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# Intravitreal Injections with Vascular Endothelial Growth Factor Inhibitors: A Practical Approach

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## ABSTRACT

Intravitreal injections with vascular endothelial growth factor inhibitors constitute the most prevalent ophthalmic procedure in developed countries. Historically, there has been steady growth in the number of treatments performed of this kind, and projection studies estimate further growth in such treatments in the future. We provide a practical

approach to intravitreal injections and discuss important aspects relating to the setting, the patient, the procedure, and the information given to the patient.

**Keywords:** Anti-VEGF therapy; Clinical practice; Intravitreal injection; Practical approach

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### Key Summary Points

#### Why carry out this study?

Intravitreal injections (IVIs) with vascular endothelial growth factor inhibitors represent the most prevalent ophthalmic procedure in developed countries.

This paper aims to provide a practical approach to IVIs.

#### What was learned from the study?

We describe important aspects relating to the setting, the patient, the procedure, and the information given to the patient.

We outline a best practice protocol for the procedure.

## INTRODUCTION

Intravitreal injection (IVI), a means of accessing the retina for therapeutic purposes, has been performed for over a century [1, 2]. It gained considerable popularity in 1970s with the administration of intravitreal antibiotics and steroids [2]. Research efforts during the 1990s elucidated that ocular neovascularization is related to vascular endothelial growth factor (VEGF) expression [3, 4]. This finding sparked an impressive effort to develop VEGF-targeted therapy, which led to the introduction of VEGF inhibitors (anti-VEGF) delivered through IVI. The therapeutic indication was initially neovascular age-related macular degeneration—the most prevalent cause of irreversible vision loss in developed countries [5]. Since then, the therapeutic indication has been extended to a number of other prevalent retinal diseases, such as retinal vein occlusion, diabetic macular edema, and choroidal neovascularization due to other conditions [6]. Overall, these developments have dramatically changed the number of IVIs performed worldwide: according to records in the American Medical Association

Specialty Society Relative Value Scale Update Committee database, the number of injections performed increased more than 500-fold during the period from 2000 to 2012 (from 4500 to 2.3 million injections per year) [7], and similar developments have been reported in the United Kingdom (UK) [8]. Due to population aging in many developed countries, forecasting studies on retinal diseases indicate that we should expect an ever-increasing number of patients who need this treatment [9–11]. These circumstances contribute to the fact that IVIs with anti-VEGF constitute an important, high-volume procedure of any ophthalmic service. In this paper, we provide a practical approach to IVIs with anti-VEGF. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## SETTING

The predominant setting for IVI differs across countries for reasons that include regulations, reimbursement considerations, and traditions. For example, an operating theater with air filtration systems is an official requirement for a setting in which IVIs are performed according to Swiss regulations [13]. In Italy, the National Society of Ophthalmologists guidelines recommend that IVIs should be performed in operating theaters under sterile conditions [14]. In the UK and the Netherlands, most clinics administer IVIs in a dedicated clean room [15] that has high hygiene standards but does not have air filtration systems. Compensation rates for IVIs can vary by almost a factor of ten across Europe [13]. In Germany and Denmark, IVIs are restricted to large public hospitals [13], which impacts the perceived burden of treatment on patients from rural areas [16]. There are also differences in whether there are organizational incentives to increase or decrease the number of IVIs (which can be obtained through different treatment regimens) or the waiting times for patients [13]. In the Netherlands, there are marked differences in the IVI procedure across the country: sterile gloves are worn during the

procedure in some hospitals whereas no gloves are used in other hospitals.

### Operating Theater Versus Office

Whether to perform the IVIs in an operating theater or in an office has been debated. The theoretical rationale for performing IVIs in operating theaters is that air filtration systems can help to remove contaminants from the air and reduce the risk of infection from airborne particles [12].

