TURCZYNOWICZ, Magda, LEWANDOWSKA, Karina, JANIKOWSKI, Wojciech, JÓŹWICKA, Agnieszka, RADWAŃSKA, Natalia, GÓRSKA, Weronika and KRÓL, Jerzy. Complications associated with the use of hyaluronic acid and their management - a literature review. Quality in Sport. 2025;40:59462. eISSN 2450-3118.

https://doi.org/10.12775/QS.2025.40.59462 https://apcz.umk.pl/QS/article/view/59462

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.

Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).

Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.

Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

© The Authors 2025;

This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Polan d

Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike. (http://creativecommons.org/licenses/by-nc-sa/4.0/) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 14.03.2025. Revised: 01.04.2025. Accepted: 04.04.2025 Published: 07.04.2025.

# Complications associated with the use of hyaluronic acid and their management - a literature review

## Magda Turczynowicz

Medical University of Warsaw, Zwirki I Wigury 61, 02-091 Warszawa <u>magda.turczynowicz@gmail.com</u> <u>https://orcid.org/0009-0009-3116-5565</u>

### Karina Lewandowska

Medical University of Warsaw, Zwirki I Wigury 61, 02-091 Warszawa karina.lewandowska93@gmail.com https://orcid.org/0009-0004-5298-1426

## Wojciech Janikowski

Medical University of Warsaw, Zwirki I Wigury 61, 02-091 Warszawa wojtekjanikowski12@gmail.com https://orcid.org/0009-0008-4078-9698

## Agnieszka Jóźwicka

Medical University of Warsaw, Zwirki I Wigury 61, 02-091 Warszawa agnieszka.jozwicka@onet.eu https://orcid.org/0009-0008-1130-1518

# Natalia Radwańska

Medical University of Warsaw, Zwirki I Wigury 61, 02-091 Warszawa natalia.radwanska5@onet.pl https://orcid.org/0009-0000-8298-1081

## Weronika Górska

Medical University of Warsaw, Zwirki I Wigury 61, 02-091 Warszawa weronika.maslow@gmail.com https://orcid.org/0009-0005-3155-9573

## Jerzy Król MD

Stanisław Zeromski Hospital in Cracow, Department of Dermatology Jagiellonian University Medical College jerzy.krol@uj.edu.pl https://orcid.org/0000-0003-0783-764X

## Abstract

**Introduction:** Aesthetic medicine is a rapidly growing field, as evidenced by statistics from the American Society of Plastic Surgeons. Like any medical procedure, treatments with hyaluronic acid (HA) fillers carry a risk of complications or adverse effects. These complications can be broadly categorized into non-vascular and vascular events. Non-vascular complications include nodules, granulomas, oedema, Tyndall effect, infections, and biofilm formation. Vascular complications encompass ischemia, necrosis, and severe outcomes such as blindness or other visual impairments.

**Purpose:** This study aims to compile and analyze current data on HA filler treatments and their associated complications within the scope of aesthetic dermatology.

**Materials and Methods:** A comprehensive manual review of scientific databases, including Scopus, EMBASE, and Medline, was conducted for articles published up to November 2024. **Summary:** This review underscores the spectrum of complications related to HA fillers, emphasizing the importance of prevention, early diagnosis, and appropriate management. Although HA fillers are generally regarded as safe, the potential for complications persists. This reinforces the necessity of meticulous preparation, adherence to established guidelines, and continuous education for clinicians. Such measures can significantly minimize the incidence and severity of adverse events, thereby improving patient outcomes.

Keywords: hyaluronic acid, complications, hyaluronidase

## Introduction

Aesthetic medicine represents a rapidly expanding field of medical practice, as evidenced by data from the American Society of Plastic Surgeons. Comparative analyses of annual reports demonstrate a significant increase in the number of aesthetic procedures performed globally, rising from approximately 15 million in 2013 to over 27 million in 2023 [1, 2].

Among these procedures, treatments involving hyaluronic acid (HA) fillers have gained notable popularity, contributing over 5 million interventions in 2023 alone [1, 2]. This widespread adoption can be attributed to the perceived safety and efficacy of HA fillers in enhancing physical appearance [3]. Moreover, their reversibility through the administration of hyaluronidase provides an additional layer of reassurance for patients and practitioners alike [4, 5].

Despite their safety profile, HA filler treatments, like all medical interventions, carry inherent risks of complications or adverse effects. As the frequency of these procedures increases, the likelihood of clinicians encountering complications within their practice also rises. It is, therefore, imperative for healthcare professionals to possess the necessary skills to identify and manage these complications effectively. This underscores the importance of a thorough understanding of the potential adverse outcomes associated with HA fillers.

Adverse reactions to HA filler treatments may result from various factors, including improper injection techniques, inadequate aseptic conditions during the procedure, individual anatomical variations, or immunological responses to the injected material. These complications can be broadly categorized into two groups: non-vascular and vascular. Non-vascular complications encompass nodules [6-8], granulomas [8-10], oedema [11], the Tyndall effect [8, 12], infections [13], and biofilm formation [8, 13]. In contrast, vascular complications include ischemia, necrosis [8, 14], and severe outcomes such as blindness or other visual impairments [8, 14]. The objective of this study is to comprehensively examine the spectrum of complications associated with HA fillers, with a particular focus on their etiology, clinical manifestations, and management strategies, as informed by current literature.

