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DELAYED INFLAMMATORY REACTIONS AFTER DERMAL FILLERS: THE ROLE OF BIOFILM, IMMUNOLOGY, AND ANTIBIOTIC STEWARDSHIP

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ABSTRACT

Dermal fillers have seen a marked increase in use over recent decades, becoming integral to both aesthetic and reconstructive medical practice. Although generally considered safe, delayed inflammatory reactions (DIRs) have emerged as clinically significant complications, exhibiting heterogeneous presentations and complex pathogenesis. This review provides a comprehensive analysis of the mechanisms, clinical features, diagnostic strategies, and treatment approaches associated with DIRs following dermal filler injections.

The present review is grounded in a structured analysis of current scientific literature, with particular emphasis on immunological mechanisms, biofilm formation, and clinical management of delayed complications.

Available evidence indicates that DIRs arise from multifactorial interactions between filler-related properties, host immune responses, and microbial factors. Biofilm formation plays a central role by enabling bacterial persistence, resistance to antimicrobial therapy, and chronic low-grade inflammation. Concurrently, immune-mediated processes—including foreign body reactions, delayed-type hypersensitivity, and adjuvant-like effects—contribute to the diversity of clinical manifestations. Clinically, DIRs may present as nodules, granulomas, abscesses, edema, or induration, with a delayed, often recurrent onset. Accurate diagnosis requires integration of clinical evaluation, imaging modalities such as ultrasonography, and, when necessary, microbiological or histopathological assessment. Treatment is based on a stepwise approach combining antibiotic therapy, hyaluronidase administration, corticosteroids, and, in selected cases, surgical intervention.

In summary, DIRs constitute complex complications that require individualised management strategies. Enhanced understanding of biofilm-related mechanisms and immune responses is essential for optimising prevention, diagnosis, and treatment. Further research is warranted to standardise diagnostic criteria and develop evidence-based therapeutic protocols.

KEYWORDS

Delayed Inflammatory Reactions, Dermal Fillers, Biofilm, Hyaluronic Acid, Granuloma, Aesthetic Medicine

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1. Introduction

The use of dermal fillers has increased substantially over recent decades, making them one of the most frequently performed minimally invasive procedures in aesthetic medicine worldwide (Bachour et al., 2021; Broder & Cohen, 2006). Hyaluronic acid (HA)-based fillers are particularly favoured because of their biocompatibility, reversibility, and favourable safety profile (Christensen, 2007). Nevertheless, despite their widespread use, an increasing number of complications have been reported, including both early and delayed adverse events (Bachour et al., 2021; Rohrich et al., 2010).

Among these, delayed inflammatory reactions (DIRs), including delayed-onset nodules (DONs), represent a clinically significant and challenging group of complications (King et al., 2016; De Boulle & Heydenrych, 2015). These reactions may develop weeks to months after injection and present as nodules, induration, edema, abscesses, or granulomatous inflammation (Ledon et al., 2013; Baranska-Rybak et al., 2024). Their variable clinical presentation and delayed onset frequently contribute to diagnostic uncertainty and complicate management (King et al., 2016; Artzi et al., 2020).

Historically, delayed complications were primarily attributed to hypersensitivity reactions or foreign body responses (Lee & Kim, 2015; Anderson et al., 2008). However, current evidence suggests that the pathogenesis of DIRs is multifactorial and involves interactions between filler properties, host immune responses, and infectious processes, particularly those associated with bacterial biofilm formation (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019; Zhang et al., 2024).

Biofilms are structured microbial communities embedded within a self-produced extracellular matrix that enables resistance to immune responses and antimicrobial therapy (Zhang et al., 2024; Alhede et al., 2014). Their ability to persist in a dormant state before reactivation makes them particularly relevant in delayed filler

complications. Immunological mechanisms, including foreign body reactions, delayed-type hypersensitivity, and adjuvant-like effects, further complicate these reactions (Lee & Kim, 2015; Alijotas-Reig et al., 2008).

The recognition of both infectious and immune-mediated mechanisms has important clinical implications (Sadeghpour et al., 2019). Inappropriate corticosteroid use in the presence of underlying infection may worsen clinical outcomes (Artzi et al., 2020; Shalmon et al., 2020). Moreover, growing concerns regarding antimicrobial resistance highlight the importance of rational antibiotic use and antibiotic stewardship in aesthetic practice (Artzi et al., 2020; Shalmon et al., 2020).

Despite growing awareness, standardised diagnostic and treatment algorithms for DIRs remain limited (King et al., 2016; Artzi et al., 2020). This underscores the need for a comprehensive understanding of the underlying mechanisms and risk factors associated with these complications (Sadeghpour et al., 2019; Decates et al., 2021).

This review offers a comprehensive overview of delayed inflammatory reactions following dermal filler injections, with particular emphasis on biofilm formation, immunological mechanisms, and antibiotic stewardship. Current evidence regarding risk factors, clinical manifestations, diagnostic approaches, and treatment strategies relevant to clinical practice is also summarised.

2. Methodology

This structured narrative review is based on a comprehensive analysis of peer-reviewed scientific literature concerning delayed inflammatory reactions following dermal filler injections.

A literature search was conducted using PubMed, PubMed Central, and Google Scholar. Additionally, the reference lists of relevant review articles, consensus statements, and expert recommendations were manually screened to identify further pertinent publications.

The literature search was performed between April 2026 and May 2026.

The following search terms and their combinations were used: “dermal fillers”, “hyaluronic acid fillers”, “delayed inflammatory reactions”, “delayed-onset nodules”, “late inflammatory reactions”, “foreign body granuloma”, “biofilm”, “filler complications”, “immune-mediated reactions”, “hyaluronidase”, “antibiotic therapy”, and “antibiotic stewardship”.

Eligible publications included peer-reviewed articles published in English that addressed the pathogenesis, clinical manifestations, diagnosis, prevention, or management of delayed complications following dermal filler injections. Priority was given to systematic reviews, consensus statements, expert recommendations, clinical reviews, original studies, and clinically relevant case series.

Publications were excluded if they focused exclusively on immediate adverse reactions, vascular complications, or allergic reactions unrelated to delayed inflammatory responses. Conference abstracts without full-text availability, duplicate publications, and non-scientific sources were also excluded.

Titles and abstracts were screened initially, followed by full-text evaluation of potentially relevant publications. Studies were selected based on their scientific relevance, methodological quality, recency, and contribution to the understanding of delayed inflammatory reactions associated with dermal fillers.

As this article represents a structured narrative review rather than a systematic review or meta-analysis, no formal risk-of-bias assessment or quantitative synthesis was performed.

The principal limitation of this review is the heterogeneous nature of the available evidence, which consists predominantly of observational studies, case series, expert recommendations, consensus statements, and narrative reviews. Consequently, the conclusions presented should be interpreted as a synthesis of current clinical knowledge rather than evidence derived from pooled quantitative analysis.

3. Dermal Fillers in Modern Medicine

Dermal fillers have become an integral component of modern medical practice, with applications extending beyond aesthetic enhancement to include reconstructive and therapeutic indications (Broder & Cohen, 2006; Lemperle et al., 2006).

Dermal fillers are commonly classified as biodegradable (temporary) or non-biodegradable (permanent) materials (Broder & Cohen, 2006; Christensen, 2009). Biodegradable fillers are gradually resorbed over time and generally exhibit a more favourable safety profile. Among these, hyaluronic acid (HA) remains the most widely used filler because of its high biocompatibility, reversibility, and predictable clinical outcomes (Christensen, 2007; Christensen, 2009). Other biodegradable fillers include calcium hydroxyapatite (CaHA) and poly-L-lactic acid (PLLA), which also stimulate neocollagenesis and tissue remodelling (Lee & Kim, 2015).

In contrast, non-biodegradable fillers such as polymethyl methacrylate (PMMA) provide long-lasting results but are associated with a greater risk of delayed complications (Lee & Kim, 2015; Kadouch et al., 2013). The persistence of these materials within tissues may lead to chronic inflammation, prolonged immune activation, and the formation of foreign body granulomas (Lee & Kim, 2015; Lemperle et al., 2009). Consequently, complications associated with permanent fillers are often more difficult to manage than those related to temporary materials (Shalmon et al., 2020; Lemperle & Gauthier-Hazan, 2009).

From a clinical perspective, dermal fillers are used for soft-tissue augmentation, wrinkle correction, facial contouring, and restoration of age-related volume loss (Broder & Cohen, 2006). Beyond cosmetic applications, fillers are also used in reconstructive medicine, including the correction of congenital anomalies, post-traumatic deformities, and tissue defects following oncological treatment (Lemperle et al., 2006). Their versatility and minimally invasive nature have contributed to their widespread use across multiple medical specialities.