A number of European retrospective studies have reported the incidence of endophthalmitis after IVI in operating theaters with laminar airflows [17–19]. In two Swiss centers, three cases of endophthalmitis were reported after a total of 40,011 IVIs (incidence of 0.0075%) [17]. In a Danish center, no cases of endophthalmitis were reported after 20,293 IVIs [18]. In a multicenter European study, 10 cases of endophthalmitis were reported after a total of 134,701 IVIs (incidence of 0.0074%) [19]. Studies on the incidence of endophthalmitis after IVI in an office setting are mostly based on data from the United States. A single-center study from New York reported three cases after 10,254 IVIs (incidence of 0.029%) [20]. Results from the multicenter Comparison of Age-Related Macular Degeneration Treatments Trials found 11 cases after 18,509 IVIs (incidence of 0.059%) [21]. In a large multicenter study of five retina practices, 183 cases of endophthalmitis were reported after 503,890 IVIs (incidence of 0.036%) [22]. Taken together, endophthalmitis rates seem higher for office-based settings. Abell et al. from Australia were able to compare the risk of endophthalmitis after performing IVIs in an operating theater versus an office in the same center, and they found that endophthalmitis rates were significantly lower in the operating theaters [operating theater: 0 cases in 8,873 (0%); office: 4 cases in 3376 IVIs (0.12%);  $P = 0.006$ ] [23]. Dossorps et al. retrospectively investigated factors influencing the incidence of endophthalmitis in 25 French centers [65 cases in 316,576 IVIs (0.021%)] and found a borderline-significant trend towards a lower risk of endophthalmitis in settings with filtration

airflow when compared with settings without filtration airflow ( $P = 0.079$ ) [24]. Bande et al. systematically reviewed studies investigating the incidence of endophthalmitis after IVIs and performed a meta-regression which indicated that there was no significant difference in endophthalmitis incidence after IVIs were performed in operating theaters versus an office-based setting [25]. In conclusion, determining a gold standard for the setting to use for IVI is difficult. Randomized clinical trials are needed to before any firm conclusions can be drawn about the superiority or noninferiority of one setting compared to the other. Patients with incident endophthalmitis after an IVI may be at an increased risk of developing endophthalmitis again after IVI in the future. If these patients change clinic after the endophthalmitis, a retrospective study conducted at that clinic may show an incorrectly low incidence of endophthalmitis. Thus, prospective controlled clinical studies are needed. Looking at the clinical evidence available so far, it is important to realize that the risk of endophthalmitis after IVIs—regardless of the setting—is very low. Additionally, when asked, patients do not seem to have any clear pattern of preference for the operating theater or office [26].

### Who Should Perform the Injection?

Around the world, regulations and traditions strongly influence who performs the injection. While some centers allocate consultant ophthalmologists or only allow vitreoretinal surgeons to perform the injection, others allocate this task to residents. Because of the increasing demand for this procedure, its simplicity, and the generally low prevalence of complications, some centers have employed nurses to perform the IVIs [27]. Experiences so far from centers in Denmark [28, 29], the UK [30], Norway [31], and New Zealand [32] suggest that this is feasible (in terms of training, implementation, capacity improvements, and patient satisfaction) and safe (in terms of complication rates compared with IVIs given by physicians) [27, 29, 31].

## Use of Injection-Assisting Devices

A number of IVI-assisting devices exist [33], among which the InVitria Injection Assistant (FCI Ophthalmics, Paris, France) is one of the more widely used. The use of such devices ensures that the desired distance from the limbus is achieved, and may facilitate a faster procedure with fewer steps. The incidence of endophthalmitis after IVI in which an assisting device was used is yet to be documented.

## Optimizing Patient Comfort

Preparations can be made to optimize patient comfort. Patients receiving an IVI for the first time should be allocated more time to learn about the injection and monitored for unexpected reactions. Gomez et al. studied patient comfort during IVIs and found that favorable strategies were the presence of an extra staff member during the injection, the use of a neck pillow, and the provision of a verbal warning prior to the IVI [34]. When bilateral IVIs were necessary, the majority of the patients preferred to have them performed on the same day [34]. In addition, patients between 30 and 60 years of age preferred to have their hand held during the IVI and to have background music playing during the injection [34]. Music is played in operating theaters in many surgical specialties. Specifically for IVIs, Chen et al. documented that classical music in the waiting room and in the operating theater led to decreased anxiety and increased patient satisfaction [35]. However, classical music did not influence pain perception [35]. Irrigating the eye after the IVI leads to less epithelial staining but has no impact on redness, lacrimation, or the sensation of pain, burning, or grittiness [36]. In line with this, several centers apply lubricant drops after the IVI to help reduce the sensation of pain and grittiness and thus further improve patient comfort. After performing the IVI, it is recommended that any information regarding the patient's specific reaction to any part of the protocol should be noted, as should adjustments made to the protocol. This approach can

allow a certain degree of individualization, further optimizing patient comfort.