# Complications following vascular administration of HA

# **Blindness/Visual Disturbances**

Blindness, or visual loss, represents the most severe complication associated with facial hyaluronic acid (HA) injections. HA is widely utilized as a facial filler due to its long-lasting effects and lower immunogenicity compared to other temporary fillers. Additionally, its reversibility through enzymatic degradation with hyaluronidase contributes to its appeal in aesthetic medicine. Despite these advantages, numerous reports document cases of temporary or permanent blindness resulting from HA filler migration into the anterior chamber of the eye or ocular circulation [15].

The severity of visual impairment caused by HA injections is often linked to vascular occlusion. Clinical observations suggest that treatments such as retrobulbar hyaluronidase injection are insufficient in reversing visual loss. Research indicates that injecting as little as 0.08 mL of HA into a facial artery can induce central retinal artery embolism, underscoring the need for precise injection techniques. Preventive strategies, such as limiting the volume per injection, have been suggested as potential prophylactic measures [16].

The physiology of retinal photoreceptor cells reveals a critical vulnerability to ischemia, with irreversible necrosis occurring within 90 minutes of embolic occlusion if untreated. As such, vascular occlusions affecting the retina should be regarded as medical emergencies requiring immediate intervention [16].

A review of 29 studies identified 32 cases of blindness following aesthetic procedures. In 15 cases, the blindness occurred after adipose tissue injections, while the remaining 17 were linked to a variety of materials, including corticosteroids, paraffin, silicone oil, calcium hydroxyapatite, and, most frequently, hyaluronic acid [17]. Another study reported three cases of vision loss due to central retinal artery occlusion following filler injections, with one patient showing significant recovery after aggressive therapeutic intervention.

Facial injections inherently carry the risk of material entering the ophthalmic artery or retinal circulation through high-pressure retrograde flow from the supratrochlear, supraorbital, or dorsal nasal arteries. Cases involving HA-based fillers have demonstrated sudden vision loss, retinal whitening, and the presence of a cherry-red spot on the retina-hallmark features of arterial occlusion [18].

Given the devastating and often irreversible nature of such outcomes, it is crucial to inform patients of these risks before performing facial injections. Ocular arterial occlusion remains a rare complication; however, its severe consequences necessitate heightened vigilance and preventive measures during filler procedures.

## Partial and Total Ischemia/Necrosis

Vascular complications, though relatively rare, can arise as adverse effects of hyaluronic acid (HA) filler injections. These complications range from early to late adverse reactions and may lead to severe outcomes such as necrosis, blindness, or even cerebral infarction.

Necrosis, characterized by irreversible cell death, results in non-viable tissue and manifests as necrotizing lesions or wounds. The extent of ischemic damage following arterial occlusion can vary significantly depending on the time of diagnosis and intervention. Delayed diagnosis (e.g., days after the procedure) may present with a spectrum of ischemia, including areas that recover rapidly and others where necrosis is more advanced and challenging to manage [19, 20]. The identification and management of vascular complications are critical components of clinical practice and demand a high level of competence from practitioners. These adverse outcomes often represent significant stress for clinicians and patients alike, underscoring the need for immediate and effective intervention [19, 21].

One of the primary vascular complications of HA fillers is vascular occlusion, which occurs when HA is inadvertently injected into a blood vessel. This leads to ischemia, where reduced blood flow causes tissue necrosis. Furthermore, ischemia may be compounded by vasospasm triggered by the HA filler acting as a noxious stimulus. This vasospasm can intensify ischemic damage and worsen tissue outcomes. If left untreated, the ischemic process progresses in stages, influenced by factors such as the size of the occlusion, the anatomical area, collateral vascular supply, the patient's healing capacity, and the presence of infection [19].

Common injection-related symptoms include pain, ecchymosis, erythema, bruising, and bleeding [21]. The likelihood and severity of vascular complications are contingent on the injection site. Facial areas such as the nose, glabella, temple, and forehead are particularly high-risk zones due to their vascular anatomy. The risk stratification of facial regions highlights the need for clinicians to exercise heightened caution in these critical areas.

The clinical signs of ischemia typically appear immediately or within a few hours but may sometimes manifest days later. Prompt assessment of capillary refill time (CRT) is essential in identifying ischemic changes and determining the extent of tissue involvement. CRT is evaluated by compressing the affected area and observing the time taken for blood flow to return; a delay beyond two seconds may indicate vascular insufficiency. Skin pallor, followed by a reticulated purple discoloration as deoxygenated blood accumulates, is an early indicator of ischemia. The progression to necrosis necessitates urgent intervention to prevent permanent tissue damage [19].

Vision impairment, a serious consequence of vascular infarction, can occur when emboli obstruct the retinal vasculature. This may result in permanent blindness or paradoxical ischemia affecting distant regions. Such cases are often associated with high-pressure injections that lead to retrograde embolism into cerebral or orbital arteries. Early signs include blurred vision, periorbital discomfort, or sudden visual loss [20].

To minimize the risk of vascular complications, clinicians should carefully select appropriate HA products and adopt safe injection techniques. A comprehensive understanding of injection-related anatomy and a detailed patient history, including previous filler treatments or medical conditions, are essential. Injections in high-risk areas should be performed cautiously, with preference for blunt cannulas over needles when possible. Additionally, aspiration before injection and the use of minimal doses are strongly recommended [21].

