

Delayed-Onset Complications of Facial Soft Tissue Augmentation with Permanent Fillers in 85 Patients

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OBJECTIVE To evaluate factors influencing the onset and type of adverse events in patients injected with permanent fillers in the face and to propose a therapeutic strategy for these complications.

METHODS A prospectively attained series of 85 patients with delayed-onset complications after facial injection with permanent fillers underwent clinical follow-up and treatment of the complications.

RESULTS Lag times until onset and type of delayed-onset complication varied according to filler material. In 28% ($n = 24$) of the cases, patients reported the onset of complications after dental procedures, additional injections with fillers, or other invasive treatments in the facial area. Forty-eight (57%) patients required invasive treatment. Abscess formation was significantly more frequent in patients with human immunodeficiency virus infection and facial lipoatrophy ($p = .001$).

CONCLUSION The intrinsic characteristics of the injected filler and the immune status of the patient play important roles in the diversity of time of onset and type of delayed-onset adverse events observed. It seems that invasive facial or oral procedures in the vicinity of filler depots can provoke such complications. We propose a strategy for treating these complications and advise great caution when using permanent filling agents.

The authors have indicated no significant interest with commercial supporters.

In the past decade, permanent fillers have slowly gained a controversial reputation with regard to their safety.^{1–3} Although soft tissue fillers are generally regarded as having an impressive safety profile,^{4–6} numerous studies have been published describing potential adverse events after injection of permanent filler materials.^{1,6–29}

As originally proposed by Sclafani and colleagues, we categorized adverse events into one of three types: immediate-type (within 24 hours after injection of the filler), early-onset type (within 2 weeks), and delayed-type (starting after 2 weeks) complications.²⁹ This article describes 85 patients with delayed-onset complications after injections

with permanent filling materials. The majority of this cohort developed adverse events after injections with permanent fillers for esthetic reasons, although a substantial number had been treated for combination antiretroviral therapy (CART)-induced facial lipoatrophy. Table 1 depicts the currently available permanent soft tissue fillers and their potential complications as described in the literature.

Patients and Methods

Patient data

We performed a prospective case series study. From 2005 to 2011, 85 patients (40 male, 45

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TABLE 1. Currently Available Permanent Fillers and Their Complications As Reported in the Literature

<i>Filler Type</i>	<i>Brand Name and Manufacturer</i>	<i>Delayed-Onset Complications</i>	<i>Complication Rate,%</i>
Polymethylmethacrylate 20% plus bovine collagen 3.5%	Artecoll, ArteFill, Suneva Medical Inc., San Diego, CA	Persistent redness, telangiectasia, hypertrophic scarring, nodules, delayed granulomatous reactions	3
Hydroxyethylmethacrylate/ ethylmethacrylate	DermaLive, Dermatech, Paris, France	Indurations and nodules, discolorations, delayed granulomatous reactions	0.12–25
Polyacrylamide 2.5% gel	Aquamid, Contura International, Copenhagen, Denmark	Induration and nodules, infection, delayed granulomatous reactions, migration	6–21
Polyalkylimide 4% gel	Bio-Alcamid, Polymekon, Brindisi, Italy	Induration, infection and inflammation, abscesses, delayed granulomatous reactions, migration	3.3–4.8
Polymethylsiloxane (liquid injectable silicone)	Silikon 1000, Alcon Pharmaceuticals, Fort Worth, TX Adatosil 5000, Bausch & Lomb Surgical, San Dimas, CA	Induration and nodules, migration, inflammation, hyperpigmentation, delayed granulomatous reactions, cellulitis, scarring, ulceration	0.02–6

ArteFill is the only product that the Food and Drug Administration (FDA) has approved as a soft tissue filler (since 2006, for the nasolabial folds).

Preliminary results indicate that the risk of complications after injection with ArteFill appears to be lower than for Artecoll.⁶⁵

The FDA has approved Silikon and Adatosil for vitreoretinal surgery, but they are used off label for soft tissue augmentation.

