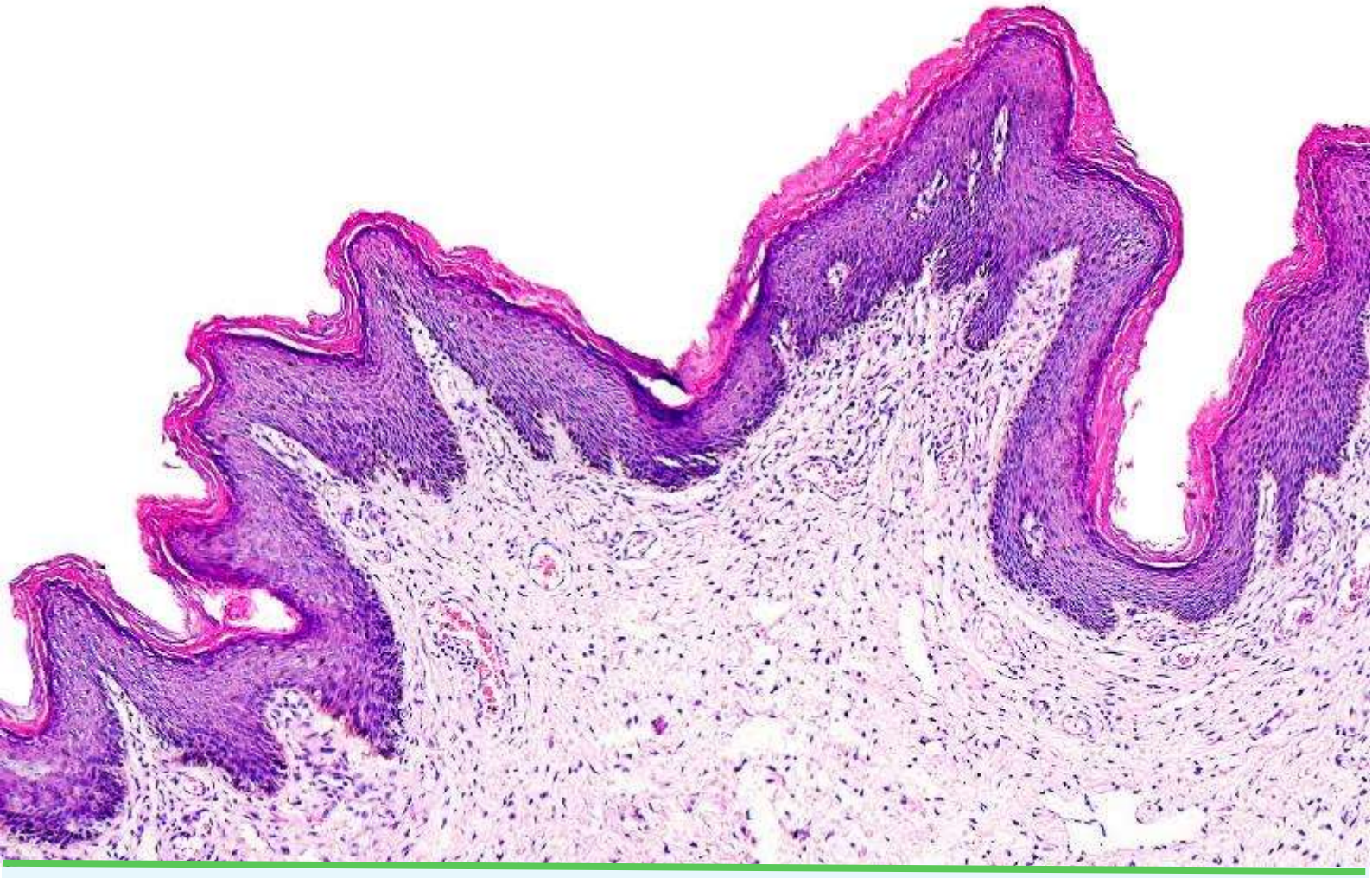
Management of Delayed Onset Nodules (DONs) and Delayed Onset Reactions (DORs) caused by soft tissue filler injections



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Seriousness		Frequency	
Minor		Common	
Minor to Moderate		Occasional	
Moderate	X	Infrequent	
Serious		Rare	X
Major		Very rare	

Management of Delayed Onset Nodules (DONs) and Delayed Onset Reactions (DORs) caused by soft tissue filler injections

Abstract:

The term DON or Delayed Onset Nodule was first coined by the Aesthetic Complications Expert Group (ACE Group) several years ago and has now been widely accepted to describe a visible or palpable unintended mass which occurs at, or close to, the site of injection of a soft tissue filler used for aesthetic procedures. However, a DON or a DOR is not a diagnosis and may include a swelling[1], lump, mass, nodule[1], region of induration[1], delayed hypersensitivity reaction, biofilm, sterile abscess[2] or granuloma[2].