Despite their favourable safety profile, dermal fillers are associated with a spectrum of adverse events, including delayed inflammatory reactions (Lee & Kim, 2015; Rohrich et al., 2010). The risk of complications is influenced by filler type, physicochemical properties, and interactions with host tissues (Lee & Kim, 2015; Christensen, 2009). Characteristics such as particle size, surface properties, and degradation behaviour may significantly affect immune responses and susceptibility to delayed complications (Lee & Kim, 2015; Baranska-Rybak et al., 2024). A thorough understanding of these properties is therefore essential for optimising clinical outcomes and minimising adverse events.

4. Delayed Inflammatory Reactions Following Dermal Filler Injections

Delayed inflammatory reactions (DIRs), also known as late inflammatory reactions or delayed-onset nodules, are adverse events that occur weeks, months, or even years after dermal filler placement (King et al., 2016; Baranska-Rybak et al., 2024; Munavalli et al., 2022). They may present as nodules, edema, induration, erythema, abscesses, or granulomatous inflammation and may be inflammatory or noninflammatory in nature (Ledon et al., 2013; De Boulle & Heydenrych, 2015).

The terminology used to describe these reactions remains inconsistent, as granulomas, sterile abscesses, hypersensitivity reactions, and biofilm-related complications may overlap clinically and pathophysiologically. Therefore, the term “delayed inflammatory reactions” is useful because it describes a broad clinical spectrum without assuming a single histopathological diagnosis (King et al., 2016; De Boulle & Heydenrych, 2015).

Although DIRs are relatively uncommon, they are clinically important because of their delayed onset, unpredictable course, recurrent nature, and potential impact on patient satisfaction and quality of life. Their development is thought to involve interactions between filler material, host immune responses, and microbial factors, particularly biofilm formation (Baranska-Rybak et al., 2024; Zhang et al., 2024; Saththianathan et al., 2017).

5. Pathogenesis

The pathogenesis of delayed inflammatory reactions (DIRs) following dermal filler injections is multifactorial and involves interactions between filler-related properties, microbial factors, and host immune responses (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019; Saththianathan et al., 2017). Although hyaluronic acid (HA) fillers are generally biocompatible, they may trigger physiological inflammatory responses that occasionally become dysregulated, resulting in chronic or delayed inflammation (Christensen, 2007; Christensen, 2009; Bachour et al., 2021).

One proposed mechanism involves degradation of hyaluronic acid into low-molecular-weight fragments capable of activating innate immune pathways, inducing oxidative stress, cytokine release, and delayed inflammatory responses (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019).

Another key factor is the formation of bacterial biofilms on the surface of injected filler material (Sadashivaiah & Mysore, 2010; Zhang et al., 2024; Alhede et al., 2014). Biofilms are structured microbial communities embedded within an extracellular matrix that protects bacteria from host immune responses and limits antibiotic penetration. Microorganisms introduced during injection, often originating from resident skin or mucosal flora, may persist in a dormant state within the filler (Zhang et al., 2024; Netsvyetayeva et al., 2018). These bacteria can remain clinically silent until triggered by local or systemic factors such as trauma, infection, or immune modulation (Sadashivaiah & Mysore, 2010; Saththianathan et al., 2017). Upon activation, biofilms may induce chronic low-grade inflammation leading to nodules, abscesses, or granulomatous reactions (Sadashivaiah & Mysore, 2010; Zhang et al., 2024). This mechanism may also explain the recurrent nature of some complications and their resistance to conventional treatment.

In addition to microbial factors, immune-mediated processes play a significant role in the development of delayed reactions (Lee & Kim, 2015; Alijotas-Reig et al., 2008; Anderson et al., 2008). Chronic foreign body responses may occur when macrophages fail to effectively phagocytose injected material, resulting in multinucleated giant cell formation and granulomatous inflammation (Lee & Kim, 2015; Anderson et al., 2008; Lemperle et al., 2009). Delayed-type (type IV) hypersensitivity reactions mediated by T lymphocytes have also been proposed, particularly in cases associated with systemic immune activation, including infections, autoimmune diseases, or vaccination (Alijotas-Reig et al., 2008; Decates et al., 2021). In some individuals, HA fillers may also act as adjuvants, amplifying innate and adaptive immune responses and prolonging inflammation (Baranska-Rybak et al., 2024).

The etiology of DIRs is therefore best understood as a convergence of multiple mechanisms rather than a single causative pathway (Sadeghpour et al., 2019; Baranska-Rybak et al., 2024). Physicochemical properties of the filler, including molecular weight, degree of crosslinking, and impurity content, may influence immunogenic potential (Lee & Kim, 2015; Christensen, 2009). Procedural factors, such as injection technique and aseptic conditions, may also determine the likelihood of bacterial contamination and subsequent biofilm formation (Sadashivaiah & Mysore, 2010; Saththianathan et al., 2017). Patient-related factors, including immune status and comorbidities, further modulate susceptibility to delayed inflammatory complications (Decates et al., 2021).

Collectively, current evidence supports a multifactorial model in which biofilm formation, immune dysregulation, and filler degradation interact to produce delayed inflammatory reactions following dermal filler injections (Baranska-Rybak et al., 2024; Zhang et al., 2024; Sadeghpour et al., 2019).

5.1 Foreign Body Reaction

The foreign body reaction represents a fundamental biological response to implanted biomaterials, including dermal fillers, and is an important mechanism in the development of delayed inflammatory reactions (DIRs) (Lee & Kim, 2015; Anderson et al., 2008). It is a non-allergic, chronic inflammatory process that occurs when the host immune system recognises the injected material as foreign and is unable to eliminate it effectively.

Macrophages are the main effector cells in foreign body reactions. Persistent or non-phagocytosable filler particles may lead to macrophage aggregation, cytokine release, fibroblast activation, fibrous encapsulation, and formation of multinucleated giant cells, ultimately contributing to granulomatous inflammation (Lee & Kim, 2015; Anderson et al., 2008; Lemperle et al., 2009).

The development and severity of the foreign body reaction are influenced by multiple factors, including particle size, surface characteristics, impurities, injection volume, and injection technique (Lee & Kim, 2015; Christensen, 2009). Although this reaction is considered a normal physiological response to implanted materials, when excessive or prolonged, it may contribute to delayed complications observed in clinical practice (Bachour et al., 2021; Anderson et al., 2008).

5.2 Immunological Mechanisms

The development of delayed inflammatory reactions (DIRs) following dermal filler implantation is associated with complex immunological processes involving both innate and adaptive immune responses (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019). These mechanisms are closely linked to the foreign body reaction and are influenced by filler physicochemical properties and host-related factors (Lee & Kim, 2015; Christensen, 2009).

Innate immune activation contributes significantly to DIRs through cytokine-mediated inflammatory pathways involving macrophages, neutrophils, and dendritic cells (Bachour et al., 2021; Baranska-Rybak et al., 2024).

Macrophages play a central role in DIRs and may promote either pro-inflammatory or tissue-remodelling responses depending on local immune conditions. Persistent stimulation may lead to chronic inflammation and granuloma formation (Lee & Kim, 2015; Lemperle et al., 2009).

Adaptive immune responses, particularly T cell-mediated delayed hypersensitivity, may also contribute to DIRs, especially after systemic immune activation such as infection or vaccination (Alijotas-Reig et al., 2008; Decates et al., 2021).

Dermal fillers may additionally act as immunological adjuvants, potentially enhancing innate and adaptive immune responses in susceptible individuals and contributing to chronic inflammation or ASIA-related mechanisms (Baranska-Rybak et al., 2024; Munavalli et al., 2022).

5.3 Adjuvant Effect of Fillers

In addition to classical inflammatory and immune responses, dermal fillers may contribute to delayed inflammatory reactions (DIRs) through potential immunological adjuvant activity (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019). Although hyaluronic acid fillers are generally considered biologically inert, increasing evidence suggests that they may modulate immune responses under certain conditions (Baranska-Rybak et al., 2024; Decates et al., 2021).

Adjuvants are substances that amplify immune responses without possessing intrinsic antigenic properties. In the context of dermal fillers, this effect may arise from both the material itself and its degradation products (Baranska-Rybak et al., 2024; Christensen, 2009). For example, low-molecular-weight hyaluronic acid fragments generated during filler degradation may activate innate immune pathways, including toll-like receptors, and promote the production of pro-inflammatory mediators. This process may contribute to the delayed onset of inflammatory reactions observed weeks to months after injection (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019).

