

Current Practices in Hyaluronic Acid Dermal Filler Treatment in Asia Pacific and Practical Approaches to Achieving Safe and Natural-Looking Results

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Abstract: Complications such as delayed inflammatory reactions (DIRs) and unnatural outcomes can sometimes arise from hyaluronic acid (HA) dermal filler treatments and can be challenging to address. Given the popularity of HA dermal fillers for aesthetic procedures, there is a need for preventive strategies to minimize these complications. Two hundred practitioners from 10 regions in Asia Pacific who administer HA fillers completed a survey on prevention of DIRs and unnatural outcomes. Thirteen global experts convened to evaluate the current practices and propose practical approaches for safe and appropriate use of HA dermal fillers. From the survey, the top three measures used to reduce the risk of DIRs included choosing an appropriate HA filler, aseptic technique, and patient selection. Key strategies employed to achieve natural-looking outcomes were treatment customization, understanding the rheological properties and behavior of different HA fillers, and being conservative in treatment approach. The panel developed a concise reference guide aimed at minimizing the risk of DIRs while achieving natural aesthetic outcomes. Five practical considerations were recommended: patient assessment and individualization of treatment plan, choice of an appropriate HA filler, adequate knowledge of facial anatomy, strict adherence to aseptic methods, and proper injection technique. The panel highlighted the need for education efforts to increase awareness of differential immunogenicity between HA fillers and to improve understanding on the importance of preserving aesthetic individuality for optimal results. These practical insights from the global experts support practitioners in optimizing safety and quality of aesthetic treatment with HA fillers.

Keywords: hyaluronic acid dermal filler, consensus, practical approaches, safe, natural-looking outcomes, current practices

Introduction

Hyaluronic acid (HA) dermal fillers are one of the most common nonsurgical modalities in aesthetic medicine due to their ease of administration, quick onset of action and minimal recovery time for patients.¹ Although HA fillers are useful for facial rejuvenation and soft-tissue augmentation,²⁻⁴ complications such as delayed inflammatory reactions (DIRs) and aesthetically unpleasant outcomes can arise, in addition to common side effects like bruising, swelling and redness.^{5,6}

While there are discrepancies in the definition of DIRs in the literature, in this article, DIRs are defined as large, tender, erythematous nodules with surrounding edema presenting ≥ 14 days after filler placement.⁷ Although DIRs are

uncommon and may resolve spontaneously, more often than not, additional interventions are required to promote resolution; they can be challenging to treat and can lead to permanent sequelae if not managed properly.^{5,7}

Aesthetically unpleasant outcomes manifest as overfilled appearance, surface irregularities, bumps/nodules, disproportionate face, distorted appearance, etc.^{5,6} They may be caused by overfilling of filler, inappropriate filler choice, and inappropriate placement of filler.^{5,6} While some of these unpleasant outcomes may resolve spontaneously, others require remedial interventions that may not necessarily restore the original anatomy and patient appearance.^{5,6}

Therefore, it is best to take precautions to avoid these undesirable complications to improve patient safety and the quality of aesthetic outcomes. This article reports the current practices in HA dermal filler treatment in Asia Pacific pertaining to the knowledge of practitioners in preventing DIRs and achieving pleasant, natural-looking outcomes. It also includes relevant recommendations and a concise reference guide to support good practices among aesthetic practitioners who administer HA fillers.

Survey on HA Dermal Filler Treatment and Panel Discussion

An online survey was conducted to understand the current practices in HA dermal filler treatment in Asia Pacific. As the survey only collected information on treatment practices, ethics approval was not required. Practitioners from 10 regions in Asia Pacific completed the online survey between May and June 2021. A panel comprising 13 clinical experts with extensive experience in using HA fillers, known as the Senior Aesthetics Filler Experts (SAFE) council, convened in a virtual meeting in July 2021 to review and discuss the survey findings, and establish a consensus for safe and appropriate use of HA dermal fillers. Specifically, they proposed recommendations and practical approaches to prevent and manage DIRs and achieve natural-looking results. The panel consisted of aesthetic physicians, dermatologists, and plastic surgeons from Australia, Germany, Hong Kong, Indonesia, Malaysia, the Philippines, Singapore, South Korea, Taiwan, Thailand, and the United States. The voting results were graded as follows: strong consensus (>95% agreement); consensus (>75% to 95% agreement); majority consent (>50% to 75% agreement); and no majority consent (\leq 50% agreement). The definition of DIR described by Artzi and colleagues⁷ was adopted for this work.

