquel® (Aspid, Mexico City, Mexico) and Permacol® (Tissue Science Labs, Aldershot, United Kingdom).

Evolve® is indicated for moderate to deep lines, wrinkles, and folds, and for the correction of contour defects. It is not used in the lips because of the possibility of nodule formation. Evolve Breeze® is used to fill fine lines and for lip enhancement. Although the information available is not extensive, it would appear that Evolve® is less immunogenic than bovine collagen. The studies in the literature show it to be a very safe dermal filler, at least for 1 year after implantation.³¹ From the clinical standpoint, some studies have reported that this product is more effective than bovine collagen in the treatment of nasolabial folds.³² However, no significant differences have been observed with respect to HA fillers.²⁸

Poly-L-lactic Acid

Poly-L-lactic acid is a temporary dermal filler composed of a biocompatible and biodegradable synthetic polymer. No pretreatment skin test is required. The only commercially available product of this type is marketed in the United States under the brand name Sculptra® (Dermik Laboratories, Berwyn, PA, USA) and in Europe as New Fill® (Sanofi Aventis, Paris, France). Poly-L-lactic acid belongs to the category of fillers that produce their effect by stimulating new collagen formation through fibroblast activation.³³ As a result, the volume increases in the treated area over time. This effect has been studied in a murine model and has been described in isolated cases in humans in series reported in the literature. The amount of collagen present has been found to continue to increase on follow-up at 3 and 6 months; after a longer interval, between 8 and 30 months, breakdown of the poly-L-lactic acid is observed but type I collagen continues to increase.³⁴ The poly-L-lactic acid continues to break down 9 to 24 months after its introduction. Degradation is not enzymatic but rather involves metabolism into water and carbon dioxide. The de novo collagen may, however, remain in tissue, and its presence has been detected up to 24 months after treatment.^{34,35} As the effect develops over a prolonged period, reinjection is not advisable when no immediate clinical effect is observed following initial treatment. The efficacy of this filler material in the treatment of facial

lipoatrophy in patients with human immunodeficiency virus (HIV) infection has been clearly established.³⁶ The cosmetic results are also satisfactory.^{34,37}

Calcium Hydroxylapatite

The calcium hydroxylapatite filler is Radiesse® (Bioform Medical, San Mateo, CA, USA), a product formerly marketed under the brand name Radianse FN®. Although Radiesse is a temporary filler, it has a longer duration of effect than either HA or collagen fillers, leading some authors to classify it as semipermanent.¹ Radiesse is composed of microspheres of synthetic calcium hydroxylapatite (a chemical composition identical to that found in teeth and bone) suspended in a water-based carboxymethyl cellulose gel carrier. The microspheres are very smooth and vary in size from 25 to 45 µm. As the product is totally biocompatible, no pretreatment skin test is required. In addition to the direct volumizing effect produced by the presence of the filler itself, this product also stimulates endogenous collagen production, an effect that can be observed months after treatment as a consequence of the attempts of macrophages to break down the calcium hydroxylapatite; macrophages have been observed to engulf the calcium hydroxylapatite microspheres.³⁸ This filler remains in tissue for as long as 1 year or even 18 months in some studies,⁴⁰ exceeding the longevity of HA. It is indicated for the correction of moderate to severe facial wrinkles and oral and maxillofacial defects and for the treatment of HIV-associated facial lipoatrophy. Radiesse is also used for radiographic tissue marking and vocal cord augmentation. The incidence of associated complications is low, and there are no reports of calcification or osteogenesis at injection sites.

Permanent Dermal Fillers

Polymethyl Methacrylate Microspheres

Polymethyl methacrylate microspheres can be suspended in either bovine collagen (Artecoll® and Artefill®) or HA (Dermalive® and Dermadeep®). The characteristics of each of these 2 types of dermal fillers are detailed below.