Following on from the initial ACE Group guidance[3], we have now introduced the term DOR or Delayed Onset Reaction to help differentiate between the different management pathways for various skin manifestations that can occur weeks to months after the injection of a soft tissue filler.

ACE Group World have produced a collection of evidence-based and peer reviewed guidelines for the management of common and serious complications experienced in non-surgical aesthetic practice as well as concise algorithms to help the aesthetic practitioner and improve patient safety and outcomes.

Keywords:

Delayed Onset Nodule, Delayed Onset Reaction, Delayed Inflammatory Reaction, Soft Tissue Filler, Dermal Filler, Complication, Lump, Nodule, Biofilm, Granuloma, Cosmetic Medicine.

Definition:

A visible or palpable unintended mass or swelling which occurs at, or close to, the site of injection of a soft tissue filler at least 2 weeks post-treatment in the absence of any previous mass, swelling or inflammation in the same area. Swelling may be persistent or may be relapsing and remitting due to ongoing trigger factors or a temporary response to treatment.

Introduction:

Soft tissue augmentation with filler is the second most popular non-surgical cosmetic treatment worldwide with over 4 million procedures being performed in 2019[4]. However, with increasing numbers of patients having treatment, the number of complications has also escalated. The risk of adverse events is also further increased by unqualified, inexperienced, and lay people performing these procedures.

The ACE Group definition states that a DON or DOR appears at least 2 weeks post-treatment[5], but may manifest several months or even years later, following a period of quiescence. However, other recommendations state that 4 weeks is needed to make a diagnosis[1]. In context, the literature reports that the average time duration from injection to the appearance of a delayed reaction was 4 months[6].

For lumps, nodules, or areas of inflammation that appear immediately after treatment or within a few days, these generally have a different mechanism of action and require a particular management plan. These complications may include misplaced filler, oedema, haematoma formation, allergic reactions, and infections. Aesthetic Complications Expert Group World have produced separate guidelines for these indications.

A lump presenting at the time or within hours of treatment is likely to be due to product misplacement, adjuvant anaesthetic or oedema. Massage by the practitioner and the patient should be the immediate response to an over-correction or product placed too superficially[7,8]. This will lead to mechanical displacement and diffusion and may assist in

reducing volume effects. Vigorous massage is of benefit and will help disperse the product[9]. Injection of lidocaine or saline along with vigorous massage may give greater benefit even with non-hyaluronic acid fillers[9]. When a product is too superficial or there has been an over-correction, early massage may help smooth the skin and uniformly distribute the injected filler[5,8]. Small papules or nodules in the early stage may be amenable to aspiration[7,10] with a 21G needle or by superficial incision and extrusion[5,7,8]. If the cause is too much product or too superficial placement of a hyaluronic acid dermal filler, then this can be treated by the administration of hyaluronidase[7,9,10,11].

Lumps, masses or swelling along with features of acute inflammation (redness, heat, tenderness, pain and swelling) presenting after 3-4 days and before 14 days is likely to be due to infection and should be dealt with accordingly[12].

An abscess may develop several months following soft tissue filler treatment and may or may not be related to the previous treatment. However, an abscess will have characteristic findings that the practitioner should be familiar with, and this should be dealt with by incision and drainage[1] and should not be managed in the same way as a DON or DOR.

The practitioner also needs to be aware that changes in the skin or a skin mass in an area that has previously been injected with a soft tissue filler may be completely unrelated and may represent a benign or malignant skin condition or lesion or be a manifestation of other systemic disease. If the diagnosis is uncertain, it is important to refer on to a more experienced practitioner or conduct further investigations to determine the nature of the lesion which may include ultrasound or biopsy.

Incidence:

The incidence of DONs and DORs following the injection of hyaluronic acid filler appears to be on the increase. In 2002, Friedman et al[13] reported that the incidence of delayed nodule formation following non-animal stabilised hyaluronic acid (NASHA) was as low as 0.02% which is similar to the results published by Andre in a 4-year retrospective study reporting an incidence of 0.6-0.8%[14]. However, in 2016, Artzi et al[15], reported the rate of late inflammatory reactions may be as high as 4.25% in a cohort of 400 patients which is far higher than the 1% of patients developing a delayed onset nodule published by Sadeghpour et el[16] in 2019.