Current Practices in HA Dermal Filler Treatment in Asia Pacific

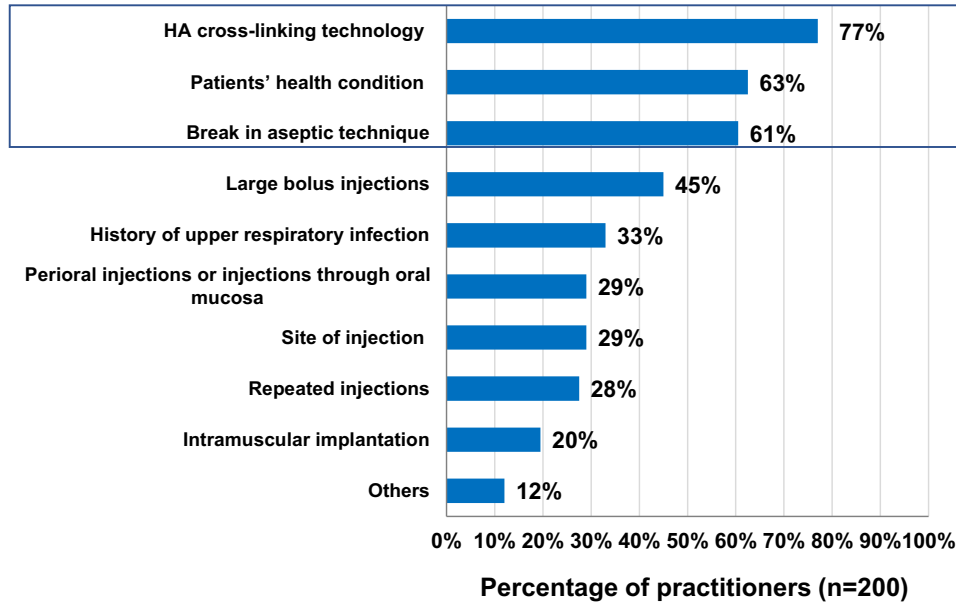
Two hundred practitioners in Asia Pacific took part in the survey. They had an average of 9.4 (SD 4.8) years of experience in using HA fillers. Practitioners from South Korea (33%), Thailand (20%), and Taiwan (15%) made up 68% of the survey participants, whereas those from the Philippines (7%), Australia (6%), Indonesia (6%), Hong Kong (5%), Singapore (4%), Malaysia (2%), and New Zealand (2%) constituted the remaining 32%. The majority were aesthetic general physicians (64%) and the rest included dermatologists (27%), plastic surgeons (8%), and non-physician practitioners (1%).

Practitioners' Views and Practices Pertaining to DIRs

Close to three-quarters (74%) of the practitioners reported having encountered patients who had DIRs.⁷ When asked to rate the incidence of DIRs in their practice, 12% rated DIRs as common (1:100 patients), whereas 88% rated the incidence as low (1:1000 patients) or extremely low ($<$ 1:1000 patients). HA cross-linking technology, patients' health condition, and break in aseptic technique were identified as the top three risk factors for DIRs (Figure 1A). Choosing an appropriate HA filler technology and avoiding products that seem to be more prone to DIRs, aseptic technique, and patient selection were the top three measures to reduce the risk of DIRs (Figure 1B). About half (52%) viewed HA fillers with a higher composition of low molecular weight-hyaluronic acid (LMW-HA) as associated with a higher risk of DIRs (Figure 2). Half of the practitioners indicated they do not perceive any difference in the risk of DIRs between different HA filler technologies. Of those who did, two-thirds perceived Vycross[®] technology to have the highest risk of DIRs (Figure 3).

In terms of the strategies used to manage these delayed reactions, broad spectrum antibiotics, oral corticosteroids, and intralesional hyaluronidase were most frequently used as early treatment options, whereas surgical excision was used as a last resort treatment (Figure 4).

A



B

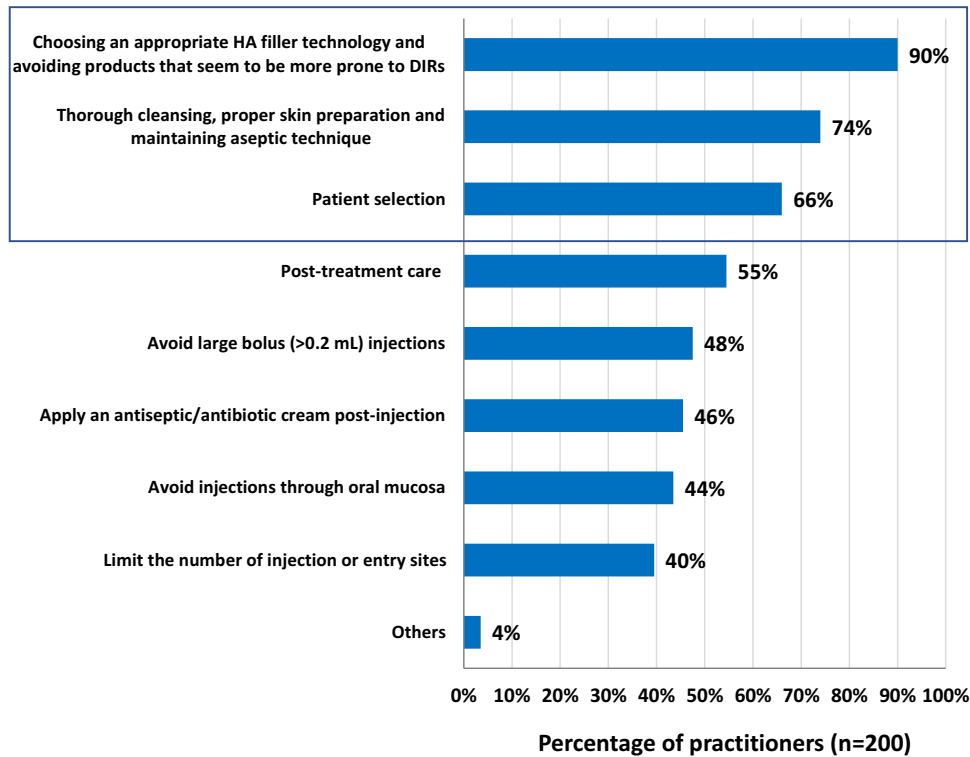


Figure 1 Practitioners' views and practices pertaining to DIRs. **(A)** Risk factors for DIRs. Top three factors are marked by the box. **(B)** Measures for reducing the risks of DIRs. Top three measures are marked by the box.