female) with complications starting 2 weeks or more after injection of permanent filling agents were included. All patients were seen in our outpatient clinic. Some had been injected with more than one type of filler, in which case all injected fillers were listed. Five patients with CART-induced facial lipoatrophy had undergone research-related soft-tissue augmentation with polyalkylimide gel (PAIG) in our outpatient clinic in 2005.³⁰ All of the other patients had been treated with permanent filling agents elsewhere. Complications were categorized as noninflammatory nodules, low-grade inflammation, abscess formation, or migration. Noninflammatory nodules were defined as firm swellings or indurations lacking clinical features of inflammation such as erythema, edema, heat, tenderness, or pain. Low-grade inflammation was defined as redness,

swelling, tenderness, or pain at the site of injection, with a clinical presentation that intrinsically varied in severity. Nodules or indurations with evidence of inflammation were categorized as low-grade inflammation. Abscesses were defined as fluctuating swellings with redness, tenderness, or pain near the injection site. Migration was reported when filler material had moved from the site of injection. Age, sex, type of injected soft tissue filler(s), treatment indication, injection site(s), time to the onset of complications, type of complication(s), and complication-provoking or triggering factors were documented. Treatment of the complications was performed upon request by the patient. In the case of recurrent or persistent low-grade inflammation or abscess formation at or near a filler depot, surgical treatment (excision of filler material and incision and drainage of the

abscess, respectively) was performed, and bacterial cultures were obtained.

Statistical analysis

Data analysis was performed using SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL). The incidence of certain complications and treatment strategies in patients with the human immunodeficiency virus (HIV) with CART-induced facial lipoatrophy were compared with those of patients without HIV using the nonparametric Mann–Whitney *U* test for independent samples. A two-tailed *p* < .05 was chosen to indicate statistical significance.

Results

Of the 85 patients (mean age 54, range 27–79) enrolled in this study, 66 (78%) had delayed-onset complications after injections with PAIG (Bio-Alcamid). Other permanent filling agents used were hydroxyethylmethacrylate and ethylmethacrylate (HEMA/EMA, Dermalive; *n* = 8, 9%), polymethylmethacrylate (PMMA, Artecoll; *n* = 7, 8%), polyacrylamide hydrogel (PAAG, Aquamid) (*n* = 6, 7%), and liquid injectable silicone (LIS; *n* = 4, 5%). Some patients (*n* = 5) were injected with more than one permanent filler in the same area. The majority of the 85 patients underwent soft-tissue augmentation for facial rejuvenation (*n* = 51, 60%), whereas 40% (*n* = 34) had HIV and had been treated for

CART-induced facial lipoatrophy. The injection sites encountered were the glabellar area (*n* = 2), marionette lines (*n* = 3), forehead (*n* = 5), chin (*n* = 5), temporal region (*n* = 8), tear troughs (*n* = 9), perioral area and lips (*n* = 11), nasolabial folds (*n* = 19), and cheeks (*n* = 58). A number of patients had received injections at more than one site. Time until onset of complications varied from 1 month to 10 years (mean 38 months). The mean onset time according to type of filler was 10 months for PAAG (*n* = 5), 38 months for PAIG (*n* = 64) and for LIS (*n* = 3), 40 months for HEMA/EMA (*n* = 8), and 57 months for PMMA (*n* = 6). Onset times could not be determined in four cases.

The most common complications were low-grade inflammation (*n* = 34, 40%) and migration (*n* = 34, 40%), followed by noninflammatory nodules (*n* = 33, 39%; Figures 1 and 2). In 25 patients (29%), we observed abscess formation at the site of the filler depositions (Figure 3). Abscesses were observed only in patients who had been injected with PAIG (25/66, 38%), whereas the other types of complications were not restricted to a certain type of filler (Table 2). Some patients presented with more than one type of complication. Migration was predominantly seen in LIS (50%), PAIG (45%), and PMMA (43%). Nodules were mostly observed in HEMA/EMA (88%), PAAG (67%), and PAIG (30%). Low-grade inflammation was mainly seen in PMMA (57%), LIS (50%), and PAIG (38%).

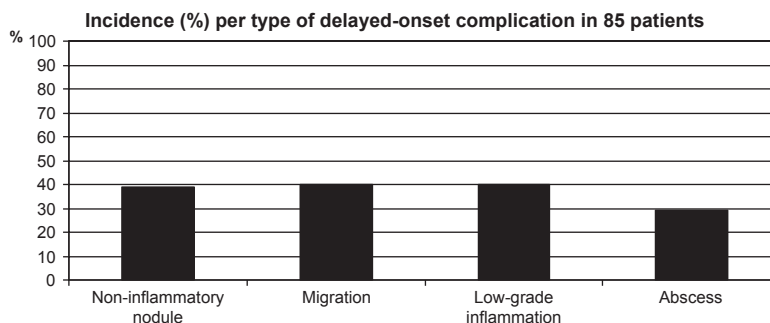


Figure 1. Type of delayed-onset complications in 85 patients. Most of the 85 patients presented to our outpatient clinic with low-grade inflammation and migration (both *n* = 34, 40%). Clinically noninflammatory granulomas occurred in 33 patients (39%), and abscesses were seen in 25 patients (29%). Some patients presented with more than one type of complication.

