Emerging Trends in Botulinum Neurotoxin A Resistance: An International Multidisciplinary Review and Consensus

Background: Botulinum neurotoxin A (BoNT-A) injection is the most widely performed aesthetic procedure and a first-line therapeutic option for various medical conditions. The potential for BoNT-A immunoresistance and secondary nonresponse related to neutralizing antibody (NAb) formation warrants attention as the range of BoNT-A aesthetic applications continues to expand.

Methods: An international multidisciplinary panel reviewed published evidence on BoNT-A immunoresistance in aesthetic and therapeutic applications and discussed best practices integrating clinical, ethical, and aesthetic considerations. Consensus statements relating to awareness, assessment, and management of the risk of NAb-related secondary nonresponse in aesthetic practice were developed.

Results: There was a consensus that, as doses used in aesthetic practice become like those in therapeutics, rates of NAb formation may be expected to increase. However, the true extent of NAb formation in aesthetics is likely underestimated due to limitations of published evidence and variability in treatment patterns of aesthetic patients. Since BoNT-A therapy is often lifelong, practitioners need to recognize immunogenicity as a potential complication that might affect future therapeutic use and strive to minimize modifiable risk factors. The selection and use of a BoNT-A product with the least immunogenic potential from the beginning may thus be advantageous, especially when treatment with high doses is planned.

Conclusions: In view of current trends in BoNT-A aesthetic use, it is essential for practitioners to conduct thorough clinical assessments, inform patients of treatment risks, and develop BoNT-A treatment plans to minimize immunogenicity. This can help preserve the option of continued or future BoNT-A treatment with satisfactory outcomes. (Plast Reconstr Surg Glob Open 2022;XX10X:e4407; doi: 10.1097/GOX.0000000000004407; Published online 20 June 2022.)

INTRODUCTION

Injection of botulinum neurotoxin A (BoNT-A) has remained the most frequently performed aesthetic procedure since 1999. It accounted for one-third of 13.3 million minimally invasive aesthetic procedures performed in 2020 in the United States. Beyond facial rhytid treatment, the range of BoNT-A aesthetic applications has expanded to include cosmetic treatment of maseteric hypertrophy and, more recently, body contouring. BoNT-A is also considered a first-line treatment for various therapeutic indications.

All authors contributed equally to this work.

Received for publication March 16, 2022; accepted May 11, 2022.

This article draws on material presented and discussed during a virtual meeting organized by Merz Aesthetics Asia Pacific.

Copyright © 2022 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of The American Society of Plastic Surgeons. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/GOX.0000000000004407
BoNT-A, a potent neurotoxin produced by Clostridium botulinum, causes muscle paralysis by blocking synaptic neurotransmission. Its therapeutic and aesthetic use derives from this ability to selectively weaken or paralyze the injected muscle group. Since the effects of BoNT-A diminish over time, repeated injections are required to maintain the treatment effect. However, repeated injections of BoNT-A may stimulate antibody formation, including neutralizing antibodies (NAbs) that counteract its biological activity. With NAB formation, the patient may develop partial or complete nonresponse to further BoNT-A treatment. This immunoresistance potentially has direct and long-term implications for future therapeutic options and should be considered in BoNT-A treatment decisions.

Three BoNT-A formulations [onabotulinumtoxinA (ONA), abobotulinumtoxinA (ABO), and incobotulinumtoxinA (INCO)] are currently approved by the US Food and Drug Administration (FDA) for therapeutic and aesthetic use. Besides ONA, ABO, and INCO, an increasing number of other formulations are commercially available around the world.

To highlight issues surrounding BoNT-A resistance and propose approaches for best practice, a multidisciplinary panel (Aesthetic Council for Ethical use of Neurotoxin Delivery) comprising 14 experts in aesthetic medicine, dermatology, plastic surgery, neurology, immunology, and bioethics was convened. This article reviews emerging concerns related to increasing numbers of patients seeking treatment and expanding off-label applications. With this growth, concerns have emerged regarding secondary nonresponse (SNR) to BoNT-A aesthetic treatment, initially highlighted in case reports. SNR refers to the reduction or absence of therapeutic effects (partial or complete SNR) after initial successful treatments. BoNT-A SNR may be related to NAB formation or other factors, including disease progression, inadequate dosage, incorrect muscle target, or improper injection technique. Typical signs of SNR include dose or interval creep, wherein higher BoNT-A doses or shorter injection intervals are required to achieve the desired therapeutic effect. However, such signs may be overlooked, resulting in underrecognition of the issue.

For therapeutic BoNT-A use, rates of NAB formation have been estimated using systematic reviews/meta-analyses (SR/MAs) and clinical studies. The reported range is 0.3%–27.6%, highest for therapeutic applications involving high-dose BoNT-A, especially dystonias (1.3%–27.6%) and spasticity (0.3%–13%) (Table 1). Reported NAB formation frequency was lowest for therapeutic indications: INCO (0%–1.1%), followed by ONA (0.3%–5.6%) and ABO (0%–13.3%) (Table 2). These overall estimates warrant careful interpretation because patients can integrate relevant biological, clinical, ethical, and aesthetic considerations.