Abbreviations: DIRs, delayed inflammatory reactions; HA, hyaluronic acid.

Practitioners' Views and Practices Pertaining to Natural Outcomes

Nearly all practitioners indicated it is very important (92%) or rather important (5%) to create a natural outcome for their patients. Practitioners viewed overfilling (90%), surface irregularities (88%), bumps/nodules (86%), disproportionate face

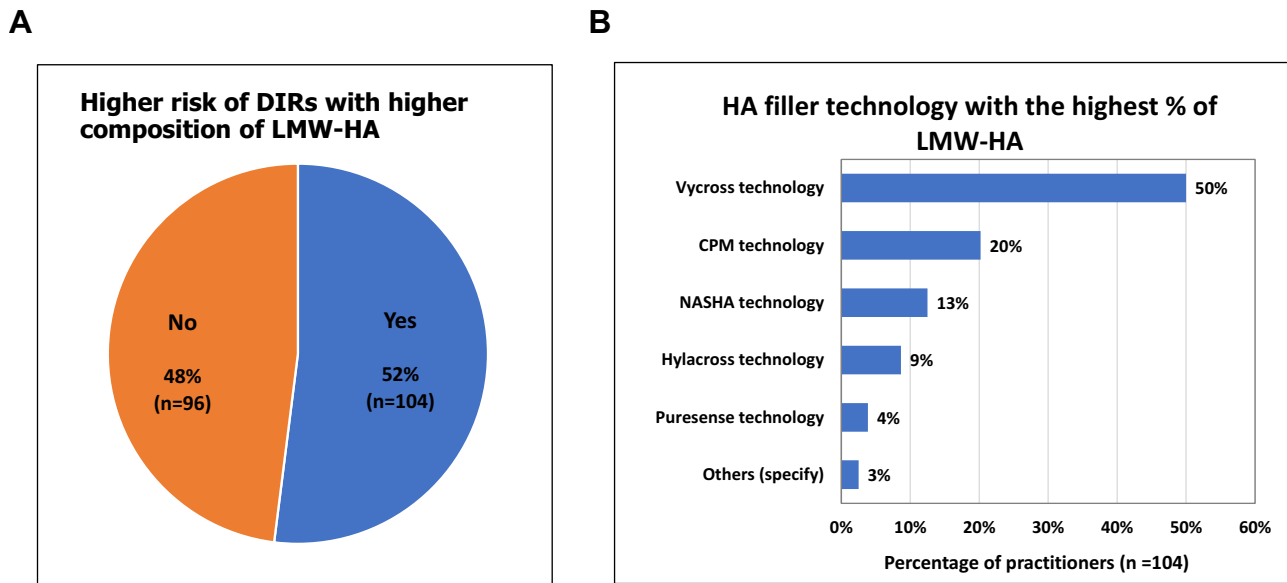


Figure 2 Practitioners' perception on the association between (A) LMW-HA and risk of DIRs, and (B) LMW-HA and HA fillers.
Abbreviations: CPM, cohesive polydensified matrix; DIRs, delayed inflammatory reactions; LMW-HA, low molecular weight-hyaluronic acid; NASHA, nonanimal stabilized hyaluronic acid.

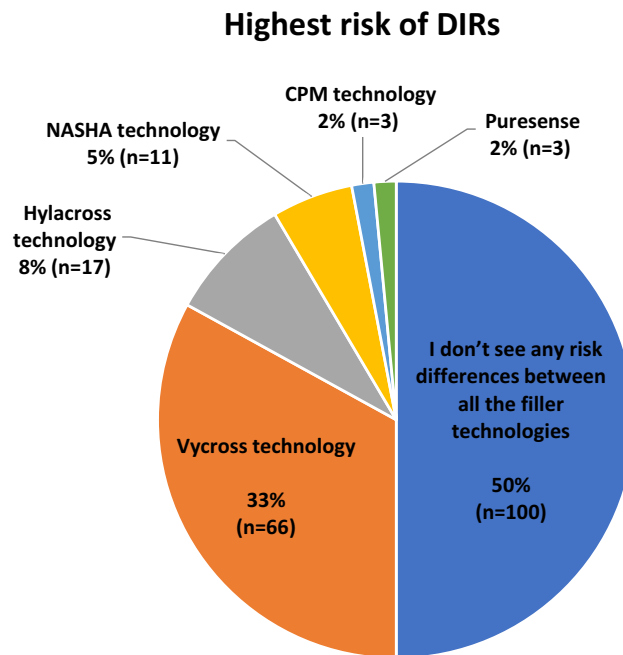


Figure 3 Practitioners' perception on the risk of DIRs among different HA fillers technologies.
Abbreviations: CPM, cohesive polydensified matrix; DIRs, delayed inflammatory reactions; HA, hyaluronic acid; NASHA, nonanimal stabilized hyaluronic acid.