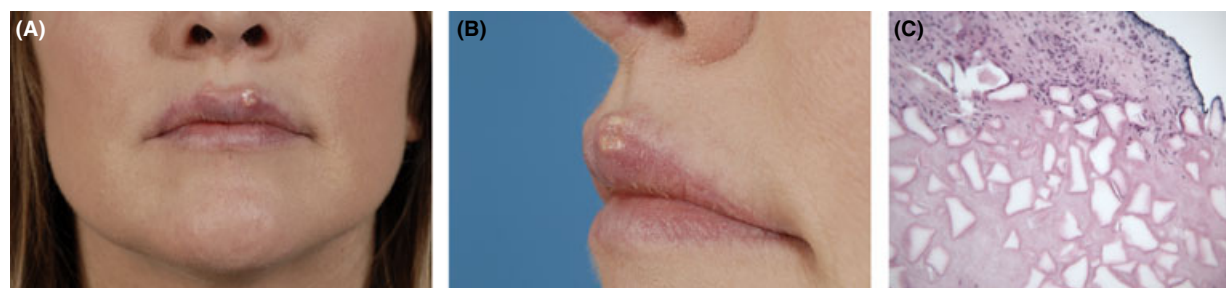


Figure 2. Nodule on the upper lip. A 42-year-old woman after injection of hydroxyethylmethacrylate and ethylmethacrylate (HEMA/EMA) in the lips for esthetic reasons. After 10 months, a clinically noninflammatory nodule appeared (A and B). This was treated with excision by direct surgical approach. (C) Histological appearance of “broken glass” particles corresponding to the HEMA/EMA filler material surrounded by an inflammatory response of mainly histiocytes.

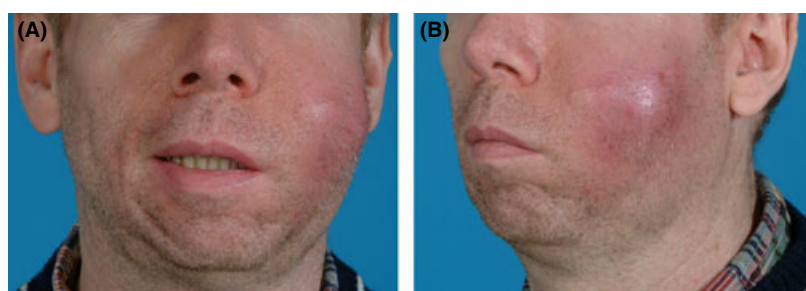


Figure 3. Abscess of the left cheek. A 55-year-old man with a fluctuating swelling of the left cheek. This complication occurred 18 months after injections of polyalkylimide gel for treatment of facial lipoatrophy, without an apparent provoking event. Bacterial cultures were positive for *Staphylococcus aureus* and *Streptococcus sanguinis*. Treatment was performed by incision and drainage under antibiotic therapy (see Figure 4).

TABLE 2. Incidence of Complications According to Filler Material in Our Patients

Filler Type	Noninflammatory Nodule N (%)	Low-Grade Inflammation	Abscess	Migration
Polyalkylimide gel	20 (30)	25 (38)	25 (38)	30 (45)
Polyacrylamide hydrogel	4 (67)	2 (33)	0 (0)	1 (17)
Polymethylmethacrylate	2 (29)	4 (57)	0 (0)	3 (43)
Hydroxyethylmethacrylate and ethylmethacrylate	7 (88)	2 (25)	0 (0)	1 (13)
Liquid injectable silicone	0 (0)	3 (75)	0 (0)	2 (50)

The majority of the complications appeared to occur spontaneously ($n = 61$, 72%), although 11 patients (13%) experienced the onset of complications after a visit to a dentist or oral hygienist. In 10 patients (12%), additional filler injections in the same area preceded the inflammatory response. In other cases, complications arose after blepharoplasty ($n = 2$) and tattooing of the eyebrows ($n = 1$).

