CMAC UK

Complications in Medical Aesthetic Collaborative

Hyaluronidase Guideline:

Pharmacology, Allergy and Elective use

Title	**Hyaluronidase Guideline: Pharmacology, allergy and elective use**		
Author	Gillian Murray, Cormac Convery, Lee Walker, Emma Davies		
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Introduction

Cross-linked hyaluronic acid (HA) is the most commonly used filler for volume replacement and soft tissue augmentation. Endogenous hyaluronic acid is ubiquitous through the body being a major structural component of the extracellular matrix. It is found within the skin and acts to support tissue architecture and maintain hydration due to its hygroscopic nature[1].

Hyaluronidase is a soluble protein that functions as an enzyme. It is used within cosmetic medicine for both elective and emergency procedures however it has been used within the sphere of medical practice since the 1949. It is commonly used in sectors including anaesthesia and pain, cardiology, radiography, oncology, ophthalmology, plastic surgery and now laterally, within the past 15 years, aesthetic medicine to dissolve crosslinked hyaluronic acid. It has a diverse range of clinical applications due to its unique ability to facilitate the dispersion and/or absorption of fluids and many medicines. It has also been used for niche indications such as treating keloids scars as an alternative to steroids, dissolution of haematomas and treatment of lymphoedema.[1,2] Hyaluronidase breaks down complex hyaluronan glycosaminoglycan polysaccharides by a hydrolysis reaction. Hyaluronidase targets the breakdown of the C1 and C4 bond between the glucosamine and glucuronic acid components causing the complex molecule to unfold and break down[3]. Its primary function within cosmetic medicine is to dissolve crosslinked hyaluronic acid (HA) dermal fillers, however it can also be used to improve resistant oedema given its ability to increase capillary and tissue permeability[4].

It is important that in medical aesthetics, the practitioner understands the clinical application of hyaluronidase in practice, risks associated with its use including allergy, storage, and directions for administration.

Practical application of hyaluronidase in aesthetic medicine

Vascular Occlusion

It may be necessary to dissolve crosslinked HA in the event of a vascular occlusion (VO). Accidental intravascular injection, resulting in a VO, is a time sensitive but not a time critical event unless there is visual or neurological disturbance. Failure or delay in dissolution could lead to tissue necrosis and scarring, blindness or cerebrovascular accident. Please refer to the CMAC Guideline: Guideline for the management of hyaluronic acid filler induced vascular occlusion, for more information.

Tyndall

Tyndall effect is a phenomenon seen when particulate fillers are injected into a superficial plane. It has been postulated that this effect is due to shorter wavelengths (blue) being preferentially scattered by the filler particles creating a blue hue which is visible to the naked eye. Historically Tyndall has been attributed to the scattering of light when it is passes through particles with a smaller wavelength than light itself. HA molecules are much larger than the wavelength of light, meaning this theory seems unlikely. Recent evidence has suggested that the HA alters the tissue physiology, allowing deeper absorption of red light. The effect of this makes the tissue appear ‘more blue’[5].

Late and Delayed Onset Nodules

'Lumps' or delayed nodules may appear weeks or months after injection of the dermal filler and can be caused by any soft tissue filler including crosslinked HA. Understanding the underlying pathophysiology of these nodules is challenging due to the limited access to investigations coupled with patients' reluctance to permit tissue sampling.

Delayed (type IV) hypersensitivity reactions, granulomas and biofilms are possible causes, and there may be mixed pathology. When the filling agent is HA, there is a significant advantage in being able to dissolve the nidus of the problem. When there is a significant inflammatory component, hyaluronidase should be administered only under broad-spectrum antibiotic cover.

Poor Aesthetic Outcome

Incorrect placement of filler, excess filler or migration/redistribution can lead to a poor aesthetic outcome and patient distress. Good product knowledge, a deep appreciation of 3-dimensional anatomy, and correct technique are vital for an optimal aesthetic outcome.

As crosslinked hyaluronic acid breaks down in the tissue its physicochemical properties alter. These changes can affect all rheological parameters of the filler. As the hyaluronic acids properties change, by virtue of the tissue condition and being subjected to hydrolytic degradation, the aesthetic outcome may begin to change. This change in its physicochemical properties may also contribute to some dermal fillers migrating in areas high muscle activity[6].