(81%), and distorted appearance (79%) as unnatural outcomes. They cited poor technique (such as large bolus injections and wrong layer of injection), and the use of HA fillers that do not integrate well into the underlying tissue as the main causes of unnatural outcomes in treatment with HA filler (Figure 5A). When were asked about the treatment strategies used to achieve natural outcomes with HA fillers, treatment customization, understanding the rheological properties and behavior of different HA fillers, and being conservative in treatment approach were the key strategies reported (Figure 5B).

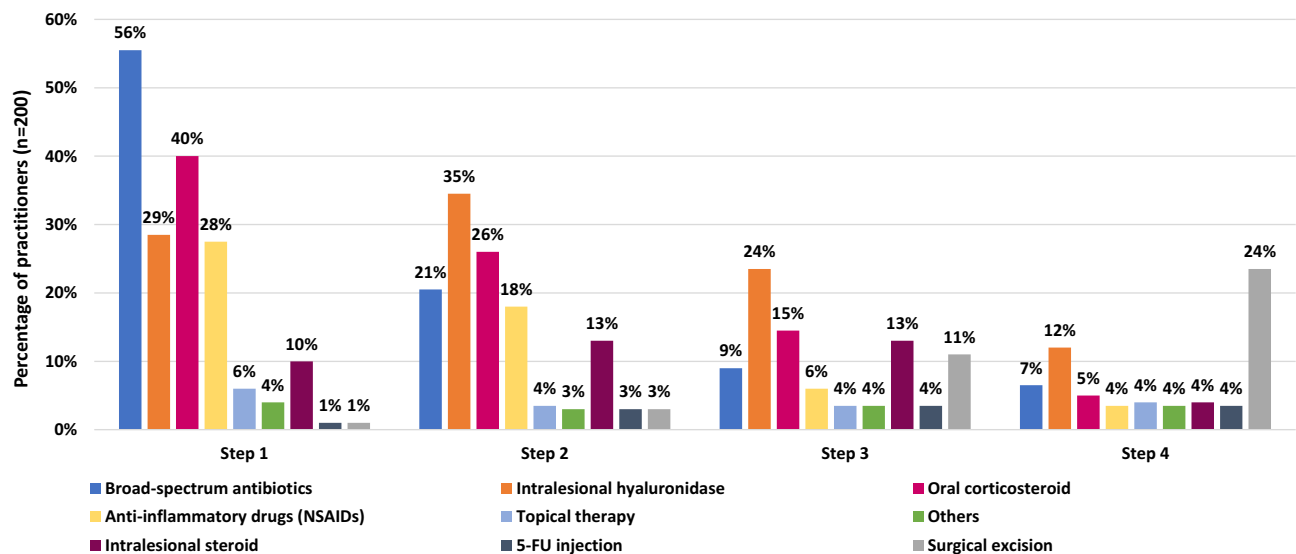


Figure 4 Strategies employed by practitioners to manage DIRs.

Abbreviations: DIRs, delayed inflammatory reactions; 5-FU, fluorouracil; NSAIDs, nonsteroidal anti-inflammatory drugs.

Panel Perspectives

Overall, the panel shared that the views and practices of practitioners in Asia Pacific are largely in line with their experience. The panel added that although choosing an appropriate HA dermal filler and ensuring strict adherence to aseptic technique are important measures for minimizing the risk of DIRs, it is also essential for practitioners to have an adequate knowledge of facial anatomy, and to use proper injection techniques. Collectively, these measures are fundamental for achieving safe and natural outcomes for patients.^{5,8–11}

The survey revealed limited awareness of differential immunogenicity between different HA fillers and the relevant influencing factors among practitioners in Asia Pacific despite published evidence.^{12–18} Although practitioners recognized the importance of choosing HA fillers that are less prone to DIRs for treatment, close to half did not perceive high composition of LMW-HA as relating to higher risk of DIRs and half did not seem to be aware of any difference in the risk of DIRs between different HA filler technologies (Figures 1B, 2 and 3). The panel acknowledged the need for educational efforts to improve knowledge on the different HA filler technologies and their associated risk of DIRs among practitioners in Asia Pacific to support them in making informed decisions when selecting an appropriate HA filler for their patients.

Consensus and Practical Approaches to Achieving Safe and Natural-Looking Results with HA Dermal Fillers

The panel shared their experiences and expertise with HA dermal filler treatment, and established a consensus for the safe and proper use of HA fillers. The consensus statements (Table 1)^{12–19} and the panel's recommendations relating to HA filler treatment (described in the sections below) are summarized into a concise reference guide (Figure 6). The guide is not intended to provide detailed instructions on how to prevent DIRs or attain natural-looking results, which are already available in published literature,^{5,6,8–11,20,21} but rather to highlight practical considerations to support practitioners in customizing their treatment plans based on the unique conditions and needs of the individual patient.