Of the 85 patients seen in our outpatient clinic, five chose to be treated elsewhere; 48 of the 80

remaining patients (60%) required invasive treatment and underwent intralesional corticosteroid injections ($n = 3$) with 40 mg/mL of triamcinolone-acetonide, evacuation of the filling material using an 18-gauge needle ($n = 8$, including 3 patients with abscesses), excision of the filling material ($n = 17$), or incision and drainage of an abscess ($n = 20$; Figure 4). Two patients with abscesses were among the five treated elsewhere. Fifteen patients needed repetitive surgery in the same area because of recurrent or persisting complications, mostly

because of abscess formation in the PAIG group ($n = 10$). The use of intralesional corticosteroid injections was restricted to the treatment of noninflammatory nodules, because it was not suspected that pathogenic microorganisms caused these lesions. Of the patients receiving surgical treatment (evacuation with 18-gauge needle, excision of filler material, incision and drainage of an abscess), 69% (31/45) had a low-grade inflammation or an abscess. Twenty-four bacterial cultures were performed in this subgroup; cultures were sterile in 42% ($n = 10$). Seven of the 18 cultured abscesses did not show bacterial growth. Positive cultures identified *Staphylococcus aureus* ($n = 13$) as the predominant pathogen, followed by *Enterobacter aerogenes* ($n = 2$), *Streptococcus sanguinis* ($n = 1$), *Pseudomonas aeruginosa* ($n = 1$), *Escherichia coli* ($n = 1$), and *Streptococcus agalactiae* ($n = 1$).

Next, we studied differences in complications and treatment results between HIV-positive patients with CART-induced facial lipoatrophy and HIV-negative patients treated with fillers for esthetic reasons. Although only 40% ($n = 34$) of our patients were HIV-positive, they were over-represented in the subgroups with abscess formation (17/25, 68%, $p = .001$), in patients requiring surgical treatment

($n = 23/45$, 51%, $p = .03$), and in patients who needed repetitive surgery (10/15, 67%, $p = .02$; Figure 5). As noted previously, PAIG was the only filler associated with abscess formation. When comparing the incidence of abscesses in the 66 patients treated with PAIG, this complication still occurred more frequently in the HIV-infected subgroup (17/34 vs 8/32, $p = .04$).

Discussion

The use of permanent fillers for soft-tissue augmentation has been shown to be associated with adverse events, including delayed-onset complications such as described in our study.^{1,6-29} It has been more than a decade since Lemperle and colleagues stated that a foreign body immune-mediated reaction might occur with implants.³¹ Since then, several studies have hypothesized that minor trauma or low-grade infections may trigger a delayed pathologic immune reaction.^{32,33} This could explain the varying times of onset observed in our study. Granulomatous reactions to LIS have been shown to occur years to decades after injection.²²⁻²⁶ A significant variation in onset time has also been shown for complications with other types of fillers (Table 1).^{4,10,12-14,17-19,21,28} An explanation for the

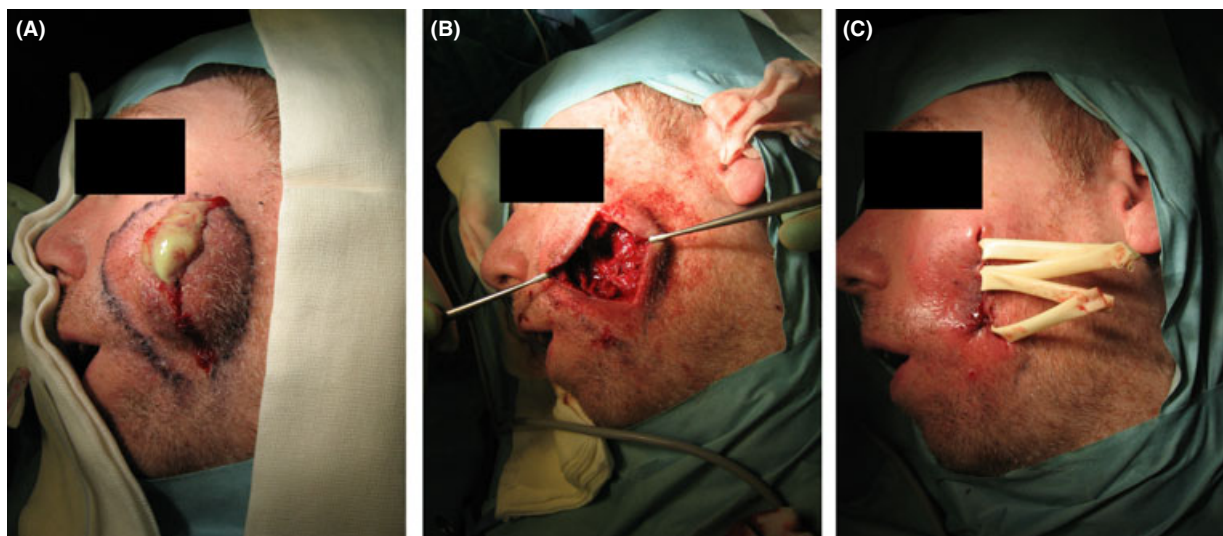


Figure 4. Incision and drainage of an abscess. Incision and drainage of an abscess of the left cheek in the patient described in Figure 3. A drain was left during wound closure (C). The patient received concurrent antibiotic treatment.