Polymethyl Methacrylate Microspheres in Bovine Collagen

The 2 most widely known fillers in this group are Artecoll®, a second generation product, and, more recently Artefill®, a third generation product. Arteplast®, the original polymethyl methacrylate filler, is no longer in use. Artefill® (Suneva Medical Inc, San Diego, CA, USA) is composed of polymethyl methacrylate microspheres suspended in a bovine collagen matrix mixed with 0.3% lidocaine. Consequently, pretreatment skin testing is required if this product is chosen. Artefill®, unlike the other polymethyl methacrylate products, has highly uniform microspheres and less than 1% of particles are smaller than 20 µm, a characteristic that gives rise to a lower rate of adverse effects compared to other

polymethyl methacrylate fillers.⁴¹ Once injected, the microspheres act as a matrix, stimulating the patient's own fibroblasts to produce collagen and encapsulate each microsphere. The bovine collagen, in addition to being the carrier of the polymethyl methacrylate microspheres, prevents the needle from becoming obstructed during injection and has the effect of stimulating the growth of tissue in which it is deposited. This product is mainly used as a filler for nasolabial folds.

Hydroxyethyl Methacrylate in Hyaluronic Acid

The products based on a combination of hydroxyethyl methacrylate and HA are Dermalive[®] and Dermadeep[®] (Dermatech, Paris, France). Dermalive[®] is a mixture of 60% crosslinked HA fluid produced by fermentation in bacterial culture and 40% hydroxyethyl methacrylate and ethyl methacrylate particles. The particles have an irregular surface and vary in size from 45 to 65 µm. This filler must be implanted in the deep dermis and is not indicated for the treatment of superficial rhytides. Dermadeep[®] must be implanted even more deeply, in the hypodermis or periosteum. The use of these materials is not very widespread because of the high incidence of associated adverse effects.

Polyacrylamide Gel

The 2 most widely known polyacrylamide gel products are Bio-Alcamid[®] and Aquamid[®]. Bio-Alcamid[®] (Polmekon, Milan, Italy) is composed of 96% water and 4% polyalkylimide. It is generally used for the treatment of deep defects. Aquamid[®] (Contura International, Copenhagen, Denmark) is a hydrogel, composed of 2.5% polyacrylamide and 97.5% water, that is not absorbed. This product is also used to correct deep defects. Since Aquamid has a high complication rate and its use is often associated with the formation of granulomas, its use is increasingly rare.² Other products in this group have different molecular weights and, therefore, different levels of viscosity. They include Interfall[®] (Interfall Ltd., Kiev, Ukraine), Formacryl and Argiform[®] (Bioform, Moscow, Russia), Outline[®] (ProCytech, Bordeaux, France), and Amazing Gel[®] (FuHua Ltd, ShenZhen, China).

Silicone

Injectable liquid silicone was one of the permanent fillers most used in the past. There are various products on the market, including Adato SIL-OL 5000[®] (Bausch & Lomb, Rochester, NY, USA), Silikon 1000[®] (Alcon Laboratories, Fort Worth, TX, USA), and SilSkin 1000[®] (Richard-James Development Corp, Peabody, MA, USA). There is also a product, marketed under the brand name Bioplastique[®] (Uroplasty BV, Netherlands), that consists of solid silicone particles suspended in a polyvinylpyrrolidone carrier. All these materials must be implanted in the deep dermis or on the dermis-panniculus adiposus plane. As well as affording an immediate effect due to the volume of the injected silicone, these products also induces the formation of fibroplasia in the long term. However, since complications

are frequent, these products are now rarely used for facial rejuvenation.

Other Permanent Products

Other permanent products on the market include Metacrill[®] (Nutricel Laboratories, Rio de Janeiro, Brazil), composed of polymethyl methacrylate spheres suspended in a carboxygluconate gel; Advanta[®] (Atrium Medical Corporation, NH, USA), containing expanded polytetrafluoroethylene; and Profill[®] (Laboratoires Filorga, Paris, France), composed of polyoxyethylene and polyoxypropylene.

New Dermal Fillers

Current research into new dermal fillers is focused on obtaining products with a longer duration of effect that provide better cosmetic results without complications. Some of the most recently developed fillers are discussed below.

