

INTRAVITREAL INJECTION TECHNIQUE AND MONITORING

Updated Guidelines of an Expert Panel

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Purpose: To review evidence and provide updated guidelines on intravitreal (IVT) injection technique and monitoring.

Methods: A review of the published literature on IVT injection from 2004 to 2014 formed the basis for round table deliberations by an expert panel of ophthalmologists.

Results: The dramatic increase in the number of IVT injections has been accompanied by a comparable increase in evidence surrounding IVT practice patterns and techniques. The expert panel identified a number of areas that have evolved since publication of the original IVT injection guidelines in 2004, the most notable of which were a lack of evidence to support the routine use of pre-, peri-, and postinjection antibiotics to reduce the risk of endophthalmitis, and the role of aerosolized droplets containing oral contaminants from the patient and/or providers as a potential source of infection. The panel emphasized the continued importance of applying povidone-iodine to and avoiding eyelid contact with the intended injection site and needle.

Conclusion: Updated guidelines on IVT injection technique and monitoring are proposed based on a review of published literature and expert panel deliberations.

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Guidelines Synopsis

The following guidelines were based on round table deliberations conducted after a review of published studies regarding intravitreal (IVT) injection technique and monitoring. The guidelines presented in this document are relevant to the basic principles of IVT injection and, therefore, generally applicable across therapeutic indications and agents. As with the previous document,¹ the expert panel selected the term “guidelines” over the term “recommendations” in recognition of the fact that many of these conclusions were developed through expert panel consensus.

This guideline update is organized similarly to the previous guidelines to encompass pre-, peri-, and postinjection issues. Preinjection issues address a number of specific clinical situations of potential relevance to the IVT injection, including preexisting ocular hypertension and glaucoma, recent cataract surgery,

preexisting ocular or medical conditions, and use of anticoagulant agents. New or revised sections related to pre- and peri-injection decision-making include guidelines regarding setting (office vs. clinic vs. operating room), the practice of bilateral injections, management of potential aerosolized droplet contamination, and the effective use of topical anesthetics in conjunction with povidone-iodine to minimize the risk of endophthalmitis. As with the previous publication, postinjection guidelines address issues related to monitoring, patient discharge, and protocols for appropriate follow-up.

An additional section, “General Considerations Before IVT Injections,” has been incorporated at the beginning of these guidelines to address overarching issues related to the injection process. The most notable of these is the guideline related to antibiotic use, which marks a substantial change from the 2004 publication. Based on a review of the growing body of evidence surrounding endophthalmitis risk, the conclusion of the

panel was that there is insufficient evidence to support the use of pre-, peri-, or postinjection antibiotics to

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These guidelines were based on the best available data as interpreted by a panel of knowledgeable health professionals. These guidelines are general and meet the needs of most patients but cannot possibly meet the needs of every patient. Adherence to these guidelines will not ensure a successful outcome in every situation. These guidelines should not be deemed inclusive of all proper methods of intravitreal injection or exclusive of other methods of obtaining the best results for a given patient. It may be necessary to approach different patients' needs in different ways. The injecting physician must make the ultimate judgment regarding the propriety of care of a particular patient in light of all of the circumstances presented by that patient. The panelists specifically disclaim any and all liability for injury or any damages of any kind from negligence or otherwise for any and all claims that may arise out of the use of any guidelines or other information contained herein.

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attempt to reduce the risk of endophthalmitis. A second general consideration incorporates the need to use best clinical judgment to tailor these guidelines to the individual patient.

Although the conclusions reached for each of the issues considered during the round table discussion have been summarized, the panel discussions and comments themselves were instructive. We have included, therefore, not only the evidence on which each guideline was based but also selected points discussed during the panel session so as to provide additional context where appropriate.

General Considerations Before IVT Injections

Individual Tailoring of Treatment

The guidelines mentioned below should be tailored to the individual patient as necessary in the best clinical judgment of the injecting physician.

Antibiotic Use

There is insufficient evidence to support the routine use of pre-, peri-, or postinjection antibiotics to reduce the rate of endophthalmitis.

Guidelines for Care and Prophylaxis Before Injection

Specific Clinical Situations

There are no absolute contraindications to IVT injections. However, there are certain situations that require the injecting physician's best clinical judgment.

1. Ocular hypertension/glaucoma: 1) Patients with preexisting ocular hypertension/glaucoma should be managed by the treating physician according to standard of care or preferred practice patterns; 2) IVT injection should not be denied or withheld from patients with a history of ocular hypertension/glaucoma if such therapy is deemed important to preservation of vision; 3) Before performing IVT injection, the injecting physician should conduct a thorough risk assessment based on standard medical practice, including monitoring of intraocular pressure (IOP) before and after injection; 4) Routine anterior chamber paracentesis is not recommended.
2. Preexisting ocular conditions/previous ocular surgeries: Preexisting ocular conditions and previous ocular surgeries should be considered, but do not preclude IVT injection if the injection is otherwise indicated.

Injecting physicians should avoid injecting in the area of previous incisional glaucoma surgery.

3. Recent postcataract surgery patients: The injecting physician should use best clinical judgment with IVT injection in recent cataract surgery patients.
4. Complex medical or ocular conditions: In patients with complex medical or ocular conditions, care should be coordinated with the patient's entire medical team.
5. Patients on anticoagulation: There is minimal risk involved with IVT injections in patients on anticoagulation. Therefore, IVT injection is not contraindicated in these patients.
6. Allergy to Povidone–Iodine: True povidone–iodine allergy is rare. Anaphylaxis has not been reported after ophthalmic application of povidone–iodine.
7. Active external infection, including active infection in blepharitis: Postpone injection until the infection has been treated and cleared, unless, in the best judgment of the injecting physician, the benefits of injection clearly outweigh the increased risk of endophthalmitis.
8. Eyelid, adnexal, and ocular surface abnormalities: Consider eyelid, adnexal, and ocular surface abnormalities as possible risk factors for endophthalmitis.

Guidelines for Pre- and Peri-Injection Management

Clinical Setting for Injection

Intravitreal injections may be safely performed in an office setting, in a treatment room, or in an operating room.

Bilateral Injections

The injecting physician should exercise caution when considering bilateral injections in the same sitting. When bilateral injections are performed, the injection for each eye should be considered to be a separate procedure and should be performed accordingly, using separate site preparation and individual syringes, needles, etc. When administering compounded medications, a different medication batch should be considered for each eye. Pharmaceutical compounding standards are available under United States Pharmacopeia Chapter 797.

Gloves and Draping

Although the use of gloves has not been shown to reduce the risk of endophthalmitis, sterile or nonsterile gloves may be used as consistent with modern office practice. There is no evidence to support the routine use of a drape when performing IVT injections.

Talking and Use of Masks

The spread of aerosolized droplets containing oral contaminants from the patient and/or staff should be minimized to reduce infection risk. This may be achieved by minimizing speaking and/or by the use of surgical masks during the injection preparation and procedure.

Application of Povidone–Iodine to the Ocular Surface and Eyelids

Povidone–iodine (5–10%) should be the last agent applied to the intended injection site before injection. Povidone–iodine may also be applied to the eyelids, including the eyelid margins and eyelashes, but eyelid scrubbing or eyelid pressure adequate to express material from the meibomian glands should be avoided. If a gel anesthetic is used, povidone–iodine should be applied both before and after application of gel, as retained gel may prevent povidone–iodine from contacting the conjunctival surface at the injection site. After the final application of povidone–iodine, the eyelashes and eyelid margins should not be allowed to come into contact with the injection site until the injection has been completed.