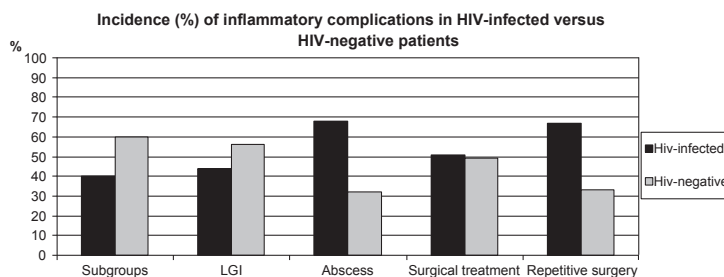


Figure 5. Higher incidence of inflammatory complications in human immunodeficiency virus (HIV)-positive patients. Although the HIV-positive subgroup constituted only 40% ($n = 34$) of our patient population, HIV-positive patients were significantly over-represented in the subgroups with abscess formation (68%, $n = 17/25$) and in the subgroups requiring surgery (51%, $n = 23/45$) or repetitive surgery (67%, $n = 10/15$).

observed variation in onset times between the different fillers remains to be elucidated. Different structural properties of the injectable fillers, such as chemical composition, electrical charge, surface irregularities, and particle size; the presence of contaminants; and implantation site may influence the onset and extent of complications.^{34,35} The possible role of “external” triggering factors will be discussed later in this section.

In this study the observed complications could be categorized into noninflammatory nodules, low-grade inflammation, abscesses, and migration. Nodules can have different origins. They can be caused by incorrect positioning of filler material, muscle induced displacement, capsular contraction or result from a granulomatous reaction to the filler depot.^{28,35} After injection, all filler materials induce some form of inflammatory reaction and fibrous capsule formation.^{35,36} Excessive capsule formation and capsular contraction are believed to be a patient-dependent entity instead of a filler-specific side effect.¹⁷ The trigger leading to the generation of foreign body granulomas is a matter of debate. Some authors postulate that all granulomatous reactions to fillers are delayed-type hypersensitivity reactions.¹⁴ Others believe that low-grade infections cause all delayed-onset complications, including foreign body granulomas, and that the intrinsic characteristics of the injected filler material mainly determine the type of complication that arises.^{1,37,38} Low-grade infections are defined as contaminated filler depots in which bacteria have

organized into a biofilm, having low bacterial activity, little host response, and high antibiotic resistance.^{38,39} “Activated” biofilms are thought to result in complications presenting as late-onset deeply erythematous and painful nodules.^{4,39} We preferred the term “low-grade inflammation” for such complications, because in most cases, cultures were not taken, and infection was not proven. A continuous foreign body reaction could also generate such inflammatory symptoms.^{35,38} Filler abscesses are almost exclusively found after injection with nonabsorbable hydrogel polymers, namely PAIG.^{17,18,28,38} The biocompatible nature of these filler materials is thought to make them suitable for bacterial contamination and infection, with potential secondary abscess formation.³⁸ Some authors, however, prefer to speak of pseudo-abscesses since bacterial cultures are often negative.¹⁹ In these cases, an immune-mediated hypersensitivity reaction is suggested as a possible provoking factor.^{19,40} Migration is thought to result from muscle- or gravity-induced displacement of the filler material.⁴¹ A deficient or absent fibrous capsule facilitates displacement of filler material, by micromigration within the directly surrounding tissue or remote macromigration.^{35,39,42} PAAG, PAIG, and LIS are specifically known for inducing little inflammatory reaction and thin fibrous capsules, which explains their migratory potential.^{35,43}

In our study, the risk of specific complications appeared to depend on the type of filler used. Noninflammatory nodules were observed mainly in

patients injected with HEMA/EMA and PAAG, whereas low-grade inflammation was mostly seen with PMMA and LIS. Migration was mostly observed in LIS and PAIG, whereas formation of abscesses occurred only after injection with PAIG. These results are in agreement with the literature, with nodules and granulomas being the most frequently reported delayed-type complication in HEMA/EMA, PMMA, PAAG, and LIS.^{8-12,14,16,25-28} As stated earlier, PAIG and LIS are known for their tendency to migrate from the original injection site.²⁰⁻²³ Low-grade inflammatory reactions are the most frequent complication of PAIG, but they are also seen with LIS and PMMA.^{10,20,21,43} Several studies have shown that PAIG is the principal filler material associated with abscess formation.^{17-21,28} Our results confirm the risk of abscess formation in patients injected with PAIG, including the particular risk of this complication occurring in HIV-positive patients with facial lipoatrophy. In addition, 87% of the recorded complications were associated with filler materials that the Food and Drug Administration had not approved (HEMA/EMA, PAAG, PAIG).

