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REVIEW ARTICLE

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Improving aseptic injection standards in aesthetic clinical practice

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Abstract

The rise in popularity and demand for nonsurgical injectable aesthetic procedures is inherently accompanied by an increase in reported complications, particularly those related to infection. Aseptic technique is under the control of aesthetic practitioners and can be modified to minimize the potential for cross-contamination and infection. This should be a key consideration during all clinical procedures, particularly those involving breach of the skin's natural defenses and the use of soft tissue filler. A consensus group of five UK expert aesthetic clinicians were convened to discuss current best practice for aseptic techniques in medical aesthetics. The aim of the consensus group was to recommend a step-by-step procedure to achieve optimal aseptic practice in private clinics, and define important considerations for reducing infection risk during the whole patient journey: pre-, during- and postaesthetic procedure. Recommendations were based on current evidence and extensive clinical experience. Various procedure recommendations were made to achieve and maintain a high standard of asepsis and infection control. Guidance was divided into three phases for patients and health care professionals, covering preprocedure (including patient selection), during-procedure, and postprocedure considerations. Although adherence to standard hospital guidance on handwashing and cleanliness measures is a cornerstone of controlling cross-contamination, aesthetic clinics carry a high potential risk of infection—particularly as popular treatments with dermal fillers primarily involve the face. This expert consensus guidance recommends procedures to mitigate the potential risks of asepsis.

KEYWORDS

aesthetic, aseptic, clinic, services, standards

1 | INTRODUCTION

Aesthetic service providers are facing new and unique challenges as healthcare systems transition from essential, urgent care to resuming routine and elective services.[1] During this unprecedented time, when we are dealing with a new transmissible infection with significant inherent risks as well as risk to complicate treatments, aseptic practice becomes all the more crucial.

However, practice is variable and minimum standards for asepsis are not clear.

Injectables for facial aesthetics include a range of products, both pharmaceutical and non-pharmaceutical in nature. Botulinum toxin is a prescription only medicine, and may only be dispensed and used by medically qualified professionals.[2-4] Currently, in the EU, regulatory authorities class dermal fillers as medical devices, which do not undergo the same level of clinical scrutiny as medicinal products and require only the Conformité Européene (CE) mark to receive a product license.[5] Dermal fillers, particularly hyaluronic acid-based products, are no longer the domain of superficial treatment of skin lines and wrinkles and are better described as soft tissue fillers (STF). There has been a paradigm shift in their use with deeper and higher volume treatments, allowing practitioners to achieve 3D panfacial volumisation with in-office procedures that have little downtime.[6]

To obtain EU approval, dermal fillers require positive testing in only 10 to 20 patients with a 6-month follow-up; there are over 160 EU-approved dermal fillers available within the UK market,[5] at a value of Euro 53 million (2016).[7] Lack of clinical regulation and an escalation in both filler accessibility and subject exposure has produced a concurrent increase in the number of complications.[8,9]

Although the frequency of serious occurrences are probably underreported, a 2017 audit report by the SaveFace group recorded 934 complaints regarding unregistered practitioners, and 616 related to use of dermal fillers; mainly associated with lip procedures.[10] Furthermore, the British Association of Aesthetic Plastic Surgeons (BAAPS) highlights that such survey findings do not adequately convey the unethical methods aesthetic treatments are marketed to Millennials.[11] Complications reported following the application of STF include infection, delayed inflammatory nodule formation,[12] granulomatous reactions, pigmentary changes, hypersensitivity reactions, vascular occlusion,[13] and rarely blindness.[14] All of these complications can be further complicated by secondary infection[15,16]; it is therefore recommended that practitioners consider methods of improving aseptic techniques, including pre- and posttreatment advice to patients.[17]

Aseptic technique minimizes the potential for cross-contamination and infection, ensuring that only uncontaminated equipment and products come into contact with susceptible treatment areas. It should be used during any clinical procedure that bypasses the body's natural defenses, such as with injections using needles and cannulae.[18]

In a pandemic-focused era, where infection is high on the agenda, techniques to protect both the clinician and patient from an array of complications are also an important aspect of day-to-day care and management. The aims of this paper are to provide expert consensus guidance for practices performing injectable treatments, particularly with STF, to reduce the risk of complications secondary to infection.