Atlean[®]

Atlean[®], formerly marketed by ABR Development in France and currently owned by Stiefel Laboratories, is classified as a dermal filler and volumizer. It contains HA and tricalcium phosphate particles that are biodegradable and biocompatible and thus cause no allergic reactions. There is prior experience of this product in the literature related to its use in the regeneration of fractured bones. The HA component produces an immediate clinical effect and tissue subsequently forms around the particles, with formation of new collagen. Atlean is injected subcutaneously or supraperiosteally and has the advantage over other dermal fillers that the injection is less painful. The material remains in tissue from 12 to 15 months.³⁰ It is used in the nasolabial folds, marionette lines, facial contour remodeling, chin folds, cheekbone remodeling, and lipotrophy.

Laresse[®]

Laresse[®] (FzioMed, Inc, London, United Kingdom) is a biodegradable and biocompatible filler composed of a polymer of carboxymethyl cellulose and polyethylene oxide. It is used to treat nasolabial folds, marionette lines, and lip lines, and in cheek contouring. One of the advantages of Laresse over HA is that superficial injection of the product does not leave a blue discoloration. The material remains in tissue for about 6 months.³⁰

Easy Agarose[®]

Easy Agarose[®] (Dermacare Aps, Denmark) is a polymer composed of D-galactose and 3,6 anhydro-L-galactose. Two preparations are available: Easy Agarose L.D.[®] (low density) is used to treat superficial rhytides, and Easy Agarose H.D.[®] (high density) is used to treat deeper lines and folds and to correct volumes. The duration of action is 8 to 11 months.³⁰

Esthélis®

Esthélis® (Laboratorios Anteis, Geneva, Switzerland) is manufactured using cohesive polydensified matrix (CPM®) technology, a crosslinking process that produces a totally homogeneous, cohesive, and elastic HA gel of different densities. The 2 formulations of Esthélis® on the market differ in the degree of crosslinking and the percentage of high and low density areas. The AH CPM Basic® version has an HA concentration of 22.5 mg/mL and a high percentage of high density areas with double crosslinking, while AH CPM Soft® formulation has a lower concentration of HA (20 mg/mL) and a higher percentage of single crosslinking. The chief advantage of HA gels obtained using CPM® technology is their excellent dermal biointegration and the more natural clinical effect they obtain, including a certain lifting effect because the larger spaces in the dermis are filled with the high density part of the gel and the smaller interfibrillar spaces with the low density material. The risk of formation of aggregates is very low. AH CPM Basic® is injected into the reticular dermis and is indicated for deep lines, while AH CPM Soft® is implanted below the papillary dermis and is indicated for periocular lines.³⁰

Macrolane®

Macrolane® (Q-Med AB, Uppsala, Sweden) is a stabilized, biocompatible and resorbable HA product indicated for improving body contours and augmenting the volume of areas of larger dimensions. It is used to treat atrophic defects caused by liposuction and to correct concave body deformities. It is currently being used experimentally for breast tissue augmentation.³⁰ The product remains in tissue for approximately 12 months. The 2 available formulations are Macrolane 20® and Macrolane 30®, the latter having a higher density. The filler material must be implanted deeply in the subcutaneous or subperiosteal tissue. Large volumes of up to 120 mL are injected per treatment area.³⁰

Complications Associated with Dermal Fillers

Unlike permanent filler materials, temporary dermal fillers are associated with a very low incidence of complications.^{12,42} Most complications are mild and of limited duration. A potential complication common to all dermal fillers is an asymmetrical appearance caused by the injection of different amounts of material on either side. Each patient must be individually assessed because facial asymmetry may be present before treatment. Alternatively, one area may be overtreated or undertreated. As a general rule, undertreatment is preferable to overtreatment since the latter is more difficult to correct.

Complications Associated with Temporary Fillers

Complications that may appear immediately are local redness, inflammation, and bruising.^{6,42} Both erythema and edema are due to inflammation after trauma caused by the injections but may also be related to the

hygroscopic properties of the injected material. While erythema usually resolves within a few hours, edema may persist for 2 to 3 days. The risk of edema can be minimized by limiting the number of percutaneous punctures, by using anesthetics containing epinephrine, by applying ice or cold compresses after the procedure, and by avoiding treatments during menstruation.⁴³ Bruising is caused when a vessel is accidentally punctured by the needle or when pressure is exerted on the vessel by the filler. In many cases, bruising appears immediately after the injection; it resolves within 5 to 10 days. To reduce the incidence of this complication, it is important to have the appropriate side lighting and to clean the treatment area with alcohol. If a vessel breaks, immediate compression with a dressing on the area can reduce the size of the hematoma. Very rarely, a larger vessel may be punctured, making cauterization necessary. Some HA products incorporate an anesthetic, such as lidocaine. Owing to the vasodilator effect of this ingredient, such products may be associated with more bleeding and subsequent hematomas. In any case, none of these immediate complications will affect the final cosmetic result.