Management of vascular occlusion involves a multifaceted approach:

- 1. Pharmacological Interventions: High-dose hyaluronidase is the primary treatment for vascular occlusions. A dose of 1500 units per 1 mL of reconstituted hyaluronidase is recommended, applied in a pulsed fashion to maximize diffusion and restore blood flow.
- 2. Anti-inflammatory and Antithrombotic Therapy: Nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin (300 mg orally) may help alleviate inflammation and prevent thrombosis.
- 3. Hyperbaric Oxygen Therapy (HBOT): Although evidence is limited, HBOT has been reported to improve ischemic outcomes, particularly in cases involving visual impairment.
- 4. Supportive Measures: Local massage, warm compresses, and careful monitoring of ischemic regions are essential to manage early signs of vascular compromise.

Timely and systematic treatment of vascular occlusion can prevent or reduce irreversible damage. While vascular complications of HA fillers are rare, their severity necessitates meticulous technique and preparedness to manage adverse outcomes effectively.

## **Complications Following Non-Vascular Administration of HA: Chronic Oedema**

Chronic oedema, a relatively rare complication in aesthetic dermatology, is characterized by the persistent accumulation of interstitial fluid. This condition arises from an imbalance between capillary fluid filtration and lymphatic drainage [22, 23]. It is associated with multiple pathological mechanisms directly or indirectly linked to hyaluronic acid (HA) injections, including compression or damage to lymphatic vessels, inflammation, increased capillary permeability, a type IV Gell-Coombs hypersensitivity reaction, and the hydrophilic nature of HA. These factors collectively contribute to interstitial fluid retention within the tissues.

While chronic oedema may initially present as mild swelling, it can progress to more severe complications, such as fibrosis, localized or systemic infections, and irreversible tissue damage if not promptly addressed [21, 23].

Complications related to HA administration are reported in approximately 0.01–1% of patients [24]. Chronic oedema typically develops between two weeks and several months post-injection and is often linked to improper filler placement, excessive filler volume (overcorrection), pre-existing vascular conditions, inflammation, or hypersensitivity reactions. Thin-skinned areas, such as the periorbital region (with skin thickness ranging from 0.3 to 0.5 mm), are particularly vulnerable [25, 26]. Oedema may persist for up to 18 months and often requires multifaceted interventions to resolve [27].

Certain patient-related factors, such as obesity, prior surgeries, trauma history, or pre-existing vascular or lymphatic disorders, increase susceptibility to chronic oedema. Furthermore, improper injection techniques heighten the risk. Chronic oedema can also lead to visible tissue alterations, including skin thickening, which may adversely impact aesthetic outcomes and patient satisfaction [23].

# **Management of Chronic Oedema**

Prompt diagnosis and early intervention are critical in managing chronic oedema. First-line treatments typically include manual lymphatic drainage (MLD) and compression therapy, which aim to enhance lymphatic flow and reduce fluid accumulation [28-30].

For more severe cases, hyaluronidase administration is recommended, in line with consensusbased guidelines and clinical practice. According to Signorini et al., hyaluronidase treatment should begin with 10–20 units injected intradermally or subcutaneously in small areas, adjusted for regional sensitivity and skin thickness. Smaller incremental doses are recommended for regions exceeding 2.5 mm, whereas single injections suffice for areas smaller than this threshold [21].

In Poland, current recommendations advocate for hyaluronidase doses of 5–50 units per 1 mL. Reassessment should be performed 48–72 hours after the initial administration, and if oedema persists, additional treatments with the same dose should be considered every 7–10 days [21, 25].

Additional pharmacological interventions include systemic or topical corticosteroids, intralesional triamcinolone, arnica creams, oral loratadine, and nonsteroidal anti-inflammatory drugs (NSAIDs). Prior to hyaluronidase treatment, a skin test should be performed to rule out hypersensitivity reactions, as some patients may exhibit allergic responses to the enzyme [21, 23, 25, 28].

Adjunctive therapies, such as radiofrequency (RF) treatments, may also be employed to reduce swelling, promote lymphatic drainage, and accelerate filler degradation [31]. If chronic oedema is accompanied by signs of infection, appropriate antibiotic therapy is required. In extreme cases where other treatments fail, surgical excision of the filler may be necessary [21].

Although chronic oedema is an uncommon complication, it poses a significant challenge in aesthetic dermatology. Effective management is essential to mitigate its impact on patient satisfaction and long-term aesthetic outcomes.

# **Tyndall Effect**

The Tyndall effect refers to the scattering of light, which can result in a bluish discoloration of the skin following dermal filler injections. This phenomenon is most commonly observed in the subocular region due to the thin skin in this area [32]. The bluish hue arises from the superficial placement of hyaluronic acid (HA) filler, as shorter wavelengths of light, such as blue, scatter more readily than longer wavelengths. Additionally, large filler deposits placed too superficially in the tear trough region further increase the likelihood of this complication [33].

To minimize the risk of the Tyndall effect, cross-linked HA fillers should be injected at the periosteal level or at least within the suborbicularis plane to ensure proper placement and reduce the likelihood of light scattering [34].

Management of the Tyndall Effect

Several techniques have been proposed to address the Tyndall effect. These include:

- 1. Massage: Effective in early stages, massage can redistribute the filler and reduce visible discoloration within a few days.
- 2. Hyaluronidase Injection: This enzyme can dissolve the superficial filler, effectively resolving the discoloration.
- 3. Aspiration and Stab Excision: In some cases, mechanical removal of excess filler using a needle may be required.
- 4. Camouflage with Makeup: Temporary masking of the bluish hue using corrective cosmetics.
- 5. Laser Therapy: The Nd

1064 nm laser has been explored as a potential treatment. While there is no established chromophore for HA fillers, some studies, such as that by Cho et al., report near-complete resolution of bluish discoloration in the nasolabial fold using Q-switched Nd lasers [35].

