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Management of Delayed Onset Nodules

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Definition

For the purpose of these guidelines, a delayed onset nodule (DON) is a visible or palpable unintended mass that occurs at or close to the injection site of dermal filler.

Lumps, masses, nodules, regions of induration, delayed hypersensitivity reactions, biofilms, sterile abscesses[1] and granulomas[1] are all terms used to describe a delayed onset nodule. These categories are prone to substantial overlap, as reflected in the treatment options. To avoid a focus on largely unhelpful histological categories, the term DON is adopted by the Aesthetic Complications Expert Group. A granuloma is actually a histological diagnosis and no lump or nodule should be named as this unless there is histological evidence.[2]

Seriousness of complication		Frequency of complication	
Minor complication		Common	
Worrying complication		Occasional	
Moderate complication		Infrequent	X
Serious, but not major	X	Rare	
Major complication		Very rare	

Incidence

A four-year retrospective study reported a 0.6- to 0.8-percent incidence of hypersensitivity reactions including nodules to hyaluronic acid dermal fillers.[6] True foreign body granulomas are rare with an estimated incidence of between 0.01 and one percent. They can occur with all injectable dermal fillers and usually appear after a latent period of several months to years after treatment.[3,4] One study reported the incidence of granulomatous foreign body reactions with bovine collagen at 1.3 percent.[5]

Risk Factors

(A) Patient factors. Delayed onset nodules are more common in immune-reactive patients and particularly those with active autoimmune diseases.[7] Although lacking robust evidence, it would seem prudent to approach with caution patients with rheumatoid diseases, atopic diseases (severe eczema, asthma, hayfever), autoimmune syndrome induced by adjuvants (ASIA),[7] multiple medications (especially immunomodulatory agents, corticosteroids, chemotherapeutic and hematological drugs, interleukins, systemic antifungals, novel antidiabetic agents, and disease modifying anti-rheumatic drugs), significant allergies, and previous reactions of any kind to dermal fillers. 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 percent of HIV patients in one study.[5] Injections in highly mobile areas, such as the lips, increase the risk of delayed-onset noninflammatory nodules.[4]

(B) Practitioner factors. The risk of complication is greater for less experienced practitioners and there needs to be a greater focus

on anatomy, injection technique, and product-specific variables. Improper injection technique[4,7] 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 nodule.

(C) Product factors. The increased immunogenicity of the product increases the risk of a DON, and this is a function of viscosity, roughness,[9] hydrophobicity,[9] charge,[9] particle size,[9] particle shape,[4] and surface porosity.[9]

Complications appear to be more frequent with particulate fillers[4] (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.[1] The microparticles of poly-L-lactic acid gel are likely to continuously provoke a host response as long 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.[1]

Although rarely used nowadays, in one 2008 study, there was an 80-percent incidence (16 out of 20) of nodule formation when using porcine collagen for lip augmentation and collagenase was ineffective in dissolution of these nodules.[7]

Minimizing 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, as ever, crucial. Select patients with expectations that can be met, absence of significant comorbidty 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[2] (See ACE Group guidelines on Management of Acute Skin Infections).

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[4,7] facilitated by appropriate assessment and marking up of the target anatomical region where needed.

Areas of Caution

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.

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, which can cause product clumping and extrusion.[7]

Treatment

If a patient develops a delayed onset nodule, initial assessment needs to include the impact it has on the patient. Some DONs may be palpable within the skin, but not visible and they may be best left alone with watchful waiting. Some nodules may be "disguised" by the injection of dermal filler around the area. If the DON 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 recordkeeping with photography.

A lump presenting at the time or within hours of treatment is likely to be due to product misplacement, adjuvant anesthetic or edema. Massage by the practitioner and the patient should be the immediate response to an over-correction or product placed too superficially.[5,8] 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.[4] Injection of lidocaine or saline along with vigorous massage may give greater benefit even with nonhyaluronic acid fillers.[4]

Lumps, masses or swelling along with features of acute inflammation (redness, heat, tenderness, pain, and swelling) presenting after 3 to 4 days and before 14 days is likely to be due to infection and should be dealt with accordingly (See ACE Group guidelines on Management of Acute Skin infections).