### Table 1. Reported NAB Formation Frequency by Therapeutic Indication

| Indication          | NAB Formation Frequency (%) | No. Publications |
|---------------------|----------------------------|------------------|
| Dystonias           | 1.3–27.6                   | 17,21–23,25      |
| Spasticity          | 0.3–13                     | 17,21–23,25      |
| Hyperhidrosis       | 0.4–14                     | 21,22,25         |
| Bladder disorders   | 2.6–6.2                    | 21,25            |
| Blepharospasm       | 5.4                        | 1,25             |
| Not specified       | 0.5–17                     | 4,21,22,23,28    |

### Disclosure

Dr. Ho serves as a consultant for Merz Aesthetics. Dr. Albrecht reports grants and/or personal fees and/or nonfinancial support from Novartis, Biogen, Merz, Teva, Ipsen, Allergan, Celgene/Bristol Myers Squibb, Janssen Cilag, Roche, Merck, and Sanofi Genzyme outside of the submitted work. Ms. Corduff is a speaker and clinical investigator for Merz Aesthetics. Prof. Martin served as an ad-hoc consultant and speaker for Merz. Dr. Tseng served as a speaker, trainer, and advisory board member for Merz Aesthetics, AbbVie, Bausch & Lomb, Cynosure, Galderma, and Solta. Dr. Vachiramon serves as a speaker for Merz Aesthetics, LG Chem, Leo Pharma, Briersdorf, and L’Oreal, and as an advisory board member for Merz Aesthetics, AbbVie, and L’Oreal. Dr. Won currently receives grants from BMI Korea, Huons, Inhibio, and Metyox. Dr. Yu serves as a key opinion leader for Merz Aesthetic Philippines. Dr. Dingley is/was a speaker and advisor for and has received funding from Merz Aesthetics, Galderma, and Allergan. All authors received honoraria from Merz Aesthetics for participation in the expert panel and article preparation/development. The other authors have no financial interest to declare.

**Takeaways**

**Question:** How can aesthetic practitioners minimize risks of NAB formation and SNR with BoNT-A treatment?

**Findings:** An international multidisciplinary panel reviewed published evidence on BoNT-A immunoresistance and established a consensus on the need for awareness, assessment, and management of NAB-related SNR risks. The panel advocates for practitioners to recognize the potential impact of immunogenicity on future treatment options and strive to minimize modifiable risk factors.

**Meaning:** Since BoNT-A therapy is often lifelong, it is important for practitioners to minimize the risk of immunogenicity by using a highly purified BoNT-A and injecting the lowest dose required at appropriate intervals.
could have previous exposure to BoNT-A formulations other than those addressed in these studies. However, a similar trend is apparent when considering patients who exclusively used specific formulations: the percentages of patients with NAbs were 0%, 0.6%, and 5.3% with exclusive use of INCO, ONA, and ABO, respectively (Table 3).22,23,26,28

Although it is recognized that NAb-related SNR may arise in patients receiving high doses of BoNT-A for chronic medical conditions, the extent and clinical relevance of NAb formation in aesthetic treatment has been questioned, citing reasons such as the lower doses typically used in aesthetics.29 There may also be a perception that the issue is not of substantive clinical concern because NAbs/SNR arose. Nevertheless, considering only patients treated exclusively with one formulation, no cases of NAb-related SNR have been reported with exclusive INCO aesthetic use. This is consistent with observations for therapeutic indications, even those requiring high BoNT-A doses.23,26,28,37,37

We note certain caveats in interpreting these estimates. First, the summary estimates reported in SR/MAs are based on data aggregated from randomized controlled trials and observational studies, and are limited by the heterogeneity of study designs and measured outcomes. Such estimates are convenient for overall description but may obscure meaningful variation due to differences in the design and intent of studies. For example, one SR/MA noted differences between studies that were or were not primarily designed to detect NAbs.25 Second, all the published aesthetic studies on NAb formation and SNR evaluated only approved indications, such as glabellar lines,21,22,25,43 whereas a large proportion of real-world BoNT-A use includes off-label applications involving higher BoNT-A doses. Third, follow-up periods were relatively short, ranging from 4 to 16 months, whereas it is known that NAbs typically develop over a more extended period of years.24 For a complete view of NAb formation and SNR in clinical practice, one should consider the full range of published literature, including evidence from case reports and case studies.

Table 3. Reported NAb Formation Frequency in Therapeutic Indications, by Formulation (Exclusive Use*)

| Formulation | Patients with NAbs or Whose Use Nonresponders (n) | Total Number of Patients (N) | Percentage of Patients with NAbs or Nonresponders (n/N, %) | No. Publications |
|-------------|------------------------------------------------|-----------------------------|----------------------------------------------------------|----------------|
| ABO*        | 21                                              | 399                         | 5.3                                                      | 621,23,26,28    |
| ONA†        | 19                                              | 2859                        | 0.6                                                      | 321,26,28       |
| INCO‡       | 0                                               | 529                         | 0                                                       | 321,26,28       |

*Estimates in these studies may be associated with either overall use or exclusive use of the BoNT-A formulations studied.
†This publication did not distinguish between the old and new formulations of ONA.
‡Most patients had previously received ABO and/or ONA.

http://links.lww.com/PRSGO/C78. We identified 18 relevant publications with data on NAb-related SNR with aesthetic use (Table 4). SR/MAs reported overall rates of NAb formation with aesthetic BoNT-A use ranging from 0.2% to 0.4%, lower than for therapeutic indications.21,22,25

Except for one SR/MA focusing on ONA, these estimates represent various BoNT-A formulations and aesthetic applications.