Hyaluronidase is often the preferred treatment for managing the Tyndall effect. According to a survey by Olaiya et al., over 26% of respondents reported using hyaluronidase to treat the Tyndall effect, as well as related complications such as inflammatory nodules, asymmetry, vascular occlusion, and filler over-correction [36].

Proper injection techniques and accurate placement of fillers are critical to preventing the Tyndall effect. Clinicians must ensure an understanding of facial anatomy and adjust their approach according to the specific needs of each treatment area to achieve optimal outcomes and minimize complications.

# Infections

Hyaluronic acid (HA) injections, like other procedures that breach the skin barrier, carry an inherent risk of infection. These infections are predominantly bacterial, though viral and fungal pathogens have also been reported. Streptococcus and Staphylococcus species are the most frequently implicated bacteria in skin and soft tissue infections following dermal filler injections [37, 38]. Complications related to HA injections can be categorized into early- and late-onset infections. The primary source of infection often stems from inadequate sterilization techniques, which may introduce pathogens during the procedure.

Additional risk factors include the use of non-sterile or contaminated HA fillers, pre-existing skin infections, and immunocompromised patients.

The clinical presentation of infections related to HA injections typically includes erythema, swelling, pain or tenderness, acneiform eruptions, nodules, and abscess formation [39]. Management of mild cases involves the use of oral antibiotics, with broad-spectrum agents like tetracycline, doxycycline, and clindamycin, which have high skin penetration, being commonly prescribed. In more severe cases, cultures should be obtained to guide antibiotic therapy, and hospitalization with intravenous antibiotics may be required [40, 41].

Herpes simplex virus (HSV) reactivation, while less common than bacterial infections, presents a significant complication in some patients. Viral reactivation is thought to be triggered by direct axonal injury caused by needle penetration during facial dermal filler procedures [42, 43]. In cases where a patient has a known history of HSV infection, prophylactic antiviral therapy is recommended. This typically consists of acyclovir at a dose of 400 mg, administered orally three times daily for seven days [44]. Given the potential for HSV reactivation, a thorough medical history is essential to assess the risk of prior herpes outbreaks before undergoing HA injections.

## Biofilm

Biofilm formation has been increasingly recognized as a significant factor contributing to adverse reactions following dermal filler injections, with recent scientific literature highlighting its impact on clinical outcomes. Biofilms are structured communities of microorganisms that adhere to surfaces and form multiple layers encased in a hydrated extracellular matrix. These biofilms are primarily composed of microorganisms such as Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus viridans, Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa. Their presence at injection sites can lead to persistent inflammatory responses due to continuous immune activation elicited by the microorganisms within the biofilm matrix [45, 46].

Biofilm-related infections manifest as chronic inflammation, which can present as erythema, swelling, and pain at the injection site. This ongoing inflammatory response not only compromises the aesthetic outcomes but also impacts patient satisfaction, making biofilm management critical in the post-injection care of patients [47].

The treatment of biofilm-associated infections requires a comprehensive and multifaceted approach, involving early diagnosis, appropriate pharmacotherapy, and in some cases, surgical intervention. The persistent nature of biofilm infections is largely attributed to the microorganisms' ability to evade the host immune system and their resistance to conventional antibiotic treatments [48]. Current guidelines recommend the use of a thick needle for aspiration and subsequent drainage of the infected material, followed by the administration of hyaluronidase at a dose of 15–30 IU twice weekly for 2–3 weeks to dissolve any remaining filler and reduce biofilm-associated complications [49]. Empirical antibiotic therapy is also essential, with recommendations suggesting a broad-spectrum regimen that targets both Grampositive and Gram-negative bacteria. A combination of at least two antibiotics is typically prescribed for a minimum duration of three weeks to ensure adequate bacterial coverage and reduce the risk of infection recurrence [50, 51].

This combined therapeutic approach is crucial for effectively managing biofilm-associated infections and minimizing their long-term impact on patient outcomes following filler injections.

### Granulomas

Hyaluronic acid dermal fillers, which are generally deemed low-risk, may occasionally result in rare late-onset reactions that manifest between 3 and 4 months postinjection, and in some instances, as early as 24 hours postinjection [52]. One of the late reactions of complications associated with hyaluronic acid fillers is granuloma. Granulomas are typically a chronic inflammation caused by a foreign body. All dermal fillers are recognized by the immune system as foreign bodies, and inflammation surrounding the filler is a common reaction. The reactions can range from minor, involving limited macrophage infiltration, to significant, resulting in a granulomatous reaction with fibrosis. Foreign body reactions to implants are an immediate response that does not involve an adaptive immune response, while T-cell-mediated granulomas (i.e., due to hypersensitivity type IV) are a type of late-onset reaction [52]. The immune response may be triggered by an extended foreign body reaction. The inflammatory phase of the reaction is usually replaced by a healing phase, which facilitates tissue regeneration and repair. However, in certain individuals, the transition to the anti-inflammatory phase may be impaired, which may lead to chronic inflammation and granuloma formation [52]. The most commonly reported filler utilized was silicone, followed by hyaluronic acid, subsequent to lip augmentation using dermal fillers [53]. The permanent fillers (non-HA), especially silicones and polyacrylamides, have higher infection and inflammation risks when other fillers are layered on top. Inflammation may result from trauma or disruption to the existing filler, triggering an immune response and potentially leading to persistent granulomas. Conversely, infection may arise from a disruption in the surrounding bacteria caused by a needle. It is also advised against the practice of cross-brand layering in order to minimize any potential complications [52]. An ineffective aseptic technique was identified as the third biggest risk factor for delayed-onset reaction. While skin sterilization is impossible due to the presence of bacteria in deep skin layers that are impenetrable by topical antiseptics, maintaining an adequate aseptic technique can effectively reduce the risk of nodules with a bacterial etiology [52]. Regarding the injection technique, bolus and pillar injections have been associated with granulomas. Moreover, a rapid rate of injection, an aggressive fanning technique, and a substantial bolus size all contribute to the likelihood of late-onset reactions in general. The use of large filler volumes can cause significant inflammation, which is another risk factor. Trauma has the potential to stimulate quiescent biofilms, thereby intensifying the inflammatory response and potentially leading to infection [52].