Since patients follow a regimen involving multiple IVIs, patients receiving IVIs often visit the clinic several times per year. Organizing an IVI service may lead to less time spent at the clinic or hospital [37], which is important from a patient perspective since the perceived burden of treatment may influence the adherence to therapy. One example of organizing an IVI service that reduces the time spent on the patient is to arrange for the retinal assessment and IVI to be performed on the same day [37]. In a Danish study of patients with neovascular age-related macular degeneration who were aged 90 years or more and were predominantly resident in rural areas of Denmark, approximately 15% of the patients discontinued treatment because the patients' perceived burden of treatment was too high [16].

## PATIENT

### Contraindications

#### *Hypersensitivity*

If the patient is known to have hypersensitivity reactions towards the drug or any of the substances in the drug solution, IVI administration is contraindicated.

#### *Preexisting Ocular Conditions*

- IVI therapy is contraindicated in patients with any ocular or periocular infection at the time of the IVI [38]. Infections must be treated and followed by a new assessment prior to IVI.
- IVI is not contraindicated in eyes with prior intraocular or periocular surgery [38]. However, caution is advised for eyes with prior glaucoma surgery such as trabeculectomy or a drainage device to avoid injection at the site of the filtering bleb or shunt. Some evidence suggests that pharmacokinetic properties may be different in previously vitrectomized eyes, with a shorter half-life of the anti-VEGF drug [38], which is no contraindication for IVI but may influence the frequency of IVIs needed.

- In patients with glaucoma, several studies have documented a rise in the intraocular pressure (IOP) after IVIs. Although the rise in IOP may be slightly higher in eyes with glaucoma, the IOP elevation is rarely alarmingly high [39]. Rare cases with an unacceptable IOP elevation after IVI can be managed [40].
- In cases with a history of previously unacceptable IOP elevation after IVI, lowering the IOP prior to the IVI should be considered.

### ***Preexisting Medical Conditions***

- Infections elsewhere and any fever in general should prompt caution, as there may be a risk of introducing systemically circulating microorganisms through IVIs. Whether IVI can be performed should be considered on a case-by-case basis and by discussing the risks with the patient. There is no clinical evidence in this regard, so this is more of a theoretical consideration.
- Since anti-VEGF administered through IVIs can be detected systemically [41], there have been debates regarding its use in patients with recent cardiovascular or cerebrovascular events as to whether it could worsen a potentially life-threatening condition [42, 43]. Studies do not prove that IVIs with anti-VEGF increase the risk of cardiovascular or cerebrovascular events [42, 43]. In a systematic review and meta-analysis, Reibaldi et al. did not find any strong evidence suggesting a relationship between IVI with anti-VEGF and increased mortality [44]. In an interesting study of published systematic reviews and meta-analyses on systemic adverse events after IVI with anti-VEGF, Thulliez et al. showed that different meta-analyses found different signals, i.e., some studies found an association with an increased risk of cardiovascular events whereas others did not [45]. One important perspective is that only patients identified as being at high risk of a future cardiovascular event prior to anti-VEGF therapy may have an increased risk of developing a cardiovascular event after the commencement of anti-VEGF therapy [46]. Hence, from a practical

perspective, caution is advised in cases with a recent vascular event [47] and, if possible, the IVI should be postponed until  $\geq 3$  months after the vascular event. In severely vision-threatened cases involving patients with a recent vascular event, the use of an anti-VEGF agent with a shorter half-life should be considered, e.g., ranibizumab instead of aflibercept.

- There are no known drug interactions with IVI-administered anti-VEGF. Anticoagulants do not increase the risk of complications after IVIs [48, 49].

