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DONS AND DORS

Dr Martyn King discusses Delayed Onset Nodules and Delayed Onset Reactions Related to soft tissue filler treatments

Delayed Onset Nodules or DONs were first described as a later onset complication of soft tissue fillers over 10 years ago and have now been widely reported in the literature for most products on the market.

A DON or DOR is used to describe the pattern of signs and symptoms that may appear because of filler injection, but it is not a diagnosis. They may include swelling, nodules[1], masses, areas of induration[1], biofilms, a sterile abscess[2] or granulomas.[2] They can be defined as a visible or palpable unintended mass which occurs at, or close to, the site of injection of a soft tissue filler at least two weeks post treatment in the absence of any previous mass, swelling or inflammation in the same area[3] and where other causes can be excluded.

There are differences in opinion amongst experts for the time period between injection and the development of a DON or DOR with some suggesting one week is sufficient and others requiring four weeks.[1] However, they may not appear for several months or even years after treatment with an average length of four months from treatment to signs and symptoms.[4] As well as this, DONs, and more commonly DORs, may have a relapsing and remitting behaviour, likely due to exposure to trigger factors at certain intervals or due to a temporary response to interventions.

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MANAGEMENT

Although the distinction between a DON or DOR is useful as presentation and aetiology may be different[1], the management of these complications should be on an individual basis based on clinical history and findings.

Watchful waiting[1,5] may be the best approach for a DON or DOR if it is palpable but not visible on the skin, if the patient has medical conditions that may preclude further management or if the aesthetic appearance is acceptable to the patient and they are content to let it settle spontaneously over time. The management may lead to medication side-effects, bruising, swelling, loss of volume, asymmetry, skin or fat atrophy or may not be successful, so before embarking on a treatment regime, it is important that the patient is aware of all these factors so that an informed decision can be made. Even when the appropriate management plan is followed, it can take several weeks or months for a DON or DOR to resolve.[6,7]

Despite extensive research, it remains unclear whether delayed onset nodules are caused, at least in part, by bacterial contamination or biofilm formation.

Bacterial remnants have been identified by various laboratory testing methods in sub-infective quantities in the presence of a DON. Certain bacteria can hide themselves from the host immune system and the action of pharmacological agents by the secretion of an extracellular matrix of exopolysaccharides, which can include hyaluronic acid, to form their own microenvironment.[3] These bacteria can remain dormant in a planktonic state, only to become active when conditions are favourable for replication, such as disease or illness in the host or tissue disruption due to the administration of further soft tissue filler or other invasive procedure. When these conditions do arise, it can result in granulomatous inflammation, abscesses and nodules.[13] Bacteria that have been commonly implicated in biofilm formation include S. epidermidis and P.acnes.[8]

Whether it is the anti-microbial effect or their immunomodulatory and anti-inflammatory[4,9] properties, it is well documented that antibiotics have a large role in the management of DONs and DORs and should often be used as first line treatment.

The antibiotic of choice is usually a tetracycline[4,9] (e.g. Doxycycline 100mg OD or Minocycline 100mg OD) although a macrolide[3,9,10] could also be considered (e.g. Clarithromycin 500mg BD). It is important that practitioners are familiar with these antibiotics including interactions, side-effects, and contra-indications.

Tetracyclines are active against both Gram positive and negative bacteria and as well as their anti-bacterial properties, they are also anti-inflammatory and help to modify the body's immune response. They are highly lipid soluble so can penetrate areas of soft tissue filler placement. They inhibit bacterial protein synthesis and are bacteriostatic (inhibiting bacterial replication). They should not be used in pregnancy or breast feeding and can also lead to photosensitivity.

Macrolides also suppress bacterial protein synthesis and accumulate in adipose tissue.[9] They are particularly helpful in the management of DONs and DORs as these agents can restrain quorum sensing – this is the mechanism by which bacteria can modify their behaviour according to their surrounding environment, including from entering a replication state from being dormant. They can cause side-effects including abdominal pain, diarrhoea, nausea, and vomiting. It is recommended to use macrolides second-line, as dual therapy, or first-line if tetracyclines are contra-indicated.