Thirteen cases of NAb-related SNR emerging during aesthetic BoNT-A treatment were identified in case series or case reports, which would have been excluded from SR/MAs (Table 5).17–19,40–41 Across these cases, we noted a pattern of regular repeated treatments (with the same or different formulations) before detection of SNR, usually with clear signs of dose and/or interval creep. In all cases, patients had initially or exclusively received ABO or ONA; three patients were switched to INCO after partial or complete SNR with previous treatments. Duration of therapy before NAb detection varied considerably (2–72 months). Systematic testing was uncommon, and it was unclear precisely when NAb formation first occurred in most cases. These observations illustrate the difficulty of identifying precisely when and how NAbs/SNR arose. Nevertheless, considering only patients treated exclusively with one formulation, no cases of NAb-related SNR have been reported with exclusive INCO aesthetic use. This is consistent with observations for therapeutic indications, even those requiring high BoNT-A doses.23,26,28,37,37

We note certain caveats in interpreting these estimates. First, the summary estimates reported in SR/MAs are based on data aggregated from randomized controlled trials and observational studies, and are limited by the heterogeneity of study designs and measured outcomes. Such estimates are convenient for overall description but may obscure meaningful variation due to differences in the design and intent of studies. For example, one SR/MA noted differences between studies that were or were not primarily designed to detect NAbs.25 Second, all the published aesthetic studies on NAb formation and SNR evaluated only approved indications, such as glabellar lines,21,22,25,43 whereas a large proportion of real-world BoNT-A use includes off-label applications involving higher BoNT-A doses. Third, follow-up periods were relatively short, ranging from 4 to 16 months, whereas it is known that NAbs typically develop over a more extended period of years.24 For a complete view of NAb formation and SNR in clinical practice, one should consider the full range of published literature, including evidence from case reports and case studies. The frequency of BoNT-A NAb formation and SNR in real-world aesthetic practice...
may be higher than published estimates suggest. Although the reported frequency of NAb-related SNR appears relatively low for aesthetic versus therapeutic use of BoNT-A, the issue warrants further attention because of current aesthetic treatment trends and the potential implications of immunoresistance on access to future therapeutic options.

**BoNT-A NAb Formation and Resistance: An Immunological Perspective**

Although the true extent of NAb-related SNR in real-world practice remains unclear, the underlying biological process (how the immune system assesses and responds to the presence of BoNT-A or other biologic products) is well understood. This understanding can guide practitioners in evaluating the risk of immunogenicity and taking measures to manage that risk.

Immune system activation by BoNT-A (or any other antigen) is controlled via two key decision points (Fig. 1A, B). Both are necessary to stimulate classical T-helper cell-dependent antibody production. The first decision is made by DCs, which determine whether an antigen is potentially dangerous. Toll-like receptors (TLRs) on DCs recognize characteristic microbial cell surface features (e.g., flagellin) as “danger signals.” This triggers phagocytosis of the microbe or other “dangerous” particles by the DCs, which migrate to lymph nodes to act as antigen-presenting cells (APCs). APCs process the microbe or other “dangerous” particles and present the “dangerous” peptide antigens to naive T-helper cells while providing costimulatory signals to trigger clonal expansion of antigen-specific T-cells. The second decision involves antigen-specific T-cells that recognize presented peptide antigens as “foreign.” Fully activated antigen-specific T-helper cells expand clonally and then support antigen-specific B-cell activation as well as their clonal expansion, finally producing antibodies against the original antigen. These two decisions are strictly hierarchical since naive T-helper cells always require peptide-antigen presentation by a fully activated DC.

The physiological BoNT-A supramolecular complex produced in nature by *C. botulinum* comprises the core 150-kDa neurotoxin and various neurotoxin-associated proteins (NAPs), including hemagglutinins (HAs) and non-HAs. Of the FDA-approved formulations, ONA and ABO are known to include NAPs and/or other unnecessary bacterial proteins, whereas INCO contains only the core 150-kDa neurotoxin (Fig. 1C). If a highly purified BoNT-A formulation is injected, peptides derived from the BoNT-A core neurotoxin subunits could be identified as “foreign” by naive T-helper cells. However, the pure bioactive 150-kDa core neurotoxin lacks the comitent “danger signals” required to fully activate DCs to become APCs. Without these signals, the first decision-maker (the DCs) would not register BoNT-A core neurotoxin subunits as “dangerous,” escaping the immune cascade. In contrast, NAPs, such as HA-33, and other bacterial contaminants, particularly flagellin, inactive/denatured toxin, and clostridial DNA, can trigger an immune response. HA-33 is reported to be an immune response stimulator, whereas flagellin and clostridial DNA are adjuvants that bind readily to TLR5 and TLR9 on DCs, respectively, activating the immune cascade. In the context of BoNT-A treatment, NAPs have no therapeutic role and merely enhance the immunogenicity of the injected product.

It is, thus, clear that antigen-specific immune activation by BoNT-A is not determined by the indication (therapeutic versus aesthetic) for which it is administered. Instead, factors that could influence the risk of Nab formation with a given BoNT-A formulation include its purity, dose administered, and the number and interval between injections. These factors are generally modifiable within a BoNT-A treatment plan. As noted, the purity of

---

**Table 4. Identified Publications with Data on BoNT-A NAb-related SNR in Aesthetic Applications**

| Publication | Type         | Application(s)                                                                 |
|------------|--------------|--------------------------------------------------------------------------------|
| Borodic et al | Case report  | Facial lines                                                                  |
| Borodic et al | Case report  | Facial lines                                                                  |
| Cohen and Scuderi | SR         | Glabellar lines; crow’s feet                                                  |
| Dressler et al | Case series | Facial lines (four cases)                                                     |
| Fabbri et al | SR/MA        | Ax: glabellar lines                                                           |
| Fischer et al | Clinical study (interventional) | Tx: dystonia, spasticity, urologic conditions, and hyperhidrosis |
| Helmsatder et al | Clinical study (chart review) | Facial lines                                                                  |
| Imhof and Kühne | Clinical study (interventional) | Glabellar lines                                                              |
| LacroczyDesmazes et al | SR | Ax: glabellar lines                                                           |
| Lawrence and Moy | Secondary analysis (safety and efficacy) of clinical trial data | Tx: dystonia, blepharospasm, spasticity, and urological indications          |
| Lee | Case report | Glabellar lines                                                              |
| Naumann et al | SR/MA        | Ax: glabellar lines                                                           |
| Rahman et al | SR/MA        | Tx: dystonia, urologic conditions, spasticity, and hyperhidrosis              |
| Srinoulprasert et al | Clinical study (interventional) | Ax: glabellar lines and crow’s feet                                           |
| Stengel and Bee | Case report  | Tx: dystonia, urologic indications, spasticity, facial hemispasm, blepharospasm, and hyperhidrosis |
| Stephan et al | Case report  | Aesthetic indications (various)                                                |
| Torres et al | Case series  | Glabellar lines                                                              |
| Wanitphakdeedecha et al | Clinical study (interventional) | Facial rejuvenation (four cases)                                               |