Globe Softening

Globe softening before IVT injection is generally not required but may be considered in persons with advanced glaucomatous optic neuropathy and in those for whom the risk of a prolonged postinjection IOP spike is high or in whom any given IOP spike might result in visually significant damage to the optic nerve. If globe softening is used, the injecting physician should apply pressure to the globe itself and not to the eyelids or ocular adnexa.

Dilation

Committee members had differing opinions regarding the need for pupillary dilation. Although some believed that the documented presence of formed vision after injection was sufficient, others believed that pupillary dilation and postinjection examination of the posterior segment was important.

Topical Anesthetics

Topical anesthetics should be applied to minimize patient discomfort as indicated by standard medical practice. In addition, supplemental subconjunctival anesthetics may be considered. Injecting physicians should be aware that the use of anesthetic gel may interfere with povidone–iodine contact with the

conjunctival surface, thereby limiting its antimicrobial activity. If anesthetic gel is used, povidone–iodine should be applied to the intended injection site both before and after application of gel.

Use of a Speculum

It is important to prevent contact of the eyelashes and eyelid margins with both the injection site and the injection needle after final application of povidone–iodine and especially during the actual injection. Although use of a speculum is the most common way to prevent such contact, other techniques may be used to maintain this separation, including manual lid retraction.

Site of Injection

Intravitreal injections should be given between the horizontal and vertical rectus muscles at the pars plana, 3.5 to 4.0 mm posterior to the limbus. Quadrant selection should be dictated by both patient-specific considerations and injecting physician preference. Although oblique and tunneled approaches to scleral penetration have been described to minimize drug reflux after injection, a simple perpendicular injection approach is both convenient and preferred in most settings.

Needle Gauge and Length

Needle gauge should be selected based on the drug to be injected. A 30-gauge or smaller needle is generally preferred for nonviscous solutions. Larger bore needles can be considered for suspensions and for solutions of higher viscosity. Needle length should be 5/8 inch (18 mm) or shorter but long enough to allow for complete penetration of the pars plana.

Protocol: Sequence of Events

An appropriate sequence of steps for IVT injection is to perform the following:

1. Either surgical masks should be used or both the patient and providers should minimize speaking during the injection preparation and procedure;
2. Take a procedural time-out to verify patient, agent, and laterality;
3. Apply liquid anesthetic drops to the ocular surface;
4. Apply povidone–iodine to the eyelashes and eyelid margins (optional, most use 10%);
5. Retract the eyelids away from the intended injection site for the duration of the procedure;
6. Apply povidone–iodine (most use 5%) to the conjunctival surface, including the intended injection site, at least 30 seconds before injection;

7. If additional anesthetic is applied, reapply povidone–iodine to the intended injection site immediately before injection (most use 5%);
8. Insert the needle perpendicular to the sclera, 3.5 to 4.0 mm posterior to the limbus between the vertical and horizontal rectus muscles.

Guidelines for Postinjection Management

Intraocular Pressure

Monitor IOP after injection and provide therapy when persistently elevated IOP warrants intervention.

Patient Discharge

The injecting physician should confirm the presence of formed vision before the patient leaves the office. 24-hour emergency contact information should be provided to the patient. No special precautions are required before discharge of a patient who has had an uneventful IVT injection, but patients and/or caregivers should be educated to avoid eye rubbing and to recognize the signs and symptoms of endophthalmitis, retinal detachment, or intraocular hemorrhage. These include increasing eye pain, discomfort, light sensitivity, or redness; worsening vision; or loss of all or part of central or peripheral vision.

Guidelines for Follow-up

Follow-up Protocol

Postinjection follow-up should be tailored to the individual patient.

Background

The use of IVT injection therapies represents one of the most exciting and dynamic areas of growth in ophthalmology over the past decade. Before 2002, IVT injections were performed relatively uncommonly: from 2000 through 2002, the volume of IVT injections reflected in the AMA/Specialty Society RVS Update Committee (RUC) Database remained stable at approximately 4,500 per year, used primarily for the treatment of endophthalmitis.^{2,3} Ten years later, in 2012, this same database reported more than 2.3 million IVT injections. Taking into account the current growth estimates and other payors, it is expected that the number of IVT injections may reach more than 4 million in 2013 and nearly 6 million in 2016 (Figure 1).²

The published literature reflects this rapid adoption of IVT injections. A search of PubMed reveals

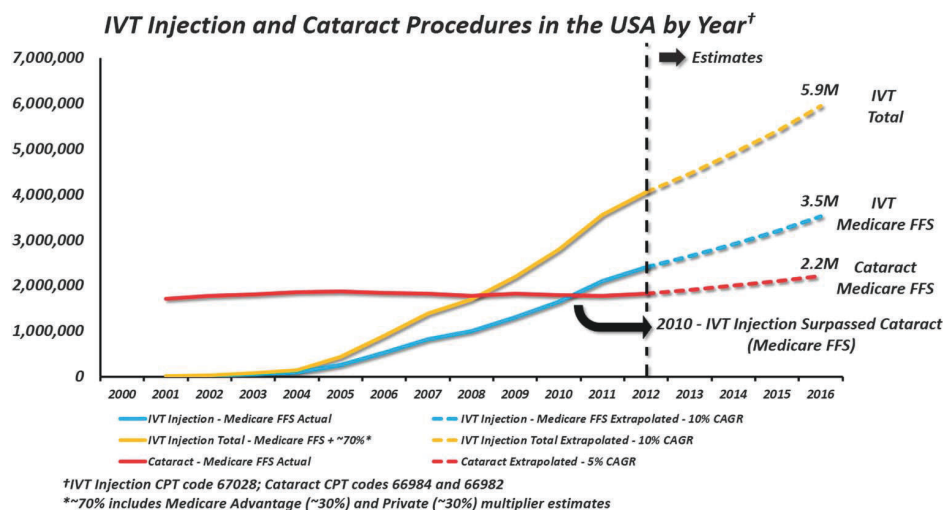


Fig. 1. Intravitreal injection and cataract procedures in the United States, by year. FFS, fee for service; CAGR, compounded annual growth rate. Modified from Williams.²

approximately 1,400 articles (including 7 randomized controlled trials) published through the end of 1999. In the years since, the number of articles has increased 5-fold to more than 7,500 and the number of randomized controlled trials has increased to more than 375.