Initial management of a DON or DOR, unless there has been an acute inflammatory response to a known trigger, should be with antibiotics and these should be continued for at least 48 hours[8,9] before any further intervention is commenced. Experts recommend that in most situations, antibiotics should be prescribed for a week to assess therapeutic benefit before proceeding with additional or alternative treatment.[3] The aetiology and severity of the DON and DOR will dictate how quickly and aggressively this complication will be managed.

If there has been no clinical improvement after a one-week course of antibiotics, the practitioner should consider prescribing a second-line antibiotic, dual therapy[10] or alternative adjunctive treatments. However, if intralesional hyaluronidase or steroid treatment is being considered, this should be conducted whilst the patient is receiving antibiotic therapy due to the risk of worsening or spreading the problem.
If there has been some improvement, but it has not resolved entirely, antibiotics can be continued for a longer period, and it may be acceptable to remain on antibiotics for several weeks to allow complete resolution. Alternatively, dual therapy or adjunctive treatment may be a better option to successfully manage the complication.

If first and second-line antibiotics have failed to make a clinical difference or if there is a contra-indication or they are not tolerated, a fluoroquinolone (e.g. Ciprofloxacin 500mg BD) may be used as a third-line alternative.[3] However, due to their extensive potential side-effects, including aortic rupture, tendon rupture, antibiotic-associated colitis, and cardiovascular toxicity, their use should be limited. The mechanism of action is inhibition of bacterial enzymes responsible for DNA replication, transcription, repair, and recombination. They should not be prescribed for periods more than 60 days.[11]

Although penicillins are used for many skin and other infections, there is very little evidence for their use in the management of DONs and DORs and they are not recommended.

Hyaluronidase should not be used first line due to lack of clinical improvement[12] and the risk of spreading infection into surrounding tissue,[13,14] unless the problem is filler misplacement or migration without any hallmarks of a DON or a DOR. It should only be considered after at least 48 hours of antibiotic cover when the causative product is a hyaluronic acid filler.[4,15] If it is used without antibiotics, the treatment is unlikely to be successful.[3]

There are different formulations of hyaluronidase commercially available globally, which vary in their source (commonly ovine, bovine or recombinant), their units per ampoule and their potency. Different hyaluronidases are not directly interchangeable, and up to three-fold dosages may be required to obtain the same effect.[15] The author, based in the UK, has experience in the use of Hyalase® 1500 IU (Wockhardt, UK) which is ovine in origin and compared to its bovine counterpart, is more potent in nature and less likely to cause inflammatory reactions, including erythema and burning sensation.[19]

Although somewhat dependent on the size of the DON or DOR and whether they are solitary or multiple, it is recommended to dissolve 1500 IU Hyalase® in 5ml of saline and to treat to clinical effect, where the practitioner can palpate the nodule and notice changes in its size, firmness, and consistency.[3] Although many papers have agreed that 20-30 units of hyaluronidase are required to dissolve 0.1ml of hyaluronic acid filler, there are many factors that can affect this amount[16] including product used, cross-linking, location, size, and DONs are inherently more resistant to break down. Often 30-250 of hyaluronidase is needed to deal with a single delayed onset nodule,[9] but this dosage may need to be doubled if a more resistant filler has been used, such as Vycross™ technology.[9] Nodules should be injected with a suitable length and gauge needle, from multiple angles and depths to ensure the DON or DOR is fully penetrated and the contents are fully exposed to the hyaluronidase, antibiotics, and the body's immune system. Firm massage should be used during the procedure to assist in mechanical breakdown of the nodule or swelling.[3]

Sometimes only partial benefit is achieved, or the DON or DOR can re-appear soon after treatment and the procedure can be repeated at weekly intervals until complete resolution is achieved. After three attempts at hyaluronidase, assuming correct dosage and technique was applied, further management may be needed if the complication persists. However, a combination of broad-spectrum antibiotics and repeated high-dose hyaluronidase is a proven, effective management strategy for the management of DONs and DORs.[20]