For non-hyaluronic acids, there is little data on reported DONs and DORs although only 'a handful of cases' has been reported for calcium hydroxylapatite in 10 years of clinical use[17] and an incidence of 0.45% of temporarily palpable lumps, which may or may not include DONs and DORs, in a study of 1111 treatments for polycaprolactone[18].

In the absence of larger clinical trials and the distinct lack of reporting complications in this sector, it is difficult to state an actual incidence of DONs and DORs following soft tissue filler injection, but it does appear to be on the rise. There are likely to be multiple factors leading to the rise in these adverse events, including the increased demand for these treatments, treatments being performed by less experienced and non-medical injectors, a vast increase in the number of injectable product ranges entering the market, non-FDA and non-CE approved products as well as counterfeit products becoming available, increased risk factors in patients seeking treatment (such as recent vaccination or infections), lack of standardisation of training companies and a lack of regulation as a whole in non-surgical aesthetic practice.

Differentiation of DONs and DORs:

Although there is sometimes some overlap between DONs and DORs making the diagnosis more difficult, there are certain characteristics which help the practitioner to differentiate between them (Table 1). Generally, DORs have an inflammatory component to them and will present with the classic signs of erythema (rubor), oedema (tumour), heat (calor) and tenderness (dolor), although these signs

and symptoms may be minor or absent completely. DONs are typically more inert and well-defined with a more defined mass and shape.

TABLE 1: Differentiation of DONs and DORs

Characteristic	DON	DOR
Firmness	Hard to firm	Firm to soft
Size	Usually smaller (<1cm)	Usually larger (>1cm)
Boundary	Usually well-defined	Can be more diffuse
Tenderness	Usually none or mild	Often mild to moderate
Inflammation	None or mild	Often some erythema and irritation
Heat	None	May be warm
Time of onset	Usually later, months	Usually sooner, weeks
Trigger	Trigger may not be identified	May be a trigger factor beforehand
Permanence	Often persistent	May be cyclical (relapsing and remitting)

Risk factors:

(a) Patient factors

Autoimmune disease: DONs and DORs are more common in immune-reactive patients and particularly those with active autoimmune diseases[19]. Prior to treatment, patients should be counselled regarding the increased risk of these complications, and it should be documented on the consent form. The practitioner should consider not performing soft tissue filler treatment or consider an alternative. Caution should be taken in patients with rheumatoid diseases, atopic diseases (severe eczema, asthma, hayfever), and autoimmune syndrome induced by adjuvants (ASIA)[19].

Medication: Multiple medications, especially those taking immunomodulatory agents, corticosteroids, chemotherapeutic and haematological drugs, interleukins, systemic antifungals, novel antidiabetic agents and disease modifying anti-rheumatic drugs are at an increased risk of DONs and DORs[3].

Allergies: Patients who have significant allergies or have had any previous reaction of any kind to soft tissue fillers will be at increased risk and the practitioner needs to consider the benefits versus the risk of treatment.

Infection/Inflammation: Localised or systemic infection and localised inflammation of the skin are contra-indications to soft tissue filler treatments and will have an increased risk of adverse events. The underlying infection or inflammation needs to be treated and a sufficient recovery time elapsed prior to any procedure where the skin is breached. Chronic infections also pose an increased risk to patients. For example, the risk of granuloma formation is more common in patients with human immunodeficiency virus (HIV) compared to the normal population when injecting poly-L-lactic acid and occurred in 8.6% of HIV patients in one study[7].

Dental procedures: Due to the risk of bacteraemia and the spread of infection into the tissue planes during dental procedures, the risk of an acute infection and DOR[1,20] is increased, and treatment should be avoided until sufficient time has elapsed to minimise the risk. Similarly, dental procedures can trigger a DON or a DOR several weeks or months post-treatment in a patient who has undergone soft tissue filler augmentation.

Previous filler treatment: Patients who have previously had a soft tissue filler treatment in the same area which has not had sufficient time to have been eliminated by the body, particularly when using a different brand of filler that was used previously, may be at an increased risk of DONs or DORs[1]. This may be due to the presence of a quiescent biofilm which becomes active with subsequent treatment.

Viral infections: It is well documented that DORs can appear within 2 weeks of a viral

illness, such as a flu-like illness[21] or SARS-CoV-2[22], and ACE Group World recommends that soft tissue filler treatments should be delayed for 2 weeks after a viral infection. However, viral infections can trigger a delayed onset reaction in fillers that had been injected several months previously via a Type IV hypersensitivity reaction[21]. Further evidence to support viral infections as a trigger factor, is the higher incidence of these complications occurring in the autumn and winter months[1].