Dermal fillers may also interact with external stimuli, serving as additional adjuvant triggers. Clinical observations indicate that delayed inflammatory reactions can be precipitated by systemic or local events such as infections, trauma, dental procedures, medications, or vaccinations (Bachour et al., 2021; Munavalli et al., 2022). These stimuli may activate the immune system directly or enhance the adjuvant effect of previously injected filler material, leading to a localised inflammatory response.

The concept of autoimmune/inflammatory syndrome induced by adjuvants (ASIA), also known as Shoenfeld's syndrome, has been proposed as a framework for understanding these phenomena. According to this hypothesis, exposure to adjuvant substances, including biomaterials such as dermal fillers, may trigger immune dysregulation in susceptible individuals (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019). This may result in immune-mediated responses ranging from localised inflammation to systemic manifestations resembling autoimmune disease.

Several factors may influence the likelihood of adjuvant-related reactions, including genetic predisposition, cumulative exposure to multiple adjuvant stimuli, and the balance between innate, adaptive, and regulatory immune responses (Baranska-Rybak et al., 2024; Decates et al., 2021). Sequential exposure to different adjuvants, such as repeated filler injections combined with infections or vaccinations, has been suggested to increase the risk of abnormal immune activation (Bachour et al., 2021; Munavalli et al., 2022).

Despite growing interest in the adjuvant hypothesis, the role of dermal fillers in systemic immune disorders remains incompletely understood, and current evidence is largely based on observational studies and theoretical models (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019).

5.4 Role of Biofilm in Delayed Reactions

Biofilm formation is increasingly recognised as an important mechanism in DIRs, as dermal fillers may serve as substrates for microbial adhesion and colonisation (Sadashivaiah & Mysore, 2010; Zhang et al., 2024; Saththianathan et al., 2017). Microorganisms introduced during injection may persist within the filler material in a dormant biofilm state, protected from host immune responses and antimicrobial therapy (Sadashivaiah & Mysore, 2010; Alhede et al., 2014; Netsvyetayeva et al., 2018).

Biofilm development involves bacterial attachment, microcolony formation, maturation, and dispersion. Within mature biofilms, bacteria may enter a low-metabolic “persister” state that promotes immune evasion, antibiotic resistance, and negative conventional cultures despite ongoing inflammation (Sadashivaiah & Mysore, 2010; Alhede et al., 2014).

Biofilm-associated infections may become clinically apparent after disruption of the local microenvironment. Triggering factors such as trauma, subsequent injections, systemic infections, or immunological changes can activate dormant bacteria, leading to the release of microorganisms and inflammatory mediators (Zhang et al., 2024; Munavalli et al., 2022). This process may result in nodules, abscesses, granulomas, or chronic low-grade inflammatory reactions that recur despite initial treatment (Sadashivaiah & Mysore, 2010; Saththianathan et al., 2017).

Several microbial species have been implicated in biofilm-associated filler complications, particularly opportunistic pathogens such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, and atypical mycobacteria (Zhang et al., 2024; Saththianathan et al., 2017). However, their exact role remains debated, as their presence may represent either true infection or an immunological trigger in a previously sensitised environment.

Biofilms contribute to persistent inflammation by impairing phagocytosis, reducing antibiotic penetration, and promoting chronic immune activation. These mechanisms may sustain macrophage recruitment and granulomatous inflammation, particularly after degradation of filler material releases previously sequestered bacteria (Sadashivaiah & Mysore, 2010; Zhang et al., 2024; Alhede et al., 2014).

From a clinical perspective, recognising biofilm as a potential underlying mechanism has important diagnostic and therapeutic implications (Sadashivaiah & Mysore, 2010; Zhang et al., 2024). Standard microbiological cultures may be insufficient to detect biofilm-associated microorganisms, and advanced techniques such as molecular diagnostics or fluorescence in situ hybridisation may be required. Therapeutically, suspected biofilm involvement may support prolonged antibiotic therapy with agents that can penetrate biofilm structures, whereas corticosteroids should be used cautiously because they may exacerbate infection if administered prematurely (Sadashivaiah & Mysore, 2010; Marusza et al., 2019).

6. Clinical Presentation

Delayed inflammatory reactions (DIRs) following dermal filler injections present with a heterogeneous spectrum of clinical manifestations, reflecting their multifactorial pathogenesis (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019). They typically occur weeks to months after treatment, although onset may range from a few weeks to several years depending on the underlying mechanism (De Boulle & Heydenrych, 2015; Munavalli et al., 2022). Clinically, DIRs may manifest as nodules, induration, edema, erythema, tenderness, abscess formation, granulomatous lesions, or, less commonly, post-inflammatory hyperpigmentation (Ledon et al., 2013; Lemperle et al., 2009).

A commonly used clinical framework divides delayed-onset lesions into non-inflammatory and inflammatory nodules (King et al., 2016; De Boulle & Heydenrych, 2015). Non-inflammatory nodules are usually firm, painless, and non-erythematous, whereas inflammatory nodules are associated with erythema, tenderness, swelling, infection, biofilm activation, or immune-mediated mechanisms (King et al., 2016; Ledon et al., 2013; Baranska-Rybak et al., 2024; Zhang et al., 2024).

From a temporal perspective, early-onset reactions usually occur within hours to days after injection and are more often related to acute hypersensitivity or procedural factors, whereas delayed reactions are more commonly associated with T-cell-mediated immune responses, chronic inflammation, or biofilm-related processes (Alijotas-Reig et al., 2008; Decates et al., 2021). Late-onset reactions may include granuloma formation, which typically develops months to years after injection and is characterised by accumulation of macrophages and multinucleated giant cells (Lee & Kim, 2015; Lemperle et al., 2009).

It is important to distinguish nodules from foreign body granulomas and delayed hypersensitivity reactions, as these entities differ in pathogenesis, clinical course, and treatment approach (Lee & Kim, 2015;

King et al., 2016; De Boulle & Heydenrych, 2015). Nodules are often localised and related to procedural factors, whereas granulomas may involve multiple sites and can exceed the volume of the injected material. Delayed hypersensitivity reactions, in contrast, are immune-mediated and may resolve spontaneously or respond to systemic therapy (Alijotas-Reig et al., 2008; Baranska-Rybak et al., 2024).

The anatomical location of filler placement also influences clinical presentation. Areas such as the lips and periorbital region are particularly prone to complications due to anatomical complexity, mobility, vascularity, and bacterial colonisation (King et al., 2016; Zhang et al., 2024). Repeated injections, use of multiple filler types, higher injection volumes, injection depth, and technique may further increase the risk and severity of delayed manifestations.

6.1 Nodules

A commonly used clinical framework divides delayed-onset lesions into non-inflammatory and inflammatory nodules (King et al., 2016; De Boulle & Heydenrych, 2015). Non-inflammatory nodules are usually firm, painless, and non-erythematous, whereas inflammatory nodules are associated with erythema, tenderness, swelling, infection, biofilm activation, or immune-mediated mechanisms (King et al., 2016; Ledon et al., 2013; Baranska-Rybak et al., 2024; Zhang et al., 2024).

From a clinical perspective, nodules are broadly classified into non-inflammatory and inflammatory types, a distinction that is important for diagnosis and management (King et al., 2016; De Boulle & Heydenrych, 2015).

Non-inflammatory nodules are usually firm, well-defined, painless, and covered by normal-appearing skin without erythema or warmth. They are most commonly associated with technical factors, including superficial injection, overcorrection, filler migration, or improper material placement. In some cases, they may also be related to filler physicochemical properties such as particle size and cohesivity (Lee & Kim, 2015; Christensen, 2009). Non-inflammatory nodules may remain stable or resolve spontaneously over time, although persistent lesions may require intervention.

In contrast, inflammatory nodules present with erythema, tenderness, swelling, and sometimes pain (King et al., 2016; Ledon et al., 2013). They may arise from infection, biofilm activation, foreign body reaction, or immune-mediated mechanisms (Baranska-Rybak et al., 2024; Zhang et al., 2024; Anderson et al., 2008). These lesions often develop after a clinically silent period and may be triggered by systemic infection, trauma, dental procedures, or immune activation (Bachour et al., 2021; Munavalli et al., 2022). Compared with non-inflammatory nodules, they are more likely to progress, recur, and require active treatment.