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.[8,9] Small papules or nodules in the early stage may be amenable to aspiration[2,5] with a 21G needle or by superficial incision and extrusion.[5,8,9] 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[2,4,5] (See

ACE Group guidelines on The Use of Hyaluronidase in Aesthetic Practice). Hyaluronidase should be used with caution if infection is also suspected since this may lead to the infection spreading further along the tissue plane.[2]

Capsular contracture around tissue fillers is rare, but can occur. This is when a large bolus of filler has been injected and a capsule develops around the surface exposed to the host tissue. This capsule subsequently contracts creating a nodule or a lump that can be painful. This can be treated by local anesthetic and aspiration with or without hyaluronidase.[2]

DONs present after weeks or months and may be divided into either noninflammatory or inflammatory.

Noninflammatory DONs

Noninflammatory nodules are often characterized 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.

The initial management is with basic mechanical displacement and diffusion using saline and/or lidocaine, matching the volume of product injected which you wish to disperse. Subcision may also be attempted using a sharp needle although caution needs to be adopted not to cause further problems with fibrosis or scarring. If this fails to resolve the problem, proceed as for inflammatory lesions.

Inflammatory DONs

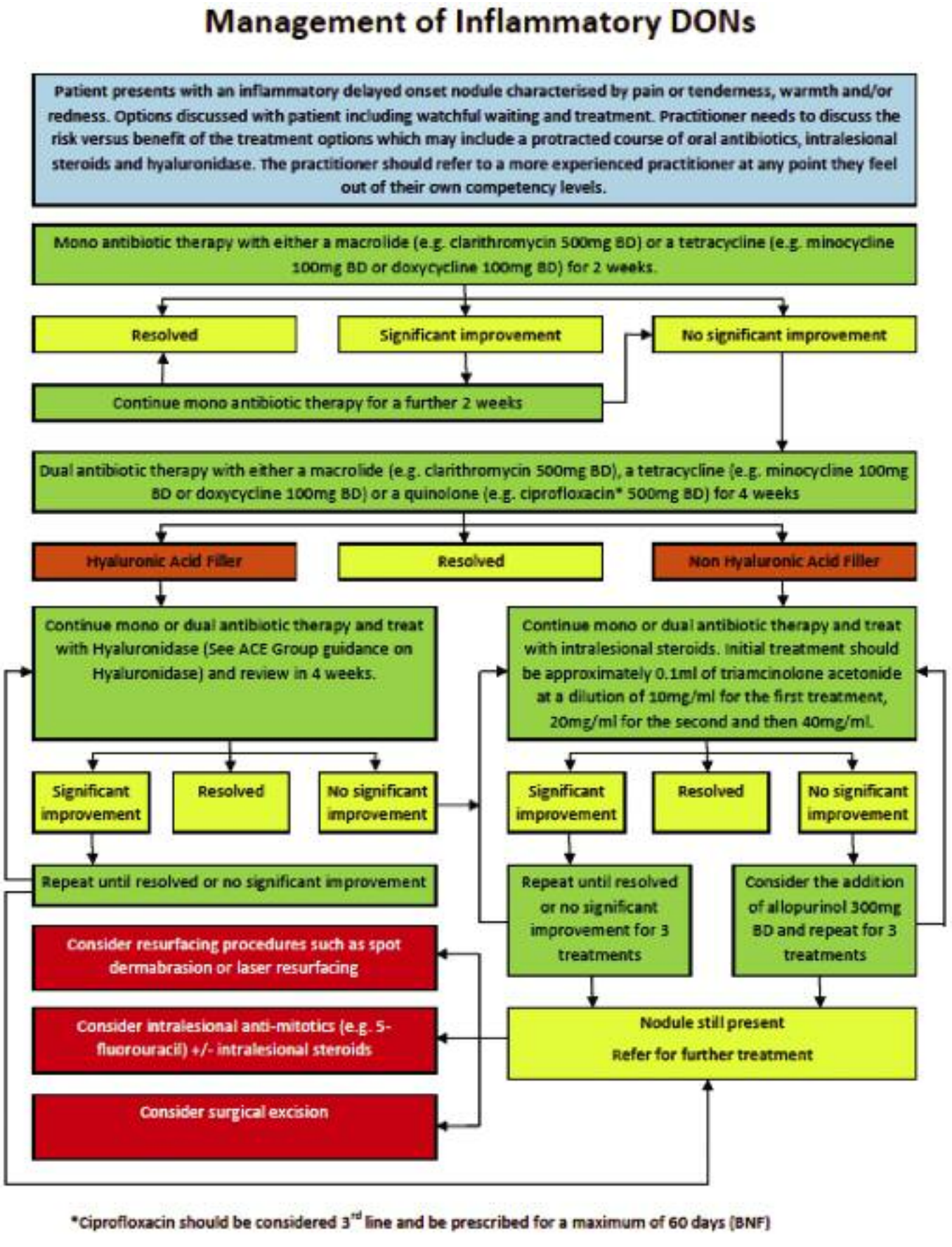
Inflammatory nodules will usually have the characteristics of pain, tenderness, or redness.[9] One study observed 55 adverse reactions to polyacrylamide gel out of 40,000 injected patients and that the likely cause was contamination with low-virulence bacteria. When these reactions were treated with steroids or high-dose nonsteroidal anti-inflammatory medication without antibiotics, the prognosis was significantly worse and intensive antibiotics or surgery was sometimes required; however, if the antibiotics were used in the first instance, the outcomes were more favorable.[1,4] There is considerable debate about whether biofilms are a cause and whether bacterial contamination is a trigger to a DON; however, whether it is the antibacterial effect of antibiotics that improve the outcome or the immunomodulatory and anti-inflammatory[7] properties of these drugs instead is academic. Some bacteria are capable of secreting an extracellular polymeric substance to protect themselves from the action of the immune system or drugs and to enter a dormant, planktonic state only to reawaken when conditions are favorable 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.[2]