Vaccination: Vaccinations, particularly mRNA vaccinations such as many of the SARS-CoV-2 vaccines, are highly immunogenic[23] by increasing protein translation and modulating innate and adaptive immunogenicity, and therefore can activate an immune response in foreign body implants[22]. ACE Group recommends that injections of soft tissue filler should be delayed for 2 weeks prior to vaccination and 3 weeks post innoculation[22].

Genetic: There is a genetic predisposition in certain patients that transform an expected physiological foreign body response following soft tissue filler injection into an inflammatory granulomatous process by virtue of a T-lymphocyte reaction in susceptible patients[24,25]. If a patient has developed a DON or DOR from their first injection of filler material or suffered with this complication on more than one occasion, it would be wise to avoid further treatment.

(b) Practitioner factors

Infection control: The single most important risk factor for the prevention of a DON or DOR is infection control and ensuring that treatment is conducted in a clean environment and as aseptic as possible[1,24]. Practitioners should refer to the ACE Group World Guideline on Infection Control[26]. Measures include environmental disinfection, skin disinfection, hand hygiene, personal protective equipment, and aseptic technique. Alcohol alone is not sufficient for disinfection due to various pathogens having tolerance to alcohol-based products. Continuous cleaning should be adopted, thorough removing of make-up, followed by double disinfection, ideally using more than one disinfectant agent, and ensuring all areas of the face are appropriately cleaned. Gauze used during the procedure should have disinfectant applied to it and sterile dressing packs used. Changing gloves after initial make-up removal is advised and changing needles if there are multiple injections during the procedure as laboratory studies confirm the risk of bacterial contamination with every needle pass through the skin, although rapid degradation and phagocytosis by the immune system will often prevent contamination becoming infection[27]. However, this clearly will increase the risk of a DON, or a DOR. Additional attention should be taken if treating the peri-oral region and gloves should be changed if contact is made inside the oral cavity[1].

Injection technique: The risk of complication is greater for less experienced practitioners and there needs to be a greater focus on anatomy, injection technique[20] and product specific variables. Improper injection technique[9,19] may result in nodule formation, surface irregularities, overcorrection and asymmetry[8]. Injection pressure, needle diameter and number, depth and angle of penetration sites can all be factors that may increase the risk of developing a DON and DOR as well as the number of times a needle is passed through the skin[28]. The injection of large boluses (greater than 0.2ml[1]) of soft tissue filler can lead to greater mechanical irritation that may subsequently trigger an inflammatory cascade and delayed onset nodule or reaction[27]. Larger boluses may also lead to nodules by causing capsular contraction[10].

Aftercare: Post-procedure contamination needs to be avoided, patients should disinfect their hands, avoid touching their face and a strict no make-up policy for at least 6 hours.

(c) Product factors

Complications appear to be more frequent with particulate fillers[9] (combination gels) although any injected foreign body elicits a reaction from the host tissue, the magnitude of which

depends on the nature of the product[2]. The increased immunogenicity of the product increases the risk of a DON or DOR and this is a function of viscosity, roughness[5], hydrophobicity[5], charge[5], particle size[5], particle shape[9] and surface porosity[5]. Hyaluronic acid fillers with a low-molecular weight have higher proinflammatory activity and the potential to increase the risk of a DON or DOR further[16]. Furthermore, low quality products are more likely to cause a delayed inflammatory reaction[20].

The micro-particles of poly-L-lactic acid gel are likely to continuously provoke a host response as the degradation takes place and subunits are released, leading to a comparatively high frequency of granulomatous nodules up to 14 months (or more) after injection[2].

Sadeghpour et al[16] (2019) also demonstrated that hyaluronic acid fillers comprising Vycross™ technology have a higher incidence of DONs which appeared to be late-onset, immunogenic, non-infectious, and non-biofilm in nature and responded best to intralesional steroid injections, rather than the more well adopted methods of treatment.

If the patient has experienced a previous DON or DOR following soft tissue filler augmentation, experts recommend that a different hyaluronic acid brand of filler or a non-hyaluronic acid filler should be used for subsequent treatments[20]. However, treatments using a combination of different products may also be a risk factor for DORs[20] so if the patient has not had a prior reaction, using the same brand of filler for subsequent treatments may be prudent.

Minimising the risk

DONs carry the potential to produce long-term disfigurement and dissatisfaction for the patient. They tend to occur in visible regions and can be difficult to conceal with make-up. Patient selection and preparation is crucial. Select patients with expectations that can be met, absence of significant co-morbidity and polypharmacy or the use of immunomodulatory drugs which may make later management difficult were it necessary.