The temporal pattern of nodule development is clinically relevant. Early nodules, occurring within days of injection, are more often associated with technical errors or acute inflammatory responses (King et al., 2016; Rohrich et al., 2010). In contrast, delayed nodules appearing weeks to months after treatment are more suggestive of DIRs and may involve biofilm formation, immune dysregulation, or chronic foreign body response (Baranska-Rybak et al., 2024; Zhang et al., 2024; De Boulle & Heydenrych, 2015).

Differential diagnosis is essential, as similar clinical presentations may correspond to distinct pathological entities. Nodules should be distinguished from foreign body granulomas, abscesses, and delayed hypersensitivity reactions (Lee & Kim, 2015; King et al., 2016; De Boulle & Heydenrych, 2015). Unlike granulomas, which often involve multiple injection sites and may enlarge beyond the original volume of injected material, nodules are typically localised and closely associated with the injection site. Moreover, granulomas represent a histopathological diagnosis, whereas nodules are primarily defined clinically.

The anatomical location of filler injection also influences the risk of nodule formation. The lips and periorbital region are particularly prone to complications because of their anatomical complexity, mobility, vascularity, and bacterial colonisation (King et al., 2016; Zhang et al., 2024). Procedural factors, including injection depth, technique, and volume, further contribute to nodule development.

6.2 Foreign Body Granulomas

Foreign body granulomas represent a distinct and clinically significant manifestation of delayed inflammatory reactions (DIRs) following dermal filler injections (Lee & Kim, 2015; Lemperle et al., 2009). Unlike nodules, which are defined clinically, granulomas are histopathological diagnoses characterised by chronic granulomatous inflammation in response to persistent foreign material (Lee & Kim, 2015; King et al., 2016).

Granuloma formation results from the immune system's ineffective attempt to eliminate persistent foreign material. The process is mediated by macrophages, which fuse into multinucleated giant cells and,

together with lymphocytes, form granulomatous structures that isolate the filler material (Lee & Kim, 2015; Anderson et al., 2008).

Histologically, foreign body granulomas consist predominantly of macrophages, multinucleated giant cells, inflammatory infiltrates, fibroblast activation, and fibrous capsule formation, reflecting persistent immune stimulation caused by retained filler material (Lee & Kim, 2015; Lemperle et al., 2009).

Clinically, granulomas typically present as firm, sometimes progressively enlarging lesions that may develop months to years after filler injection (Lee & Kim, 2015; Lemperle et al., 2009). In contrast to nodules, granulomas may occur at multiple injection sites simultaneously and can exceed the original volume of injected material. Patients may present with induration, swelling, erythema, tenderness, or discomfort, although clinical presentation varies depending on filler type and the intensity of the inflammatory response (King et al., 2016; Baranska-Rybak et al., 2024).

The incidence of foreign body granulomas after dermal filler injections is relatively low and depends partly on the material used. Biodegradable fillers such as hyaluronic acid are associated with a lower incidence of adverse events than permanent or semi-permanent fillers, which tend to provoke more sustained immune responses due to their long-term tissue persistence (King et al., 2016; Lemperle et al., 2009). Injection volume, repeated procedures, particle size, surface characteristics, and impurities may further influence the risk of granuloma formation (Lee & Kim, 2015; Christensen, 2009).

It is essential to differentiate granulomas from other delayed complications, particularly inflammatory nodules and delayed hypersensitivity reactions (Lee & Kim, 2015; King et al., 2016; De Boulle & Heydenrych, 2015). Nodules are typically localised and related to procedural factors, whereas granulomas reflect a chronic immune response to persistent foreign material. Delayed hypersensitivity reactions involve T cell-mediated mechanisms and may resolve spontaneously or respond to systemic therapy, whereas granulomas tend to persist and require targeted intervention (Alijotas-Reig et al., 2008; Baranska-Rybak et al., 2024).

From a therapeutic perspective, foreign body granulomas can be challenging to manage due to their chronic, often diffuse nature. Intralesional corticosteroid injections are considered a primary treatment modality, as they suppress macrophage activity and reduce fibroblast proliferation (King et al., 2016; Lemperle & Gauthier-Hazan, 2009). Additional options include intralesional antimetabolic agents such as 5-fluorouracil, systemic therapies in refractory cases, and, rarely, surgical intervention. However, surgical excision is often limited by poorly defined lesion borders and the risk of incomplete removal.

6.3 Abscesses

Abscess formation is a less frequent but clinically significant manifestation of delayed inflammatory reactions (DIRs) following dermal filler injections (King et al., 2016; Beleznyay et al., 2015). Unlike nodules and granulomas, which may be predominantly inflammatory or immune-mediated, abscesses are typically associated with infection, though differentiation can be difficult due to overlapping clinical features.

An abscess is a localised collection of purulent material within tissue resulting from microbial infection and subsequent inflammatory response (Sadashivaiah & Mysore, 2010; Alhede et al., 2014). In the context of dermal fillers, abscesses may develop after bacterial contamination during injection or secondary activation of dormant microorganisms, particularly in association with biofilm formation (Zhang et al., 2024; Saththianathan et al., 2017). Filler material may facilitate bacterial persistence by providing a protective environment that supports microbial colonisation and impairs immune clearance.

Clinically, abscesses usually present as painful, erythematous, and fluctuant masses at or near the injection site (King et al., 2016; Beleznyay et al., 2015). Associated features may include warmth, swelling, and, in some cases, systemic symptoms such as fever. Palpable fluctuation is a key clinical sign suggesting fluid accumulation and helps distinguish abscesses from solid inflammatory nodules or granulomas. However, biofilm-related infections may present more subtly and mimic non-infectious inflammatory lesions (Sadashivaiah & Mysore, 2010; Zhang et al., 2024).

The timing of abscess formation may vary. Early abscesses, occurring within days to weeks after injection, are more likely to result from acute bacterial contamination during the procedure (King et al., 2016; Rohrich et al., 2010). Delayed abscesses may arise weeks to months later and are often linked to biofilm activation or secondary infection triggered by systemic or local factors (Zhang et al., 2024; Munavalli et al., 2022). Such delayed presentations may complicate diagnosis because they can initially resemble inflammatory nodules.

Accurate diagnosis is essential for appropriate management. Clinical evaluation should be complemented by imaging, particularly ultrasound, which can identify fluid collections and guide intervention

(Urdiales-Gálvez et al., 2021). When abscess formation is suspected, aspiration of purulent material for microbiological culture is recommended to identify causative organisms and guide targeted antibiotic therapy (Sadashivaiah & Mysore, 2010; Marusza et al., 2019). However, cultures may be negative, particularly in biofilm-associated infections.

Management of abscesses requires both antimicrobial therapy and procedural intervention. Incision and drainage or needle aspiration are fundamental in fluctuant lesions, as antibiotics alone are often insufficient due to limited penetration into purulent collections and biofilm structures (Sadashivaiah & Mysore, 2010; Alhede et al., 2014). Broad-spectrum antibiotics are usually initiated empirically and then adjusted according to culture results. In cases involving hyaluronic acid fillers, adjunctive hyaluronidase may be considered to facilitate degradation of the filler material and reduce the substrate for bacterial persistence (King et al., 2016; Zhang et al., 2024).

Corticosteroids should be used cautiously in the presence of active infection because they may suppress immune responses and exacerbate the infectious process (Sadashivaiah & Mysore, 2010; Marusza et al., 2019). Therefore, they are generally avoided until infection has been excluded or adequately controlled.

6.4 Edema and Induration

Edema and induration are common clinical manifestations of delayed inflammatory reactions (DIRs) following dermal filler injections and often coexist with nodules, granulomas, or other delayed complications (King et al., 2016; De Boulle & Heydenrych, 2015). Although they may appear as isolated findings, they frequently reflect underlying inflammatory, immunological, or infectious processes (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019).

Edema is the accumulation of interstitial fluid within tissues and may present as localised or diffuse swelling at or near the injection site. Clinically, it may range from mild transient swelling to persistent or recurrent enlargement of the affected area (King et al., 2016; Baranska-Rybak et al., 2024). In the context of DIRs, edema may develop days to months after the procedure and can persist for prolonged periods. It may be associated with erythema, tenderness, or a sensation of tightness, although it may also remain painless.

The pathophysiology of edema in DIRs is multifactorial. Inflammatory mediators released by activated immune cells increase vascular permeability, leading to fluid extravasation into surrounding tissues (Bachour et al., 2021; Anderson et al., 2008). Lymphatic disruption or impaired lymphatic drainage, particularly in anatomically sensitive areas such as the periorbital region, may also contribute to persistent swelling (King et al., 2016; Zhang et al., 2024). External triggers, including systemic infections, trauma, or immune activation, may exacerbate these processes and precipitate delayed-onset edema (Baranska-Rybak et al., 2024; Munavalli et al., 2022).