Consensus on HA Dermal Filler Treatment Pertaining to DIRs

The panel expressed high level of agreement with statements 1–6 (Table 1). They recognized that most practitioners will encounter DIRs in their practice and pointed out that it is important for practitioners to adopt a proactive approach to avoid these complications, and be able to recognize and manage them when they do occur. The panel noted three important risk factors for DIRs—fillers with higher immunogenic potential, break in aseptic technique, and poor injection

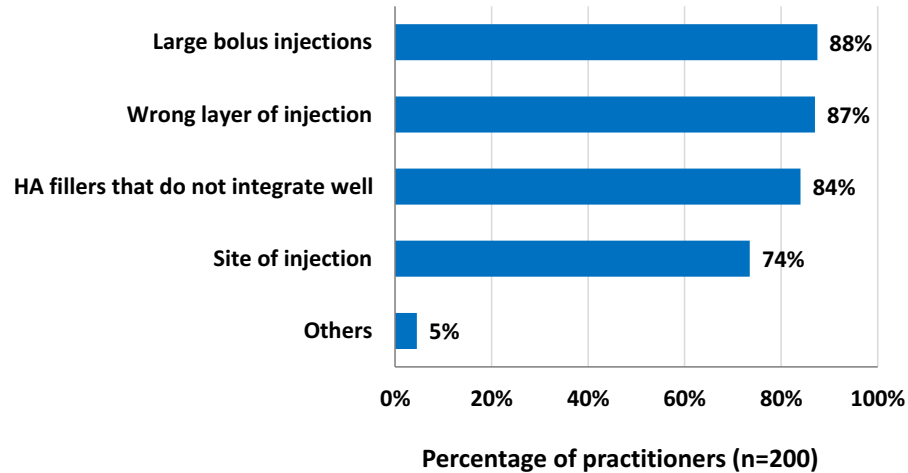
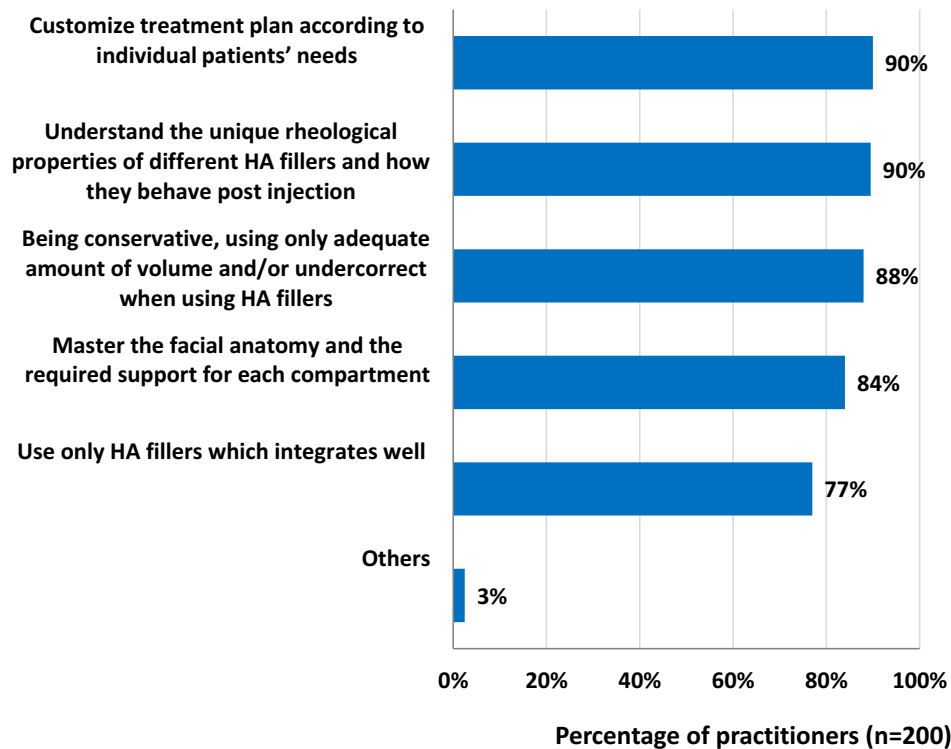
A**B**

Figure 5 Practitioners' views and practices pertaining to unnatural outcomes. **(A)** Causes of unnatural outcomes. **(B)** Strategies for avoiding unnatural outcomes with HA fillers.

Abbreviation: HA, hyaluronic acid.

technique. In addition, the panel acknowledged that any condition or procedure that can cause a systemic or localized immune response such as known ongoing infections, dental procedures, vaccinations, etc, can also trigger the onset of DIRs. It was recommended that practitioners consider patients' medical history and other medical procedures when creating a treatment plan for their patients^{8–10} (Figure 6). In the case of patients with an ongoing infection, filler treatment should be deferred until the condition is resolved. For patients who have other medical procedures such as dental procedures, vaccinations (including COVID-19 vaccinations), etc, it was recommended that such procedures be