Although no particular events or other factors provoking delayed onset of complications could be defined in the majority of our patients, 24 (28%) had undergone a facial or oral invasive procedure before occurrence of the complication. Events preceding complications included dental treatment, blepharoplasty, and additional filler touch-ups. The exact mechanisms responsible for provoking complications after invasive procedures in the vicinity of filler depots is unknown, but it seems likely that bacterial contamination of the filler material plays a role. Several authors have suggested that delayed-onset complications could have occurred in response to earlier infections (e.g., bronchitis, sinusitis), (facial) injuries, or invasive treatments in the vicinity of the filler depots, thus adhering to the biofilm theory.^{1,4,5,17} The role of biofilm formation in (permanent) soft tissue fillers has been described previously.^{1,37-39,44-48} Biofilms are defined as a structured community of micro-organisms encapsulated within a self-developed matrix and

irreversibly attached to a living or inert surface. Biofilms are known to cause an impaired exposure to the immune system of the host and allow for up to 1,000 times greater resistance to antibiotics.⁴⁶ Once a biofilm has been established, it is said to be impossible to eradicate completely. Analogous to other prostheses and implants, soft tissue fillers (especially the long-lasting and permanent fillers) also have the potential for biofilm formation.^{1,37} The role of bacterial contamination of filler depots and biofilm formation gained even more interest after Bjarnsholt and colleagues demonstrated that bacteria could be detected in biopsies from culture-negative nodules using a combination of Gram-stain and fluorescence in situ hybridization.³⁷ *Staphylococcus aureus*, as well as other bacterial species found in our cultures such as *Streptococcus sanguinis*, *Pseudomonas aeruginosa* and *Escherichia coli*, have been identified within biofilms.^{44,47} Bacteria present in biofilms may persist in a dormant state for a long time.⁴⁴⁻⁴⁷ It has been suggested that they emerge from their biofilm after activation by an external triggering factor such as trauma or manipulation and cause low-grade infections, resulting in granulomas and abscesses.⁴⁴⁻⁴⁷ Some studies have shown that invasive introduction of bacteria is not necessary to cause contamination of deeper tissues.^{1,49,50} They suggest that commensal bacteria present in hair follicles, sebaceous glands, sweat glands, lacrimal glands, or lactiferous glands can penetrate deeper, underlying tissues. Biofilms pose a problem in the treatment of delayed-onset adverse events. They can be difficult to establish and are resistant to antibiotic treatment. Steroid treatment has also been shown to promote the development of a bacterial biofilm community within PAAG if not treated simultaneously with antibiotics directed specifically against the biofilm bacteria.³⁷ Therefore, supporters of the biofilm theory advise restraint in treatment of filler complications with corticosteroids or nonsteroidal anti-inflammatory drugs and advocate for the use of real-time polymerase chain reaction as part of the standard laboratory examination when the presence of a biofilm is suspected.^{37,44,45} Not all authors are convinced of the supposedly major role of biofilms in

filler-related adverse events. Some are of the opinion that detection of a few bacteria on histologic slides is insufficient proof of the role of biofilms in filler complications. They suggest that the only way to prove this role is to demonstrate a biofilm with hundreds of bacteria in the wall of a sterile abscess.⁴⁸ Although anti-inflammatory treatments have been found to aggravate delayed-onset complications,⁵¹ nodules and granulomas resolving after intralesional corticosteroid injection are a well-known phenomenon and are not likely to contain a well-established biofilm.²⁹ Other authors believe that the primary causative factor for delayed granulomatous reactions are a delayed-type of hypersensitivity reaction,¹⁴ but filler depots contaminated with bacteria have been shown to elicit an enlarged foreign-body response mimicking a type IV allergic reaction, clinically and histologically.^{1,38} More research on this is needed. From our point of view, delayed onset of nodules, (low grade) inflammations, and abscesses after dental procedures or other invasive treatments in the facial area (in the vicinity of the filler depots) can be explained in six ways.