Induration refers to localised hardening or thickening of tissue resulting from chronic inflammation and fibrosis (Lee & Kim, 2015; Anderson et al., 2008). Clinically, it presents as firm, poorly compressible areas that may or may not be associated with visible swelling. Induration often develops in association with persistent inflammatory processes, including foreign body reactions, granuloma formation, or chronic low-grade infection (Lee & Kim, 2015; Zhang et al., 2024; Lemperle et al., 2009).

From a pathophysiological perspective, induration reflects fibroblast activation and extracellular matrix deposition, particularly collagen, in response to sustained inflammatory signalling (Lee & Kim, 2015; Anderson et al., 2008). This process may be driven by cytokines released by macrophages and other immune cells, leading to progressive tissue remodelling and fibrosis. In some cases, induration may represent an early stage of granuloma formation or coexist with other delayed complications.

The temporal pattern of edema and induration may provide important diagnostic clues. Acute or early-onset edema is commonly associated with procedural trauma or transient inflammatory responses, whereas delayed or persistent edema and induration are more suggestive of DIRs (King et al., 2016; Rohrich et al., 2010). Recurrent or fluctuating symptoms may indicate biofilm activation or immune dysregulation (Zhang et al., 2024; Munavalli et al., 2022).

Differentiation between inflammatory and non-inflammatory causes is essential for appropriate management. Non-inflammatory edema may result from product characteristics, such as hydrophilicity or osmotic effects, whereas inflammatory edema is typically associated with erythema, warmth, and tenderness (King et al., 2016; Christensen, 2009). Similarly, induration due to fibrosis should be distinguished from palpable nodules or granulomatous lesions (Lee & Kim, 2015; Lemperle et al., 2009).

Management strategies depend on the underlying etiology. Mild non-inflammatory edema may resolve spontaneously or require conservative measures, whereas persistent or inflammatory cases may require pharmacological intervention, including anti-inflammatory treatment or therapy directed at infection or immune-mediated mechanisms (King et al., 2016; Beleznyay et al., 2015). Accurate clinical assessment is therefore critical for guiding appropriate therapeutic decisions.

7. Risk Factors for Delayed Inflammatory Reactions

The development of delayed inflammatory reactions (DIRs) following dermal filler injections is multifactorial and reflects interactions among patient-, product-, and procedure-related factors (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019; Munavalli et al., 2022). DIRs are not attributable to a single cause but arise from the interplay between host immune status, filler physicochemical properties, and technical aspects of the injection procedure (King et al., 2016; Christensen, 2009). Identification of these risk factors is essential for understanding pathogenesis, optimising prevention, and improving patient selection (King et al., 2016; Urdiales-Gálvez et al., 2018).

7.1 Patient-related factors

Individual patient characteristics play an important role in susceptibility to DIRs, mainly by modulating immune system activity (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019; Decates et al., 2021). Patients with autoimmune or autoinflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, or vasculitis, appear to be at increased risk of delayed reactions. This predisposition is likely related to dysregulated immune responses, which may promote exaggerated or prolonged inflammation after exposure to foreign biomaterials (Sadeghpour et al., 2019; Anderson et al., 2008).

Systemic immune activation is another important trigger. Acute infections, viral illnesses, and immune stimulation following vaccination have been associated with the onset of delayed inflammatory reactions (Baranska-Rybak et al., 2024; Munavalli et al., 2022). These events may disrupt immune homeostasis and activate inflammatory pathways around previously quiescent filler deposits.

Bacterial translocation from distant sites is also considered clinically relevant. Dental procedures, sinus infections, or other sources of bacteremia may facilitate microbial seeding into filler-containing tissues (Sadashivaiah & Mysore, 2010; Zhang et al., 2024; Marusza et al., 2012). In the presence of implanted biomaterial, microorganisms may persist in a dormant state or contribute to biofilm formation, which can later become clinically active (Zhang et al., 2024; Saththianathan et al., 2017; Alhede et al., 2014).

Certain patient populations may also be predisposed to biofilm-related complications. Conditions associated with impaired immune defence or chronic inflammation may facilitate bacterial persistence within filler material (Sadashivaiah & Mysore, 2010; Zhang et al., 2024). Patients with prior filler-related complications may also be at increased risk of recurrence, suggesting individual susceptibility to abnormal host responses (King et al., 2016; Baranska-Rybak et al., 2024).

7.2 Product-related factors

The physicochemical properties of dermal fillers play a central role in determining their biological behaviour and immunogenic potential (Lee & Kim, 2015; Christensen, 2009). Molecular weight, particle size, surface characteristics, degree of cross-linking, and impurities may significantly influence host-material interactions.

One key mechanism involves the degradation of hyaluronic acid fillers into low-molecular-weight fragments, which may exhibit proinflammatory properties. These degradation products can activate innate immune pathways through pattern recognition receptors, including toll-like receptors, thereby contributing to delayed inflammatory responses (Bachour et al., 2021; Baranska-Rybak et al., 2024).

Particulate fillers, such as poly-L-lactic acid and calcium hydroxyapatite, may be associated with a higher risk of granuloma formation than non-particulate or more homogeneous materials (King et al., 2016; Christensen, 2009). This is partly related to their tissue persistence and to macrophages' inability to phagocytose larger particles effectively, leading to chronic foreign body reactions (Lee & Kim, 2015; Morhenn et al., 2002; Anderson et al., 2008).

Surface properties of fillers, including roughness, charge, and hydrophobicity, influence protein adsorption and subsequent immune activation (Lee & Kim, 2015; Anderson et al., 2008). Impurities introduced during manufacturing or cross-linking processes may further increase immunogenicity (King et al., 2016; Christensen, 2009).

Repeated exposure to different filler types or layering of products within the same anatomical region may lead to cumulative immune stimulation. This repeated antigenic or adjuvant-like exposure may contribute to chronic inflammation or abnormal immune responses, including mechanisms resembling autoimmune/inflammatory syndrome induced by adjuvants (ASIA) (Baranska-Rybak et al., 2024; Sadeghpour et al., 2019).

Thus, product-related factors contribute to DIRs primarily by influencing immune activation, degradation behaviour, and tissue persistence (Lee & Kim, 2015; Baranska-Rybak et al., 2024).

7.3 Procedure-related factors

Technical aspects of the injection procedure are critical and modifiable determinants of complication risk (King et al., 2016; Urdiales-Gálvez et al., 2018). Among these, aseptic technique is particularly important. Inadequate skin disinfection or breach of sterile technique may facilitate the introduction of resident skin or mucosal microorganisms into the injection site, promoting bacterial colonisation and biofilm formation (Sadashivaiah & Mysore, 2010; Zhang et al., 2024; Saththianathan et al., 2017).

The risk of contamination increases with repeated injections, multiple needle passes, and large injection volumes. Each additional tissue manipulation may introduce microorganisms or disrupt local tissue integrity, thereby increasing susceptibility to infection and inflammation (Zhang et al., 2024; Saththianathan et al., 2017; Marusza et al., 2019).

The injection technique also plays a crucial role in clinical outcomes. Injection depth, pressure, and filler distribution influence both mechanical and biological responses (King et al., 2016; Urdiales-Gálvez et al., 2018). Superficial placement, overcorrection, or uneven distribution may result in product accumulation, migration, and local tissue irritation, predisposing to nodule formation and inflammatory reactions (King et al., 2016; De Boulle & Heydenrych, 2015).

Certain anatomical regions are inherently more susceptible to complications. Highly mobile areas, such as the lips, are exposed to greater mechanical stress and a higher density of resident microbiota, which may facilitate product displacement and microbial contamination (King et al., 2016; Zhang et al., 2024). Similarly, deeper injection planes may create environments that favour bacterial persistence due to reduced immune surveillance (Zhang et al., 2024; Saththianathan et al., 2017).

Procedures performed in areas with pre-existing inflammation, such as acne or dermatitis, are associated with increased complication risk because disruption of the skin barrier facilitates microbial entry (Zhang et al., 2024; Netsvyetayeva et al., 2018). Reinjection into previously treated or complicated areas should also be approached cautiously, as these sites may harbour residual inflammation or biofilm (Zhang et al., 2024; Saththianathan et al., 2017).

Overall, the risk of delayed inflammatory reactions is determined by the interaction of multiple factors rather than a single causative element. A comprehensive understanding of patient characteristics, filler properties, and procedural techniques is essential to minimise complications and ensure safe, effective aesthetic outcomes (King et al., 2016; Baranska-Rybak et al., 2024; Urdiales-Gálvez et al., 2018).