Although the dramatic growth in IVT injections is related in part to innovative use of existing agents, such as corticosteroids, the majority of expansion has come from the advent of new therapies. In 2004, the only agent specifically approved by the United States Food and Drug Administration for IVT delivery, and since then removed from the US market—was foscarnet for cytomegalovirus retinitis in association with acquired immune deficiency syndrome. As of the end of 2013, there were a total of 6 approved agents: ranibizumab (for the treatment of diabetic macular edema, neovascular age-related macular degeneration [AMD], and macular edema after retinal vein occlusion); aflibercept (neovascular AMD, macular edema after central retinal vein occlusion, and diabetic macular edema); pegaptanib (neovascular AMD); ocriplasmin (vitreomacular adhesion); triamcinolone acetonide (sympathetic ophthalmia and uveitis); and dexamethasone (in an implant form for macular edema after branch or central retinal vein occlusion and noninfectious uveitis of the posterior segment).^{4–9} These therapies have given injecting physicians the ability to minimize vision loss in more than 90% of patients with new onset neovascular AMD and to improve vision in approximately 40% of patients over a period of years.¹⁰ Similar treatment benefits have been achieved in central retinal vein occlusion and diabetic macular edema.^{11–13}

The broad and rapid expansion in IVT injections has also been fostered by the growing literature on the acceptable tolerability of this method of delivering

therapy. Experience over the past decade has shown the incidence of the most serious adverse sequela of IVT injection, endophthalmitis, to be rare, regardless of the clinical setting in which the injection is performed. Additional complications associated with IVT injection include retinal detachment, intraocular hemorrhage, uveitis/iritis, sustained ocular hypertension, and hypotony.¹⁴

In 2004, a similar expert panel published consensus guidelines for IVT injections.¹ At the time, the guidelines were based largely on clinical experience and empiric observation, as there was little published literature, and a relative lack of clinical trial evidence to inform decision-making. Ten years on, the evidence landscape has changed, and our knowledge regarding certain aspects of IVT injection has grown accordingly. Nowhere is this more apparent than in our understanding of endophthalmitis risk and the role that antibiotics may or may not play in reducing this risk. At the time the last guidelines were published, considerable attention was devoted to the question of whether antibiotics have an important role in reducing endophthalmitis risk, and if so, how they may best be used.¹ There is now sufficient evidence to support the notion that the use of topical antibiotics is not associated with a reduced incidence of endophthalmitis in the context of IVT injections^{15–19} and could contribute to drug resistance.^{20,21} Other aspects surrounding IVT injections that now have a substantial body of evidence include the use of povidone-iodine, the safety of injections in various settings (i.e., office, treatment room, or operating room),^{16,22–26} no-talking policies, the effective use of anesthetics, and speculum use versus manual eyelid separation.^{26,27}

In light of this new evidence, an expert panel reconvened in December 2013 to revisit the

conclusions of the original guidelines and make appropriate additions and/or revisions where dictated by the evidence and the past decade of clinical experience. As in the previous guidelines, the goal of this document was to outline steps for safe delivery of IVT injection by establishing where there is evidence, where there is consensus, and where there may be controversy. These guidelines not only facilitate a best practice approach to IVT injection but also outline areas in which additional investigation is warranted.

General Considerations Before IVT Injections

Individual Tailoring of Treatment

Guideline: The guidelines below should be tailored to the individual patient, as necessary, in the best clinical judgment of the injecting physician.

Comment: As with the previous document, the goal of these guidelines is to outline steps for safe IVT injection. The guidelines are meant to facilitate a best practices approach to IVT injection but are not intended to substitute for the injecting physician's best clinical judgment. The panel anticipated that multiple instances may arise in actual clinical practice in which the injecting physician might need to tailor the recommendations summarized below based on specific circumstances and individual patient requirements.

Antibiotic Use

Guideline: There is insufficient evidence to support the routine use of pre-, peri-, or postinjection antibiotics to reduce the rate of endophthalmitis.

Evidence for Guideline: Ten years after the original publication of IVT injection guidelines,¹ retrospective data from the Diabetic Retinopathy Clinical Research Network reported a numerically higher rate of endophthalmitis with the use of topical antibiotics (6/4,694 injections; 0.13%) compared with no antibiotic use (1/3,333 injections; 0.03%).^{15,16} Antibiotics also conferred no clinical benefit in other large retrospective series involving either postinjection application¹⁷⁻¹⁹ or preinjection prophylaxis.²⁸

Although routine use of topical antibiotics before, during, and after IVT injection has, in the past, been associated with a very low rate of endophthalmitis,²⁹ this fact in and of itself should not be interpreted to indicate that antibiotic use per se produced such low infection rates. In fact, the preponderance of evidence would now suggest that routine use of pre-, peri-, and postinjection antibiotics does not materially lower

postinjection infection risk and so should not be used routinely.^{15,17,19,30,31} That said, a number of studies have shown that 3 days of topical antibiotics does decrease bacterial colonization of the conjunctiva^{30,32,33} prompting some to consider the discretionary use of pre-, peri-, and postinjection antibiotics in selected patients who are either unable to use povidone-iodine or who are believed to be at increased risk of infection. The panel emphasized throughout the day-long discussion that the use of appropriately applied topical povidone-iodine was perhaps the single most important step in endophthalmitis prevention, and that the use of topical antibiotics alone should not be viewed as an effective substitute for povidone-iodine.

Comment: Although some physicians continue to use pre- or postinjection topical antibiotics as part of IVT injection protocols, the preponderance of accumulated evidence since publication of the initial guidelines suggests that the use of antibiotics does not contribute to a lower incidence of endophthalmitis. It needs to be emphasized that in all studies that have examined this issue, the rate of endophthalmitis was extremely low, regardless of whether antibiotics were used. The single largest contributor to this low endophthalmitis rate seems to have been meticulous attention to antiseptic techniques during IVT injections, including the appropriate use of povidone-iodine. It is important to take this lack of benefit, the potential for antibiotic resistance, and cost into account when considering the use of pre-, peri-, or postinjection antibiotics.

Guidelines for Care and Prophylaxis Before Injection

Specific Clinical Situations

Guideline: There are no absolute contraindications to IVT injections. However, there are certain situations that require the injecting physician's best clinical judgment.

Comment: The overall risk of complications with IVT injections is low when the injections are administered by experienced ophthalmologists. The panel considered a number of clinical situations that require the ophthalmologist to exercise his or her best clinical judgment when choosing whether to administer an IVT injection but concluded that there is a lack of evidence supporting an absolute contraindication to injection for any specific situation (the panel noted, however, that each approved IVT agent carries relative contraindications as outlined in the respective package inserts⁴⁻⁹).

Ocular Hypertension/Glaucoma

Guideline: 1) Patients with preexisting ocular hypertension/glaucoma should be managed by the treating physician according to standard of care or preferred practice patterns; 2) IVT injection should not be denied or withheld from patients with a history of ocular hypertension/glaucoma if such therapy is deemed important to preservation of vision; 3) Before performing IVT injection, the injecting physician should conduct a thorough risk assessment based on standard medical practice, including monitoring of IOP before and after injection; 4) Routine anterior chamber paracentesis is not recommended.

Evidence for Guideline: Although several retrospective studies have suggested an increased risk of sustained ocular hypertension in patients receiving prolonged anti-VEGF therapy,³⁴ including those with preexisting glaucoma,^{35,36} at least 2 retrospective studies of patients treated repeatedly with anti-VEGF agents concluded that preexisting glaucoma was not a risk factor for sustained ocular hypertension.^{37,38} Moreover, a post hoc analysis of data from the randomized MARINA and ANCHOR trials found no association between elevations in IOP and the number of injections.³⁹ Because the risks of an IOP-related complication from IVT injection may outweigh the benefits in a given patient with uncontrolled ocular hypertension/glaucoma, the panel consensus was that caution should be exercised and additional postinjection IOP surveillance should be considered in eyes with advanced glaucomatous optic neuropathy and/or visual field loss at fixation.