Oral corticosteroids are useful to reduce the signs and symptoms of inflammation often associated with a DOR although they do not manage the cause of the problem and once they are stopped, the problem tends to reappear as a rebound effect.[1] Prescribing steroids in this situation may lead to a lengthy and protracted course as whenever they are reduced or stopped, symptoms and signs recur, leading to a vicious cycle of continuing steroids which can create longer-term problems. If they are prescribed for a period of greater than three weeks, they should be gradually reduced rather than stopped abruptly.[17]

They can be particularly useful if there is an area of inflammation and swelling over an area previously treated with soft tissue fillers with no discrete mass and initiated by a known trigger factor, such as a viral infection or vaccination.[17] If the trigger factor has a bacterial cause, steroids can worsen the situation by its immunosuppressive action, leading to a worsening of infection. Caution also needs to be adopted if they trigger factor was a vaccination, as oral corticosteroids can diminish the immune response to inoculation, leading to vaccine failure.[17] Ideally, steroids should not be prescribed until at least three weeks after vaccination.[17]

Oral corticosteroids may also be considered if there has been an extensive inflammatory response at initial presentation.[9] The recommended dosages are Prednisolone 40mg once a day for seven to 21 days[9] or Dexamethasone 4mg a day. A shorter course of Dexamethasone may be sufficient due to its longer half-life. Practitioners should consider co-prescribing gastroprotection (an H2 receptor antagonist or proton pump inhibitor)[21] while on steroids due to the risk of dyspepsia and gastric ulceration. Other side effects from corticosteroids include severe psychiatric reactions, sleep disturbance, immunosuppression, and adrenocortical insufficiency.

Intralesional immunosuppressive drugs should only be considered when other options have been exhausted[3] and again, should only be administered under the cover of antibiotics. They may be a better option when non-hyaluronic acid fillers have been injected.[10,13,18] The literature recommends the use of triamcinolone acetonide 40mg/ml (Kenalog™, Bristol-Myers Squibb, Dublin), diluted in either saline or water for injection. Initial concentration should be 10mg/ml, increasing to 20mg/ml and 40mg/ml on repeated cycles depending on response and injecting 0.1ml per nodule[13] at two to four weekly intervals.[9] The risk of intralesional steroids includes skin and fat atrophy (20-30%[33]) and the development of telangiectasia[10] at the sites of injection. This risk may be minimised by the addition of the anti-mitotic agent, 5-flurouracil,18 in a ratio of 80:20 (5-FU:triamcinolone).1

Other treatment options that have been used for the management of DONs and DORs include non-steroidal anti-inflammatory drugs (NSAIDs), antihistamines, allopurinol, platelet rich plasma and intralesional antibiotics. NSAIDs can lessen some of the symptoms and signs, but like oral corticosteroids, do not deal with the underlying problem. They may offer some short-term symptom relief in an exacerbation that is expected to settle spontaneously in a short period.

Delayed hypersensitivity reactions are mediated by a T-cell lymphocyte response and do not respond to oral antihistamines[22] and so should generally not be used unless the patient is displaying additional signs or symptoms of an acute histamine reaction. Allopurinol is a xanthine-oxidase inhibitor, and it is principally used to lower uric acid levels in the body. Its mechanism of action in the management of delayed onset nodules is little researched or understood, but there is some evidence that it may be of benefit when other measures have been unsuccessful.[18] Platelet rich plasma has anti-microbial action, diminishes hyaluronic acid and can be effective against biofilms,[14] but there is only weak evidence that it can help manage a DON or DOR. Similarly, although intralesional antibiotics have been cited as treatment modalities for the treatment of filler related nodules, there is not enough evidence to recommend their wider use.tional lasers have been used to try and disrupt nodules and there is limited evidence to support their use in the under eye and lip areas[18] and more recently intralesional radiofrequency[1] has also been proposed as an alternative.