Select the correct product for the indication that you are treating. Always use a product that has evidence for its use and safety documentation. Ensure you receive your product from a trusted source and that it has been appropriately transported and stored.

The administration of dermal fillers requires an aseptic technique. Thorough cleansing followed by disinfection with 2% chlorhexidine gluconate in 70% alcohol, full removal of skin debris, thorough hand sanitation, and wearing sterile gloves[10]. Reduce trauma by using the correct gauge needle or cannula appropriate for the chosen product. Ensure injections are in the correct tissue plane and not too superficial and not intramuscular[9,19] facilitated by appropriate assessment and marking up of the target anatomical region where needed.

Areas of caution

The lips appear to be more prone to developing nodules, either due to the thin mucosa, increased amounts of bacterial flora or the underlying hypermobile muscles[9], which can cause product clumping and extrusion[19]. The periorbital region is a challenging area due to a combination of vascular factors, interpenetrating lymphatics, bony prominences, superficial fat compartments and reduced skin thickness and should only be treated by experienced practitioners.

Trigger Factors

Approximately 40% of delayed onset nodules may have an identifiable trigger[6] prior to their appearance. Trigger factors for a DON or a DOR include the following:

- Systemic bacterial infection[24,28], localised infection[1], sinusitis[20]
- Viral infections[1,20]
- Dental procedures[16,20]
- Vaccination[29]
- Immunosuppressive therapy or chemotherapy (including interferon treatment[24])
- High UV exposure

DONs

DONs are thought to be caused by low-grade filler reactions[1] and are characterised by a cool, firm, discrete, regular surface and are likely to be due to product misplacement or migration and associated chronic immune-inflammatory reaction and possibly low-grade bacterial infection. Although more inert than their counterparts, DORs, they may still have biofilm present and by not considering this detail, outcome may be worsened if antibiotics are not given prior to other treatments.

DORs

DORs will usually have the characteristics of pain, tenderness or redness[5] and have the histopathology of biofilm[1] or foreign body reactions[1]. When compared to a DON, they are more likely to be associated with a trigger factor, although this will be absent in more than half of cases. They are usually less well defined and more diffuse than a DON.

Management

Late onset swellings, lumps and nodules have been classified into either a Delayed Onset Nodule or Delayed Onset Reaction for simplicity and to help practitioners with the correct management, however, it is recognised that clinical presentation and aetiology can be variable[1] and that an individual treatment plan based on clinical history and findings should be adopted.

If a patient develops a delayed onset nodule, initial assessment needs to include the impact it has on the patient. Some DONs and DORs may be palpable within the skin but not visible and they may be best left alone with watchful waiting[1,6]. It may take several weeks or months for the successful resolution of a DON or DOR, even when the appropriate treatment is undertaken[3,30].

If the DON or DOR requires treatment, the patient needs to understand the risks versus benefits of treatment and the possible side-effects from intervention before making an informed decision and consent. Ensure good record keeping with photography.

Antibiotics

Experts are divided about whether biofilms or bacterial contamination are a cause of a DON or DOR, however there is good evidence that certain antibiotics can help resolve these complications which may be due to their anti-microbial effect or their immunomodulatory and anti-inflammatory[5,20] properties. Some bacteria can secrete an extracellular matrix of exopolysaccharides, that can include hyaluronic acid, to form a microenvironment[30] conferring protection from the action of the immune system or drugs and to enter a dormant, planktonic state only to reawaken when conditions are favourable for replication. This may occur following periods of illness or by repeated injections. When they do arise, they can cause granulomatous inflammation, abscesses and nodules[10]. Bacteria that have been implicated in the formation of biofilms include *S. epidermidis* and *P. acnes*[24] and these organisms can survive in vitro on a hyaluronic acid medium[28].

For the majority of DONs and DORs, initial treatment should be with an antibiotic, either a tetracycline[5,20] (e.g. minocycline 100mg OD or doxycycline 100mg OD) or a macrolide[2,9,20] (e.g. clarithromycin 500mg BD). It is important that the practitioner is familiar and competent with prescribing antibiotics and aware of potential interactions, side-effects, and contra-indications. Although penicillins are often used first line for acute skin infections, there is very little evidence in the literature to support their use for the management of DONs or DORs and therefore not recommended.

Antibiotics need to be taken for at least 48 hours[20,24] before embarking on any other treatment although ACE Group World recommend waiting a week after commencing antibiotics to assess the response. DONs are likely to need adjunctive treatment to the

antibiotics whereas a DOR may resolve using antibiotics alone. The severity of the delayed reaction will have an impact on how timely other treatments should be delivered.