Comment: The primary goal of managing ocular hypertension/glaucoma is the preservation of visual function. Preexisting ocular hypertension/glaucoma should be managed appropriately before IVT injection, according to current standards of care (guidelines for glaucoma management have been published elsewhere and are beyond the scope of this document⁴⁰). However, IVT injection should not be denied or withheld from patients with a history of ocular hypertension/glaucoma. It is important for physicians who are performing IVT injections in patients with ocular hypertension/glaucoma to have documented the presence or absence of optic nerve damage and, if present, the degree of damage because in advanced disease, even transient elevations in IOP can have effects on the optic nerve. Occasionally, patients are given injections but their glaucoma is not being appropriately monitored over time. Consideration should be given before treating patients with baseline IOP >25 mmHg before the injection.

Treatment options for acute IOP elevations include α_2 -adrenergic agonists, such as brimonidine and

apraclonidine, β -adrenergic antagonists, such as timolol, and oral or topical carbonic anhydrase inhibitors. As with any intraocular procedure, anterior chamber paracentesis, although generally safe,⁴¹ is associated with a low rate of endophthalmitis.^{42,43} The panel recognized this risk and recommended that manual globe softening be considered as the first technique for prophylactically lowering IOP, and that prophylactic paracentesis not be done routinely but rather be considered only when, at the injecting physician's discretion, an acute postinjection rise in IOP might pose an imminent and irreversible threat to vision.

Preexisting Ocular Conditions/Previous Ocular Surgeries

Guideline: Preexisting ocular conditions and previous ocular surgeries should be considered but do not preclude IVT injection if the injection is otherwise indicated. Injecting physicians should avoid injecting in the area of previous incisional glaucoma surgery.

Comment: This is an addition to previous guidelines covering specific clinical situations to address questions regarding the impact of preexisting ocular conditions (e.g., glaucoma) or previous ocular surgeries (e.g., penetrating keratoplasty) on the decision to administer an IVT injection. Although the patient's general health and particular ocular conditions should be taken into account, the panel agreed that there is no evidence that these should preclude IVT injection if the injection is otherwise warranted. Injection should be avoided in the area of previous incisional glaucoma surgery (e.g., in the area of a filtering bleb or shunt).

Recent Postcataract Surgery Patients

Guideline: The injecting physician should use best clinical judgment with IVT injection in recent cataract surgery patients.

Comment: The panel agreed that recent cataract surgery, in and of itself, should not preclude IVT injection if the injection is otherwise indicated. In making the decision to inject, the injecting physician should use his or her best clinical judgment, taking into account the patient's overall health and particular ocular conditions.

Complex Medical or Ocular Conditions

Guideline: In patients with complex medical or ocular conditions, care should be coordinated with the patient's entire medical team.

Comment: This is an addition to previous guidelines covering specific clinical situations, to address questions regarding the use of IVT injections in those who

may have complex underlying medical or ocular diseases. The panel recognizes the value of consulting with the patient's other physicians and coordinating care among them to positively impact care and to determine the best course of treatment.

Patients on Anticoagulation

Guideline: There is minimal risk involved with IVT injections in patients on anticoagulation. Therefore, IVT injection is not contraindicated in these patients.

Evidence for Guideline: Since the initial publication of these guidelines, several reports have addressed the issue of administering IVT injections to patients on anticoagulation. In a retrospective case series of 1,710 injections for neovascular AMD performed in 228 eyes in 191 patients, vitreous or subretinal hemorrhage occurred in 3 patients on systemic anticoagulation and 1 patient not on anticoagulation. The difference was not statistically significant.⁴⁴ In a retrospective chart review of 220 patients who received IVT ranibizumab, diabetes and the combination of diabetes/hypertension were risk factors for macular hemorrhage but the use of an anticoagulating agent was not.⁴⁵ In a retrospective study of 31 patients (32 eyes) on warfarin anticoagulation who underwent 102 pegaptanib injections, there were no intraoperative or immediate postoperative hemorrhagic complications.⁴⁶

Comment: This addition to the guidelines addresses concerns regarding patients on anticoagulation. There was overall agreement among the panelists that current evidence does not suggest an increased risk of intraocular bleeding complications after IVT injection in patients who are on anticoagulant therapy.

Allergy to Povidone–Iodine

Guideline: True povidone–iodine allergy is rare. Anaphylaxis has not been reported after ophthalmic application of povidone–iodine.

Evidence for Guideline: Patients may experience irritant effects of povidone–iodine (in proportion to the duration of exposure) and contact dermatitis.^{47–49} True cases of povidone allergy, however, are rare.^{41,47} Anaphylaxis to povidone–iodine used in conjunction with IVT injection has yet to be documented, although cases have been reported after application to open wounds or mucous membranes.^{47,50,51}

Comment: Use of povidone–iodine is an important component of IVT injection preparation. Since publication of the initial guidelines, studies in patients undergoing IVT injection have supported the effectiveness of topical povidone–iodine in reducing the number of conjunctival bacteria.^{52,53} In addition, in a retrospective review of 15,144 IVT injections, no

cases of endophthalmitis occurred using a preparation regimen that included the application of povidone–iodine to the skin and conjunctiva.²⁹ Commonly, patients develop contact dermatitis or surface irritation, which they may equate incorrectly with allergy. In addition, a history of systemic iodine allergy does not typically translate to allergy with povidone–iodine. A skin patch test may be considered in a patient with an undocumented claim of povidone–iodine allergy to determine whether there is a reaction; however, skin redness per se in response to the test should not necessarily be interpreted as evidence of an immune-mediated hypersensitivity response or preclude the use of povidone–iodine before IVT injection. For these reasons, the panel did not support the routine use of a skin test to screen for povidone allergy before IVT injection, although this skin test may be useful in convincing some patients that the ocular use of povidone–iodine is safe for them. Postinjection irritation may be minimized by irrigating residual povidone–iodine from the ocular surface using sterile saline after the procedure.

Active External Infection, Including Active Infection in Blepharitis

Guideline: Postpone injection until the infection has been treated and cleared, unless, in the best judgment of the injecting physician, the benefits of injection clearly outweigh the increased risk of endophthalmitis.

Evidence for Guideline: Endophthalmitis is one of the most serious complications of IVT injection. Rigorous precautions to reduce this risk of infection are warranted. There are no controlled data demonstrating a reduced risk of endophthalmitis with treatment of external infections before IVT injection. In a prospective observational case study of 47 cases of postinjection anti-VEGF endophthalmitis who were compared with 200 control cases, blepharitis, present in 6.5% of cases, was a significant risk factor for endophthalmitis ($P = 0.006$).⁵⁴

Comment: This is unchanged from the previous guidelines. Panel consensus was that patients undergoing IVT injection should meet the same general guidelines and considerations as those undergoing intraocular surgery, including postponing the injection until active external infection has resolved. This approach is consistent with good medical practice.

Eyelid, Adnexal, and Ocular Surface Abnormalities

Guideline: Consider eyelid, adnexal, and ocular surface abnormalities as possible risk factors for endophthalmitis.

Evidence for Guideline: In a study evaluating the risk of endophthalmitis after intraocular lens implantation

relative to other intraocular surgeries, endophthalmitis was associated with preoperative eyelid abnormalities, as well as diabetes mellitus, transscleral suture fixation of posterior chamber intraocular lenses, polypropylene haptics, reentry of eye through a previous wound, and postoperative wound defects. Most cases were caused by *S. epidermidis*.⁵⁵

Guidelines for Pre- and Peri-Injection Management

Clinical Setting for Injection

Guideline: IVT injections may be safely performed in an office setting, in a treatment room, or in an operating room.