2 | METHODS

A consensus group of five UK expert aesthetic clinicians, including an oculoplastic surgeon and a plastic surgeon, all with significant experience in the prevention and management of complications, convened in a virtual meeting on the April 14, 2020 to discuss current best practice for aseptic techniques in medical aesthetics. The aim of this consensus group was to recommended steps to achieve optimal aseptic practice, based on current evidence and extensive clinical experience.

The specific objectives of the meeting were to produce a step-by-step procedure for achieving and maintaining a high standard for aseptic conditions for treatment/injecting rooms in private clinics, highlight and address procedural challenges, and define important considerations for reducing infection risk during the whole patient journey: pre-, during and postaesthetic procedure.

The virtual meeting was led by a chairperson (DE) and contemporaneous notes were recorded by the manuscript writer (AJ). Prepared questions designed in conjunction with a member of the advisory board (DE) were introduced to structure the meeting and answers were sought from all the group (Appendix S1). A consensus was obtained when there was 80% or greater agreement. Following the consensus meeting, further minor refinements were permitted in a discussion of the recorded responses from the meeting. The discussion offered clarification and refinement of the consensus but did not alter the accepted consensus statements. The final consensus recommendations were agreed unanimously by the group.

The recommendations were also checked and supported by a review of the current literature pertaining to each recommendation.

3 | RESULTS

Various recommendations were made to provide a step-by-step procedure to achieve and maintain a high standard of asepsis and infection control. The recommendations were divided into three phases for patients and health care professionals, covering preprocedure (including patient selection), during-procedure, and postprocedure considerations.

3.1 | Patient selection

Selecting appropriate patients and, critically, not treating inappropriate patients is crucial for avoiding complications with STF.[19] Obtaining a thorough patient history of skin conditions, as well as allergies, systemic disease, current medication, and previous procedures is mandatory clinical practice.[17]

Although infections following treatment with STF are uncommon,[20] skin conditions and infections can be exacerbated, causing complications following dermal filler procedures.[19] In general, there are several broad areas of infection risk to consider before injecting a patient: viral, bacterial, and fungal (usually *Candida*) species, which may also occur as polymicrobial infections.[21]

Disruption of the skin due to inflammatory or infective conditions, such as rosacea, dermatitis or *Herpes simplex*, may also permit infection[17] and pretreatment of underlying conditions may be important to enable adequate healing time to restore the skin's barrier function.[22] *H. simplex* is a common viral infection following dermal injection,[21,23] and patients with a history of cold sores or fever blisters

may be pretreated with antivirals such as acyclovir, famciclovir, or valacyclovir to reduce the severity and duration of cutaneous herpes infections.[19,21,23] To prevent virus reactivation, prophylactic treatment may be of value for patients with a known history of *H. simplex* infection, especially when injecting in the perioral area and lips.[19] In cases of active inflammatory dermatitis, including atopic dermatitis, allergic contact dermatitis, and seborrheic dermatitis, the clinician must make their best judgment for treatment based on the severity of the condition and its proximity to the treatment area.[19]

Excessive amounts of *Propionibacterium acnes* may also make patients unsuitable for STF augmentation. Recommendations from a consensus review of dermal filler complications suggests the presence of resistant *P. acnes* at the edges of topically treated areas may play a role in the formation of infective biofilms; the "safe distance" for filler placement relative to an area of acne is unknown.[19]

Patients with remote infections or other local procedures, such as influenza, sinusitis, periodontal disease, ear, nose, or throat infections, dental abscesses, or recent dental surgery, are also candidates for treatment deferment until condition resolution.[17,24,25] Emerging clinical evidence suggests that these normally nonvirulent infections might subsequently invade implanted filler areas, triggering a delayed hypersensitivity immune response and formation of late-onset nodules.[26] Dental surgeons have reported patients with orofacial swelling secondary to dental infection or dental procedures when performed near the region where injectable filler materials were used.[25]

Caution should be used when considering dermal fillers in patients with compromised immune systems, such as with HIV, cancer treatment, immunotherapy, or poorly controlled diabetes. In the event of infection in immunocompromised patients, the possibility of *Candida* species infection should be considered for those not responding to treatment with antiviral agents and antibiotics alone.[21]

3.1.1 | Consensus recommendation: full medical assessment

- Contact/email the patient asking them to attend clinic alone; reducing the number of people in waiting or treatment rooms may help reduce viral/URTI transmission.[27]
- Full patient history should be taken, including drug history, previous procedures or dental work, and an examination of the areas to be treated.
- Patients with an active skin infection (eg, cold sores or bacterial/fungal infection) should not be treated until the condition has resolved or the risks actively mitigated.[28]
- Patients with acne[19] or sebaceous skin types[16,17,19] may be at a higher risk of posttreatment inflammatory reactions.