Table I Consensus Statements on HA Dermal Filler Treatment Pertaining to DIRs and Natural Outcomes

| Statements | Agreement (%) |
|--|---------------|
| DIRs | |
| 1. Most doctors will encounter DIRs in their practice, so they should be aware of how to recognize and manage them | 100 |
| 2. Different HA-cross linking technologies produce HA dermal fillers of varying immunogenicity. Using HA dermal fillers with high immunogenicity is the most important factor for the development of DIRs, followed by break in aseptic technique, and poor injection technique. | 100 |
| 3. Any condition that can cause a systemic or localized immune response such as viral exposure or dental procedures may trigger the development of DIRs. | 100 |
| 4. The SAFE expert panel echoed the assessment by ASDS ¹⁹ that DIRs very rarely occur with both HA and non-HA dermal fillers. | 92 |
| 5. The SAFE expert panel agreed with the ASDS recommendation ¹⁹ that patients who have received dermal filler treatment should not be discouraged or precluded from receiving vaccines of any kind, and vice versa. | 100 |
| 6. Patients who have received COVID-19 vaccination should be advised to delay HA dermal filler treatment for at least 2–4 weeks post vaccination. | 100 |
| 7. HA dermal fillers with a higher composition of LMW-HA (<1000 KDa) are associated with a higher risk of DIRs. ^{12,13} | 100 |
| 8. Published evidence suggests increased incidence of DIRs with Vycross [®] technology HA dermal fillers. ^{12,16–18} One hypothesis for the greater inflammatory response relates to the high composition of LMW-HA in Vycross [®] fillers. ^{12,16–18} | 100 |
| 9. As LMW-HA is associated with increased proinflammatory activity which could trigger DIRs, ^{14,15} practitioners should consider choosing a HA dermal filler containing a lower percentage of LMW-HA for treatment. | 100 |
| 10. Choosing HA dermal fillers that are more immunologically inert, ensuring strict adherence to aseptic technique, and using proper injection technique are key measures that can be taken to reduce the risk of DIRs. | 100 |
| 11. DIRs can present as a spectrum of reactions that require physician assessment and appropriate tailored responses, which can range from the use of broad-spectrum antibiotics, oral steroids, and/or intralesional hyaluronidase to surgical excision to manage these reactions. | 100 |
| 12. For severe DIRs, a combination of broad-spectrum oral antibiotics, intralesional hyaluronidase, and oral steroids can be used to manage the symptoms. | 85 |
| 13. The approach for managing recalcitrant DIRs can include intralesional hyaluronidase injection under ultrasound guidance or a combination of intralesional hyaluronidase and 5-FU, with surgical extraction reserved as a last resort. | 100 |
| Natural outcomes | |
| 14. Unnatural outcomes are characterized by overfilling, surface irregularities, bumps/nodules, disproportionate face, and distorted appearance. | 100 |
| 15. Attaining natural outcomes is a very important consideration when performing HA filler treatment. | 100 |
| 16. Poor technique (large bolus injections, wrong layer of injection, etc) and inappropriate selection of HA fillers are causes of unnatural outcomes in HA filler treatment | 100 |
| 17. Filler treatment plan should be individualized, respecting patient's anatomical structure and avoiding one-size-fits-all treatment approach that can produce unnatural outcomes. | 100 |
| 18. Safety and natural outcomes are more important factors to consider when choosing a HA dermal filler than longevity of a filler. | 100 |
| 19. Using HA dermal fillers with excellent tissue integration leads to a more natural outcome. | 100 |
| 20. Treatment customization, understanding the HA dermal filler rheological properties and behavior, and being conservative in treatment strategy are important measures to avoid unnatural outcomes. | 100 |
| 21. Proper education to improve the understanding of the importance of preserving aesthetic individuality is vital for achieving optimal outcomes. | 100 |
| 22. As physicians, we have a non-maleficence duty of care to educate patients on the importance of safe injection procedures and avoiding unnatural treatment outcomes. | 100 |

Abbreviations: ASDS, American Society for Dermatologic Surgery; DIRs, delayed inflammatory reactions; 5-FU, 5-fluorouracil; HA, hyaluronic acid; LMW-HA, low molecular weight-hyaluronic acid; SAFE, Senior Aesthetics Filler Experts.

performed at least 2–4 weeks before or after filler treatment to minimize the risk of complications. The development of a DIR following COVID-19 vaccinations has been postulated to occur via the inactivation of angiotensin-converting enzyme receptor 2 (ACE2). Published case reports suggest the use of ACE inhibitors as a possible alternative to oral