Evidence for Guideline. Numerous large-scale analyses have documented the excellent safety of performing IVT injections in an office setting, in a treatment room, or in an operating room. A meta-analysis of US literature from 2005 to 2009, encompassing 16 studies and 105,536 injections, found 52 cases of endophthalmitis (0.049% rate). Twenty-six of these cases (52%) were culture-positive.⁵⁶ Studies of US cohorts published since that meta-analysis have found consistently low rates of endophthalmitis in the clinic setting with IVT injection of various agents, ranging from 0.02% to 0.09%.^{16,22-26} European series have also reported very low rates of endophthalmitis after IVT injections performed in the operating room setting with a Swiss study of anti-VEGF injections reporting 3 cases over a total of 40,011 injections (0.0075%)⁵⁷ and a Danish study reporting no cases in 20,293 injections (0%).⁵⁸

Studies that have compared rates of endophthalmitis in the office versus the operating theater have found the incidence in both settings to be extremely low. In a retrospective comparison of patients treated with ranibizumab or bevacizumab in an office procedure room or an operating theater, the rates of endophthalmitis were 4/3,376 (0.12%) in the office setting and 0/8,873 for the operating theater ($P = 0.006$).⁵⁹ In a second retrospective case series involving ranibizumab, bevacizumab, and triamcinolone acetonide, endophthalmitis occurred in 3/8,647 (0.04%) office-based injections and in 2/3,063 (0.07%) operating room-based injections.⁶⁰

Comment: The issue of where to perform IVT injections is addressed for the first time in these guidelines. Regardless of the specific injection setting, (office setting, treatment room, or operating theater), the risk of endophthalmitis has been consistently very low. The majority of IVT injections to date have been performed in the outpatient office setting, and this seems to confer no additional risk compared with the operating room setting.

Bilateral Injections

Guideline: The injecting physician should exercise caution when considering bilateral injections in the same sitting. When bilateral injections are performed, the injection for each eye should be considered a separate procedure and should be performed accordingly, using separate site preparation and individual syringes, needles, etc. When administering compounded medications, a different medication batch should be considered for each eye. Pharmaceutical compounding standards are available under United States Pharmacopeia Chapter 797.

Evidence for Guideline: Although the safety of bilateral same-day IVT injections is well documented,⁶¹⁻⁶⁴ several studies have reported outbreaks of infectious endophthalmitis with the use of drugs prepared by compounding pharmacies. In one series, 12 eyes of 12 patients developed endophthalmitis after IVT injections of bevacizumab from syringes prepared by a single compounding pharmacy. Outcomes at 12 months were poor, with 7 patients requiring enucleation or enucleation.⁶⁵ Other outbreaks were reported in patients receiving IVT injections of triamcinolone acetonide⁶⁶ and a combination of bevacizumab and triamcinolone acetonide.⁶⁷ In each instance, the medication was prepared by a compounding pharmacy.

Comment: Compounded drugs are commonly used for IVT injections (Table 1). The issue of bilateral IVT injections is addressed for the first time in these guidelines regarding concerns over accidental contamination of one or both eyes when bilateral injections are performed and to minimize the risks that may arise from batches of compounded drugs in particular. The issue of compounded drugs was highlighted in 2012, after an outbreak of fungal meningitis traced to epidural injections of betamethasone from a single compounding center in New England. Fifty-one deaths were tied to the

Table 1. Commonly Compounded Drugs Delivered by IVT Injection*

Amikacin	0.4 mg/0.1 mL
Amphotericin B	0.005 mg/0.1 mL
Bevacizumab	1.25 mg/0.05 mL
Cefazolin or ceftazidime	2.25 mg/0.1 mL
Clindamycin	1.0 mg/0.1 mL
Dexamethasone	0.4 mg/0.1 mL
Foscarnet	2.4 mg/0.1 mL
Ganciclovir	2.0 mg/0.05 mL
Methotrexate	0.4 mg/0.1 mL
Tobramycin	0.1 mg/0.1 mL
Triamcinolone	4.0 mg/0.1 mL
Vancomycin	1.0 mg/0.1 mL
Voriconazole	0.05–0.1 mg/0.1 mL

*Pharmaceutical compounding standards are available under United States Pharmacopeia Chapter 797.⁶⁸

contaminated drug.⁶⁹ This outbreak and the endophthalmitis outbreaks tied to IVT injections^{65–67} raised issues regarding the safety of bilateral injections, especially with compounded drugs. Pharmaceutical compounding standards are available under United States Pharmacopeia Chapter 797. These include the use of a laminar flow hood, sterile gown and gloves, and credentialed pharmacy staff.⁶⁸ Bilateral IVT injections can safely be performed during the same session when appropriate, and may be preferred by patients over separate day injections.⁶² In addition, each injection should be treated as a separate procedure and should be performed accordingly, using separate site preparation and individual syringes, needles, etc. When administering compounded medications, a different medication batch should be considered for each eye.

Gloves and Draping

Guideline: Although the use of gloves has not been shown to reduce the risk of endophthalmitis, sterile or nonsterile gloves may be used as consistent with modern office practice. There is no evidence to support the routine use of a drape when performing IVT injections.

Evidence for Guideline: There are no controlled data confirming the efficacy of wearing gloves to reduce the risk of infection after IVT injection, but this is a reasonable extrapolation of the use of gloves as a part of general infection control practice. In 2 prospective randomized controlled trials performed by the Diabetic Retinopathy Clinical Research Network that did not require the use of gloves or a drape, the endophthalmitis rate was 0.078% (3/3,838 injections).¹⁵ An endophthalmitis rate of 0.057% was reported in a retrospective case series of 15,895 IVT injections involving ranibizumab, bevacizumab, triamcinolone acetonide, and pegaptanib, in which gloves were not used.¹⁸ Similarly, an endophthalmitis rate of 0.029% was reported in a retrospective, interventional, single-center case series of 10,254 anti-VEGF injections with a protocol that did not use a drape (there was no mention of glove use).⁷⁰ In nonophthalmic surgical procedures, a Cochrane review of 5 randomized controlled trials involving 3,082 patients found that use of a plastic adhesive drape was associated with a significant increase in surgical site infections (RR, 1.23; 95% confidence interval, 1.02–1.48; $P = 0.03$).⁷¹

Comment: The package inserts for all agents currently approved for IVT injection by the US FDA cite the use of sterile gloves and a sterile drape as part of the injection protocol.^{4–9} Nevertheless, there is little evidence of benefit for sterile gloves and drapes⁷² and it is commonplace not to use either. In a survey of 765 retina specialists, 58% reported use of gloves, and of

those, 58% used sterile gloves. Only 12% reported use of a sterile drape.⁷³

Although the use of gloves is not strictly required by either evidence-based studies or regulations, many patients and physicians find the use of gloves, either sterile or nonsterile, to be consistent with modern office practice. Regardless of the use or nonuse of gloves, careful handwashing before and after patient contact and attention to aseptic injection technique is recommended for IVT injection.

The use of a drape may be more problematic in that it has the potential to create patient anxiety and discomfort. In a survey of 42 patients undergoing IVT injection, drape application ranked second only to insertion of the needle in terms of the level of discomfort, and 18% of patients reported that the drape caused significant discomfort.⁷⁴

Talking and Use of Masks

Guideline: The spread of aerosolized droplets containing oral contaminants from the patient and/or staff should be minimized to reduce infection risk. This may be achieved by minimizing speaking and/or by the use of a surgical mask during the injection preparation and procedure.