- The invasive procedure activates the locoregional (innate) immune system, which also targets the sterile filler depot.^{32,33,44}
- After an invasive procedure, unknown triggering mechanisms activate preexisting dormant bacteria in filler biofilms.
- An invasive procedure near the site of the filler depot causes an infection that spreads to the previously sterile depot.
- An invasive procedure at the site of the filler depot (additional injections of soft tissue fillers) causes contamination of the filler material by direct inoculation.
- By mere coincidence. The complication is not related to the invasive procedure and is possibly caused by:
 - Commensal bacteria present in hair follicles, sebaceous glands, sweat glands, or lacrimal glands that have penetrated underlying tissues, contaminating the filler depot.^{1,49,50}
 - Analogous to late-onset infections in prosthetic joints, bacterial contamination is developed hematogenously in the setting of an infection at another, distant site.^{52,53}

The possibility of bacterial contamination of a filler depot during an invasive treatment poses a problem for the use of permanent fillers. Aging and CART-induced lipoatrophy are dynamic, on-going processes that always will need “touch ups.” Additional injections at the site or in the direct vicinity of an existing permanent filler depot will always involve the risk of infection.

Of the 85 patients with delayed-type complications, 34 (40%) were HIV-positive patients who had been treated with permanent fillers for CART-induced facial lipoatrophy. In these patients, the incidence of abscesses was significantly higher, and surgical intervention was required more often than in HIV-negative patients. Ocampo-Candiani and colleagues have suggested that in HIV-positive patients, the altered cellular immune response may result in a different reaction to permanent filler-implants.⁵⁴ Our findings support the view that the risk of infection is higher in HIV-positive patients.^{54,55} Future research should be directed toward elucidating the underlying immunologic mechanisms responsible for the diversity in delayed-onset complications after injection with permanent soft tissue fillers.

Strategy and treatment options

Forty-eight of our patients required invasive treatment (56%). From our experience with facial complications after injection of PAIG and other permanent filling agents, we propose the treatment strategy outlined in Figure 6. Although the different permanent fillers are associated with different types of adverse events, we feel that most complications can be treated using this algorithm. The main exception is patients injected with LIS in a microdroplet fashion. Microdroplet injection of highly purified 1,000-centistoke silicone oil has been