Ax, aesthetic indications; Tx, therapeutic indications.
each formulation and the presence of potential adjuvants are product-specific features. High doses or repeated injections increase the exposure to potentially “dangerous and foreign” material. Thus, a risk-based approach, such as that outlined by the FDA and European Medicines Agency (EMA), seems eminently applicable to evaluate and manage the risk of immunogenicity associated with therapeutic protein products when used for aesthetics.

Navigating the Complex Landscape of BoNT-A Treatment Decision-making

Advances in BoNT-A treatment have engendered new aesthetic enhancement possibilities and challenges for everyday practice, particularly in terms of decision-making. For example, practitioners must carefully consider the patient’s treatment history, which could be potentially complex, including extensive prior BoNT-A treatment for multiple indications from different practices, and weigh the implications of specific treatment choices throughout a patient’s medical history. Considering the risk of immunoresistance, we suggest that it is clinically prudent to minimize the risk of NAb formation to facilitate continued clinical response over time.

Since aesthetic and medical treatments are associated with distinct contexts and expectations, aesthetic patients’ clinical course and behaviors may be expected to differ from therapeutic patients (Fig. 2A). BoNT-A use in both aesthetic and therapeutic contexts becomes “complicated” in cases where injection patterns in one setting have clinical implications within the other. For example,

Table 5. Summary of BoNT-A NAb Formation and Secondary Nonresponse Reported in Aesthetic Cases

| No. | Publication | Age | Sex | Condition | Treatments | Intervention | Results | Duration of Treatment before NAb Detection |
|-----|-------------|-----|-----|-----------|------------|--------------|---------|------------------------------------------|
| 1   | Borodic     | 48  | F   | Facial lines | 1–14 ONA | ONA | Cycles 1–14: response lasted for 3–4 mo Cycle 15: no response, no effect on forced frown | Unclear when NAb test was done. Duration (first to last treatment): 72 mo |
| 2   | Borodic     | 44  | F   | Facial lines | 1–14 ONA | ONA | Cycles 1–5: normal response Cycles 6–9: PSNR Cycle 10: CSNR Cycle 1: normal response | Unclear when NAb test was done. Duration (first to last treatment): 60 mo NAb detected (7.0 mU/mL) at cycle 10 |
| 3   | Dressler et al | 53 | F   | Facial lines | 1–10 ABO | 10–180 MU | Cycles 1–5: normal response Cycles 6–9: PSNR Cycle 10: CSNR Cycle 1: normal response | NAb detected (2.7 mU/mL) at cycle 6 |
| 4   | Dressler, 2010 | 46 | F   | Facial lines | 1–3 ONA | 80 MU | Cycles 2: PSNR Cycles 3: CSNR Cycles 5–6: CSNR | NAb detected (1.0 mU/mL) at cycle 12, and (>10.0 mU/mL) at cycle 13 NAb detected (>10.0 mU/mL) at cycle 7 |
| 5   | Dressler et al | 51 | F   | Facial lines | 1–9 ONA | 30 MU | Cycles 1–11: normal response Cycles 12: PSNR Cycle 13: CSNR Cycle 3: PSNR Cycle 5: CSNR | NAb testing was not available |
| 6   | Dressler et al | 45 | F   | Facial lines | 1–6 ONA | 25–105 MU | Cycles 1–3: response lasted for 4–5 mo Cycles 4–5: response lasted for 1.5 mo Cycles 6–7: no response Cycles 1–2: response lasted for 4–8 mo Cycles 3–11: response lasted for 5–4 wk | NAb testing was not available |
| 7   | Lee et al | 20 | F   | Massesteric hypertrophy | 1–6 ONA | 70 MU | Cycles 1–3: partial response (>2 mo), required high-dose booster injections Cycle 3: partial response with even shorter duration of efficacy | NAb testing was not available |
| 8   | Stengel and Bee | 41 | F   | Glabellar lines | 1–5 ONA | 9–28 U | Cycles 1–3: partial response (>2 mo), required high-dose booster injections Cycle 3: partial response with even shorter duration of efficacy | NAb testing was not available |
| 9   | Stephan et al | 51 | F   | Facial lines | 1–3 ONA | 75 U | Cycles 1–3: partial response (>2 mo), required high-dose booster injections Cycle 3: partial response with even shorter duration of efficacy | NAb testing was not available |
| 10  | Torres et al | 55 | F   | Facial rejuvenation | 1–2 ONA | 33 U | Cycles 1: no response Cycles 2: mild response lasting 3 mo | Unclear when NAb test was done. |
| 11  | Torres et al | 54 | F   | Facial rejuvenation | 1–8 ONA | 25–180 U | Cycles 1–7: normal response Cycle 8: loss of efficacy Cycle 10: no effect after 4 wk Cycle 11: no effect after 2 wk Initial response lasted for 6–8 mo, decreased to 3 mo at later treatments Cycle 3: CSNR | Unclear when NAb test was done. Duration (first to last treatment): 96 mo |
| 12  | Torres et al | 43 | F   | Facial rejuvenation | 1–6 ONA | 100–260 U | Cycles 1–7: normal response Cycle 8: loss of efficacy Cycle 10: no effect after 4 wk Cycle 11: no effect after 2 wk Initial response lasted for 6–8 mo, decreased to 3 mo at later treatments Cycle 3: CSNR | Unclear when NAb test was done. Duration (first to last treatment): 96 mo |
| 13  | Torres et al | 38 | M   | Facial rejuvenation | 1–3 ONA | 120–250 U | Cycles 1–7: normal response Cycle 8: loss of efficacy Cycle 10: no effect after 4 wk Cycle 11: no effect after 2 wk Initial response lasted for 6–8 mo, decreased to 3 mo at later treatments Cycle 3: CSNR | Unclear when NAb test was done. Duration (first to last treatment): 96 mo |