If no clinical improvement has occurred following first-line antibiotics, the practitioner should consider switching to a second-line antibiotic or prescribing dual-therapy[9] and considering other adjunctive treatments. Third-line antibiotics should only be considered if there is a contra-indication to first- and second-line options or they are not tolerated due to side-effects.

If there has been an improvement, but the DON or DOR has not completely resolved, it would be advisable to continue the antibiotics for a further 2 weeks and then review. Depending on the response, antibiotics can be continued for a longer period, dual-therapy may be considered or an additional adjunctive treatment added to the regime.

Even if the DON or DOR has not completely resolved, if the outcome is acceptable to the patient and practitioner, treatment may be stopped, and a watchful waiting approach taken.

1. Tetracyclines (1st Line)

As well as exerting an anti-microbial effect on both Gram-positive and Gram-negative bacteria, they also have additional anti-inflammatory and immunomodulatory effects[19,20] making them particularly useful for the management of DONs and DORs as well as having a high degree of lipid solubility. They are bacteriostatic and exert their effects by inhibition of protein synthesis. They should not be used in pregnant or breast-feeding women and used cautiously in hepatic or renal impairment. Tetracyclines can also cause photosensitivity so patients should be advised on the use of sun protectant.

2. Macrolides (2nd Line)

Macrolides are considered beneficial due to their ability to restrain quorum sensing and they accumulate in adipose tissue[20]. Quorum sensing is thought to be particularly important regarding biofilms as bacteria in a dormant state can communicate and change their behaviour according to the surrounding environment. They exert their effect by the suppression of protein synthesis in susceptible bacteria. The most common side effects caused by macrolides include abdominal pain, diarrhoea, nausea, and vomiting.

3. Fluoroquinolones (3rd Line)

Due to the potential side effects of quinolones[20] including aortic rupture, antibiotic-associated colitis, cardiovascular toxicity, tendon and muscle damage and prolonging the QT interval, ACE Group World recommends that these drugs are used as 3rd line agents if there is intolerance, allergy or other contra-indication for macrolides and tetracyclines. They work by inhibition of bacterial enzymes responsible for DNA replication, transcription, repair, and recombination. Ciprofloxacin should not be prescribed for a longer duration than 60 days (British National Formulary).

Hyaluronidase

Hyaluronidase should not be considered first line treatment for a DON or DOR, unless the cause of the problem is due solely to filler misplacement or migration, due to a lack of clinical improvement[16] when used first line. It should be considered if there has been no significant improvement after at least 48 hours of antibiotics and the DON or DOR is a result of injection with hyaluronic acid dermal filler[5,31] (See ACE Group World guidance on The Use of Hyaluronidase in Aesthetic Practice).

Most experts agree that hyaluronidase should not be used until at least 48 hours[20,24] after commencing an antibiotic, due to the potential risk of spreading infection into adjacent tissue[10,28]. Hyaluronidase has successfully led to the resolution of a “true hypersensitivity and granulomatous reaction” 5 months after the injection of hyaluronic acid within 24 hours where injected cortisone and topical tacrolimus failed to do so[32]. Either mono or dual antibiotic therapy should be continued when considering treatment with hyaluronidase with many

experts reporting the failure of hyaluronidase in the successful management of a DON or DOR if not used in combination with other treatments[1].

There are different types of hyaluronidase available globally, varying in their source (commonly, bovine, ovine or recombinant) and the amount of units per ampoule. In the UK, Hyalase® 1500 IU (Wockhardt, UK) is commercially available, and ACE Group World recommend reconstitution 1500 IU in 5mls of bacteriostatic saline and injecting between 20-30 units to dissolve 0.1ml of hyaluronic acid. Nodules should be injected with a suitable length and gauge needle to penetrate the lesion from multiple angles and depths. The practitioner should attempt to mechanically disrupt the nodule as much as possible to allow greater exposure of the contents to the hyaluronidase, antibiotics, and the immune system. Although 20-30 units of hyaluronidase are advocated per 0.1ml of hyaluronic acid filler, there are multiple factors that can affect this amount[11] and practitioners should treat to clinical effect which they can assess with examination and palpation. In clinical practice, often 30-250 units[20] of hyaluronidase are used with good success. This dosage may need to be doubled if a more resistant filler has been injected[20], such as Vycross™ technology. As hyaluronidase is administered, the practitioner should apply firm pressure and massage to the mass or nodule to assist its breakdown and resolution. If there has been an improvement with hyaluronidase, this can be repeated at weekly intervals until complete resolution, or the patient has received a satisfactory outcome. A combination of broad-spectrum antibiotics with repeated high-dose hyaluronidase has been proven to be an effective treatment for the management of DORs[15].