3.1.2 | Consensus recommendation: pandemic screening

- Prior to attending clinic, patients should be screened for potential infection and nonadherence to local self-isolation protocols.[29]
- Temperature checking (tympanic or infrared device) on entry to the clinic is also recommended.[1,27,29-31]
- Several publications have previously highlighted the safety considerations for patients seeking aesthetic treatments and procedures following the return-to-work phase of a viral pandemic.[1,27-30,32] Recommendations include attending alone, organization of predetermined in-office routes and personal safety, and treatment of only one patient per session.[1,27,29,30] These recommendations are applicable for improving asepsis well beyond the pandemic and provide a gold standard to measure future practice.

3.2 | Preprocedure considerations

The level of personal protective equipment (PPE) recommended for use in Primary Care should be considered a robust standard for protection for both the patient and practitioner, and part of the prevention and control measures that can limit the spread of respiratory viral infection.[33] Current interim guidance from the World Health Organization suggests the use of face masks is an integral part of any comprehensive preventative package and can be used either for protection of healthy persons (worn to protect when in contact with an infected individual) or for source control (worn by an infected individual to prevent onward transmission).[33] Eye goggles or a visor are also recommended as viral transmission is a risk from and to the ocular surface.[34]

Meta-analyses in systematic literature reviews have reported that the use of N95 respirators do not provide a significantly lower risk of clinical respiratory illness outcomes for laboratory-confirmed influenza or viral infections compared with the use of surgical masks.[35] Studies showing reductions in risk with N95 or similar respirators have been confounded by important design limitations.[36]

The distance from a patient that respiratory viruses are infective, and the optimum person-to-person physical distance is uncertain. For the current foreseeable future, prevention and mitigation of respiratory infection will be a priority in conjunction with aseptic technique for complication prevention. Decreased transmission of viruses at physical distances of 1 m of greater, compared with closer distances, has implication for any profession working near patients' faces.[36] Face mask and eye protection could result in a large reduction in risk of infection.

Prior to any procedure, patients should be advised to attend clinics with a clean face and without cosmetics. Hair should be kept away from treatment areas to reduce contamination risks, with hairbands used for both patient and injecting practitioner, if necessary. Common antiseptics for cutaneous preparation include isopropyl alcohol, povidone-iodine, and chlorhexidine.[37] The practitioner should note that isopropyl alcohol may cause irritation, is flammable,[37] and can produce severe ocular burns[38]; it should not be used near the eye or peri-ocular area. Povidone-iodine is rapidly effective but neutralized by contact with blood or sputum, with the added complication of dying hair and clothing.[37] Chlorhexidine provides a sustained antiseptic effect, but poses a risk to the middle ear and has the potential to

irreversibly damage the cornea following minimal splash exposure[37,39]; increasingly, chlorhexidine has been associated with reports of hypersensitivity and anaphylaxis.[40] Hypochlorous acid has advantages for skin asepsis, including a well-tolerated non-alcohol base, efficacious in reducing microbial loads, and with benefits of specific preparations for peri-oral and peri-ocular asepsis.[37,41] Products such as Clinsept+ (CHT Ltd), a high purity hypochlorous solution, are compatible with skin pH. A pH neutral preparation for mucus membranes and another for eye treatment are also available and can be used as a mouth wash prior to peri-oral treatment and antimicrobial for peri-ocular treatment, respectively. If a nasal procedure is required, hypochlorous solution or 0.23% povidone-iodine solution may be used in a dosage of two sprays per nostril before entering the office.[27] Purifeyes by FaceRestoration can be instilled directly onto the conjunctival surface or sprayed over the periocular area for antimicrobial cleansing prior to facial treatments where the eyes cannot be covered. Challenges from PPE include discomfort, fogging of eye protection, high resource use linked with potentially decreased equity, equipment shortages, and less clear communication.