### **Pregnancy and Postpartum**

Angiogenesis plays a major role in the development of the placenta and the fetus. There is limited evidence on the use of intravitreal anti-VEGF in pregnancy, and the available literature can mostly be categorized as low-grade evidence (case reports, case series, expert recommendations) [50]. Since anti-VEGF administered through IVIs can be detected systemically, there is an important reason for caution. In rats, teratogenic effects of IVI with anti-VEGF peak during the first trimester [51]. Case reports of IVI with anti-VEGF in the first trimester show that 4 out of 13 cases resulted in fetal demise or a complicated birth [50]. No sequelae were reported for the 7 patients who received IVI with anti-VEGF during the second or third trimester. However, it is difficult to extrapolate these few cases to decisions in real life. McFarland et al. investigated breast milk levels of anti-VEGF after IVI therapy with bevacizumab and did not find detectable levels with a threshold level of 3 ng/mL [52]. Taken together, there are reasons to avoid IVI therapy using anti-VEGF during pregnancy, whereas possible side effects of this therapy during the postpartum period are more unclear. In some cases, steroid-based IVIs or laser-based therapy are feasible substitutes due to their better documented and tolerated safety profiles [53].

## Bilateral Injections

Same-day bilateral injections have been debated due to concerns regarding an increased risk of local and systemic complications [54]. However, from the patient's point of view, treatment of bilateral disease on different days may increase the perceived burden of treatment [34]. Studies have investigated the safety profile of same-day bilateral injections and found that rates of endophthalmitis and systemic vascular events were comparable to those for unilateral injections [54]. It is recommended that each injection should be considered a separate procedure. Separate instruments and medication vials should be used for each eye to decrease the risk of potential bilateral contamination.

## PROPOSED PROCEDURE

The proposed procedure for anti-VEGF IVI is described in Table 1. Various aspects of the procedure are discussed in more detail below.

### Face Masks, Gloves, and Drapes

Studies of post-IVI acquired endophthalmitis show that the most commonly cultured bacteria are *Staphylococcus* species followed by *Streptococcus* species [55]. Staphylococci may reside in conjunctival membranes and are often part of the flora of the patient [56], whereas streptococci reside in the oronasal cavities and the upper respiratory system but are uncommon in the conjunctival membranes [56]. Therefore, it is logical to minimize the aerosolization of oropharyngeal droplets by using face masks during the procedure.

Hand hygiene and the use of gloves are a fundamental practice in medicine, and World Health Organization guidelines state that hand hygiene and surgical gloves are required for all surgical interventions [57]. Nevertheless, according to a survey of retinal specialists in the United States, clinical practices vary: 54% used a single or double pair of gloves whereas 46% used no gloves [56]. One retrospective study in a center where no gloves were used reported an

endophthalmitis rate after office-based anti-VEGF IVI of 9 cases in 15,895 (0.057%) [58], which is similar to office-based incidence rates reported elsewhere.

The EURETINA Expert Consensus Statement recommends the use of face masks and gloves [38]. There is no evidence or theoretical rationale for using a sterile drape. Drapes are also considered optional in the EURETINA Expert Consensus Statement [38].

### Topical Anesthesia

There is no gold standard for the choice of topical anesthesia. Shiroma et al. systematically reviewed studies on topical anesthesia prior to IVI and the patient pain experience and found it to be generally mild regardless of the anesthetic employed [59]. Studies reviewed included proparacaine, tetracaine, cocaine, lidocaine pledget or gel, and subconjunctival injection of 2% lidocaine or 0.75% levobupivacaine [59]. The authors found that among these interventions, subconjunctival injection of 2% lidocaine may provide the greatest pain reduction [59]. However, considering that another noninvasive topical anesthesia often suffices, the subconjunctival injection of 2% lidocaine should only be considered in select cases where other options provide insufficient anesthesia. Considering the number of IVI treatments and treatment intervals, general anesthesia is not a feasible option and should only be considered for the very rare cases where topical anesthesia cannot be used under any circumstances, e.g., in cases of severe manifest syringe phobia.

### Topical Disinfection

Povidone-iodine is considered the gold standard for preoperative surface preparation because of its microbicidal properties and fast preparation time [38]. The povidone-iodine concentration plays a role in its disinfectant effects. Friedman et al. investigated the contact time of 5% povidone-iodine in conjunctiva and the number of colony-forming units upon sampling and culturing [60]. The number of colony-forming units did not decrease significantly at 15 s but