Initial treatment should be with an antibiotic, either a macrolide (e.g., clarithromycin 500mg twice daily) or a tetracycline[9] (e.g., minocycline 100mg twice daily or doxycycline 100mg twice daily) for two weeks and then review. It is important that the practitioner is familiar and competent with prescribing oral antibiotics and aware of potential interactions, side-effects, and contraindications.

After two weeks, if there is significant improvement, but it has not completely resolved, it would be advisable to continue the antibiotics for a further four weeks and then review. If there has not been any significant improvement, then dual antibiotic therapy should be prescribed.[4] Antibiotics that should be considered are a macrolide (e.g., clarithromycin 500mg twice daily), a tetracycline (e.g., minocycline 100mg twice daily or doxycycline 100mg twice daily), and/or a quinolone (e.g., ciprofloxacin 500mg twice daily). Due to the potential side effects of quinolones including antibiotic-associated colitis and prolonging the QT interval, the ACE Group recommends that these drugs are used as third-line agents if there is intolerance, allergy, or other contraindication for macrolides and tetracyclines. Ciprofloxacin should not be prescribed for a longer duration than 60 days (British National Formulary). Dual antibiotic therapy should continue for four weeks and the patient should be reviewed again.

If there has been no significant improvement after four weeks and the DON is a result of injection with hyaluronic acid dermal filler, then hyaluronidase should be considered[9,11] (See ACE Group guidelines on The Use of Hyaluronidase in Aesthetic Practice). Hyaluronidase has successfully led to the resolution of a "true hypersensitivity and granulomatous reaction" five months after the injection of hyaluronic acid within 24 hours where injected cortisone and topical tacrolimus failed to do so.[10] Either mono or dual antibiotic therapy should be continued during this process at the judgement of the practitioner. If there has been a moderate to significant improvement with hyaluronidase, this can be repeated at four weekly intervals until complete resolution or the patient has received a satisfactory outcome. If there is no real improvement, the DON should be treated the same as a non-hyaluronic acid filler.

For non-hyaluronic acid fillers, inflammatory DONs can be treated with intralesional steroid injection with good effect.[2–4,8,9] The majority of evidence recommends the use of triamcinolone acetonide 40mg/mL and this can be diluted to lesser dilutions using water for injection or sodium chloride. DeLorenzi[2] 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 four weekly intervals. There is a risk of post-treatment soft tissue atrophy (20–30%[3]) and telangiectasia[4] when administering intralesional steroids, and the patient will need counselling to this effect. If there has been no significant