Hyaluronidase

In the UK, Hyaluronidase, produced by Wockhardt is a prescription only medicine. It is licensed to enhance the permeation and uptake of subcutaneous or intramuscular injections, local anaesthetics and subcutaneous infusions, and to promote the resorption of excess fluids and blood in the tissues. Its use in aesthetic medicine to dissolve cross linked hyaluronic acid is an 'off- license' indication7. As part of the consent process, the patient must be advised of its off-license status. (Please see the CMAC Hyaluronidase consent form.)

The manufacturers data sheet from Wockhardt states that the product must be stored at temperatures of less than 25oC to ensure formulation stability. The product features an expiry date and can be used until the last day of the month its due to expire, if correctly stored. When stored at temperatures consistently above 25°C the product's expiry date will be affected. Once the ampoule is opened, it must be used immediately, and any unused contents discarded[7].
If the clinician resides outside of the UK, with access to other brands of hyaluronidase, the manufacturers data sheet must be followed for specific storage instructions.

Hyaluronidase can be reconstituted with most common infusion fluids, however for use in medical aesthetics it is most frequently reconstituted with bacteriostatic NaCl 0.9% which is less painful on injection. Bacteriostatic and non-preserved NaCl 0.9% have similar pH values (pH 4.5-7)[8,9], which is important as enzyme activity is pH sensitive and bovine/ovine extracted Hyaluronidase has a bimodal activity with maximum activity of pH 4.5 and 7.5[10]. However, in the event of a vascular occlusion, where there may be pain due to ischaemia, it is recommended that it is reconstituted with a local

anaesthetic without adrenaline to make the experience more comfortable for the patient. Hyaluronidase is physically compatible with lidocaine in solution, and in ocular and spinal anaesthesia it is commonly used in combination with local anaesthetic agents and administered as part of anaesthetic blocks[7].

Allergic Risk Associated with Hyaluronidase treatment

Incidence of allergy

There is a growing concern amongst practitioners that an anaphylactic (type I hypersensitivity) reaction may occur when injecting hyaluronidase, with many practitioners performing skin tests to screen for these reactions. The British Society of Allergy and Clinical Immunology (BSACI)[11] state that 'skin tests' must always be interpreted within the appropriate clinical context and not used to screen for drug allergy[12,13]. The BSACI further elaborate that they should not be used to screen for drug allergy in the absence of a clinical history compatible with an IgE mediated allergy, otherwise known as a type I hypersensitivity[11]. Skin testing in general is usually done in specialist centres where there is a clinical history of drug allergy[14], despite this, skin testing is frequently used in aesthetic medicine when there is no reason to suspect allergy. In such circumstances it is deployed as a method of 'reassuring' the practitioner that the patient will not develop anaphylaxis, which is against BSACI recommendations for appropriate allergy testing[11]. Considering the incidence of allergy to hyaluronidase, since 1949 there have been 4 case reports of allergy requiring adrenaline. The incidence, therefore, is extremely small. The incidence of hypersensitivity is often widely quoted as approximately 0.1%, unless large intravenous doses (in excess of 200,000 units) have been given, where treatments yielded a type I reaction rate of 33%[15,16]. However rates of allergy reported include 'all allergy', not specifically type I hypersensitivity. Combining the information in the case reports/series the incidence of overall 'allergy' is actually very small (table 1). The allergic responses consist mainly of localised type IV reactions, if defined as reactions occurring at 1 hour or later, unless large doses are injected intravenously[17,18]. It is also important to state that the incidence rates of allergy do not specify rates for first exposure compared to subsequent exposure, and allergy was almost exclusively linked to prior exposure to hyaluronidase or bee/wasp venom[19,20,21,22,23,24,25,26,27,28,29,30,31,32].

Specifically addressing the risk of allergy in aesthetic medicine there are only 3 case reports of 'allergy' after hyaluronidase injection to dissolve cross-linked hyaluronic acid filler[19,20,21], totalling 4 patients in the literature. However, the incidence may be under-reported.