Hyaluronidase can be used to treat granulomatous reactions to hyaluronic acid fillers. It is imperative to consider the efficacy of empiric antibiotic therapy. After infection is ruled out or the granulomas are quiescent, they may respond to oral or intralesional steroids. An intralesional steroid may be utilized in conjunction with hyaluronidase. In instances of persistent failure of alternative therapies, surgical excision is the preferred treatment option for foreign-body granuloma. The literature additionally contains a description of laser-assisted evacuation of filler material and inflammatory and necrotic debris of granulomata [21].

### Nodules

Changes in nodules are considered to be a rare complication of hyaluronic acid administration. They occur up to 4 weeks post HA injection to the specific area. Nodules can be classified according to the time of appearance following the injection: early (hours or days) and subacute or delayed (months or years later) [54]. Delayed onset nodules are more common in immunereactive patients and especially those with active autoimmune diseases [55]. Most frequently, the nodules are classified as firm and limited. Other common clinical signs reported by patients are swelling during induration [56]. Those changes remain until the time they are absorbed, removed or successfully treated. Ways to eliminate the nodule include massage, puncture, mechanical extrusion of acid or an injection of hyaluronidase [28]. This enzyme is considered as generally effective for resolving such nodules, however it can interfere with the favorable aesthetic effects of filler treatment [57]. which may be distressing to both patient and clinician. Rare delayed granulomatous reactions complications have been well documented in medical publications and have been associated to hypersensitivity reactions that may be caused by impurities developed during the bacterial fermentation process [58]. The nodules should be always distinguished from inflammatory processes that may be due to an infection or immunological reaction [54].

Important factors of the risk of appearing the nodules are following-less experienced practitioners, not sufficient focus on anatomy, injection technique, and product-specific variables. Improper injection technique may result in nodule formation, surface irregularities, overcorrection, and asymmetry [55]. Injection pressure, needle diameter and angle of penetration may also increase the risk of developing a nodule.

Delayed-onset inflammatory nodules have recently been reported with the use of HA fillers.[1] To present the scale of that matter, there was a study, in which in over 68 months over 4,500 treatments were performed using Hyaluronic Acid. A number of 23 patients (0.5%) experienced delayed-onset nodules. The median time from injection to reaction was 4 months, and the median time to resolution was 6 weeks. Nine of the 23 (39%) had an identifiable immunologic trigger such as flu-like illness before the nodule onset [59].

Any dermal filler has the potential to produce an inflammatory response, as it will be recognized as a foreign body [54]. Although inflammatory nodules are more common with permanent fillers such as silicone, inflammatory nodule development following administration of temporary fillers such as hyaluronic acid and collagen has also been reported.

## CONCLUSIONS

Hyaluronic acid (HA) has become one of the most commonly used fillers in aesthetic medicine, primarily due to its perceived safety and the ability to reverse its effects. However, like any medical procedure, HA injections carry certain risks and it is crucial for clinicians to be prepared to manage potential complications. This review highlights the spectrum of both non-vascular and vascular complications associated with HA fillers, stressing the importance of prevention, early diagnosis and appropriate treatment.

Non-vascular complications, such as nodules, granulomas, and infections, while typically manageable, require timely intervention using treatments like hyaluronidase, antibiotics, or drainage techniques. The formation of biofilms poses a more persistent challenge, necessitating a combination of high-dose antibiotics and the removal of the filler.

Although rare, vascular complications can have severe and sometimes irreversible consequences, including ischemia, necrosis, and even blindness. Rapid identification and immediate intervention—such as the administration of hyaluronidase or hyperbaric oxygen therapy—are critical in mitigating tissue damage and preserving function.

These findings underscore the necessity for practitioners to possess not only a thorough understanding of facial anatomy and proper injection techniques but also the ability to promptly recognize the early signs of adverse reactions. Additionally, ensuring that patients are wellinformed about potential risks, particularly in high-risk anatomical areas, is essential for obtaining informed consent.

In conclusion, while hyaluronic acid fillers are generally considered safe, the potential for complications remains, reinforcing the need for careful preparation and continuous education for clinicians. By adhering to established guidelines and remaining vigilant, the incidence and severity of adverse events can be minimized, ensuring better patient outcomes.