Finally, surgical removal may be considered, but as granulomatous reactions develop finger-like projections into the surrounding tissue[14], surgery is difficult, often incomplete, likely to result in scarring and should only be considered as a last resort.[1,9]

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Algorithm: Protocol for the management of DONs and DORs (Reproduced with permission from the Aesthetics Complications Expert Group)

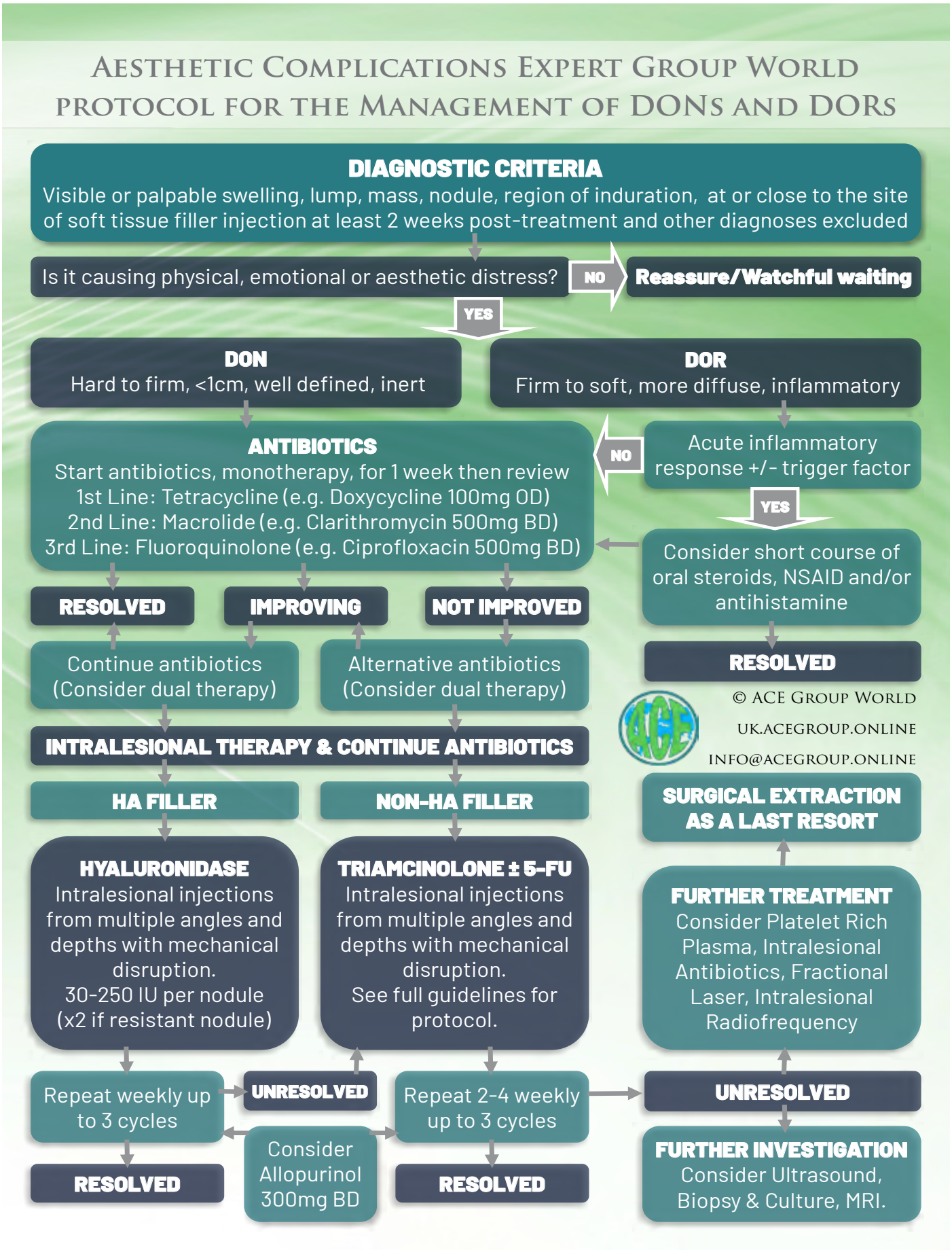

Image provided by author

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