Table 1. Incidence rates of allergy to hyaluronidase

Study	Route	Overall incidence rate
Zamora- Alejo et al[22]	Peribulbar	0.05%
Leibovitch et al[17]	Peribulbar	0.13%
Kempeneers et al[23]	Retrobulbar	0.05%
Eberhart et al [24]	Peribulbar	0.69%
Escolano et al[33]	Peribulbar	0.03%
Szefalusi et al[15]	Intravenous	31.25%
Raichura et al[18]	Peribulbar	0.006% (first exposure)/0.016% second exposure

Formulation and allergy

Hyaluronidase is used globally, with most formulations being derived from ovine or bovine testes. In the UK, for example, the Wockhardt product is ovine derived. It is important to note that some countries use compounded (pharmacy formulated) hyaluronidases, containing more protein impurities than the ovine or bovine derived products, while the US use recombinant hyaluronidase 'Hylenex' which is known to be the purest formulation[2]. Much of the literature, based around case reports, assumes that that the problematic protein in the hyaluronidase formulation is the enzyme itself. However, a contributing factor to the allergic response, that is difficult to quantify, is the presence of protein impurities within the formulation. Thimerosal, a preservative used in some hyaluronidase preparations, has long been known to cause allergic reactions. However other protein impurities, that have not been quantified and can be present, could also be the cause of allergic responses[2]. Hyaluronidase produced by Wockhardt in the UK does not contain a preservative, or any other excipients, but will contain impurities by virtue of the formulation process. There has never been a study which has isolated and tested protein impurities within all the hyaluronidase products and established links to allergy, or whether the allergy is potentiated by the combination of the hyaluronidase and the preservative/ protein impurities. Of note, there have been no documented cases of allergy with Hylenex (human recombinant rHuPH20)[34] produced by Halozyme. It was also found that on comparison to animal derived hyaluronidases, Hylenex had 100 times more activity per milligram of total enzyme protein[2], however the clinical significance of this fact is not yet understood. Another factor to consider is the use of bacteriostatic sodium chloride 0.9% when reconstituting hyaluronidase. It is preserved with benzyl alcohol with an allergy rate of 1.3%[35]. This is greater than the average allergy risk to hyaluronidase. It therefore remains up for discussion, whether the hyaluronidase enzyme has been the direct cause of allergy in the all the cases of hyaluronidase allergy reported in the literature.

Dose/route and allergy

The small number of cases/case reports pertaining to allergy in the literature, suggest that route of administration and dosage may be a factor in the severity of allergic reaction. In general, when dose ranges of less than 1500 units are injected at a local site, allergic reactions to hyaluronidase are confined to localized responses (oedema, erythema, urticaria) in the injection area without generalized symptoms[23]. There appears to be a dose dependant effect on administering hyaluronidase. When doses range from 1,500 to 200,000 IU and /or are injected intravenously, most allergic patients described in the literature present with more generalized symptoms[19,20,21,22,23,24,25,26,27,28,29,30,31,32].

The rates of allergy after ocular administration dominate the literature. This may be partly due to the drugs pharmacokinetic profile in the tissues. Hyaluronidase is known to have a plasma half-life of around 2 minutes. However, it is important to consider the alpha distribution phase (time for the drug to distribute through the tissues) in the ocular tissue. Residence time in ocular tissue has been reported to be longer than in other tissues that have a denser vascular network. It is thought that the alpha elimination phase is 60-120 hours in ocular tissue meaning the tissues may have a greater exposure to the drug before it reaches the plasma, where the terminal half-life (beta elimination) is

around 2 minutes[36]. Greater exposure to the drug may allow for a greater degree of primary sensitisation. There is a relatively higher risk of apparent type IV hypersensitivity to hyaluronidase when given as part of an ocular block, due to sensitisation or coadministration with other drugs.

Side effects

Hyaluronidase at concentrations greater than 1:10 (1500:10 ml) can be irritant. Erythema at the injection site is a commonly known side effect. Side effects are type A adverse reactions, meaning they are predictable by virtue of the drugs pharmacology, but they are not allergies, which are classed as type B adverse reactions. High dose hyaluronidase can provoke hypersensitivity-like responses, such as non-infectious swelling and inflammation whilst skin allergy tests are normal[14,20]. This injection site reaction would typically include erythema and some swelling disappearing within 24 hours, and in the authors' experience can occur when injecting hyaluronidase. This would indicate a type A adverse reaction, and not a type B reaction, as seen in an allergy presentation.

Intradermal Testing

Skin allergy testing is prevalent in the practice of medical aesthetics, however valuable information to the clinician is the medical history, drug history, allergy history, prior exposure and consideration to the dose used. There are certain groups of patients who, on having a type I reaction, will have a more significant reaction. Examples of these patients include those on an ACE inhibitor, those with mast cell disorder and high trypsin levels, allergic atopic individuals, C1 esterase deficiency, hereditary angioedema, and those on a beta blocker[11,14] where it will be more difficult to restore haemodynamic stability during anaphylaxis. It is therefore important to ensure the medical and drug history is accurately taken in the first instance.