**Table 1** Proposed procedure for intravitreal injections

1. Prepare setting	Operating theater with laminar air flow and a dental chair for the patient. The chair can help the elderly patient move from a sitting to a supine position for the injection, and then from a supine to a sitting position afterwards. All rooms have two members of the medical staff on hand for the injection, music available, and neck pillows. Medical staff use face masks and gloves for all sterile procedures
2. Ensure patient identification, consent, and eligibility	Talk with the patient to ensure identification and to discuss any contraindications, allergies, and consent, as well as to confirm eye laterality for treatment and the treatment drug
3. Prepare medication	Prepare the relevant drug under sterile conditions using a large 27-gauge needle and then change the needle used to a smaller 30-gauge needle. For prefilled syringes, simply prepare the 30-gauge needle. Remove dead space and ensure that there is only 0.05 mL of the drug in the syringe
4. Apply topical anesthesia	Apply topical tetracaine twice, with a 60-s interval between applications
5. Apply topical disinfection	Apply topical disinfectant once to conjunctiva, lids, and lashes and then wait for 30 s
6. Lid speculum	Insert a sterile lid speculum
7. Mark injection location	Mark the location corresponding to the pars plana in the superotemporal quadrant. Mark a distance to the limbus of 3.5 mm for pseudophakic eyes and 4.0 mm for phakic eyes
8. Coordinate gaze direction	Ask the patient to look in the direction opposite to the injection. For example, when injecting into the superotemporal quadrant of the right eye, ask the patient to look downwards and to the left
9. Hold the prepared syringe and a Q-tip	Hold the prepared syringe in the dominant hand and a sterile Q-tip in the nondominant hand
10. Place the Q-tip	Place the Q-tip close to the area of injection and displace the conjunctiva slightly
11. Insert the syringe	Insert the syringe perpendicularly at the marked area of insertion in one smooth motion. Insert the short 30-gauge needle about 1/2 of its length, ensuring that it extends beyond the subretinal space and into the vitreous. Inject the medicine slowly and remove the syringe
12. Remove lid speculum and consider irrigation and/or lubricant	Remove the lid speculum. Consider irrigation and/or lubricant drops
13. Review alarm signs with the patient	The patient should expect slight discomfort during the day of the intravitreal injection, but significant pain, redness, or acute vision loss should prompt contact with emergency eyecare



did after 30 s and beyond. In line with these findings, concentrations of povidone-iodine of between 2.5% and 10% applied for 30–120 s produce a sufficient bacteriocidal effect that lasts throughout the entire IVI procedure [38]. Povidone-iodine for conjunctival administration is typically given at a 5% concentration, and it should be administered upon the conjunctiva. It should be noted that the preferred concentration of povidone-iodine for use on skin is higher, typically 10%. Chlorhexidine 0.1% can be used for patients with unacceptable irritation or hypersensitivity towards povidone-iodine, but requires a contact time of 5 min or longer to exert its full bacteriocidal effects on *Staphylococcus aureus* and *Escherichia coli*, and provides a narrower antimicrobial spectrum than povidone-iodine [38].

### Topical Antibiotics

Theoretically, the use of topical antibiotics should decrease the bacterial load, but clinical evidence does not show any clear benefit of using topical antibiotics in conjunction with IVIs [61]. Indeed, since IVIs are given multiple times in the same eye, repeated exposure to topical antibiotics is thought to promote the development of resistant bacterial cultures and to, paradoxically, lead to an increased incidence of post-IVI endophthalmitis [62, 63]. Hence, topical antibiotics are recommended neither prior to nor after an IVI.

### Needle Type

The appropriate needle gauge to use for IVI should theoretically range between 27 and 33. It is important to minimize structural damage in order to avoid vitreous incarceration or reflux of the medicine [38]. Several randomized clinical trials have explored the relationship between needle gauge, pain experience, and post-IVI IOP [64–66]. The use of a smaller needle may reduce the pain experienced by the patient, but the difference is not clinically significant. Smaller needle sizes are also associated with a larger rise in IOP after IVI, although this temporary rise in IOP is small and not of clinical significance. The

force required to penetrate the sclera with a 27-gauge needle is almost double that required with a 30-gauge needle [67]. Thus, for practical purposes, smaller needle sizes are preferred. The EURETINA Expert Consensus Statement recommends a 30-gauge or thinner needle of length 13–18 mm [38].

### Lid Speculum

The use of a lid speculum or lid retractor can help to avoid involuntary lid closure and contact between the injection needle and lids or lashes. Clinical evidence suggests that not using a sterile lid speculum increases the risk of post-IVI endophthalmitis [68]. Therefore, a sterile lid speculum is recommended.