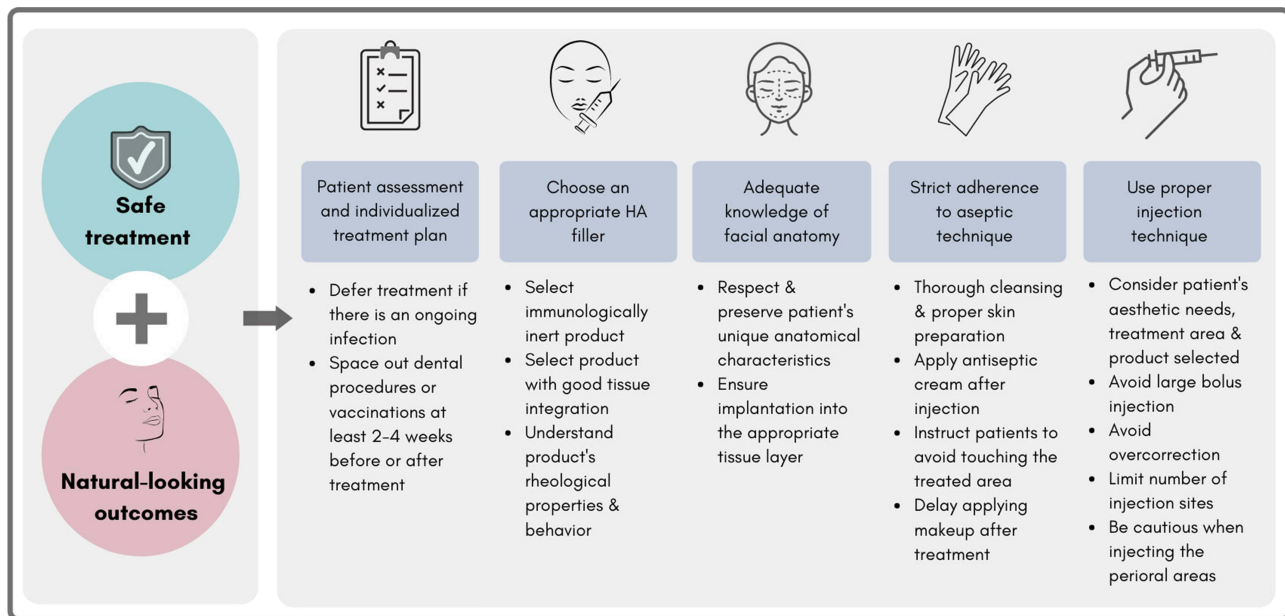


Figure 6 Practical considerations for creating an individualized treatment plan to achieve safe and natural-looking results.

Abbreviation: HA, hyaluronic acid.

steroids for managing the reaction should it arise.^{22,23} The panel concurred with the recommendations from the ASDS guidance that was issued in response to reports of COVID-19 mRNA vaccine-related adverse events in patients with dermal filler.¹⁹ The majority of the panel members agreed that the risk of developing DIRs following filler treatment is rare. Hence, there was a strong consensus that such potential complications should not hinder patients from taking vaccines (including COVID-19 vaccines).

The panel pointed out that although HA fillers are generally well tolerated and have a favorable safety profile, there is differential immunogenicity between different HA fillers, which is influenced by several factors including the molecular weight of HA, crosslinking and manufacturing technologies, etc.²⁴ The incidence of DIRs to HA filler treatments has been reported to range from around 0%–4.3% across different HA filler products.^{16,17} Hence, the panel recommended that practitioners be aware of the immunogenicity of different HA fillers and the influencing factors when selecting an appropriate filler for their patients. Reports have shown that HA dermal fillers with a higher composition of LMW-HA (<1000 kDa) are associated with a higher risk of DIRs.^{12,13} Published evidence suggests increased incidence of DIRs with Vycross[®] technology HA dermal fillers.^{12,16–18} One hypothesis for the greater inflammatory response relates to the high composition of LMW-HA in Vycross[®] fillers, which is proinflammatory and could trigger DIRs.^{12,14–18} Hence, it was recommended that practitioners consider a filler product containing a lower percentage of LMW-HA for treatment (Table 1).

The panel recommended three measures that are fundamental for avoiding DIRs—choosing an appropriate HA dermal filler with low immunogenic potential, ensuring strict adherence to aseptic technique, and using proper injection technique which requires an adequate knowledge of facial anatomy, in particular of deep spaces, different fat compartments, and muscle–bone relationship^{8–10} (Figure 6) (Table 1). The panel stressed that strict adherence to aseptic technique is important for minimizing the risk of DIRs. Injections can increase the chance of bacteria passing through the skin and causing a biofilm infection, which can induce the development of chronic nodules and granulomatous inflammation.²⁵ Hence, it was recommended that patients' skin be thoroughly cleaned and disinfected before injection. Aseptic technique should be adhered to throughout the procedure and practitioners should exercise continuous vigilance against possible contamination. Patients should be advised to delay putting on makeup and avoid touching the treated area for at least 12 hours after injection. The panel also addressed the importance of proper injection technique to avoid DIRs. Due to high numbers of bacteria in the perioral areas, practitioners are advised to take additional precaution when

injecting these areas, and avoid injecting through the oral mucosa. Studies show that large bolus filler injections can trigger the occurrence of DIRs, and multiple injections can increase the risk of bacterial contamination,^{25,26} hence the panel recommended limiting filler volume and the number of injection sites, according to patient's aesthetic needs, treatment area, and product selected. In line with published guidance,^{5,8} the panel pointed out that it is pertinent for practitioners to have a thorough knowledge of facial anatomy and a clear understanding of the appropriate depth and plane of injection. It is also important to understand how each filler intercalates with the skin at different depths.^{27–32} For example, what can be placed superficially and what will easily intersperse with fat in areas like the mid face.