Another complication seen in the short and medium term is the presence of visible filler material in the form of whitish papules or palpable or visible nodules. This complication is usually caused by poor technique, when the filler material is injected very superficially. It has also been suggested that nodules may develop later as a result of local inflammation or an inflammatory foreign body response. Filler visibility occurs very rarely with HA formulations but may be associated with a bluish discoloration.⁴⁴ In the case of poly-L-lactic acid fillers, the incidence of nodules can be greatly reduced by reconstituting the product in at least 5 mL of sterile water at room temperature and leaving the preparation to stand for 2 hours before use.⁴⁵ The injection of small amounts of filler (0.1-0.2 mL at a time) using the tunneling technique is recommended. Some authors add 0.1% lidocaine with epinephrine to the filler, shaking the mixture just before injection.⁴⁶ Nodules may also appear after treatment with calcium hydroxylapatite, particularly in the lips, making the use of this type of dermal filler in the lips inadvisable.⁴⁷ All types of nodules can be treated by firmly massaging the tissue. If the problem does not resolve, nodules can be pricked with a needle and drained^{42,48} or injected with corticosteroids. If they persist despite these measures, systemic treatment with corticosteroids can be considered. Treatment with oral allopurinol has been shown to be effective in isolated cases.⁴⁹ If nodules should appear after treatment with an HA filler, hyaluronidase can be injected to attempt to eliminate them.⁵⁰ Hyaluronidase is sold by the following companies: Amphastar Pharmaceuticals (Amphadase; Rancho Cucamonga, CA, USA) and Ista Pharmaceuticals Inc (Vitrase; Irvine, CA, USA). In any case, most nodules are more palpable than visible, and they will resolve spontaneously without treatment. Surgical excision should only be used as a last resort.

It is not clear whether a hypersensitivity reaction can be produced by the implantation of temporary dermal

fillers or whether the complications observed are local irritations due to the volume of the product injected or poor placement of the filler material. Temporary fillers are generally biocompatible and rarely cause this type of reaction. HA has the best safety profile and very rarely gives rise to this complication. When such a reaction occurs it could be due to the crosslinking agent rather than HA. Isolated cases have been described of delayed hypersensitivity reactions characterized by inflammatory nodules, induration, and facial edema.⁵¹ In some studies, a localized cutaneous reaction has also been reported in humans following a skin test with HA.^{52,53} Finally, serum antibodies against certain types of HA have been found, although these have not been associated with any apparent clinical manifestations.⁵² Improvements in the processes used to purify the different types of HA have reduced the incidence of this type of reaction, making its occurrence highly unlikely.¹² Other fillers, such as bovine collagen, are associated with a high incidence of allergic reactions, making a prior skin test always necessary when these products are used.

Necrosis at the injection site is a rare but severe complication.^{6,54,55} It may occur when the material is injected into the angular artery of the nasolabial fold or the supratrochlear artery in the glabellar region. Compression of the supratrochlear vessels during injection of the filler could, hypothetically, minimize this complication. Since necrosis in the glabellar region has been reported after the implantation of bovine collagen²⁷ and calcium hydroxylapatite, the use of these materials in this region is not recommended. Exceptionally, isolated cases of necrosis with HA have been described.^{6,55} A violet discoloration and pain are immediately observed in the area and this is followed by subsequent erosion and ulceration. Because of its vasodilatory properties, topical nitroglycerin could reduce necrotic spread.^{6,42} If this complication occurs after injection of HA, hyaluronidase can be injected.⁵⁶ Subcutaneous injection of low molecular weight heparin has also been used successfully in a case of severe necrosis.⁵⁵

Other reported complications, such as headache, sinusitis, and respiratory symptoms, are difficult to relate to the use of dermal fillers. More infrequently, isolated cases have been reported of facial paralysis and collagen disease.⁴² One case in the literature reports generalized scleromyxedema, which took the form of a generalized papular eruption with thickening of the skin secondary to the injection of HA some 9 months earlier.⁵⁷ Infections caused by herpes simplex, local infections, changes in pigmentation, and small scars may occur at injection sites.¹² Antiherpetic prophylaxis is recommended only in patients undergoing lip treatment who have a history of recurrent herpes simplex.