Oral Corticosteroids

Oral steroids often help to reduce the signs and symptoms of inflammation associated with a Delayed Onset Reaction but often does not deal with the cause of the problem, resulting in a rebound effect[1] when they are discontinued. They are most useful when there is an identified, self-limiting trigger, such as a viral infection or vaccination, leading to an area of inflammation and swelling, with no discrete nodule or mass identified.

Practitioners need to be aware of the immunosuppressant effects of steroids, which can lead to a worsening scenario, if the DON or DOR has sub-clinical bacterial colonisation. Careful consideration should be taken if prescribing oral steroids following vaccination, as this can lead to failure of the vaccine in mounting an appropriate immune response[22]. Caution also needs to be taken when considering prescribing steroids, if the patient has a good symptomatic response, but the underlying cause is not dealt with, a prolonged course of steroids may then be sought by the patient which has further negative consequences. If oral steroids are continued beyond a 3-week period, the dosage should be tailed off gradually rather than abrupt withdrawal[22].

Oral steroids may be considered if there has been an extensive inflammatory response[20] at initial presentation. If oral steroids are to be prescribed, the recommended is prednisolone 40mg per day for 7-21 days[20] or dexamethasone 4mg once daily. A shorter course of dexamethasone may be sufficient due to the longer half-life of this medication. If oral steroids are to be prescribed for more than a week, the practitioner should consider co-prescribing gastric protection (a H2-receptor antagonist or proton-pump inhibitor)[21]. Side-effects include severe psychiatric reactions, adrenocortical insufficiency, immunosuppression, and sleep disturbance.

Intralesional Immunosuppressive Drugs (Steroids/Anti-Mitotic Agents)

Intralesional steroids, with or without, 5-fluorouracil should only be considered when other measures have been exhausted[1].

For non-hyaluronic acid fillers, DONs can be treated with intralesional steroid injection with good effect[5,8,9,10,28,33]. Most of the evidence recommends the use of triamcinolone

acetonide 40mg/ml (Kenalog™, Bristol-Myers Squibb, Dublin) and this can be diluted to lesser dilutions using water for injection or sodium chloride. DeLorenzi[10] recommends graduated injections of triamcinolone acetonide of 0.1ml starting with a 10mg/ml concentration and then increasing concentration to 20mg/ml and 40mg/ml at 4 weekly intervals. There is a risk of post-treatment soft tissue atrophy (20-30%[33]) and telangiectasia[9] when administering intralesional steroids and the patient will need counselling to this effect. The addition of 5-flurouracil in a ratio of 80:20 (5-FU:triamcinolone)[1] may help limit these side effects of intralesional steroids[21,33]. If an improvement is observed, this treatment may be repeated every 2-4 weeks[20].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Several authors recommend the use of NSAIDs for the management of DORs as an alternative to oral corticosteroids to help manage some of the inflammatory signs and symptoms but without the potential side-effects and immunosuppression associated with steroid usage. However, like oral steroids, these medications are not dealing with the complication, but simply masking the inflammatory aspects. They are generally not as effective as oral steroids, and their role is limited in the management of DORs. They may be considered for short term relief when there is an identified trigger factor, and it is expected that the DOR will settle spontaneously within a relatively short period. Gastric protection should also be considered if NSAIDs are taken or alternatively, a cyclooxygenase-2 (COX-2) inhibitor may be prescribed, which have less gastric irritation than traditional NSAIDs.

Antihistamines

Antihistamines may play a small part in symptom control for some patients with DORs, but they do not manage the cause[1] or resolve the situation so should only be considered for symptom relief where there is some benefit. However, due to the mechanism of action involving T-lymphocytes, delayed hypersensitivity reactions do not respond to antihistamines[34].

Allopurinol

The addition of allopurinol[33] should be considered if a DON has failed to respond to antibiotics, intralesional hyaluronidase and intralesional steroid injections. Allopurinol is a xanthine-oxidase inhibitor, and its principal mechanism of action is to lower uric acid levels. Its mechanism in the management of DONs is little researched or understood and should only be considered by practitioners who are expert in the management of complications. The recommended dosage for this indication is allopurinol 300mg twice a day.

Platelet Rich Plasma

There is a limited amount of evidence to suggest that platelet rich plasma[20] has a role in the management if a biofilm is suspected, by virtue of its antimicrobial, hyaluronic acid degradation and destruction of biofilms properties[28].