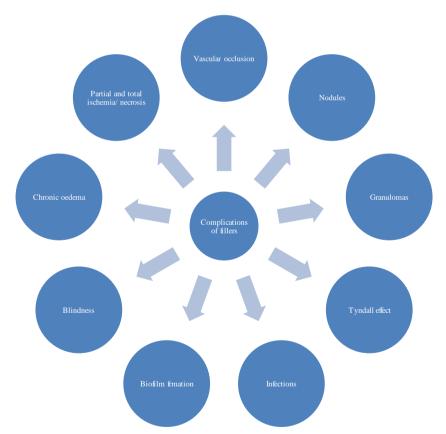


Figure 1. Graphic showing a set of complications after using HA fillers

Complication	Description	Frequency	Treatment
Nodules	Small lumps or bumps that	Rare	Massage,
	form under the skin, early		hyaluronidase
	or delayed onset.		injections,
			mechanical
~ .			extrusion.
Granulomas	Chronic inflammatory	Rare	Corticosteroids,
	reaction, often linked to		hyaluronidase,
	immune response or		surgical removal.
	impurities.		
Tyndall Effect	Bluish discoloration of the	Occasional	Massage,
·	skin due to superficial filler		hyaluronidase, Nd
	placement.		laser.
Infections	<b>Bacterial or viral infections</b>	Uncommon	Antibiotics (oral or
	at the injection site.		intravenous),
			drainage of
			abscesses, antiviral
			prophylaxis for HSV
			reactivation.
<b>Biofilm Formation</b>	Persistent inflammation	Rare	Hyaluronidase,
	due to microbial biofilm		broad-spectrum
	around the filler.		antibiotics, surgical
			intervention if
			necessary.
Vascular Occlusion	Blockage of a blood vessel	Rare but	High-dose
	causing ischemia and	serious	hyaluronidase,
	potential tissue necrosis.		anticoagulants,
			hyperbaric oxygen
			therapy, local
			massage.

Blindness	Visual impairment or loss due to filler entering the ophthalmic artery.	Very rare	Immediate retrobulbar hyaluronidase, hyperbaric oxygen therapy, and in severe cases, surgical intervention.
Partial and total ischaemia/necrosis	Vascular occlusion by HA injected into a blood vessel and vasospasm reaction leads to irreversible cell death (necrotizing lesions or wounds	Occasional	Hyaluronidase, NSAIDs and aspirin p.o. HBOT, local massage, warm compresses
Chronic oedema	Persistent accumulation of interstitial fluid caused by compression or damage to lymphatic vessels, inflammation, increased capillary permeability, a type IV Gell-Coombs hypersensitivity reaction, and the hydrophilic nature of HA	Rare	MLD and compression therapy, small dose hyaluronidase, radiofrequency, antibiotics when complicated by infection

**Figure 2.** Table showing a description, frequency and treatment of complications after using HA fillers

## DISCLOSURE

## **Authors contribution:**

Conceptualization: Magda Turczynowicz, Karina Lewandowska Methodology: Wojciech Janikowski, Agnieszka Jóźwicka, Natalia Radwańska Software: Jerzy Król, Weronika Górska, Check: Magda Turczynowicz, Agnieszka Jóźwicka FormalAnalysis: Weronika Górska, Karina Lewandowska Investigation: Magda Turczynowicz, Wojciech Janikowski Resources: Natalia Radwańska Data Curation:Agnieszka Jóźwicka, Writing-Rough Preparation: Magda Turczynowicz, Karina Lewandowska, Wojciech Janikowki, Agnieszka Jóźwicka, Natalia Radwańska, Weronika Górska, Jerzy Król Writing-Review and Editing: Weronika Górska, Magda Turczynowicz Visualization: Wojciech Janikowski Supervision: Jerzy Król, Natalia Radwańska, Project Administration: Karina Lewandowska

The authors have read and agreed with the published version of the manuscript.

## **Funding Statement:**

The Study Did Not Receive Special Funding.

## **Institutional Review Board Statement:**

Not Applicable.

**Informed Consent Statement:** 

Not Applicable.

# Data Availability Statement:

Not Applicable.

# **Conflict Of Interest:**

The authors declare no conflict of interest.

# **References:**

- 1. Surgeons, A.S.o.P., 2013 Plastic Surgery Statistics Report. 2013.
- 2. Surgeons, A.S.o.P., 2023 Plastic Surgery Statistics Report. 2023.
- 3. Bhojani-Lynch, T., et al., A Prospective, Observational Registry Study to Evaluate Effectiveness and Safety of Hyaluronic Acid-Based Dermal Fillers in Routine Practice: Interim Analysis Results with One Year of Subject Follow-Up. Clinical, Cosmetic and Investigational Dermatology, 2021. 14(null): p. 1685-1695.