Practitioners and other staff should wear clean-on uniforms or scrubs daily. UK National recommendations state that uniforms should be laundered on-site or by healthcare laundry services.[42] The consensus group considered changing scrubs or uniforms between patients was unnecessary unless soiled or contaminated.

Hand hygiene is one of the most effective measures to control contamination and support aseptic conditions,[43] and hands should be decontaminated with liquid soap and warm running water.[43,44] When clean running water is not available, alcohol-based hand rub products (containing at least 70% alcohol) should be used if the skin is not visibly soiled[43,45]; alcohol-free hypochlorous may be preferable where long-term use of alcohol, soap or chlorhexidine may result in contact dermatitis or allergy. The use of barrier creams and bar soaps containing moisturizers may be beneficial after each procedure to reduce the potential for skin dryness or irritation.[45]

Adherence to standard hospital guidance on handwashing and bare-below-elbow (BBE) procedures is considered mandatory for infection control in injecting practitioners, including absence of wrist and hand jewelry, short and clean fingernails that are free of adornment or polish, and covering of minor cuts and abrasions with water proof dressings.[18]

3.2.1 | Consensus recommendation: adhere to the principles of aseptic area preparation

- The level of PPE recommended for Primary Care is a robust standard that should be implemented across all aesthetic clinics.
- All staff should wear clean-on uniforms or scrubs, which are not changed between patients.[18]
- Handwashing and BBE standards should be adhered to, ensuring fingernails are short, clean and free of nail polish.[18]
- Patients should attend clinic with clean, cosmetics-free skin (Table 1)[17]; long hair should be managed with hairbands that can be laundered.

TABLE 1 Preprocedure preparations

Clean, degrease, and disinfect the treatment area
Remove any cosmetics and cleanse the skin
The injector should adhere to BBE procedures: remove all jewelry, wash hands, and use gloves for all injection procedures
Adhere to the principles of sterile technique: do not touch any component of the needle or cannula that penetrates the skin
Constant vigilance against possible contamination

- Hypochlorous is advantageous for skin asepsis and has demonstrated benefit with appropriate preparations for peri-oral and peri-ocular asepsis.
- The consensus recommended an application of hypochlorous-based mouthwash for at least 30 s before treating the perioral area, in particular prior to lip treatments.

3.3 | Contamination reduction and patient management

For the purposes of infection control, environmental surfaces must be properly cleaned and disinfected to prevent transmission. In a clinic setting, environmental surfaces include furniture and other fixed items inside and outside of waiting and treatment rooms, such as tables, chairs, walls, light switches, electronic equipment (including touch screens and controls), medical devices and trays, and computer peripherals.[32] However, all touchable surfaces should be disinfected and all disinfectant solutions prepared and used according to the manufacturer's recommendations for volume and contact time required to inactivate pathogens.[32] Within a treatment room, the burden for ensuring infection control rests with the injecting practitioner, or a delegated and trained assistant.

To reduce the volume and time spent disinfecting equipment between patients, the number of devices used for aesthetic procedures should be kept to a minimum within the treatment room.[45] It should be highlighted that although trolleys may enable rapid access to equipment and products during treatment, they are also a potential source of contamination that requires regular disinfection.

In the pandemic era, the Joint Council for Cosmetic Practitioners (JCCP) recommends disinfecting equipment and surfaces with dilute, hypochlorite-based products, where undissociated hypochlorous acid is active as the antimicrobial compound. Routine application of disinfectants by spraying or fogging (also known as fumigation or misting) is not recommended and has been demonstrated as ineffective in removing contaminants outside of direct spray zones, whereas also increasing the risks of irritation to eyes, skin, and respiratory system.[32] Therefore, the recommendation is direct application of a skin pH compatible high purity hypochlorous spray to the face, mouthwash, and eye-specific antimicrobial treatment; eye shields or protective glasses should also be cleaned with the same ocular surface safe spray, as alcohol-based sanitisers are toxic to the eyes.[27] It should be noted

that sodium hypochlorite (NaOCl) and hypochlorous (HOCl) are not the same clinical entity. Sodium hypochlorite is a widely used disinfectant for cleaning inanimate surfaces, but should not be confused with the purified hypochlorous safe for use on human skin and mucus membranes.[32]