CSNR, complete secondary nonresponse; F, female; M, male; MU, mouse unit; NR, not reported; PSNR, partial secondary nonresponse; SU, speywood unit; U, unit.
Fig. 1. BoNT-A treatment from the immunological perspective. A, Dangerous + foreign? Two key decisions controlling the immune response to biologics. The first decision involves DCs that determine whether or not a particle (eg, a microbe) is likely to be “dangerous.” DCs can recognize microbial surface molecules (eg, flagellin) as “danger signals.” Upon recognition of microbial danger signals, DCs will be activated and phagocytose the particle bearing the danger signal. Subsequently, these activated DCs migrate to lymph nodes and become professional APCs. The second decision involves naive T-helper cells that determine whether a particle is self or foreign. Upon encountering foreign antigen peptides presented by APCs along with co-stimulatory signals, naive T-helper cells become activated and undergo clonal expansion, leading to activation and clonal expansion of antigen-specific B cells. These mature into plasma cells that produce antibodies specific to the antigen that triggered the immune response. B, Development of BoNT-A neutralizing antibodies. C, Composition of FDA-approved BoNT-A formulations. Figure credit: Michael Martin.
extensive aesthetic treatment with high BoNT-A doses, along with frequent retreatments, results in greater exposure to potentially immunogenic material, and could, thus, increase the risk of developing NAb-related SNR. As illustrated in the hypothetical example (Fig. 2B), this potentially leads to suboptimal outcomes if this patient later develops a chronic medical condition that requires BoNT-A treatment. Furthermore, the younger a patient is when beginning aesthetic BoNT-A treatment and the more extensive the use of BoNT-A, the greater the possible lifetime exposure and risk of developing NAb-related SNR. Such cases may have medicolegal implications, especially if risks such as NAb-related SNR were not thoroughly discussed with the patient before treatment. A better understanding of patients’ awareness, attitudes, and motivations in relation to their BoNT-A treatment choices is warranted. This could help practitioners to more effectively communicate and work with their patients to manage the risk of BoNT-A resistance.

The ethical principles of medicine underpin therapeutic and aesthetic practice alike. Accordingly, it is often suggested that patient safety and empowerment in decision-making are of prime importance in good aesthetic practice. However, few published guidelines deal with ethics in aesthetic practice. The topic is usually covered only briefly within general guidance for aesthetic practitioners. Nevertheless, the applicability of core medical ethics principles is a recurring theme across the literature, including respect for patient autonomy and obtaining informed consent, comprehensive assessment of expectations within and from clinical encounters (eg, aesthetic enhancement and improved quality of life), and empathic and truthful communication of possible risks and outcomes.

Recognizing the strong influence of patient preference and choice in aesthetic medicine, we suggest that a collaborative patient-centered approach offers a better chance of achieving safe and satisfactory outcomes. In our view, a patient-centered approach in aesthetic practice encompasses not only consideration of patients’ individual preferences and circumstances but also individualized assessment, patient education, and informed
decision-making following adequate discussion of possible risks and outcomes.

There are strong clinical and ethical reasons for making thorough pretreatment assessments and informed discussions of risk/benefit integral to the aesthetic consultation process. A comprehensive treatment history (including the BoNT-A products used, number of previous injections, doses, indications, and injection intervals) would help practitioners evaluate and mitigate risks. However, with greater patient choice and “mobility” in aesthetic practice, it may prove challenging to construct a complete history and assess all relevant risk factors (Fig. 2A). Information on concurrent medical conditions or treatment may be highly relevant but may not often be solicited or volunteered. Nevertheless, it is essential to recognize clinical signs of BoNT-A resistance, know the appropriate diagnostic tests to perform, and make informed decisions on options for management.

**Consensus on BoNT-A Resistance and Implications for Aesthetic Practice**

The panel discussed the above issues surrounding BoNT-A resistance and achieved consensus on a set of recommendations (Table 6). This was achieved through a blinded voting process, in which panel members indicated their position on each statement (agree/disagree). The results were categorized as strong consensus (>95% agreement); consensus (>75%–95% agreement); majority consent (>50%–75% agreement); no majority consent (≤50% agreement).

All panel members agreed that the true extent of BoNT-A antibody-induced SNR in aesthetic applications is likely underestimated within the published literature. They noted that conclusions of SR/MAs are based on data aggregated across studies that may miss clinically relevant observations concerning individual-level data. There was a strong consensus that practitioners should refer to the full range of clinical evidence for a complete picture of antibody-induced SNR and its implications for their practice. There was also consensus that the variability of a typical aesthetic patient’s treatment journey may contribute to missed diagnoses or underreporting of BoNT-A resistance.