8. Diagnosis

Accurate diagnosis of delayed inflammatory reactions (DIRs) following dermal filler injections requires a comprehensive approach integrating clinical evaluation, imaging, and, when necessary, laboratory or histopathological investigations (King et al., 2016; Urdiales-Gálvez et al., 2021; Beleznyay et al., 2015). Because clinical presentations may overlap between infectious, inflammatory, and mechanical etiologies, precise identification of the underlying cause is essential for appropriate management (Baranska-Rybak et al., 2024; De Boulle & Heydenrych, 2015).

The initial diagnostic step is a thorough clinical assessment, including detailed medical history and physical examination (King et al., 2016; Beleznyay et al., 2015). Important elements include the time of onset relative to filler injection, the presence of triggering factors such as infections, dental procedures, or immune activation, and lesion characteristics, including size, tenderness, erythema, fluctuation, and progression over time (King et al., 2016; Munavalli et al., 2022). Differentiation between inflammatory and noninflammatory nodules is particularly important because it directly influences treatment decisions (De Boulle & Heydenrych, 2015; Beleznyay et al., 2015).

Imaging techniques, particularly high-frequency ultrasonography, have become valuable tools in aesthetic medicine (Urdiales-Gálvez et al., 2021). Ultrasound enables real-time visualisation of soft tissues and identification of filler material, its anatomical location, depth, and distribution pattern. Different fillers produce characteristic echogenic patterns, which may help distinguish materials and assess tissue integration. Ultrasound also facilitates detection of complications such as filler migration, overcorrection, vascular compromise, and fluid collections suggestive of abscess formation. In addition, ultrasound-guided procedures may improve the precision and safety of aspiration or hyaluronidase administration.

When infection is suspected, additional diagnostic measures should be considered. Fluctuant lesions may require aspiration for microbiological culture, whereas persistent or nonfluctuant nodules may necessitate biopsy and histopathological examination (King et al., 2016; Zimmermann & Clerici, 2004). Biofilm-

associated infections are frequently culture-negative because microorganisms remain in a dormant state and resist conventional detection methods (Sadashivaiah & Mysore, 2010; Saththianathan et al., 2017). In selected cases, advanced diagnostic techniques such as fluorescence in situ hybridisation may provide additional evidence of bacterial presence.

Laboratory investigations, including inflammatory markers such as C-reactive protein, may support assessment of systemic inflammation but are generally nonspecific (Baranska-Rybak et al., 2024). Therefore, laboratory findings should always be interpreted in conjunction with clinical and imaging data.

Overall, the diagnosis of DIRs relies on a multimodal approach that combines clinical judgment with imaging and targeted investigations. Accurate differentiation between infectious, immune-mediated, and mechanical causes is essential for selecting appropriate treatment strategies (King et al., 2016; De Boulle & Heydenrych, 2015; Beleznyay et al., 2015).

Table 1. Clinical characteristics of delayed inflammatory reactions following dermal filler injections

Clinical presentation	Typical findings	Most probable underlying mechanism	Initial diagnostic approach
Non-inflammatory nodule	Firm, palpable, non-tender nodule without erythema or oedema	Product accumulation, superficial placement, overcorrection, filler migration	Clinical examination; ultrasound if diagnosis is uncertain
Inflammatory nodule	Painful erythematous nodule with tenderness and swelling	Biofilm activation, low-grade bacterial infection, delayed immune-mediated response	Clinical examination; ultrasonography; assessment for possible infectious triggers
Foreign body granuloma	Persistent firm inflammatory lesion, sometimes presenting as multiple nodules developing months to years after injection	Chronic foreign body reaction with macrophage activation and multinucleated giant-cell formation	Clinical examination; imaging when indicated; histopathology examination only in selected cases
Diffuse inflammatory oedema	Diffuse swelling, erythema and tissue induration without fluctuation	Immune-mediated inflammatory response, occasionally triggered by systemic inflammatory stimuli	Clinical assessment; exclusion of infection; ultrasonography when clinically indicated
Abscess	Painful fluctuant lesion with purulent content and marked inflammation	Active bacterial infection	Ultrasonography, aspiration or drainage, microbiological culture and antimicrobial susceptibility testing

Source: Developed by the authors based on the current literature. Data synthesized from King et al. (2016), Ledon et al. (2013), Urdiales-Gálvez et al. (2018), Artzi et al. (2020), Bachour et al. (2021), and Baranska-Rybak et al. (2024).

9. Treatment

Management of delayed inflammatory reactions (DIRs) following dermal filler injections requires an individualised, stepwise approach based on the suspected aetiology, clinical severity, filler type, and careful clinical assessment, as these complications may reflect infectious, immune-mediated, mechanical, or mixed mechanisms (King et al., 2016; Shalmon et al., 2020; Urdiales-Gálvez et al., 2018; Baranska-Rybak et al., 2024; De Boule & Heydenrych, 2015; Munavalli et al., 2022).

A conservative approach may be appropriate in selected cases, particularly when lesions are small, minimally symptomatic, and likely to resolve spontaneously (King et al., 2016; Chiang et al., 2017). Watchful waiting is most often considered in noninflammatory or mildly inflammatory nodules without progressive pain, marked erythema, or fluctuation. However, persistent, painful, enlarging, or recurrent lesions usually require active intervention.

Antibiotic therapy is widely regarded as first-line treatment for inflammatory delayed reactions, particularly when infection or biofilm involvement is suspected. Macrolides and tetracyclines are commonly recommended, whereas severe cases may require combination therapy with a fluoroquinolone (King et al., 2016; Marusza et al., 2019; Sadashivaiah & Mysore, 2010; Zhang et al., 2024). Lesions with fluctuation require drainage and microbiological evaluation whenever possible.

Hyaluronidase is the treatment of choice for complications related to hyaluronic acid fillers, particularly non-inflammatory nodules, product misplacement, and retained filler material. In inflammatory reactions, timing should depend on the likelihood of infection and clinical response (King et al., 2016; Shalmon et al., 2020; Urdiales-Gálvez et al., 2018).

Corticosteroids are generally considered second-line therapy and should be used selectively (King et al., 2016; Lemperle & Gauthier-Hazan, 2009). Intralesional corticosteroids may be effective in persistent inflammatory nodules, granulomatous lesions, and foreign body granulomas, particularly when combined with agents such as 5-fluorouracil to reduce the risk of local adverse effects, including tissue atrophy (Urdiales-Gálvez et al., 2018). Systemic corticosteroids remain controversial because they may suppress inflammation while masking or worsening underlying infection (Baranska-Rybak et al., 2024; Marusza et al., 2019). Consequently, they are generally reserved for severe, disfiguring, or treatment-resistant inflammatory reactions after infectious causes have been reasonably excluded.

Additional therapeutic options may be considered in refractory cases, including aspiration of localised collections, punch biopsy for diagnostic clarification, intralesional antimetabolic agents, and, in selected situations, energy-based procedures (King et al., 2016; Urdiales-Gálvez et al., 2018). Surgical excision is typically considered a last resort, especially in true granulomatous lesions, because complete removal may be difficult and result in scarring or deformity (Lemperle & Gauthier-Hazan, 2009). In foreign body granulomas, intralesional corticosteroids remain the preferred initial treatment, whereas surgery is reserved for localised or complicated lesions.

Overall, successful management of DIRs requires an individualised, staged approach integrating antibiotics, hyaluronidase, corticosteroids, and invasive procedures when clinically indicated (King et al., 2016; Shalmon et al., 2020; Urdiales-Gálvez et al., 2018).

9.1 Antibiotic Therapy

Antibiotic therapy is a cornerstone in the management of delayed inflammatory reactions (DIRs), particularly when infection or biofilm involvement is suspected. Increasing evidence supports the role of bacterial contamination and biofilm formation in these complications, justifying antimicrobial therapy as a first-line approach (King et al., 2016; Baranska-Rybak et al., 2024; Zhang et al., 2024).

The rationale for antibiotic therapy extends beyond overt infection, as many agents also exhibit anti-inflammatory activity relevant to chronic biofilm-associated inflammation. Because biofilm-associated bacteria are often undetectable using conventional culture methods, empirical therapy is frequently initiated based on clinical presentation (Sadashivaiah & Mysore, 2010; Alhede et al., 2014).