3.3.1 | Consensus recommendation: access to a trained assistant is a vital component of infection control and patient management

- Within the treatment room, surfaces and objects should be disinfected regularly and between each patient.
- The injecting practitioner assumes responsibility for preventing cross-contamination although the availability of a trained assistant can be invaluable for maintaining patient management and infection control.
- Particular attention should be paid to environmental cleaning of high-touch surfaces and items.[32]
- Dilute, hypochlorite-based products are preferred for disinfecting equipment; use of disinfectant sprays or fogs are not recommended.[32]
- To aid in patient management and cleaning schedules, the quantity of devices used for aesthetic procedures must be kept to a minimum within the treatment room.[45]

3.4 | Considerations during aesthetic procedures

Procedural planning is essential in preventing contamination and minimizes the potential for complications.[17] Where patients request additional, unplanned procedures, these should be scheduled for a further appointment.

The principles of aseptic technique also include reducing activity in the immediate vicinity of the procedure and keeping the exposure of a susceptible site to a minimum (Table 2).[44] Ensuring the treatment area is clean and disinfected is imperative for reducing infection risk when inadvertently resting the cannula on the adjacent skin.[17]

TABLE 2 General principles of asepsis/aseptic technique

Reduce activity in the immediate area where the procedure is to be performed
Keep exposure of the susceptible treatment site to a minimum
Check all sterile treatment packs for evidence of damage or moisture penetration
Ensure all fluids and materials to be used are in date
Do not re-use single use items
Ensure contaminated/nonsterile items are not placed in a clean treatment field
Ensure appropriate hand decontamination prior to the procedure
Use sterile gloves

Single-use items, such as needles, should not be re-used and nonsterile items can quickly contaminate the treatment area if disposal is not immediate; single patient use items can be decontaminated and re-used again on the same patient, but cannot be used on another patient.[44]

In vitro testing of injections through biofilms has demonstrated that STF material can support the growth of bacterial biofilm. Thus, multiple needle passes should be avoided to reduce the risk of filler contamination and complications,[46] such as chronic granulomatous inflammation, and frequent changing of needles and cannulae is advised when utilizing multiple entry points.[17] Particular care is required when treating areas with prior STF that may be degrading, layering different products, and introducing skin flora into old residual filler.[17]

In the event of any contamination during injection compromising asepsis, the procedure must be stopped and standard principles of hand decontamination followed, including changing of gloves[18] and addressing the source of potential infection immediately; the cannula/needle should be replaced if asepsis has been breached.

3.4.1 | Consensus recommendation: considerations during aesthetic procedures

- Injectors should adhere to planned treatment procedures, with additional appointments scheduled for patients requesting unplanned treatments.
- In the event of contamination, the injector must stop the procedure, change gloves and cannula/syringe, then address the contamination.

3.5 | Considerations during immediate postaesthetic procedures

Cosmetics, especially facial cosmetics that have been used previously, have the potential to carry infection,[47] with high water-content preparations providing a greater risk of microbiological contamination compared with oil-based products.[48] Sponges and brushes used for application of cosmetics may also be a key source of cross contamination.

Following an aesthetic treatment where the dermal layer has been penetrated, the potential for infectivity, therefore, becomes a concern. Patients should not use cosmetics following any procedure to maintain the lowest possible risk of cross infection. In the event that cosmetics must be worn within 24 h of the procedure, opening a new and sealed pack or using pump-based foundations is a preferred choice over previously opened pressed powders or non-pump-based preparations. Mineral-based cosmetics are often marketed as providing non-comedogenic properties, suggesting a reduced risk of pore blockage and infection.