There was a strong consensus that BoNT-A resistance is a problem that warrants attention. The panel noted that, with expanding off-label applications and doses used in aesthetics becoming more like those in therapeutics, increased rates of NAb formation could be expected. In light of these trends, all panelists agreed that the first step toward preventing BoNT-A NAb formation is for practitioners to acknowledge immunogenicity as a potential complication that might affect future treatment options. Recognizing that BoNT-A therapy is often lifelong, there was a strong consensus that immunogenicity should be considered when making BoNT-A-related treatment decisions. All panelists agreed that using a highly purified BoNT-A formulation with the lowest immunogenicity to minimize the risk of NAb formation may be a prudent clinical decision. Where efficacy and safety are comparable, a lower immunogenicity formulation may offer advantages for further treatment, even though increasing

**Table 6. Consensus Statements**

| Statements                                                                 | % Agreement* | Consensus# |
|---------------------------------------------------------------------------|--------------|------------|
| The true extent of antibody-induced SNR in aesthetic practice is likely to be underestimated/under-reported in the medical literature | 100          | Strong consensus |
| Clinicians should refer to published literature beyond SRMAs (including single-arm studies and case reports) for real-world evidence and a more complete picture of NAb formation in clinical practice A typical aesthetic patient’s treatment journey, follow-up behavior, and treatment patterns are distinct from that of a medical patient | 100          | Strong consensus |
| The aforementioned differences further contribute to the underreporting or missed diagnosis of BoNT-A resistance | 93           | Consensus |
| Although the frequency of antibody-induced SNR for BoNT-A is low compared with other therapeutic protein products, it is a real problem that warrants further attention as the clinical applications of BoNT-A continue to expand | 100          | Strong consensus |
| As the doses used in aesthetic practice become similar to those in therapeutics owing to the rise in off-label applications, a corresponding increase in the rate of NAb formation can be expected | 100          | Strong consensus |
| The first step in preventing NAb formation against BoNT-A is for aesthetic practitioners to acknowledge that immunogenicity is a potential complication that might affect future therapeutic use | 100          | Strong consensus |
| The nature of antigen and the presence of adjuvants are modifiable risk factors for immunogenicity that are directly influenced by an injector’s choice of BoNT-A formulation | 93           | Consensus |
| Aesthetic practitioners are obliged to make treatment decisions in accordance with the key pillars of medical ethics and should strive to minimize modifiable risk factors As BoNT-A therapy is often lifelong, the risk of immunogenicity should be a key consideration in treatment decisions regarding BoNT-A formulation | 100          | Strong consensus |
| Using a highly purified BoNT-A formulation with the lowest immunogenic risk to minimize the risk of NAb formation is a prudent clinical decision Where efficacy and safety are comparable, a BoNT-A formulation that is less likely to cause antibody-induced SNR should be considered as a first-line therapy | 100          | Strong consensus |
| The FDA and EMA recommendations on assessing and mitigating adverse immunologically related responses associated with therapeutic protein products are equally applicable to BoNT-A use in aesthetics | 93           | Consensus |
| There is a need to raise public awareness on the risk of immunogenicity associated with BoNT-A therapy via patient education programs supported by health authorities and professional societies | 100          | Strong consensus |

*Cutof was as follows: strong, more than 95% agreement; consensus, more than 75%–95% agreement; majority consent, more than 50%–75% agreement; no majority consent, less than 50% agreement.

SRMA, systematic reviews/meta-analyses.
the dose and/or reducing treatment intervals can compensate for partial SNR in some patients. These views are summarized in Figure 3 and are consistent with observations suggesting that using a highly purified BoNT-A formulation and administering the lowest acceptable dose at appropriate intervals may help limit the development of immunoresistance.11–13,46

To minimize adverse immunologically related responses, the FDA and EMA have provided recommendations on immunogenicity assessment and risk-based management with therapeutic biologics.52,53 The panel concluded that these recommendations are also applicable to aesthetic BoNT-A use. In addition, the panelists discussed BoNT-A-specific advisories on NAb formation by the Korean FDA for patients, physicians, and manufacturers as examples of how regulatory bodies could provide leadership in promoting prudent use in aesthetics.56–58 These Korean Food and Drug Administration advisories provide patient education on risk factors and physician guidance on prevention strategies. Furthermore, manufacturers were recommended to conduct clinical trials assessing the immunological impact of repeated administration for at least 1 year.

As in therapeutic decision-making, the panelists concurred that treatment decisions in aesthetics should be aligned with core medical ethics principles, alongside the relevant clinical and aesthetic considerations. Given the diverse applications of BoNT-A and an increasingly complex aesthetic treatment landscape, practitioners should strive to recognize and minimize modifiable risk factors for future adverse outcomes. Finally, there was strong consensus on the need to raise public awareness of the risk of immunogenicity associated with BoNT-A therapy, as the issue can only be fully addressed with the understanding and cooperation of patients. However, the panel members acknowledged that existing resources for clinicians might be overly technical for use in patient education. Consumer advisories in lay language, such as those issued by the Korean Food and Drug Administration, may be more helpful for highlighting the issue.

**Fig. 3.** Key treatment considerations for BoNT-A use in aesthetics.
CONCLUSIONS
With millions of aesthetic BoNT-A treatments performed worldwide, especially off-label applications involving higher doses than traditional on-label indications, more practitioners may expect to encounter possible cases of NAb-related SNR. They will need to make appropriate clinical assessments and design/adjust treatment plans accordingly. A collaborative patient-centered approach and informed decision-making may offer a better chance of achieving safe and satisfactory treatment outcomes. We advocate individualized assessment and thorough discussion of BoNT-A treatment issues and risks, including immunogenicity, with patients from the outset. It may be clinically prudent to minimize immunogenic risk to preserve the option of continued or future BoNT-A treatment. The selection and use of a BoNT-A product with the highest purity and lowest immunogenicity from the beginning may be advantageous, especially when treatment with high doses is planned. We believe that this view is aligned with relevant clinical, ethical, and aesthetic considerations, and with recommendations in the therapeutic space for risk-based management of adverse immunological responses related to biologic drugs, including BoNT-A.