Management of Inflammatory DONs
Patient presents with an inflammatory delayed onset nodule characterised by pain or tenderness, warmth and/or redness. Options discussed with patient including watchful waiting and treatment. Practitioner needs to discuss the risk versus benefit of the treatment options which may include a protracted course of oral antibiotics, intralesional steroids and hyaluronidase. The practitioner should refer to a more experienced practitioner at any point they feel out of their own competency levels.
Mono antibiotic therapy with either a macrolide (e.g. clarithromycin 500mg BD) or a tetracycline (e.g. minocycline 100mg BD or doxycycline 100mg BD) for 2 weeks.
Resolved
Significant improvement
No significant improvement
Continue mono antibiotic therapy for a further 2 weeks
Dual antibiotic therapy with either a macrolide (e.g. clarithromycin 500mg BD), a tetracycline (e.g. minocycline 100mg BD or doxycycline 100mg BD) or a quinolone (e.g. ciprofloxacin* 500mg BD) for 4 weeks
Hyaluronic Acid Filler
Resolved
Non Hyaluronic Acid Filler
Continue mono or dual antibiotic therapy and treat with Hyaluronidase (See ACE Group guidance on Hyaluronidase) and review in 4 weeks.
Continue mono or dual antibiotic therapy and treat with intralesional steroids. Initial treatment should be approximately 0.1ml of triamcinolone acetonide at a dilution of 10mg/ml for the first treatment, 20mg/ml for the second and then 40mg/ml.
Significant improvement
Resolved
No significant improvement
Significant improvement
Resolved
No significant improvement
Repeat until resolved or no significant improvement
Repeat until resolved or no significant improvement for 3 treatments
Consider the addition of allopurinol 300mg BD and repeat for 3 treatments
Consider resurfacing procedures such as spot dermabrasion or laser resurfacing
Consider intralesional anti-mitotics (e.g. 5-fluorouracil) +/- intralesional steroids
Nodule still present
Refer for further treatment
Consider surgical excision
*Ciprofloxacin should be considered 3rd line and be prescribed for a maximum of 60 days (BNF)

improvement of the DON following the initial intralesional steroid injection then the practitioner may consider the addition of allopurinol[3] 300mg twice daily according to the competence and experience of the practitioner. Again either mono or dual antibiotic therapy should be continued during this process at the judgement of the practitioner.

Refer

If there has still not been any significant improvement then an expert in the management of DONs should be consulted to consider punch biopsy and anaerobic and aerobic culture,[9] resurfacing procedures such as spot dermabrasion or laser,[4,8,11] intralesional anti-mitotics (e.g., 5-fluorouracil[4]) and surgical excision.[5,11] 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.[12] Conservative management is also an option in collaboration with the patient and Carruthers and Carruthers found that all granulomas resolved within two years.[13]

Throughout the whole process, the patient should be kept fully informed and under regular review with good documentation and photography. It is recommended to speak to your medical defense organization early on as they will also be able to advise on the correct course of action and by not doing so may invalidate the policy if a claim does arise.

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Management of Delayed Onset Nodules Consensus Group: Helena Collier RN NIP; Ben Coyle, MD; Harryono Judodihardjo, MD; Sam Robson, MD

The Aesthetic Complications Expert (ACE) Group was first established in 2010 following a national conference where it became clear that although practitioners were trained in the delivery of nonsurgical cosmetic treatments, the management of complications has been woefully neglected. In the event of a complication, many practitioners find it extremely difficult to find help and expert advice has been lacking, inconsistent, and even incorrect from some companies. The ACE Group has developed evidence-based, peer reviewed guidelines to cover the majority of complications that can occur in nonsurgical aesthetic practice. The ethos of the ACE Group is not for profit to avoid any commercial conflict and the guidelines are intended to be distributed as widely as possible. Every guideline has been produced after a vast literature review and has been further reviewed by leading experts in the United Kingdom. The ACE Group will continue to review its guidelines as more evidence and consensus opinion becomes available. Additionally, the ACE Group has an expert network to help less experienced practitioners manage complications effectively. Complications in aesthetics are vastly under-reported, and the ACE Group encourages practitioners to report any complication so that as a professional body we can review and assess trends to further improve patient safety. Greater regulation in the aesthetic market is long overdue and it is hoped that producing internationally recognized guidelines in the management of complications will help raise standards within the industry and ensure early diagnosis, appropriate management, and improved outcomes for patients who suffer from complications.

—Martyn King, MD, Chairperson, Aesthetic Complications Expert Group

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