Safeguarding both the patient and clinic staff is critical to continuing care and ongoing confidence in aesthetic services. All clinic staff

TABLE 3 Consensus recommendations

Preprocedure process
Contact/email patient to attend clinic alone to decrease risk of viral transmission
Full patient history—resolve active infections before treatment
Injector to wear clean-on scrubs or uniform
Ensure availability and use of PPE appropriate for Primary Care setting
Advise patients to attend clinic without cosmetics
Hair tied away from treatment areas
Clean the face (including mouth, nose, and eyes) before starting any procedure
Regular hand hygiene and BBE procedures
During treatment procedure
Reschedule unplanned procedures
Disinfect treatment room surfaces between patients
Reduce the number of medical devices within treatment rooms
Access to a trained assistant
Utilize aseptic technique
Change cannulae and needles frequently (particularly when bone is touched)
If contamination occurs: stop, decontaminate PPE, then address infection source
Postprocedure process
Advise patient not to use cosmetics (for up to 24 h)
Adhere to standard clinical waste management procedures
Remove and dispose of gloves & contaminated PPE, clean goggles or protective glasses
Clean and disinfect all surfaces

and visitors should perform regular and thorough handwashing, with alcohol-based hand rub dispensers available in prominent places to encourage disinfection practices.[49] The WHO recommends that all surfaces and objects outside of treatment rooms should be cleaned regularly with disinfectant. Face masks and paper tissues should also be available for patient use, and use of posters promoting handwashing and respiratory hygiene are recommended.[49]

For waste management, sharps containers should be sealed and replaced when three quarters full; infectious waste bags must be closed before transport for treatment or disposal. Waste not categorized as sharp or infectious should be discarded in appropriate color-coded bags.[50]

3.5.1 | Consensus recommendation: considerations during postaesthetic procedures

- Recommendations for non-clinical areas include ensuring all surfaces are disinfected regularly, with clear promotion and access to hand sanitizing facilities for staff, patients and visitors.[49]
- Face masks and paper tissues (for sneezes and coughs) should be available, with closed waste bins for hygienic disposal.[49]
- During facial procedures where patient masks or goggles are impractical for treatment access or application, hypochlorous-based disinfecting mouthwash and antimicrobial eye drops/spray should be considered.
- Following treatment, application of cosmetics should be avoided for up to 24 h.
- Where cosmetics must be applied, pump foundations or sealed product packs are recommended to reduce the risk of cross-contamination.
- Mineral cosmetics may provide a reduced risk of pore blockage and potential for infection.

3.6 | Summary of consensus recommendations

A summary of the consensus recommendations is presented in Table 3; a printable guide for clinical asepsis in medical aesthetics is also available to assist with day-to-day management (Appendix S2).

4 | LIMITATIONS

Evidence-based medicine requires judgments that are consistent with underlying evidence, whereas consensus-based recommendations do not. Although the authors have used a widely accepted method of Expert consensus group discussion, the qualitative nature of the data and interpretation limits this study. To address this, critical appraisal of the literature and multidisciplinary analysis allows bias minimisation.

It must also be remembered that evidence changes over time and is derived from multiple sources of varying levels of credibility and levels of evidence. Where possible, systematic reviews were sought to support the recommendations in this paper. During the time of writing, the pandemic has by necessity resulted in the publication of papers with lower levels of evidence. In order to disseminate useful information for the benefit of personal and public safety, this evidence has been used support the recommendations made.

5 | CONCLUSIONS

In aesthetic practices performing injectable treatments, such as dermal fillers, the risk of inflammatory complications secondary to skin infection can be managed through robust application of the aseptic technique.

In the pandemic era, aesthetic clinics carry a high potential risk of respiratory infection, particularly as treatment with dermal fillers primarily involve the face; often in the peri-oral, nasal, and peri-ocular regions.[27]

Although adherence to standard hospital guidance on handwashing and BBE measures is a cornerstone of controlling cross-contamination,[18] this expert consensus guidance amalgamates best current evidence with experience to recommend procedures that address asepsis in the medical aesthetic clinic.

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CONFLICT OF INTEREST

All authors received honoraria from Allergan for attending the advisory board meeting.

AUTHOR CONTRIBUTIONS

Rachna Murthy has contributed to the development and clinical testing of Purifeyes by FaceRestoration. She is an International Faculty Member of the Allergan Medical Institute and on the IMCAS complications board. David Eccleston is Clinical Director and owner of MediZen. He is an International Faculty Member of the Allergan Medical Institute. Darren Mckeown reports no conflicts of interest. Apul Parikh has received honoraria as a speaker for Allergan. Sophie Shotter is a speaker for Allergan and Aesthetic Source (main distributors of Clinisept+). She is an International Faculty Member of the Allergan Medical Institute. All authors were involved in conception and development of the manuscript. Rachna Murthy produced the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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