Evidence for Guideline: There are no randomized controlled trials that specifically address the impact of wearing a mask or of a limited talking policy on infection risk after IVT injection. There is evidence from large retrospective analyses that an infection control protocol employing the use of a face mask can minimize the risk of endophthalmitis.^{29,58} In a meta-analysis of endophthalmitis cases after IVT injection, the authors noted a high rate of *Streptococcus* isolates, suggesting that causative organisms were likely to be transmitted from oropharyngeal droplets. Drawing upon the dural puncture literature, these researchers suggested that talking should be minimized or facial masks should be worn by the physician during IVT injection.⁵⁶

Two studies that simulated IVT injection procedures found that the use of a face mask and avoidance of talking both significantly reduced bacterial growth on blood agar plates positioned next to the mouth when compared with talking during the procedure.^{75,76} A third study found no significant difference in cultures sampled from IVT needles after 30 seconds of talking versus 30 seconds of silent breathing.⁷⁷

Comment: This guideline has been added to draw attention to the need to reduce the possibility of contamination with aerosolized droplets during the IVT injection procedure. Evidence supports that this risk can be addressed by minimizing speaking by the

ophthalmologist and all individuals in the room and/or the use of a mask. Some panelists expressed a preference for the use of a mask, and observed that, depending on the facility, masks may be incorporated into the IVT injection protocol.

Application of Povidone–Iodine to the Ocular Surface and Eyelids

Guideline: Povidone–iodine (5–10%) should be the last agent applied to the intended injection site before injection. Povidone–iodine may also be applied to the eyelids, including the eyelid margins and eyelashes, but eyelid scrubbing or eyelid pressure adequate to express material from the meibomian glands should be avoided. If a gel anesthetic is used, povidone–iodine should be applied both before and after application of gel, as retained gel may prevent povidone–iodine from contacting the conjunctival surface of the injection site. After the final application of povidone–iodine, the eyelashes and eyelid margins should not be allowed to come into contact with the injection site until the injection has been completed.

Evidence for Guideline: There was strong consensus among the panelists that povidone–iodine should be used to prepare the injection site for IVT injections. Compared with topical antibiotics, ocular surface preparation with povidone–iodine does not seem to promote bacterial resistance.⁷⁸ There are no controlled studies specifically examining endophthalmitis risk after IVT injections done with or without povidone–iodine, but studies from the cataract surgery literature have demonstrated significant reductions in infection risk.^{79–81}

Prospective studies have evaluated various povidone–iodine protocols in IVT injection. One study found a greater reduction in bacterial colonization with irrigation of the conjunctiva using 5% povidone–iodine, compared with drop application.⁵³ Another found that use of 5% povidone–iodine significantly reduced bacterial colony forming units after 30 seconds of exposure but not after 15 seconds.⁵²

There was consensus among the panelists that lid scrubs may increase the risk of contamination with bacteria from lids and lashes. Therefore, lid scrubs are not recommended as part of the IVT injection protocol.

Comment: The role of povidone–iodine as part of a meticulous aseptic protocol in IVT injection has been strengthened by the recent literature. The panelists noted its utility in IVT injection, taking into account its effectiveness, low cost, ready availability,⁸² and lack of association with antimicrobial resistance. There was consensus that povidone–iodine should be applied directly to the site of injection, with a number of panelists expressing a strong preference

for wider application, bathing the entire ocular surface, lids and lashes, which may provide added protection against secretions from the accessory lid glands. Regarding the duration of exposure, the panelists recognized the value of waiting at least 30 seconds after applying povidone–iodine before the injection but observed that the povidone–iodine should not be allowed to dry. Application of povidone–iodine to the lids is distinguished from a lid scrub, which may dislodge bacteria from the accessory glands and therefore should not be performed.

Globe Softening

Guideline: Globe softening before IVT injection is generally not required but may be considered in persons with advanced glaucomatous optic neuropathy and in those for whom the risk of a prolonged postinjection IOP spike is high or in whom any given IOP spike might result in visually significant damage to the optic nerve. If globe softening is used, the injecting physician should apply pressure to the globe itself and not to the eyelids or ocular adnexa.

Evidence for Guideline: Globe softening to facilitate injection is an accepted, although uncommon, practice that has been permitted in clinical trials of IVT therapies.⁸³ There are no controlled data to demonstrate that ocular massage reduces the risk of pressure-associated adverse events. However, one study of 48 patients receiving IVT injections of ranibizumab found that those randomized to application of lidocaine gel to the globe using “moderate pressure” had a significantly lower increase in IOP in the immediate postinjection period compared with those receiving lidocaine without pressure (25.7 vs. 30.9 mmHg; $P = 0.001$).⁸⁴

Comment: Panelists observed that globe softening is not common and in general is not recommended. However, they recognized that globe softening may be preferred in some patients who are at risk for high postinjection IOP elevations. Physicians who do use globe softening must be careful to limit the massage to the globe itself and avoid both the lid and the adnexa because bacteria may be released from accessory glands and, in the case of neovascular AMD, hypotony-induced bleeding can occur. Injection volumes in excess of 0.1 mL can produce dramatic increases in IOP.

Dilation

Guideline: Committee members had differing opinions regarding the need for pupillary dilation. Although some believed that the documented presence of formed vision after injection was sufficient, others believed that pupillary dilation and postinjection examination of the posterior segment were important.

Evidence for Guideline: Dilation was included in the protocols for many of the controlled trials evaluating IVT injections on the basis that this permits visualization of the needle and monitoring for perioperative complications such as impaired reperfusion of the optic nerve and retinal detachment. For example, physicians participating in the VISION studies of pegaptanib used 1% mydriacyl and 2.5% phenylephrine applied topically from new bottles to achieve adequate pupillary dilation.⁸⁵ There are no controlled trials comparing the utility of pupillary dilation on the rate of postinjection complications or their prevention. Clinical experience since the previous guidelines were published has demonstrated that dilation may not be essential for postinjection monitoring of optic nerve reperfusion or injection-related complications. However, because dilation poses no significant risks to the majority of patients and many physicians prefer to perform routine dilation to facilitate immediate postinjection examination, it may be considered optional as part of the IVT injection procedure.

Topical Anesthetics

Guideline: Topical anesthetics should be applied to minimize patient discomfort as indicated by standard medical practice. In addition, supplemental subconjunctival anesthetics may be considered. Injecting physicians should be aware that the use of anesthetic gel may interfere with povidone–iodine contact with the conjunctival surface, thereby limiting its antimicrobial activity. If anesthetic gel is used, povidone–iodine should be applied to the intended injection site both before and after application of gel.

Evidence for Guideline: Studies have evaluated various anesthetics for IVT injections, finding no significant differences in patient comfort. A randomized prospective trial of 24 patients found no difference in pain scores among 4 different anesthetic approaches (topical proparacaine, tetracaine, lidocaine pledget, or subconjunctival lidocaine).⁸⁶ Similarly, no difference in pain scores was found in a comparison of proparacaine drops, proparacaine plus lidocaine-soaked cotton swabs, and lidocaine gel.⁸⁷ A randomized trial of 28 patients did report significantly higher IVT injection pain scores with 4% topical lidocaine versus subconjunctival injections of 4% lidocaine; however, there was no difference in total pain scores when the pain of the subconjunctival injection itself was taken into account.⁸⁸ A second randomized trial of 100 patients comparing these same routes of administration with 2% lidocaine found no significant differences in pain scores.⁸⁹ Based on this, there is a lack of evidence to support recommending one anesthetic agent or application technique over another.