Wasp/Bee allergy

Prior to injecting Hyaluronidase it is important to ascertain allergy to bee/wasp stings. Allergies to bee and wasp venom, part of the Hymenoptera family, pose a significant risk of cross reactivity. When assessing allergy to wasp and bee sting it is important to assess the type of reactions, and any information known about allergy status to any of the 'Hymenoptera Family'. Small local reactions around the site of stings are a normal occurrence, and not allergy. The clinician should assess the history and the description of the reaction, if consulting a patient who has self-diagnosed their own allergy. Allergy to these stings take 2 forms:

1. A large, localised reaction, which is defined as painful swelling and erythema limited to the skin and subcutaneous tissue surrounding the sting. The affected area is large and can exceed 10cm and peaks at day 1-2 taking up to 10 days to resolve. The risk of anaphylaxis from a subsequent sting if a patient has had a Large Local Reaction (LLR) is <5%. If the patient has had an anaphylactic reaction to bees or vespidae wasps, then the risk of anaphylaxis to a subsequent sting is at least 60%.

2. Wasp and bee stings contain more than one allergen (protein), including hyaluronidase. If no specialist allergy testing has been performed on a patient with reported anaphylaxis to these stings, you would have to assume it could be the hyaluronidase based on worst case scenario. Given this, the risk of anaphylaxis on administering hyaluronidase on a background of a previous LLR, or anaphylaxis to stings, is up to 5% and 60%, respectively[37]. If the patient has had an allergy to both bee and wasp stings, it's more likely hyaluronidase is the allergen.

Performing an intradermal test on patients with a history of LLR or anaphylaxis to stings from the Hymenoptera family is an anaphylaxis risk. It is important that allergy tests in these individuals are done at an allergy clinic where full allergy testing can be undertaken to ascertain the specific allergenic substance with anaphylaxis support available.

If the decision is taken to perform an intradermal test (IDT), please note that there is no validated concentration that is used to assess hyaluronidase allergy in the UK[38]. In the literature, case reports of hyaluronidase allergy have cited doses of 15units/ ml to 150 units /ml to verify the allergy[27,39]. This is the concentration, and NOT total volume injected. The volume injected to assess a type I hypersensitivity using an intradermal test, according to allergy guidelines, is around 0.02-0.05ml[14]. This is the volume needed to achieve a 5mm bleb. If best practice was followed in these studies the number of units used in total, despite not being stated in most of the studies, may have been a fraction of this. Two papers suggested that 15 units may be used to verify the allergy, resulting in a positive IDT20[40]. One paper had to increase the concentration from 1.5u/ml to 150u/ml to achieve a positive IDT, where 1.5u/ml and 15u/ml gave negative reactions[27]. There was a lack of consistency in concentration used to verify allergies in these cases. A publication by Vartanian et al described a local reaction when 10, 20 and 30 units of hyaluronidase was injected to dissolve Restylane once injected into the volar aspect of the arm, to assess degradation. They found a dose dependant local reaction occurred in some of the test studies. However, as discussed, it is common for hyaluronidase to give rise to local irritation when injected, as a predictable type A reaction[41]. It remains to be established whether in the cases reported by Vartanian et al these were allergic type IV reactions, or predictable irritation on injecting the drug.

Warning

If a patient has a possible history of anaphylaxis to hyaluronidase or wasp/bee stings, DO NOT perform an IDT, refer to a specialist allergy centre to confirm diagnosis

In patients with a history of anaphylaxis to hymenoptera stings, performing intradermal testing with unvalidated test concentration, could result in anaphylaxis. Reliable testing must be valid and sensitive. Current skin test practice conducted by medical aesthetic clinicians is neither valid nor reliably sensitive, given there is no validated test concentration. The clinician must consider this when 'interpreting' results.

Performing an IDT

If the decision is taken to perform an IDT please follow the instruction on table 2 and 3. CMAC recommend using 15 units.

Table 2 describes the steps taken to perform an intradermal test, and Table 3 how to interpret the test. Often erythema may develop at the site either within 20 minutes or some hours later. Neither of these are positive results for type 1 hypersensitivity (anaphylaxis).