- 4. Borzabadi-Farahani, A., A. Mosahebi, and D. Zargaran, *A Scoping Review of Hyaluronidase Use in Managing the Complications of Aesthetic Interventions*. Aesthetic Plastic Surgery, 2024. **48**(6): p. 1193-1209.
- Alam, M., et al., Effectiveness of Low Doses of Hyaluronidase to Remove Hyaluronic Acid Filler Nodules: A Randomized Clinical Trial. JAMA Dermatology, 2018. 154(7): p. 765-772.
- 6. Shahrabi Farahani, S., et al., *Lip Nodules Caused by Hyaluronic Acid Filler Injection: Report of Three Cases.* Head and Neck Pathology, 2012. **6**(1): p. 16-20.
- 7. Park, T.-H., et al., *Clinical experience with Hyaluronic acid-filler complications*. Journal of Plastic, Reconstructive & Aesthetic Surgery, 2011. **64**(7): p. 892-896.
- 8. Hall, M. and B.P. Glick, *Complications of hyaluronic fillers*. Dermatological Reviews, 2020. **1**(2): p. 51-54.
- Alsaad, S.M., S.G. Fabi, and M.P. Goldman, Granulomatous Reaction to Hyaluronic Acid: A Case Series and Review of the Literature. Dermatologic Surgery, 2012. 38(2 Part 1): p. 271-276.
- 10. Alcântara, C.E.P., et al., *Granulomatous reaction to hyaluronic acid filler material in oral and perioral region: A case report and review of literature.* Journal of Cosmetic Dermatology, 2018. **17**(4): p. 578-583.
- 11. Cavallieri, F.A., et al., *Persistent, intermitent delayed swelling PIDS: late adverse reaction to hyaluronic acid fillers.* CEP, 2017. **22440**: p. 040.
- 12. Kopp, S., et al., *Delayed Migration of Hyaluronic Acid Fillers: A New Complication?* Dermatologic Surgery, 2014. **40**(1): p. 85-87.
- Abduljabbar, M.H. and M.A. Basendwh, *Complications of hyaluronic acid fillers and their managements*. Journal of Dermatology & Dermatologic Surgery, 2016. 20(2): p. 100-106.
- Aviv, U., et al., Treatment Algorithm for Hyaluronic Acid-Related Complication Based on a Systematic Review of Case Reports, Case Series, and Clinical Experience. Craniomaxillofac Trauma Reconstr, 2020. 13(4): p. 313-328.
- 15. Kim, D.Y., J.S. Eom, and J.Y. Kim, *Temporary blindness after an anterior chamber cosmetic filler injection*. Aesthetic Plast Surg, 2015. **39**(3): p. 428-30.
- 16. Zhang, L., et al., *Clinical Observations and the Anatomical Basis of Blindness After Facial Hyaluronic Acid Injection*. Aesthetic Plast Surg, 2019. **43**(4): p. 1054-1060.
- 17. Lazzeri, D., et al., *Blindness following cosmetic injections of the face*. Plast Reconstr Surg, 2012. **129**(4): p. 995-1012.
- 18. Carle, M.V., et al., *Cosmetic facial fillers and severe vision loss*. JAMA Ophthalmol, 2014. **132**(5): p. 637-9.
- 19. Murray, G., et al., *Guideline for the Management of Hyaluronic Acid Filler-induced Vascular Occlusion.* J Clin Aesthet Dermatol, 2021. **14**(5): p. E61-e69.
- 20. Wang, R., et al., *Hyaluronic acid filler-induced vascular occlusion-Three case reports and overview of prevention and treatment*. J Cosmet Dermatol, 2024. **23**(4): p. 1217-1223.

- 21. Signorini, M., et al., Global Aesthetics Consensus: Avoidance and Management of Complications from Hyaluronic Acid Fillers-Evidence- and Opinion-Based Review and Consensus Recommendations. Plast Reconstr Surg, 2016. **137**(6): p. 961e-971e.
- 22. Mortimer, P.S. and S.G. Rockson, *New developments in clinical aspects of lymphatic disease*. J Clin Invest, 2014. **124**(3): p. 915-21.
- Philipp-Dormston, W.G., et al., Consensus statement on prevention and management of adverse effects following rejuvenation procedures with hyaluronic acid-based fillers. J Eur Acad Dermatol Venereol, 2017. 31(7): p. 1088-1095.
- Beauvais, D. and E.M. Ferneini, Complications and Litigation Associated With Injectable Facial Fillers: A Cross-Sectional Study. J Oral Maxillofac Surg, 2020. 78(1): p. 133-140.
- 25. Sclafani, A.P. and S. Fagien, *Treatment of injectable soft tissue filler complications*. Dermatol Surg, 2009. **35 Suppl 2**: p. 1672-80.
- 26. Ha, R.Y., et al., *Analysis of facial skin thickness: defining the relative thickness index.* Plast Reconstr Surg, 2005. **115**(6): p. 1769-73.
- 27. Vasquez, R.A.S., et al., *Prolonged Periorbicular Edema After Injection of Hyaluronic Acid for Nasojugal Groove Correction.* J Clin Aesthet Dermatol, 2019. **12**(9): p. 32-35.
- Zegarska, B., et al., Management of complications associated with the use of hyaluronic acid fillers. Recommendations of the Aesthetic Dermatology Section of the Polish Dermatological Society. Dermatology Review/Przegląd Dermatologiczny, 2020. 107(1): p. 15-31.
- 29. Guthrie, A., et al., *A Review of Complications and Their Treatments in Facial Aesthetic Surgery*. The American Journal of Cosmetic Surgery, 2017. **34**(2): p. 73-80.
- 30. Marxen, T., et al., *The Utility of Lymphatic Massage in Cosmetic Procedures*. Aesthet Surg J Open Forum, 2023. **5**: p. ojad023.
- 31. Dayan, E., et al., *Aesthetic Applications of Radiofrequency: Lymphatic and Perfusion Assessment.* Plast Reconstr Surg Glob Open, 2020. **8**(10): p. e3193.
- 32. King, M., C. Convery, and E. Davies, *This month's guideline: The Use of Hyaluronidase in Aesthetic Practice (v2.4).* J Clin Aesthet Dermatol, 2018. **11**(6): p. E61-e68.
- 33. King, M., *Management of Tyndall Effect*. J Clin Aesthet Dermatol, 2016. **9**(11): p. E6-e8.
- 34. Niamtu, J., 3rd, *Complications in fillers and Botox*. Oral Maxillofac Surg Clin North Am, 2009. **21**(1): p. 13-21, v.
- 35. Cho, S.B., et al., *Effective treatment of a injected hyaluronic acid-induced Tyndall effect with a 1064-nm Q-switched Nd: YAG laser.* Clin Exp Dermatol, 2009. **34**(5): p. 637-8.
- 36. Olaiya, O.R., et al., *Hyaluronidase for Treating Complications Related to HA Fillers: A National Plastic Surgeon Survey.* Plast Surg (Oakv), 2022. **30**(3): p. 233-237.
- 37. Otto, M., *How Staphylococcus aureus breaches our skin to cause infection*. J Infect Dis, 2012. **205**(10): p. 1483-5.
- 38. Martinez, N., *Skin and Soft-Tissue Infections: It's More Than Just Skin Deep.* Adv Emerg Nurs J, 2020. **42**(3): p. 196-203.
- 39. Funt, D. and T. Pavicic, *Dermal fillers in aesthetics: an overview of adverse events and treatment approaches.* Plast Surg Nurs, 2015. **35**(1): p. 13-32.