Although evidence supports the equivalent efficacy of lidocaine injection, gel, and drops,⁹⁰ 2 studies, both involving blood agar plates inoculated with bacteria, concluded that applying gel before povidone–iodine can interfere with antisepsis. In one, there was no significant difference in *S. epidermidis* growth between untreated plates and those treated with 2% lidocaine gel before povidone–iodine.⁹¹ The second study found increased survivability of *S. epidermidis*, *S. aureus*, *Pseudomonas aeruginosa*, and *Haemophilus influenza* with preapplication of lidocaine gel compared with povidone–iodine alone.⁹² Based on these findings, evidence supports the application of povidone–iodine both before and after application of lidocaine gel, if used. A separate study found that subconjunctival injection of 2% lidocaine may reduce the risk of infection.⁹³

Comment: In terms of patient comfort, the panelists did not find sufficient support to recommend one anesthetic approach over another, noting that physicians have generally been given substantial discretion with choice of anesthetic in clinical trials of IVT agents. The use of the specific anesthetic and route of application (e.g., topical drop, gel, swab, subconjunctival injection) is therefore a matter of injecting physician choice. Given potential concerns over reduced effectiveness of povidone–iodine with gel anesthetic, it was observed that povidone–iodine should be applied both before and after the gel, if used. Povidone–iodine should be applied to the injection site immediately before the injection, by whichever means the injecting physician prefers (e.g., drop or pledget).

Use of a Speculum

Guideline: It is important to prevent contact of the eyelashes and eyelid margins with both the injection site and the injection needle after final application of povidone–iodine and especially during the actual injection. Although use of a speculum is the most common way to prevent such contact, other techniques may be used to maintain this separation, including manual lid retraction.

Evidence for Guideline: There is no evidence to support a preference for speculum use over other methods of maintaining separation between the ocular surface and the patient's lids/lashes during IVT injection.²⁷ In a prospective randomized study of 131 patients that evaluated the use of povidone–iodine, the placement of a lid speculum before the injection had no impact on the number of colony forming units. Two retrospective analyses encompassing more than 37,000 IVT injections found no difference in the risk of endophthalmitis with the use of a bladed speculum compared with manual eyelid retraction.^{26,27} One prospective randomized study

of 141 patients did associate speculum use with a higher risk of drug reflux.⁹⁴

Discussion: As with sterile gloves and drapes, the package inserts for agents currently approved for IVT injection by the US FDA cite the use of a speculum as part of the injection protocol.⁴⁻⁹ However, in clinical practice, it is commonplace for the physician to use either a sterile speculum or his or her fingers to direct the lids and lashes away from the injection field. There was no clear consensus by the panel on preference for a speculum over manual separation or for use of a bladed speculum over a wire speculum. Choice may be dictated by the availability of an assistant to aid in manual lid retraction, physician preference, and patient preference vis-à-vis comfort. Some unaided physicians believe that performing an injection with 2 hands, aided by a speculum, provides greater control and improved injection consistency. Conversely, some patients consider the speculum to be a source of procedure-related discomfort and the injecting physician may perform manual lid retraction.

The important goal is to prevent contact of the lids and lashes with the injection needle and ocular surface; several panelists observed that the lashes may be a primary source of some cases of endophthalmitis because of needle contact during entry into the vitreous. To this end, the physician may choose to swab the lids/lashes with povidone-iodine as part of injection preparation.

Site of Injection

Guideline: IVT injections should be given between the horizontal and vertical rectus muscles at the pars plana, 3.5 to 4.0 mm posterior to the limbus. Quadrant selection should be dictated by both patient-specific considerations and injecting physician preference. Although oblique and tunneled approaches to scleral penetration have been described to minimize drug reflux after injection, a simple perpendicular injection approach is both convenient and preferred in most settings.

Evidence for Guideline: The panel consensus was that IVT injections should generally be given between the horizontal and vertical rectus muscles at the pars plana, 3.5 to 4.0 mm posterior to the limbus, as the majority of injecting physicians have experience with this method of injection and it carries a low risk of complications. This method is also consistent with injection protocols in controlled clinical trials of drugs approved for IVT injection and is incorporated into package inserts.⁵ Several small comparative studies have reported a lower risk of drug/vitreous reflux using oblique or tunneled scleral injections.⁹⁵⁻⁹⁷ However,

notably higher increases in IOP using tunneling techniques have also been reported.⁹⁸

Comment: There is a great deal of cumulative experience with IVT injection techniques. Overall, the panel favored giving the injection between the horizontal and vertical rectus muscles at the pars plana, 3.5 to 4.0 mm posterior to the limbus, keeping the needle perpendicular to the sclera (Figure 2). Physician preference and specific patient factors (e.g., the presence of intraocular pathology or the need to avoid the site of previous incisional surgery) may influence the specific choice of quadrant.

Although studies suggest that scleral tunneling may have value in reducing the risk of reflux,⁹⁹ the panel believed that staying perpendicular to the sclera may be preferred to avoid inadvertent injury to the lens or the retina. A tunnel incision is also technically more difficult and may be more challenging for many injecting physicians.

Needle Gauge and Length

Guideline: Needle gauge should be selected based on the drug to be injected. A 30-gauge or smaller needle is generally preferred for nonviscous solutions. Larger bore needles can be considered for suspensions and for solutions of higher viscosity. Needle length should be 5/8 inch (18 mm) or shorter but long enough to allow for complete penetration of the pars plana.

Evidence for Guideline: Package inserts for FDA-approved agents (with the exception of the Ozurdex implant and triamcinolone acetonide suspension) specify the use of a 30-gauge or smaller needle for IVT

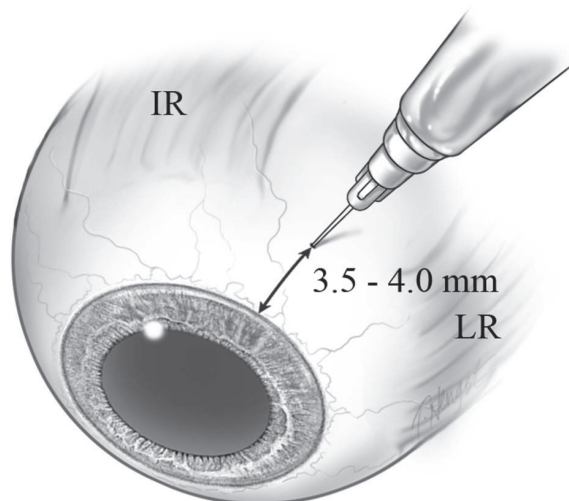


Fig. 2. Schematic of injection site technique. IVT injections should generally be given between the horizontal and vertical rectus muscles at the pars plana, 3.5 to 4.0 mm posterior to the limbus. IR, inferior rectus; LR, lateral rectus.

injection.⁴⁻⁷ There is published evidence that 30-gauge or smaller needles are associated with low pain scores and a low risk of vitreous reflux.¹⁰⁰⁻¹⁰² A larger bore needle may be selected for viscous solutions or suspensions. There are no data on which an increased risk from larger needles is well documented. There is prospective evidence that a lack of vitreous reflux is associated with a significant initial elevation in IOP that rapidly normalizes¹⁰³ and retrospective evidence that smaller bore needle sizes are associated with statistically significant IOP spikes that also normalize within 30 minutes.¹⁰⁴ The length of the needle is dictated by the goal of reducing the risk of injury to the retina or other intraocular structures from injection.