The panel recognized that DIRs can present as a spectrum of clinical manifestations with varying etiology that require distinct treatments (Table 1). It was recommended that practitioners first assess patients to differentiate DIRs from non-inflammatory nodules. The development of DIR-related nodules can be attributed to biofilm and granulomatous reactions.²⁵ The panel agreed that the strategies for treating DIRs can include broad-spectrum oral antibiotics, oral steroids, and/or intralesional hyaluronidase, with surgical excision used as a last resort.^{5,7,9,33,34} Oral antibiotics should be prescribed first, before oral steroids or intralesional hyaluronidase are considered. For severe DIRs, the majority of the panel recommended using a combination of broad-spectrum oral antibiotics, intralesional hyaluronidase, and oral steroids to manage the symptoms. However, a few panel members noted that they prefer to separate the use of oral antibiotics and oral steroids to distinguish pure hypersensitivity reaction from bacterial biofilm. For recalcitrant DIRs, it was agreed that intralesional hyaluronidase alone or in combination with 5-FU can be used for treatment. Triple combination including intralesional hyaluronidase, 5-FU, and triamcinolone can also be used, with surgical extraction reserved as a last resort. The panel recommended using ultrasonography to determine the location of the injected filler and to guide the precise delivery of hyaluronidase.³⁵ The panel recommended treatment with broad-spectrum antibiotics for a week. Treatment duration with oral steroids is recommended to be between 1 and 2 weeks, depending on the severity. If intralesional steroid is administered, it is recommended to be given at every 3–4 weekly interval. Most of the panel members recommended weekly intralesional hyaluronidase injection.

Consensus on HA Dermal Filler Treatment Pertaining to Natural Outcomes

The panel agreed to define unnatural outcomes as overfilled appearance, surface irregularities, bumps/nodules, disproportionate face, and distorted appearance that manifest after filler treatment (Table 1). Considering patients can be distressed with such unpleasant outcomes and the potential risk of permanent sequelae,^{5,6} the panel stressed the importance for practitioners to adopt proactive strategies to achieve natural outcomes for their patients when using HA fillers in aesthetic procedures. They noted two key causes of unnatural outcomes—poor technique and inappropriate selection of HA fillers—which practitioners should be aware of.^{5,6}

The panel recommended three important measures that practitioners should adopt for achieving aesthetically pleasant outcomes for their patients: choosing an appropriate HA dermal filler, having adequate knowledge of facial anatomy, and using proper injection technique^{5,8–11} (Figure 6). The panel stressed that filler treatment plans should be individualized, respecting the patient's unique anatomical structure and avoiding a one-size-fits-all treatment approach, which can produce unnatural outcomes (Table 1). When choosing a HA dermal filler for treatment, the panel advised prioritizing product safety and effectiveness in achieving natural outcomes over durability of the filler product. Use of incorrect products for an indication may result in noninflammatory nodules.⁸ Hence, it is recommended that practitioners have a good understanding of the rheological properties and behavior of different HA fillers to aid them in selecting the appropriate product to address the unique aesthetic needs of the individual patient. The panel recommended selecting products that have better tissue integration for more natural results. The panel added that it is essential for practitioners to have detailed knowledge of facial anatomy, and a thorough understanding of the appropriate depth and plane of injection to ensure correct placement of the product into the appropriate tissue layer.⁸ The panel also addressed the importance of proper injection technique for achieving natural results. It is recommended to limit filler volume and inject slowly to introduce the product gently and evenly.⁸ The panel advised physicians to take a conservative approach to undercorrect to avoid an overfilled appearance.^{11,20} It is noted that while drastic results may be desired by patients, it is important to increase awareness on the possibility of irreversible distortion of the original tissue structure and facial contours with

overcorrection.⁶ The panel acknowledged the need for educational efforts to improve understanding on the importance of preserving aesthetic individuality and proper injection procedures for optimal results.

Conclusions

This is the first report describing the current practices of HA dermal filler treatment in Asia Pacific on preventing DIRs and achieving natural-looking outcomes. The report also includes a concise reference guide for creating an individualized treatment plan aimed at minimizing the risk of DIRs while achieving natural aesthetic outcomes with HA fillers. More clinical evidence may still be needed to support the recommendations for the prevention of DIRs and unnatural results. Nonetheless, the current findings from the survey and the practical insights from the experts can raise awareness of these complications in clinical practice and support practitioners in optimizing the safety and quality of aesthetic treatment with HA fillers.

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Disclosure

Dr Corduff serves as a lecturer and clinical advisor for Merz Aesthetics. Dr Lim, Dr Suwanchinda, Dr Tseng, and Dr Ho serve as speakers and advisory board members for Merz Aesthetics. Dr Lin serves as a speaker and advisory board member for Merz Aesthetics, BTL, and AbbVie. Dr Pavicic serves as a speaker and a member of advisory boards for Merz Aesthetic, AAT, J&J, and BTL, as well as conducts clinical studies for Merz Aesthetics, LG, AAT, Galderma, and AbbVie. Dr Quiambao has received honoraria from Merz Aesthetics and Teoxane Laboratories and serves as a speaker and regional advisory board member for Merz Aesthetics. Dr Siew serves as a trainer and lecturer for Merz Aesthetic. Dr Vachiramon serves as a speaker for Merz Aesthetic, LG Chem, Leo Pharma, and Biersdorf, L'Oreal, as well as a member in advisory boards for Merz Aesthetic, AbbVie, and L'Oreal. All authors have received honoraria from Merz Aesthetics for their contributions at the advisory board meeting and subsequent manuscript preparation.

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