- 40. Christensen, L.H., *Host tissue interaction, fate, and risks of degradable and nondegradable gel fillers.* Dermatol Surg, 2009. **35 Suppl 2**: p. 1612-9.
- 41. Barańska-Rybak, W., *Powikłania po korekcji zmarszczek kwasem hialuronowym postępowanie i leczenie*. Dermatol Dypl 2015(5): p. 1-7.
- 42. Wang, C., et al., *Herpes reactivation after the injection of hyaluronic acid dermal filler: A case report and review of literature*. Medicine (Baltimore), 2020. **99**(24): p. e20394.
- 43. Gazzola, R., L. Pasini, and M. Cavallini, *Herpes virus outbreaks after dermal hyaluronic acid filler injections*. Aesthet Surg J, 2012. **32**(6): p. 770-2.
- 44. Cernik, C., K. Gallina, and R.T. Brodell, *The treatment of herpes simplex infections: an evidence-based review.* Arch Intern Med, 2008. **168**(11): p. 1137-44.
- 45. Netsvyetayeva, I., et al., *Skin bacterial flora as a potential risk factor predisposing to late bacterial infection after cross-linked hyaluronic acid gel augmentation*. Infect Drug Resist, 2018. **11**: p. 213-222.
- 46. Høiby, N., et al., *The clinical impact of bacterial biofilms*. Int J Oral Sci, 2011. **3**(2): p. 55-65.
- 47. Hall-Stoodley, L., et al., *Towards diagnostic guidelines for biofilm-associated infections*. FEMS Immunol Med Microbiol, 2012. **65**(2): p. 127-45.
- 48. Høiby, N., et al., *Antibiotic resistance of bacterial biofilms*. Int J Antimicrob Agents, 2010. **35**(4): p. 322-32.
- 49. Saththianathan, M., et al., *The Role of Bacterial Biofilm in Adverse Soft-Tissue Filler Reactions: A Combined Laboratory and Clinical Study.* Plast Reconstr Surg, 2017. 139(3): p. 613-621.
- 50. DeLorenzi, C., *Complications of Injectable Fillers, Part I.* Aesthetic Surgery Journal, 2013. **33**(4): p. 561-575.
- 51. Marusza, W., et al., *Treatment of late bacterial infections resulting from soft-tissue filler injections*. Infect Drug Resist, 2019. **12**: p. 469-480.
- 52. Baranska-Rybak, W., et al., *Late-Onset Reactions after Hyaluronic Acid Dermal Fillers:* A Consensus Recommendation on Etiology, Prevention and Management. Dermatol Ther (Heidelb), 2024. **14**(7): p. 1767-1785.
- 53. Trinh, L.N., K.C. McGuigan, and A. Gupta, Delayed Granulomas as a Complication Secondary to Lip Augmentation with Dermal Fillers: A Systematic Review. Surg J (N Y), 2022. 8(1): p. e69-e79.
- 54. Modarressi, A., C. Nizet, and T. Lombardi, *Granulomas and nongranulomatous nodules after filler injection: Different complications require different treatments.* J Plast Reconstr Aesthet Surg, 2020. **73**(11): p. 2010-2015.
- 55. King, M., et al., *Management of Delayed Onset Nodules*. J Clin Aesthet Dermatol, 2016.9(11): p. E1-e5.
- 56. Philipp-Dormston, W.G., et al., *Global Approaches to the Prevention and Management* of Delayed-onset Adverse Reactions with Hyaluronic Acid-based Fillers. Plast Reconstr Surg Glob Open, 2020. **8**(4): p. e2730.
- 57. Ostezan, L. and J. Peck, *Radial Sound (Shockwave) Therapy Resolves Delayed-onset Nodules Following Injection of Hyaluronic Acid Dermal Filler: A Case Study.* J Clin Aesthet Dermatol, 2021. **14**(12 Suppl 1): p. S15-s17.

- 58. Caldas Pozuelo, C., J. Domínguez De Dios, and X. Mota Rojas, *Multiple oral granulomatous nodules to hyaluronic acid filler*. J Cosmet Dermatol, 2020. **19**(12): p. 3453-3455.
- 59. Beleznay, K., et al., *Delayed-onset nodules secondary to a smooth cohesive 20 mg/mL hyaluronic acid filler: cause and management.* Dermatol Surg, 2015. **41**(8): p. 929-39.