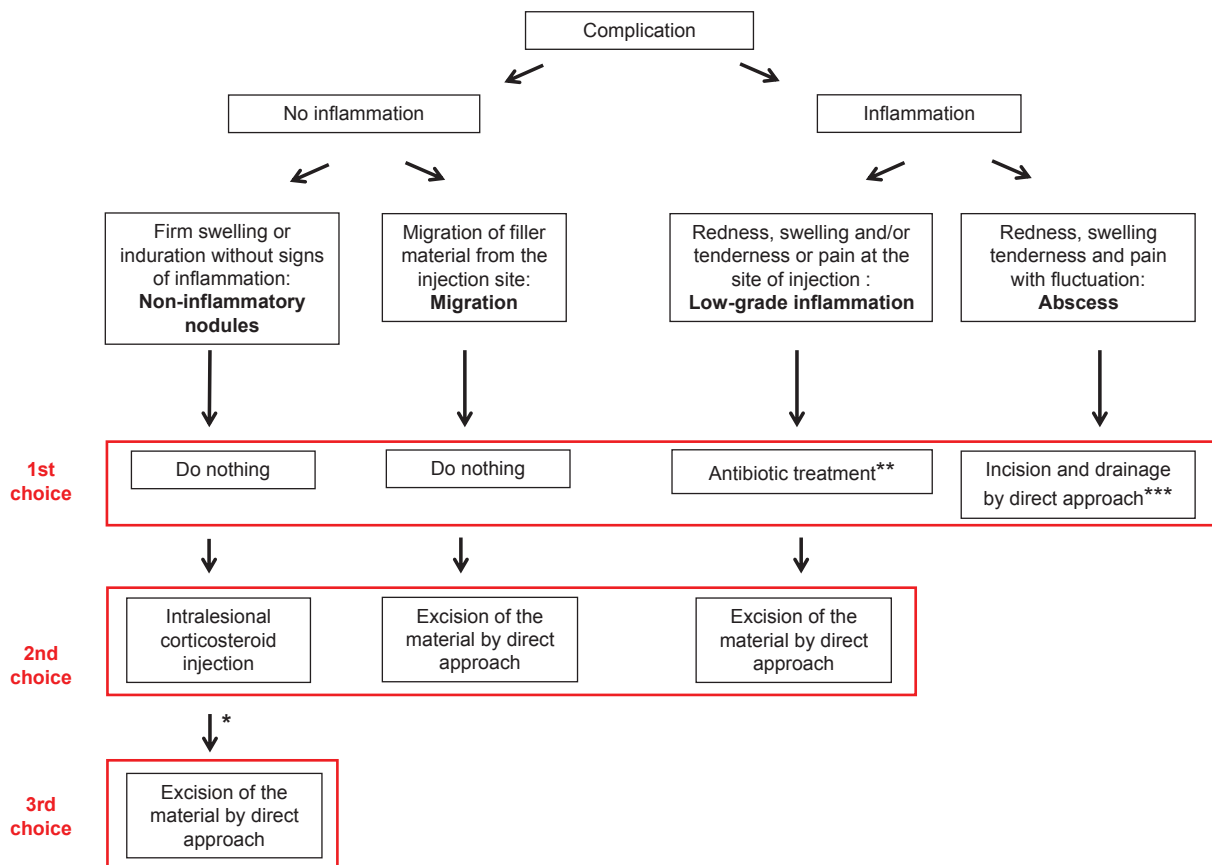


Figure 6. Flow chart for treatment of facial delayed-onset complications based on the experiences of the authors. Since the introduction of the micro-droplet technique, liquid injectable silicone is seldom injected in depots. As a consequence, excision can be unfeasible, and other treatment modalities must be considered, such as oral treatment with corticosteroids (when no inflammation is present), (immunomodulatory) antibiotics, or both. *Other treatment modalities such as topical imiquimod 5%, intralesional 5-fluorouracil injections, allopurinol, and carbon dioxide fractional laser have also been described in the literature. **In our experience, tetracyclines, such as doxycycline and minocycline, in high dosages give best results. ***In the case of an abscess, we culture its content and start with oral flucloxacillin 500 mg 3 to 4 times daily.

shown, for example, to be a safe and effective treatment option for HIV-associated facial lipodystrophy.⁵⁶ However, when complications do occur, excision can be challenging or unfeasible.

In cases of clinically noninflammatory nodules, our preferred approach is conservative. If the nodules or indurations are clearly visible and influencing the patients' quality of life, or if a patient specifically requests treatment, we start with intralesional corticosteroid injections. Excision of nodules by direct approach is performed in patients with insufficient response to intralesional corticosteroids. When clinical features of inflammation (erythema, edema, heat, tenderness, or pain) are present and infection

cannot be excluded, oral antibiotics are our treatment of choice. In such cases, we prefer tetracyclines, such as doxycycline or minocycline, at dosages of 100 to 200 mg per day, because of their dual action as antibacterial and anti-inflammatory drugs. Therefore, tetracyclines may also be effective in cases of "sterile" low-grade inflammations with negative bacterial cultures. In case of recurrent or persistent inflammation, we consider excision of the filler depot by direct approach as the only remaining option when possible. In case of an abscess, we perform incision and drainage, culture the content of the abscess, and start with oral flucloxacillin 500 mg three to four times daily, because *Staphylococcus aureus* is the predominant pathogen found in our

patients, although based on the results of bacterial cultures, we may change to another antibiotic regimen later on. Finally, in patients with filler material that has migrated from the original injection site, intralesional corticosteroid injections, antibiotic treatment and anti-inflammatory therapies are useless, and excision creates scars. We consider surgical excision only when migrated filler depots are clearly visible or troublesome for the patient.

Other treatment modalities for nodules and granulomatous complications have been described in the literature, such as topical imiquimod 5%, intralesional 5-fluorouracil injections, allopurinol, and carbon dioxide fractional laser.^{57–64} However, these publications mostly consist of case reports and small cohorts, and the authors do not have sufficient experience with these described modalities.

Conclusion

Delayed-onset complications after injection with permanent fillers in the face show an impressive diversity in time of onset and type of adverse event. The intrinsic characteristics of the injected filler may play a role in determining this observed variety. It seems that invasive facial or oral procedures in the vicinity of filler depots can provoke such complications, but the exact underlying mechanisms remain unknown. In HIV-positive patients, delayed-onset complications have a poorer course and outcome than in HIV-negative individuals. From our experience with complications after injections with permanent soft tissue fillers, we propose the treatment strategy as described in our Discussion (Figure 6).

Finally, we support the view of Duffy that the best way to minimize complications as a result of permanent filling materials is to avoid using them.⁶ We advise great caution when using permanent filling agents.

Conflict of Interest

The authors have indicated no significant interest with commercial supporters.

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