Comment: A smaller bore needle size may minimize patient discomfort and anesthesia requirements, and a 5/8 inch (18 mm) needle minimizes the risk of direct mechanical injury to posterior pole structures. Although smaller bore needles are associated with reduced vitreous reflux, they also seem to be associated with postinjection IOP spikes.

Protocol: Sequence of Events

Guideline: 1) Either surgical masks should be used or both the patient and providers should minimize speaking during the injection preparation and procedure; 2) Take a procedural time-out to verify patient, agent, and laterality; 3) Apply liquid anesthetic drops to the ocular surface; 4) Apply povidone-iodine to the eyelashes and eyelid margins (optional, most use 10%); 5) Retract the eyelids away from the intended injection site for the duration of the procedure; 6) Apply povidone-iodine (most use 5%) to the conjunctival surface, including the intended injection site, at least 30 seconds before injection; 7) If additional anesthetic is applied, reapply povidone-iodine to the intended injection site immediately before injection (most use 5%); 8) Insert the needle perpendicular to the sclera, 3.5 to 4.0 mm posterior to the limbus, between the vertical and horizontal rectus muscles.

Evidence for Guideline: Some, but not all, of these steps were mandated in clinical trials or drugs delivered by IVT injection; they represent a summary of the guidelines discussed earlier in this article. Available evidence and cumulative experience support the notion that these steps are both safe and may reduce the risk of complications. Other protocols with alternative steps may be reasonable, but this provides a structured step-by-step approach to IVT injection.

Discussion: The panelists were in agreement that modifications of the above approach are reasonable

based on individual patient differences. For example, the physician may alter this approach in an individual who is immunocompromised or has diabetes compared with a healthy young patient. Physician experience in IVT injection is also an important factor. The overall goal should always be to maximize patient comfort while minimizing the risk of complications.

Guidelines for Postinjection Management

Intraocular Pressure

Guideline: Monitor IOP after injection and provide therapy when persistently elevated IOP warrants intervention.

Evidence for Guideline: Prolonged and pronounced elevations in IOP pose a significant risk of serious vision loss. Both transient and sustained increases in IOP have been associated with IVT injection, but the risk of sustained increases in IOP is most closely associated with injection of corticosteroids.¹⁴

Discussion: Although acutely elevated IOP may produce symptomatic pain or discomfort, the panel agreed that routine monitoring of IOP is a prudent part of pre- and postinjection patient management. Committee members recommended avoiding prophylactic anterior chamber paracentesis for lowering IOP unless absolutely necessary in a patient with preexisting glaucoma. Intraocular pressure usually returns to a normal level in a short period of time (i.e., within a few minutes).

Patient Discharge

Guideline: The injecting physician should confirm the presence of formed vision before the patient leaves the office. Twenty-four-hour emergency contact information should be provided to the patient. No special precautions are required before discharge of a patient who has had an uneventful IVT injection, but patients and/or caregivers should be educated to avoid eye rubbing and to recognize the signs and symptoms of endophthalmitis, retinal detachment, or intraocular hemorrhage. These include increasing eye pain, discomfort, light sensitivity, or redness; worsening vision; or loss of all or part of central or peripheral vision.

Evidence for Guideline: Confirming the presence of formed vision ensures that the retinal artery is perfused. Once postinjection perfusion of the optic nerve has been verified and there are no specific signs or symptoms suggesting an injection-related complication, then the patient may be discharged from the office. Patients and/or their providers should be alerted to the signs and symptoms of postprocedural complications that may develop hours, days, or weeks after injection,

Table 2. Areas of General Agreement by Committee Members

Povidone-iodine (5–10%) should be the last agent applied to the intended injection site before injection. If a gel anesthetic is used, povidone-iodine should be applied both before and after application of gel, as retained gel may prevent povidone-iodine from contacting the conjunctival surface of the injection site
Pre-, peri-, or postinjection topical antibiotics are unnecessary
There is no evidence to support the routine use of a sterile drape
Avoid contamination of the needle and injection site by the eyelashes or the eyelid margins
Avoid extensive massage of the eyelids either pre- or postinjection (to avoid meibomian gland expression)
Use adequate anesthetic for a given patient (topical drops, gel, and/or subconjunctival injection)
Use of sterile or nonsterile gloves as consistent with modern office practice, combined with strong agreement regarding the need for handwashing before and after patient contact
Either surgical masks should be used or both the patient and providers should minimize speaking during the injection preparation and procedure to limit aerosolized droplets containing oral contaminants from the patient and/or provider
Monitor IOP both pre- and postinjection
Routine anterior chamber paracentesis is not recommended

such as endophthalmitis, retinal detachment, and intraocular hemorrhage. The most important signs and symptoms are increasing eye pain, discomfort, light sensitivity, or redness; worsening vision; or loss of all or part of central or peripheral vision. The patient should be provided with 24-hour emergency contact information.

Discussion: Evidence supports that IVT injection is safe when performed appropriately. Although no invasive procedure is without risk, acute complications, such as injury to the eye from injection, may be symptomatic and are usually immediately apparent with periprocedural visualization and monitoring. The late risks, such as endophthalmitis and retinal detachment, may not be evident for several days. In the absence of evidence of acute complications, there should be no obstacle to immediate discharge.

Guidelines for Follow-up

Follow-up Protocol

Guideline: Postinjection follow-up should be tailored to the individual patient.

Evidence for Guideline: Because of the relatively low risk of adverse events associated with IVT injection, it is

unlikely that different strategies for follow-up will be compared in a formal study. Postprocedural contact is important because of the small but measurable risk of serious adverse events during the recovery period, particularly endophthalmitis. The timing and nature of follow-up should be based on the physician's judgment and the needs of the individual patient. As outlined above, 24-hour emergency contact information should be provided to the patient.

Conclusion

The use of IVT injection as a means of delivering intraocular therapeutics has grown dramatically over the past decade, as has clinical experience with IVT injection techniques. Committee members addressed the multiple issues arising during IVT injection procedures and have listed areas of strong consensus versus weak consensus (Tables 2 and 3). There were limited evidence-based data to use in preparing these guidelines. However, the rapidly growing body of evidence has confirmed that appropriately performed IVT injections are associated with an extremely low rate of endophthalmitis and other serious adverse events. Nevertheless, IVT injection is associated with a low

Table 3. Areas With No Clear Consensus by Committee Members

Need for povidone-iodine application to the eyelids, including the eyelashes and eyelid margins. All agreed that when povidone-iodine is applied to the eyelashes and eyelid margins, eyelid scrubbing or eyelid pressure adequate to express material from the meibomian glands should be avoided
Use of a speculum (some prevent contact between the needle/injection site and the eyelashes and eyelids with manual lid retraction)
Need for pupillary dilation and postinjection dilated examination of the posterior segment (although some viewed the return of formed vision as sufficient, others routinely dilate the pupil and examine the posterior segment after injection)
Use of povidone-iodine flush (most preferred drops only and saw no benefit to allowing the povidone-iodine to dry before injection)

risk of injection-related loss of vision. These risks seem to increase substantially when IVT injection is not performed according to established safe practices. The updated guidelines presented in this document are designed to identify opportunities to improve the likelihood of an optimal complication-free result.

Key words: intravitreal injection, consensus guidelines, endophthalmitis, antibiotic use.

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