Adapted from: Scolaro RJ, Crilly HM, Maycock PT et al. Australian and New Zealand Anaesthetic Allergy Group Perioperative Anaphylaxis Investigation Guidelines. Anaesth Intensive Care 2017;45:5

Table 2. Performing an IDT

Performing an intradermal test
Cleanse area on volar aspect of arm and allow to dry
Stabilise the skin
Inject 0.02-0.05ml of the drug, bevel up at 15 degrees to the skin. The tip of the needle should be seen through the skin
Inject until the wheal (bleb) of drug is 5mm in diameter
Circle the injection site with a pen
Inject a control (NaCl 0.9%) as least 2cm away from the test drug

Table 3. Interpreting an IDT

Interpretation of an intradermal test
After 20 minutes examine the area for a reaction. A positive reaction is a small, raised bleb surrounded by swelling and redness.
The new 'bleb' can be marked with pen
Measure the diameter of the new bleb (P20**) and compare with the initial bleb (**Pi**)**
POSITIVITY CRITERION(EAACI): P20 = Pi + 3mm

Elective and Emergency use of hyaluronidase

Doses

For guidance on the use of hyaluronidase in the event of a vascular occlusion please refer to the CMAC Guideline: *Guideline for the management of hyaluronic acid filler induced vascular occlusion*.

In the event of elective reversal there are no set standard concentrations or doses to be used. Different brands of crosslinked hyaluronic acid (HA) may dissolve differently, some requiring more hyaluronidase and some less. Cross-linked HA's demonstrate different physicochemical properties and rheological properties that may change as residence time in the tissue increases. The volume of filler and how densely it appears in the tissue may also require the need for more or less enzyme. Various studies in the literature have compared how some of the well-known filler brands degrade in response to hyaluronidase, however the findings are inconsistent across studies and do not reflect the complete set of fillers used frequently within the UK, or different countries[43]. More research in this area is required.

As the literature describes a variety of doses used to electively dissolves cross linked HA, it is CMAC's suggestion that treating to effect is more reliable than specific doses. Use enough to treat the problem area (treat to effect). Complications data obtained by the CMAC board indicate that the doses in the literature are very conservative, and changes in cross-linked HA technology to increase HA residence time may be a contributing factor. CMAC recommend not using concentrations of less than 1500 units in 5ml. Although hyaluronidase removes native hyaluronic acid, given the rapid

turnover time, the body will restore native HA in 15-20 hours[2] and the clinician should not feel reluctant to administer what is needed on this basis.

After elective treatment with hyaluronidase the patient may be assessed after 48 hours and the treatment repeated if necessary. It may take longer than 48 hours for the post procedural swelling to subside[42], however no enzyme activity remains at this time further and crosslinked HA may 'theoretically' be administered without risk of being dissolved. However, CMAC recommend waiting a minimum of 2 weeks until the swelling has settled, longer in the event of significant post procedural swelling, to ensure more predictable aesthetic outcome.

Administration

Please refer to the CMAC Guideline: *Guideline for the management of hyaluronic acid filler induced vascular occlusion for administration in an emergency*.

Prior to injection the area should be clean, and thoroughly disinfected with an antibacterial skin solution. Palpate and mark out the area to be injected. The injections should be performed using an aseptic technique and either a cannula or needle that will reach the appropriate depth. It is important to consider the depth and site of injection of the hyaluronidase, and palpating and targeting nodules individually if present. Treat the area containing the cross-linked HA only, unless there is generalised hyaluronic acid related swelling, in which case, treat the whole area. Once injected subcutaneously the hyaluronidase will spread well through the tissues and across vessel walls.

In the event of a nodule, inject directly into the area - there may be resistance to the injection however it is important to try to penetrate the nodule to remove the filler successfully. Whilst the doses for elective dissolution following a poor aesthetic outcome are subject to response, it has been reported that does of 30-300 units may be required for an individual nodule. Repeat treatment may be required when treating delayed onset nodules. Please see the CMAC guideline: *Treatment of Late and delayed Onset Nodules*.

If there is refractory swelling around the orbit that is not amenable to treatment with hyaluronidase, or the nodule is not responding to repeat treatment, consider referring for ultrasound or MRI imaging to offer an accurate diagnosis and guide any further treatment that may be required.

Ultrasound guided dissolution is a useful tool to dissolve arterial occlusions and to improve accuracy of injection into nodules, or areas of unwanted residual cross-linked HA. Deploying imaging to assist in dissolution will result in less hyaluronidase being used.

After injection firmly massage the area to aid in the breakdown of the cross-linked HA.

Do not inject hyaluronidase in an area where botulinum toxin has been given in the past 48 hours, and do not inject into an area where there is infective sequelae unless there is thought to be a biofilm and the patient is stabilised on antimicrobial treatment.