Complications Associated With Permanent Dermal Fillers

Granulomatous reactions are much more frequent after treatment with permanent filler materials than following the use of temporary fillers; in the latter case granulomas only develop in exceptional cases (Figures 4 and 5). The development of granulomas may be delayed, for example

coming as late as 14 to 24 months after treatment with polymethyl methacrylate microspheres^{58,59} or the injection of methacrylate fillers, such as Dermalive.^{60,61} A granulomatous reaction can be defined as a chronic inflammatory response that appears at all injection sites at the same time at least 2 months after treatment; it can persist for at least a further 2 months.⁶² The real incidence of this complication is estimated to be about 0.1%.¹² Histologic findings can sometimes help to determine the type of filler used.⁶³ Reports describe various types of granulomas: cystic (palisading or inflammatory); edematous (lipogranuloma) and sclerosing.⁶² It appears that the development of these granulomas does not depend on the volume of material injected or the biocompatibility of the compound, but rather on its chemical properties, surface structure, and the greater or lesser presence of impurities.⁶² For example, granulomatous reactions are found more frequently in association with fillers that have an irregular surface, in which cases giant foreign body cells have been observed.⁶⁴ The dermis is known to be highly susceptible to immunogenic provocation, however,

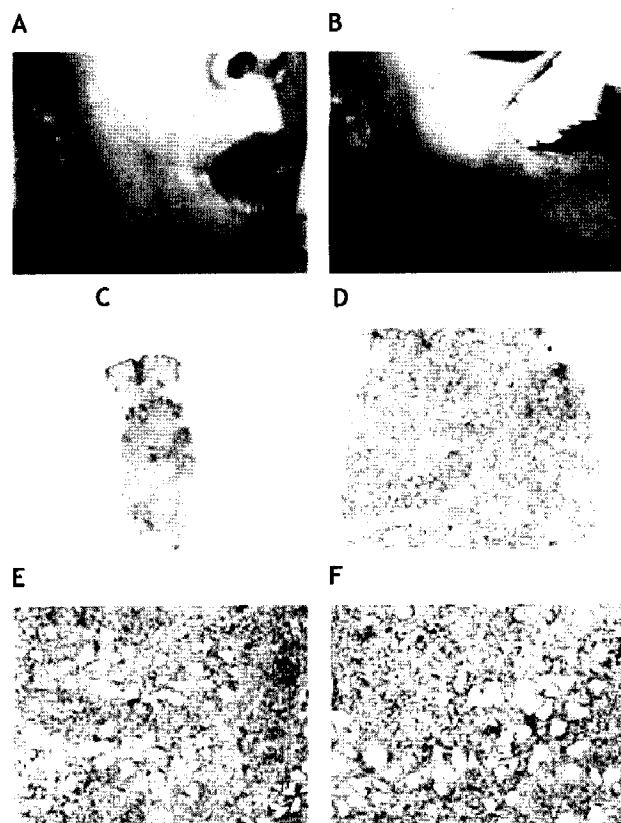


Figure 4 A and B, Patient with an intense inflammatory reaction caused by permanent dermal filler. C and D, The histologic hematoxylin-eosin stain reveals a granulomatous reaction with foreign body giant cells in the subcutaneous tissue (hematoxylin-eosin, original magnification $\times 1.25$, $\times 10$). E and F, Polygonal material can be seen, consistent with the presence of Dermalive deposits (hematoxylin-eosin, original magnification $\times 20$, $\times 40$).