Current expert recommendations support antibiotics as first-line treatment for inflammatory nodules and suspected infectious complications following filler injections (King et al., 2016; Baranska-Rybak et al., 2024; Urdiales-Gálvez et al., 2018). Combination therapy is frequently recommended, most commonly involving a fluoroquinolone with either a tetracycline or a macrolide (King et al., 2016; Marusza, Olszanski, Sierdzinski, Ostrowski, et al., 2019).

Tetracyclines, particularly doxycycline and minocycline, are widely used because of their antimicrobial and anti-inflammatory properties. Macrolides such as clarithromycin may additionally inhibit bacterial quorum

sensing and accumulate in adipose tissue (Sadashivaiah & Mysore, 2010; Marusza, Olszanski, Sierdzinski, Ostrowski, et al., 2019).

Fluoroquinolones such as ciprofloxacin and moxifloxacin are generally reserved for severe or refractory cases because of potential adverse effects, including tendinopathy (Sadashivaiah & Mysore, 2010; King et al., 2016).

Antibiotic treatment in DIRs is generally prolonged compared with standard acute infections due to the chronic and biofilm-associated nature of these infections (Zhang et al., 2024; Alhede et al., 2014). Treatment duration typically ranges from 2 to 6 weeks and should be adjusted based on clinical response and, when available, microbiological findings (King et al., 2016).

Antibiotics alone may be insufficient in cases involving abscesses or persistent filler material. In such situations, treatment should be combined with drainage, hyaluronidase administration, or surgical intervention when indicated (King et al., 2016; Shalmon et al., 2020; Urdiales-Gálvez et al., 2018).

Despite widespread clinical use, standardised evidence-based protocols for antibiotic therapy in DIRs remain limited. Current treatment strategies are largely based on expert opinion and clinical experience, highlighting the need for further research and antimicrobial stewardship (Baranska-Rybak et al., 2024; Munavalli et al., 2022).

9.2 Hyaluronidase

Hyaluronidase plays a central role in the management of complications associated with hyaluronic acid (HA) fillers, including selected delayed inflammatory reactions (DIRs) (King et al., 2016; Shalmon et al., 2020; Urdiales-Gálvez et al., 2018). By enzymatically degrading hyaluronic acid, hyaluronidase facilitates the removal of the implanted material and reduces persistent inflammatory or infectious stimuli.

The enzyme cleaves glycosidic bonds within hyaluronic acid, leading to rapid depolymerisation and tissue resorption of the filler (King et al., 2016). Reduction of filler volume may relieve tissue pressure, improve lymphatic drainage, and eliminate a potential substrate for bacterial colonisation or biofilm formation (Zhang et al., 2024; Shalmon et al., 2020).

Hyaluronidase is considered first-line treatment for non-inflammatory complications such as overcorrection, superficial placement, product misplacement, and non-inflammatory nodules (King et al., 2016; Urdiales-Gálvez et al., 2018). Early intervention may prevent progression to more complex inflammatory reactions.

Its use in inflammatory or suspected infectious reactions remains more controversial. Some authors recommend initiating antibiotic therapy before hyaluronidase administration when infection or biofilm involvement is suspected, aiming to reduce the theoretical risk of bacterial dissemination following rapid filler degradation (Sadashivaiah & Mysore, 2010; Shalmon et al., 2020). However, early hyaluronidase use may still be appropriate in severe reactions or in cases involving resistant HA formulations (King et al., 2016).

Dosing depends on lesion size, location, filler characteristics, and the degree of cross-linking. Small nodules may respond to 10–20 units per injection point, whereas larger or highly cross-linked fillers may require repeated or higher-dose treatments (King et al., 2016; Shalmon et al., 2020). Repeated injections at 2–3-week intervals are commonly recommended when necessary.

High-frequency ultrasound has increasingly been used to guide hyaluronidase injections, particularly in deep filler placement or anatomically complex areas. Ultrasound guidance improves localisation of filler deposits and may enhance both treatment precision and safety (Urdiales-Gálvez et al., 2021).

Despite its effectiveness, hyaluronidase has limitations. It is effective only for HA-based fillers and therefore cannot be used to treat complications related to non-HA materials such as calcium hydroxyapatite or polymethyl methacrylate (King et al., 2016; Shalmon et al., 2020). Potential adverse effects include allergic reactions, overcorrection, and degradation of native hyaluronic acid, although these complications are relatively uncommon.

Clinically, hyaluronidase should be integrated into a multimodal treatment strategy tailored to the underlying pathophysiology of the reaction. Optimal outcomes are often achieved by combining hyaluronidase with antibiotics, anti-inflammatory agents, or procedural interventions when indicated (Baranska-Rybak et al., 2024; Urdiales-Gálvez et al., 2018).

9.3 Corticosteroids

Corticosteroids represent an important but controversial component of treatment for delayed inflammatory reactions (DIRs) following dermal filler injections (King et al., 2016; Baranska-Rybak et al., 2024; Lemperle & Gauthier-Hazan, 2009). Their use is based on potent anti-inflammatory and immunosuppressive effects; however, concerns regarding infection and recurrence require careful patient selection and timing of administration (Sadashivaiah & Mysore, 2010; Urdiales-Gálvez et al., 2018).

Corticosteroids suppress multiple inflammatory pathways by reducing macrophage activity, inhibiting cytokine production, and decreasing fibroblast proliferation and collagen synthesis (Bachour et al., 2021; Anderson et al., 2008). These effects are particularly relevant in persistent inflammatory nodules and foreign body granulomas, where chronic immune activation and tissue remodelling predominate (Lee & Kim, 2015; Lemperle & Gauthier-Hazan, 2009).

Corticosteroids may be administered intralesionally or systemically. Intralesional corticosteroids are generally preferred for localised lesions, especially inflammatory nodules and granulomas, because they allow targeted suppression of inflammation with minimal systemic exposure (King et al., 2016; Urdiales-Gálvez et al., 2018). Triamcinolone acetonide is the most commonly used agent, typically administered in low to moderate concentrations to reduce the risk of local adverse effects such as tissue atrophy, telangiectasia, and hypopigmentation.

To improve efficacy and reduce fibrosis, corticosteroids are often combined with other agents, including 5-fluorouracil, lidocaine, or saline (Lemperle & Gauthier-Hazan, 2009). Combination therapy may be particularly beneficial in refractory or established granulomatous lesions.

Systemic corticosteroids are generally reserved for severe, extensive, or disfiguring inflammatory reactions. Their use remains controversial because systemic immunosuppression may mask underlying infection or contribute to recurrence after treatment discontinuation (Baranska-Rybak et al., 2024; Marusza, Olszanski, Sierdzinski, Ostrowski, et al., 2019). Consequently, many experts recommend limiting systemic corticosteroids to carefully selected cases after infectious causes have been reasonably excluded or treated (King et al., 2016; Urdiales-Gálvez et al., 2018).

Exclusion of active infection is a critical step before corticosteroid administration. When infection or biofilm involvement is suspected, corticosteroids should be used cautiously and preferably after initiation of antimicrobial therapy (Sadashivaiah & Mysore, 2010; Zhang et al., 2024). Premature corticosteroid use may suppress host immune responses and worsen infection.

Considerable variability remains in clinical practice regarding the timing and indications for corticosteroid therapy. Some clinicians advocate early intralesional treatment for inflammatory lesions, whereas others prefer a more conservative approach due to the overlap between infectious and immune-mediated etiologies (Baranska-Rybak et al., 2024; Munavalli et al., 2022). This variability reflects the absence of standardised treatment protocols and emphasises the importance of individualised management.

9.4 Surgical Management

Surgical management represents the final step in the therapeutic algorithm for delayed inflammatory reactions (DIRs) following dermal filler injections and is generally reserved for refractory or complicated cases (King et al., 2016; Lemperle & Gauthier-Hazan, 2009; Urdiales-Gálvez et al., 2018). Although most DIRs can be managed with conservative or minimally invasive approaches, surgical intervention may be necessary when medical treatment fails or when complications such as abscess formation, persistent granulomas, or extensive fibrosis are present.

The main indications for surgical management include failure of medical therapy, recurrent or persistent lesions, fluctuant abscesses requiring drainage, and well-defined nodules or granulomas unresponsive to pharmacological treatment (King et al., 2016; Lemperle & Gauthier-Hazan, 2009). Surgery may also be considered in cases of severe disfigurement, functional impairment, or diagnostic uncertainty requiring histopathological evaluation (Zimmermann & Clerici, 2004; Urdiales-Gálvez et al., 2018).