Mary Dingley, MBBS, FACCSM, FCPCA
The Cosmetic Medicine Centre
Toowong, QLD 4066, Australia
E-mail: drdlingy@cosmeticmedicinecentre.com.au

ACKNOWLEDGMENT
Medical writing and editorial support were provided by Tech Observer Asia Pacific Pte Ltd and funded by Merz Aesthetics.

REFERENCES
1. The Aesthetic Society. Aesthetic Plastic Surgery National Databank Statistics 2019. The Aesthetic Society. 2019.
2. American Society of Plastic Surgeons. Plastic Surgery Statistics Report 2020. American Society of Plastic Surgeons. 2020.
3. Dorizas A, Krueger N, Sadick NS. Aesthetic uses of the botulinum toxin. Dermatol Clin. 2014;32:23–36.
4. Flynn TC. Advances in the use of botulinum neurotoxins in facial esthetics. J Cosmet Dermatol. 2012;11:42–50.
5. Ahn BK, Kim YS, Kim HJ, et al. Consensus recommendations on the aesthetic usage of botulinum toxin type A in Asians. Dermatol Surg. 2013;39:1843–1860.
6. Sundaram H, Huang PH, Hsu NJ, et al; Pan-Asian Aesthetics Toxin Consensus Group. Aesthetic applications of botulinum toxin A in Asians: an international, multidisciplinary, Pan-Asian consensus. Plast Reconstr Surg Glob Open. 2016;4:e872.
7. Cheng J, Chung HJ, Friedland M, et al. Botulinum toxin injections for leg contouring in East Asians. Dermatol Surg. 2020;46(suppl 1):S62–S67.
8. Dressler D. Clinical applications of botulinum toxin. Curr Opin Microbiol. 2012;15:329–336.
9. Jankovic J. Botulinum toxin: state of the art. Mov Disord. 2017;32:1131–1138.
10. Samizadeh S, De Boulle K. Botulinum neurotoxin formulations: overcoming the confusion. Clin Cosmet Investig Dermatol. 2018;11:273–287.
11. Frevert J. Pharmaceutical, biological, and clinical properties of botulinum neurotoxin type A products. Drugs R D. 2015;15:1–9.
12. Bellows S, Jankovic J. Immunogenicity associated with botulinum toxin treatment. Toxins (Basel). 2019;11:E491.
13. Carr WW, Jain N, Sublett JW. Immunogenicity of botulinum toxin formulations: potential therapeutic implications. Adv Ther. 2021;38:5046–5064.
14. Spiegel LL, Ostrem JL, Bledsoe JO. FDA approvals and consensus guidelines for botulinum toxins in the treatment of dystonia. Toxins (Basel). 2020;12:E332.
15. Frevert J, Ahn KY, Park MY, et al. Comparison of botulinum neurotoxin type A formulations in Asia. Clin Cosmet Investig Dermatol. 2018;11:327–331.
16. Walker TJ, Dayan SH. Comparison and overview of currently available neurotoxins. J Clin Aesthet Dermatol. 2014;7:31–39.
17. Lee SK. Antibody-induced failure of botulinum toxin type A therapy in a patient with massteric hypertrophy. Dermatol Surg. 2007;33(1 Spec No.):S105–S110.
18. Stengel G, Bee EK. Antibody-induced secondary treatment failure in a patient treated with botulinum toxin type A for glabellar frown lines. Clin Interv Aging. 2011;6:281–284.
19. Dressler D, Wohlfahrt K, Meyer-Rogge E, et al. Antibody-Induced failure of botulinum toxin a therapy in cosmetic indications. Dermatol Surg. 2010;36(suppl 4):2182–2187.
20. Göschel H, Wohlfarth K, Frevert J, et al. Botulinum A toxin therapy: neutralizing and nonneutralizing antibodies–therapeutic consequences. Exp Neurol. 1997;147:98–102.
21. Fabbi M, Leodori G, Fernandes RM, et al. Neutralizing antibody and botulinum toxin type a therapy: a systematic review and meta-analysis. Neurotox Res. 2016;29:105–117.
22. Naumann M, Carruthers A, Carruthers J, et al. Meta-analysis of neutralizing antibody conversion with onabotulinumtoxinA (BOTOX®) across multiple indications. Mov Disord. 2010;25:2211–2218.
23. Walter U, Mühlenhoff C, Benecke R, et al. Frequency and risk factors of antibody-induced secondary failure of botulinum neurotoxin therapy. Neurology. 2020;94:e2109–e2120.
24. Albrecht P, Jansen A, Lee JI, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. Neurology. 2019;92:e57–e54.
25. Rahman E, Alhithi HK, Mosaihehi A. Immunogenicity to botulinum toxin type A: a systematic review with meta-analysis across therapeutic indications. Aesthet Surg J. 2022;42:106–120.
26. Mathewon I, Declenny A, Lafoont I, et al. Immunogenicity induced by botulinum toxin injections for limb spasticity: a systematic review. Ann Phys Rehabil Med. 2019;62:241–251.
27. Lacroix-Desmazes S, Moudy S, Popoff, M-R, et al. Systematic analysis of botulinum neurotoxin type A immunogenicity in clinical studies. Basel Ganglia. 2017:9:12–17.
28. Samadzadeh S, Ürer B, Braunns R, et al. Clinical implications of difference in antigenicity of different botulinum neurotoxin type A preparations: clinical take-home messages from our research pool and literature. Toxins (Basel). 2020;12:E490.
29. Dover JS, Monheit G, Greener M, et al. Botulinum toxin in aesthetic medicine: myths and realities. Dermatol Surg. 2018;44:249–260.
30. Wanitphakdeecha R, Yan C, Apinuntham C, et al. Intradermal micro-dosing of abobotulinumtoxinA for face-lifting: how long does it last? Dermatol Ther (Heidelb). 2020;10:779–789.
31. Park JY, Cho SI, Hur K, et al. Intradermal microdroplet injection of diluted incobotulinumtoxinA for sebum control, face lifting, and pore size improvement. J Drugs Dermatol. 2021;20:49–54.
32. Borodic G. Immunologic resistance after repeated botulinum toxin type A injections for facial rhytides. Ophthalmic Plast Reconstr Surg. 2006;22:239–240.
33. Borodic G. Botulinum toxin, immunologic considerations with long-term repeated use, with emphasis on cosmetic applications. Facial Plast Surg Clin North Am. 2007;15:11–16, v.
34. Cohen JL, Scuderi N. Safety and patient satisfaction of abobotulinumtoxinA for aesthetic use: a systematic review. Aesthet Surg J. 2017;37(suppl 1):S32–S44.
35. Fischer T, Sattler G, Prager W, et al. Safety, tolerability, and efficacy of repeat-dose injections of incobotulinumtoxinA in the treatment of upper facial lines: results from a prospective, open-label, phase III study. *J Drugs Dermatol.* 2020;19:461–469.