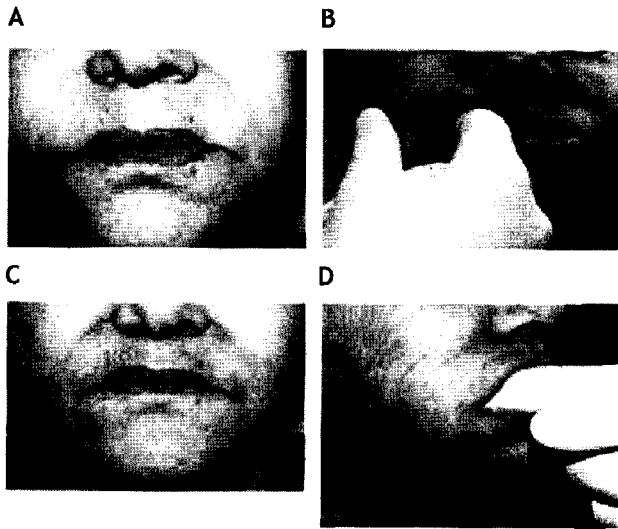


Figure 5 A and B, A patient who developed an intense inflammatory response a few months after treatment with a permanent dermal filler in whom the condition had not improved despite 3 years of treatment with oral corticosteroids. C and D, A very satisfactory response was obtained only 1 month after starting treatment with oral allopurinol.

meaning that the deeper the material is implanted, the less likely there is to be a granulomatous reaction.⁶² Although the pathogenesis is poorly understood, it has been reported that the development of granulomas is associated with the occurrence of a serious infection in the preceding months. It is therefore recommended that all patients with implants of permanent filler materials should take antibiotics during infections that develop in the 10 years following the implantation of the material.⁶²

The initial treatment for granulomas is intralesional injection of corticosteroids.⁶⁵ The number of treatments required will depend on individual response. In resistant cases, intralesional interferon can also be injected. Intralesional injection of 5-fluorouracil combined with betamethasone or triamcinolone has also been used.⁶⁶ Other treatment options include oral corticosteroids or oral antibiotics such as minocycline or doxycycline.⁶⁷ Other drugs that have been used successfully in isolated cases are allopurinol⁴⁹, colchicine,⁶⁸ and isotretinoin⁶⁹ (Figure 5). Since few patients have been treated, guidelines and specific recommendations are not available for these drugs in this setting. Surgical excision of granulomas is not recommended except as a last resort.⁶⁵

The incidence of complications associated with silicone fillers can be high when large quantities of material are used or the type of silicone used contains impurities. Cases of migration of the material to other areas of the body, cellulitis, and even death have been reported.⁷⁰ The microdroplet injection technique is recommended to minimize the complication rate. This technique involves the injection of 1 or 2 drops of the product into each one of a series of punctures. In a recent study of patients

with HIV-associated facial lipoatrophy, excellent results and no serious complications were reported using this technique.⁷¹

A final controversial question is whether exposure to certain laser or radiofrequency procedures could in some way affect injected dermal fillers. In one study no alteration of the properties or disposition of HA or calcium hydroxylapatite was observed when monopolar radiofrequencies were applied 2 weeks after injection of these fillers.⁷² Likewise, in another study using a variety of different laser and radiofrequency procedures following injection of HA dermal filler, no clinical or histologic changes were found.⁷³

Our Personal View

Dermal fillers, together with botulinum toxin treatment and certain laser procedures, have become key tools in the prevention and treatment of facial aging. An understanding of the nature of the different filler materials, their indications, and the associated complications and their respective treatments, is essential to the achievement of optimum results. To ensure a good result, treatment should always be individualized, precise indications should be established on a case-by-case basis, and the physician must inform the patient about the results that can realistically be achieved.

Dermal fillers have been used for many years to improve the appearance of lines and wrinkles by making two-dimensional changes. Today, we also use them to correct loss of volume in certain areas of the face. This volumizing effect is responsible for the increased use of fillers in recent years. Our experience with dermal fillers is aimed at achieving a natural result with few side effects. Consequently, of all the dermal fillers available to dermatologists, the material we use in most cases is HA in different densities. When facing industry pressure in this field, it is vital to follow the medical maxim that admonishes to "read up on the latest development but use the one just before that."

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