Incision and drainage are commonly used for abscesses, allowing evacuation of purulent material, reducing bacterial load, and collecting samples for microbiological analysis (Sadashivaiah & Mysore, 2010; Marusza, Olszanski, Sierdzinski, Ostrowski, et al., 2019). Drainage is usually combined with antibiotic therapy and may be guided by ultrasound to improve accuracy and reduce tissue trauma (Urdiales-Gálvez et al., 2021).

Needle aspiration is a less invasive alternative and may be used for smaller or superficial fluid collections. In addition to its therapeutic role, aspiration provides material for culture and helps differentiate infectious from non-infectious processes (King et al., 2016; Sadashivaiah & Mysore, 2010).

In cases of persistent nodules or granulomas, particularly those associated with non-hyaluronic acid fillers, surgical excision may be considered (King et al., 2016; Lemperle & Gauthier-Hazan, 2009). However, complete excision is often challenging because granulomatous lesions may be poorly defined, infiltrative, and extend beyond clinically visible borders. Incomplete removal may lead to recurrence, while surgical excision may cause scarring, tissue deformity, or additional complications, especially in aesthetically sensitive facial areas (Lee & Kim, 2015; Lemperle & Gauthier-Hazan, 2009).

Alternative procedural approaches described in the literature include mechanical extraction using needles and negative pressure, as well as adjunctive techniques such as laser therapy or dermabrasion in selected cases. These methods may reduce the volume of retained filler material and improve cosmetic outcomes, although their use is limited to specific clinical scenarios (King et al., 2016; Lemperle & Gauthier-Hazan, 2009).

Surgery may also be relevant in biofilm-associated complications. In such cases, removal of infected or colonised material may be necessary when conservative therapy is insufficient, but surgery alone is rarely curative and should be combined with appropriate antimicrobial treatment (Sadashivaiah & Mysore, 2010; Zhang et al., 2024; Alhede et al., 2014).

A multidisciplinary approach may be required in complex cases, involving dermatologists, plastic surgeons, and other specialists. Careful patient selection, preoperative planning, and consideration of aesthetic outcomes are essential to minimise complications and optimise results (King et al., 2016; Urdiales-Gálvez et al., 2018).

10. Prevention

Prevention of delayed inflammatory reactions (DIRs) following dermal filler injections relies on minimising bacterial contamination, reducing tissue trauma, and carefully selecting patients and products (King et al., 2016; Sadashivaiah & Mysore, 2010; Zhang et al., 2024). Because these complications appear to arise from interactions between filler characteristics, host immune responses, and microbial factors, preventive strategies should address all three domains (Baranska-Rybak et al., 2024; Zhang et al., 2024).

Strict aseptic technique is fundamental. Thorough skin disinfection before injection is essential, particularly in areas with high bacterial colonisation, such as the lips and perioral region (King et al., 2016; Zhang et al., 2024). Maintenance of sterility throughout the procedure is equally important, especially during multiple passes or high-volume injections, as repeated needle entry may increase the risk of bacterial inoculation. Additional caution is warranted near mucosal surfaces and in areas with acne, dermatitis, active irritation, or compromised skin integrity (Sadashivaiah & Mysore, 2010; Zhang et al., 2024).

Appropriate patient selection is another key preventive measure. Active infections, including dental, sinus, cutaneous, or remote infections, should be identified and managed before filler treatment (Sadashivaiah & Mysore, 2010; Marusza, Olszanski, Sierdzinski, Ostrowski, et al., 2019). Special caution is required in patients with autoimmune or autoinflammatory disorders, altered immune status, or a history of delayed filler-related complications (King et al., 2016; Baranska-Rybak et al., 2024). Elective dental procedures, invasive diagnostic procedures, or surgery performed within 2 weeks of the filler injection should also be considered during treatment planning. Patient education is important, including instructions to avoid unnecessary manipulation of the treated area and to report early symptoms such as tenderness, swelling, or erythema.

Product-related and technical factors also influence prevention. Filler properties, including molecular weight, degree of cross-linking, particle characteristics, and impurities, may affect immunogenicity and inflammatory potential (Lee & Kim, 2015; King et al., 2016). Repeated injections, large filler volumes, layering of different products, and reinjection into previously treated or complicated areas may increase the likelihood of late adverse events. Injection depth, pressure, bolus size, and anatomical location should therefore be carefully considered, particularly in highly mobile or anatomically complex regions such as the lips and periorbital area (King et al., 2016; Zhang et al., 2024).

Overall, prevention of DIRs requires meticulous aseptic technique, individualised risk assessment, careful procedural planning, and early recognition of warning signs. Since no single preventive measure can eliminate all delayed complications, optimal outcomes depend on integrating these principles into routine aesthetic practice (King et al., 2016; Baranska-Rybak et al., 2024).

11. Discussion and Future Directions

Despite significant advances in the understanding of delayed inflammatory reactions (DIRs) following dermal filler injections, many aspects of their pathogenesis, diagnosis, and management remain incompletely understood. Future research should focus on clarifying the interactions among biomaterials, the host immune system, and the microbiome, which appear to play central roles in these complications.

One important area for further investigation is the role of biofilm and the cutaneous microbiome in DIRs. Although microbial factors are increasingly recognised, the mechanisms by which biofilms initiate and sustain chronic inflammation remain unclear. Advanced molecular diagnostic techniques may improve the detection of biofilm-associated infections and help distinguish infectious from non-infectious inflammatory reactions.

Another priority is the standardisation of diagnostic criteria and classification systems for DIRs. The current lack of uniform terminology and diagnostic algorithms complicates clinical management and limits comparison of outcomes across studies. Consensus-based guidelines may facilitate earlier recognition, more accurate diagnosis, and more effective treatment strategies.

In treatment, high-quality clinical studies are needed to evaluate the efficacy and safety of different therapeutic approaches. Current management strategies are largely based on expert opinion and retrospective data. Prospective studies and randomised controlled trials are required to establish evidence-based protocols, particularly regarding antibiotic regimens, timing of hyaluronidase administration, and the role of immunomodulatory therapies.

Innovations in biomaterial engineering may also reduce the incidence of delayed complications. Fillers with improved biocompatibility, lower immunogenicity, and reduced susceptibility to bacterial adhesion could enhance safety profiles. Personalised aesthetic treatment that accounts for individual risk factors and immune status may further improve outcomes.

Overall, future progress will depend on interdisciplinary collaboration among clinicians, microbiologists, immunologists, and biomaterials scientists. A deeper understanding of DIR mechanisms is essential to improve prevention, diagnosis, and treatment, thereby enhancing patient safety and long-term outcomes.

12. Conclusions

Delayed inflammatory reactions (DIRs) represent complex and clinically significant complications of dermal filler procedures, characterised by variable onset, heterogeneous presentation, and multifactorial pathogenesis (Baranska-Rybak et al., 2024; Munavalli et al., 2022). Although relatively uncommon, these reactions pose diagnostic and therapeutic challenges because infectious, immunological, and mechanical mechanisms often overlap (Sadashivaiah & Mysore, 2010; Zhang et al., 2024).

Current evidence suggests that DIRs arise from interactions among filler properties, host immune responses, and microbial factors, including biofilm formation (Bachour et al., 2021; Baranska-Rybak et al., 2024; Zhang et al., 2024). Biofilm-associated microorganisms may persist in a dormant state and evade both immune surveillance and antimicrobial therapy, complicating diagnosis and management (Sadashivaiah & Mysore, 2010; Alhede et al., 2014). In parallel, immunological mechanisms, including foreign body reactions and delayed-type hypersensitivity, contribute to the diversity of clinical manifestations (Lee & Kim, 2015; Baranska-Rybak et al., 2024).

Effective management requires an individualised approach that integrates clinical assessment, imaging (e.g., ultrasonography), and stepwise therapy (King et al., 2016; Urdiales-Gálvez et al., 2021). Treatment modalities, including antibiotics, hyaluronidase, corticosteroids, and, in selected cases, surgical intervention, should be tailored to the suspected aetiology and clinical presentation (King et al., 2016; Baranska-Rybak et al., 2024).

Prevention remains equally important and should be based on strict aseptic technique, appropriate patient selection, careful product choice, and sound injection technique (King et al., 2016; Zhang et al., 2024). As dermal filler use continues to increase globally, recognition and management of delayed complications are becoming increasingly relevant in clinical practice.

Further research is needed to standardise diagnostic criteria, optimise treatment algorithms, and clarify the role of the microbiome and immune system in DIRs. A multidisciplinary approach combining clinical expertise with advances in microbiology, immunology, and biomaterials science will be essential to improve patient outcomes and ensure the long-term safety of dermal filler treatments (Baranska-Rybak et al., 2024; Zhang et al., 2024).

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