36. Helmstaedter V, Witekantl C, Hutenbrink KB, et al. Safety and efficacy of botulinum toxin therapy in otolaryngology: experience from 1,000 treatments. *Laryngoscope.* 2008;118:790–796.

37. Imhof M, Kühtre U. A phase III study of incobotulinumtoxinA in the treatment of glabellar frown lines. *J Clin Aesthet Dermatol.* 2011;4:28–34.

38. Lawrence I, Moy R. An evaluation of neutralizing antibody induction during treatment of glabellar lines with a new US formulation of botulinum neurotoxin type A. *Aesthet Surg J.* 2009;29(suppl 6):S66–S71.

39. Srinoulprasert Y, Kantaviro W, Nokdhes YN, et al. Development of inhibition ELISA to detect antibody-induced failure of botulinum toxin a therapy in cosmetic indications. *J Immunol Methods.* 2019;473:112635.

40. Stephane F, Habre M, Tomb R. Clinical resistance to three types of botulinum toxin type A in aesthetic medicine. *J Cosmet Dermatol.* 2014;13:346–348.

41. Torres S, Hamilton M, Sanches E, et al. Neutralizing antibodies to botulinum neurotoxin type A in aesthetic medicine: five case reports. *Clin Cosmet Investig Dermatol.* 2014;7:11–17.

42. Wanitphakdeedech R, Kantaviro W, Saphatsathienkul P, et al. Association between secondary botulinum toxin A treatment failure in cosmetic indication and anti-complexing protein antibody production. *Dermatol Ther (Heidelb).* 2020;10:707–720.

43. Carruthers JD, Lowe NJ, Menter MA, et al; Botox Glabellar Lines II Study Group. Double-blind, placebo-controlled study of the safety and efficacy of botulinum toxin type A for patients with glabellar lines. *Plast Reconstr Surg.* 2005;112:1089–1098.

44. Inoue K, Fujinaga Y, Watanabe T, et al. Molecular composition of clostridium botulinum type A progenitor toxins. * Infect Immun.* 1996;64:1589–1594.

45. Frevert J. Content of botulinum neurotoxin in Botox®/Vistabel®, Dysport®/Azzalure®, and Neocimi®/Bocouture®. *Drugs R D.* 2010;10:67–73.

46. Park JI, Sunga O, Wanitphakdeedech R, et al. Neurotoxin impurities: a review of threats to efficacy. *Plast Reconstr Surg Glob Open.* 2020;8:e2927.

47. Oshima M, Deitiker PR, Jankovic J, et al. Human T-cell responses to botulinum neurotoxin: proliferative responses in vitro of lymphocytes from botulinum neurotoxin a-treated movement disorder patients. *J Neurommunol.* 2011;237:66–72.

48. Bryant AM, Cai S, Singh BR. Comparative immunogenic characteristics of botulinum neurotoxin type A and its associated proteins. *Toxicon.* 2013;72:126–132.

49. Means TK, Hayashi F, Smith KD, et al. The toll-like receptor 5 stimulus bacterial flagellin induces maturation and chemokine production in human dendritic cells. *J Immunol.* 2003;170:5165–5175.

50. Yoon SI, Kurnasov O, Natarajan V, et al. Structural basis of TLR5-flagellin recognition and signaling. *Science.* 2012;335:859–864.

51. Wang L, Sun Y, Yang W, et al. Type A botulinum neurotoxin complex proteins differentially modulate host response of neuronal cells. *Toxicon.* 2014;82:52–60.

52. FDA. Guidance for Industry - Immunogenicity Assessments for Therapeutic Protein Products. Available at https://www.fda.gov/media/85017/download. Accessed October 15, 2021.

53. EMA. Guideline on Immunogenicity Assessment of Therapeutic Proteins. Available at https://www.ema.europa.eu/en/immunogenicity-assessment-biotechnology-derived-therapeutic-proteins. Accessed October 15, 2021.

54. Gillon R. Medical ethics: four principles plus attention to scope. *BMJ.* 1994;309:184–188.

55. Mousavi SR. The ethics of aesthetic surgery. *J Cutan Aesthet Surg.* 2010;3:38–40.

56. Korean Food and Drug Administration (KFDA). Information on safe use of botulinum toxin (for HCPs) (in Korean). KFDA. 2017:1-8.

57. Korean Food and Drug Administration (KFDA). Information on safe use of botulinum toxin (for Consumers) (in Korean). KFDA. 2017:1-4.

58. Korean Food and Drug Administration (KFDA). Considerations for review of Botulinum toxin preparations (for Manufacturers) (in Korean). KFDA. 2020:1-40.