Adverse events

Aside from the routine issues of post procedural pain, swelling and bruising, the CMAC board have experienced reports of local swelling on injection of the hyaluronidase. This is a known side effect

alongside erythema and itch. It is important to note that the anaphylaxis risk is extremely small and is lower than the quoted 0.1% incidence which included non-serious local and delayed reactions and secondary exposure. It is important that the medical aesthetic practitioner, when administering any medicines, not just hyaluronidase, can identify and support an anaphylactic response by administering adrenaline until the emergency services arise. It is important to remain calm and assess the patient for signs of actual anaphylaxis. In the absence of any systemic symptoms or impaired swallowing or breathing, facial swelling alone, is not an indication of anaphylaxis and can be expected to settle spontaneously within 12-24 hours.

Appendix 1 *an example of intradermal testing by EAACI*

Clinical Village – Station 2

Intradermal tests: how to perform them?

M Teresa Dordal, Blanca Andrés, Gustavo Perdomo, María Rueda, Patricia Mujal, Mireia Romero and Ramon Lleonart
CAF SCAIC (Drug Allergy Section of Catalan Allergy Society)

1. INDICATIONS:

- Drug hypersensitivity reactions
- Hymenoptera venom allergy
- Allergic BronchoPulmonary Aspergillosis (ABPA)



2. DEFINITION:

- Intradermal test (IDT) is a method of skin testing that can be used to determine whether an individual is sensitized to a specific allergen.
- The test involves the injection of a small amount of the suspected allergen under the surface of the skin.

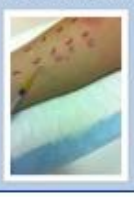
3. PREPARATION

- Make sure to verify the patient's identity and the correct allergen or drug dilution to be used. Only drugs for parenteral administration must be used.
- Some drugs may interfere with the results of IDT and should be discontinued prior to the test procedure: antihistamines, corticosteroids and some antidepressants.
- Perform hand-hygiene and put on gloves.
- Select an area on the inner forearm. Be careful with areas that have superficial blood vessels or covered with hair.
- Cleanse the area with an alcohol swab. Allow the alcohol to dry before performing the injection.


4. INJECTION METHOD

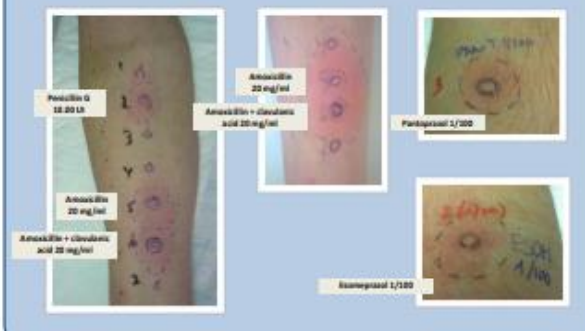
- Stabilize the skin
- Use syringes preferably with a 0.50 mm x 16 mm needle.
- Charge 0.02 ml of the allergen or drug into the syringe.
- Place the needle with the bevel side up.
- Insert the needle at a shallow angle, approximately 10-15º, when penetrating the skin. The point of the needle should be seen through the skin.
- Press in the plunger slowly injecting the agent while watching for a small wheal to appear at the injection site. The wheal must be 5 mm in diameter.
- Chart the site of the administration and circle the injection site marking the wheal with ink **(Pi)**.
- A negative control with serum saline must be carried out.





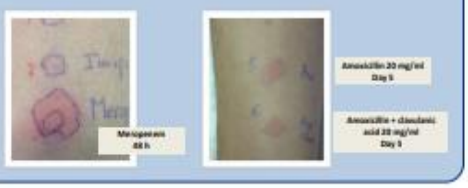
5. INTERPRETATION:

- After 20 minutes the area is examined for a reaction. A positive reaction looks like a small hive with swelling and redness.
- The new hive can be marked with ink.
- Measure the diameter of the hive **(P20)** and compare with the initial wheal **(Pi)**.
- **POSITIVITY CRITERIA (ENDA/EAACI): P20 = Pi + 3 mm**



5. SECURITY:

- All patients should be under close observation for potential anaphylactic reaction following IDT.
- Delayed positivity must be checked, specially when a delayed adverse reaction is evaluated.



Take home

- Be careful. Select properly the patient, the drug to be used and the dilution to be applied.
- Experience is mandatory in both the technique and the interpretation.

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