Intralesional Antibiotics

Although intralesional antibiotics have been cited in the literature for the management of filler-related nodules, there is insufficient evidence available to support their use as a standard therapy of the management of DONs and DORs.

Surgical Excision

Foreign body granulomas grow finger-like projections into the surrounding tissue[28], making surgical excision a more difficult option, and should only be considered as a last resort[1,20].

Outcome

Even with the correct diagnosis and treatment, it can take weeks to months[1] for a DON or DOR to resolve, with an average time of 6 weeks[6] for full resolution. In the absence of treatment and adopting conservative

management, foreign body granulomas tend to resolve within 1[18] to 2[35] years.

Further Investigations:

In most cases, the diagnosis of a DON or a DOR is clinical and further investigations are not necessary[1], however they may be important in cases where the diagnosis is in question, there is lack of response to treatment or for formulating a customised treatment strategy[1]. Aspirate or tissue biopsies may be taken for aerobic and anaerobic, bacterial, mycobacterial, and fungal culture[20]. It is important that the laboratory is notified if an atypical organism is suspected, as often these require a different and longer culture process. However, despite adequate samples being taken, the literature reports the success of identifying a causative organism to be very low. Results are improved using tissue samples and investigations including electron microscopy, polymerase chain reaction[34], and immunofluorescence.

Ultrasound is an inexpensive and relatively common tool to help identify the nature of a DON or DOR, giving further information regarding volume, depth and consistency and helps ensure intralesional therapies are administered correctly. Ultrasound is highly dependent on the skill and experience of the operator and the ultrasound device used for this purpose.

Refer

Depending on the experience of the practitioner and if standard treatments have not produced any clinically significant improvement, then an expert in the management of DONs and DORs should be consulted to consider punch biopsy and anaerobic and aerobic culture[5], resurfacing procedures such as spot dermabrasion or laser[8,9,31], intralesional anti-mitotics (e.g. 5-fluorouracil[9]) and surgical excision[7,31]. Lasers have been used to improve the appearance and help disrupt nodules and in particular there is evidence that fractional lasers have improved the visible material in the lower eyelids and lips[36]. More recently, intralesional radiofrequency has been proposed as an alternative option[1].

Throughout the whole process, the patient should be kept fully informed and under regular review with contemporaneous record keeping and photography. It is recommended to inform your medical defence organisation to ensure that the complication and subsequent treatment is covered by your indemnity insurance.

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Aesthetic Complications Expert Group World protocol for the Management of DONs and DORs

DIAGNOSTIC CRITERIA
Visible or palpable swelling, lump, mass, nodule, region of induration, at or close to the site of soft tissue filler injection at least 2 weeks post-treatment and other diagnoses excluded

Is it causing physical, emotional or aesthetic distress?

NO → **Reassure/Watchful waiting**

YES

DON
Hard to firm, <1cm, well defined, inert

DOR
Firm to soft, more diffuse, inflammatory

Acute inflammatory response +/- trigger factor

NO

YES

Consider short course of oral steroids, NSAID and/or antihistamine

RESOLVED

ANTIBIOTICS
Start antibiotics, monotherapy, for 1 week then review
1st Line: Tetracycline (e.g. Doxycycline 100mg OD)
2nd Line: Macrolide (e.g. Clarithromycin 500mg BD)
3rd Line: Fluoroquinolone (e.g. Ciprofloxacin 500mg BD)

RESOLVED | **IMPROVING** | **NOT IMPROVED**

Continue antibiotics (Consider dual therapy)

Alternative antibiotics (Consider dual therapy)

INTRALESIONAL THERAPY & CONTINUE ANTIBIOTICS

HA FILLER

HYALURONIDASE
Intralesional injections from multiple angles and depths with mechanical disruption.
30-250 IU per nodule
(x2 if resistant nodule)

Repeat weekly up to 3 cycles

RESOLVED

UNRESOLVED

Consider Allopurinol 300mg BD

NON-HA FILLER

TRIAMCINOLONE ± 5-FU
Intralesional injections from multiple angles and depths with mechanical disruption.
See full guidelines for protocol.

Repeat 2-4 weekly up to 3 cycles

RESOLVED

UNRESOLVED

FURTHER TREATMENT
Consider Platelet Rich Plasma, Intralesional Antibiotics, Fractional Laser, Intralesional Radiofrequency

UNRESOLVED

SURGICAL EXTRACTION AS A LAST RESORT

FURTHER INVESTIGATION
Consider Ultrasound, Biopsy & Culture, MRI.

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