### Injection

The injection is given through the pars plana of the retina, 3.5 or 4 mm from the limbus depending on whether the eye is pseudophakic or phakic, respectively. The injection can theoretically be safely administered in all quadrants, but is often given at the supero- or inferotemporal quadrant. It is given perpendicular to the eye surface, which allows the medicine to be administered into the vitreous. Injecting more anteriorly to the pars plana increases the risk of ciliary body hemorrhage or traumatic cataract, while injecting more posteriorly increases the risk of retinal detachment. Since many patients undergo repeated IVIs, injection at the exact same site should be avoided.

## INFORMATION

### Informed Consent Prior to Therapy

The patient should be informed about the nature of the disease, the rationale for treatment, the treatment regimen (the number of and the intervals between the injections and follow-up visits), the potential complications, and the prognosis. Patient information leaflets may be used to provide this information. Unfortunately, many patients do not remain well

informed even when they have previously signed an informed consent form. A Danish study found that the majority of patients receiving anti-VEGF have poor health literacy levels [69]. A German study found that, among patients receiving anti-VEGF, 64% expected an improvement in visual acuity after the IVI, 42% did not know what was given in the IVI, and 69% did not know about the risk of endophthalmitis [70].

### Alarm Signs After Therapy

The patient should be aware of common post-IVI complications (discomfort, pain, and subconjunctival hemorrhage), as well as uncommon but important post-IVI complications: traumatic cataract in < 0.1% [27], retinal tear or detachment in < 0.1% [27], severe IOP elevation (rarely), vitreous hemorrhage (rarely), and endophthalmitis in < 0.02%. The patient should expect slight discomfort during the day of the IVI, but significant pain, redness, or acute

vision loss should prompt contact with emergency eyecare, as they may be signs of important complications that require timely management, such as endophthalmitis, severe IOP elevation, or retinal tear/detachment. Information to be provided to the patient regarding complications is listed in Table 2. After IVI therapy, IOP measurements are performed in some clinics on either a regular basis or for select patients (e.g., those with glaucoma or a previous acute increase in IOP). In some clinics, counting fingers after IVI therapy is used as a simple way to check for the presence of severe IOP elevation and vision loss due to retinal artery occlusion.

### What Should Be Avoided After the Injection?

There is no clinical evidence on what to avoid; however, from a theoretical point of view, attempts should be made to avoid a high load of microorganisms at the area of injection

**Table 2** Information to be provided to the patient regarding complications after intravitreal injection therapy with anti-vascular endothelial growth factor

<i>Common</i>	
Discomfort and pain	Foreign body sensation and mild ocular discomfort is not unusual, especially as the topical anesthetics wear off
Subconjunctival hemorrhage	Subconjunctival hemorrhage can look dramatic, but is common and harmless
<i>Uncommon</i>	
Traumatic cataract	Needle-induced damage to the lens during an intravitreal injection can lead to a traumatic cataract. This occurs in less than 1 out of 1000 injections
Retinal tear or detachment	The procedure may facilitate a tear or detach the retina. This occurs in less than 1 out of 1000 injections
Severe intraocular pressure elevation	The pressure in the eye may increase after an injection. In rare cases, this increase may require medical attention and intervention
Vitreous hemorrhage	In rare cases, a vitreous hemorrhage may occur after an injection
Endophthalmitis	Severe pain, red eye, and blurry vision can be a sign of infection in the eye, which should prompt the patient to seek emergency eyecare. This occurs in less than 1 out of 5000 injections

immediately after the IVI. Because of this, we recommend avoiding the following activities for 24 h after the IVI: rubbing eyes, swimming, gardening, wearing eye makeup, or performing dusty work. Ongoing treatment with eye drops can continue, but a new bottle should be opened after the IVI.

## CONCLUSION

IVI with anti-VEGF is an important, high-volume procedure for any ophthalmic service. In this paper, we have provided a practical approach to this procedure and considered various aspects of the procedure, including the setting, the patient, the procedure, and information provided to the patient. In addition, we have outlined our own protocol for treatment that addresses these considerations. From a procedural perspective, it is important to understand that there is clinical evidence (albeit not level 1 evidence) for some, but far from all, of what we practice regarding IVI.

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**Compliance with Ethical Guidelines.** This article is based on previously conducted studies and does not contain any studies with human

participants or animals performed by any of the authors.

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