



Preventive factors, diagnosis, and management of injection-related endophthalmitis: a literature review

Rupali Singh¹ · Samaneh Davoudi² · Steven Ness²

Received: 30 November 2021 / Revised: 14 February 2022 / Accepted: 21 February 2022 / Published online: 12 March 2022
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Abstract

Background Intravitreal medication injections represent the gold standard treatment for a variety of potentially blinding chorioretinal vascular diseases. Despite their excellent safety profile, they are associated with the feared complication of injection-related endophthalmitis (IRE). Though the overall incidence of IRE is low, due to the ever-increasing number of injections being performed, it is a complication that all retina specialists are likely to encounter. This article reviews various factors that could potentially influence the risk of IRE and discusses evidence-based strategies for management.

Method PubMed was searched for keywords “intravitreal injection” and “endophthalmitis” from the period of 1995–2021. Relevant articles were reviewed and selected articles were analyzed with respect to the incidence, potential preventive factors, clinical presentation, microbial profile, management, and outcomes for IRE.

Results There is strong consensus supporting the use of povidone iodine topical antiseptic, eyelid retraction away from the injection site, and avoiding treatment of eyes with active surface or eyelid disease, but there is less agreement on the use of face masks versus “no-talking” policies and optimal anesthetic technique. Current evidence comparing tap and inject or early vitrectomy for treatment of IRE is inadequate to determine an optimal treatment strategy.

Conclusion Intravitreal injections are sight saving, but even using established prophylactic measures there remains a small but real risk of infectious injection-related complications. Further investigations comparing tap and inject versus vitrectomy may help to establish optimal treatment, although the rarity of IRE makes designing adequately powered prospective trials a difficult task.

Key Messages:

- Intravitreal injections of antivascular endothelial growth factors agents (anti-VEGF) represent the gold standard treatment for a variety of chorioretinal vascular diseases. While the overall incidence of injection related endophthalmitis (IRE) is low, due to the ever-increasing number of injections being performed, it is a complication that all retina specialists are likely to encounter.
- Coagulase-negative Staphylococcus is the most frequent infectious organism, but cases caused by Streptococcal species found in oropharyngeal flora are particularly devastating.
- Use of povidone iodine topical antiseptic, eyelid retraction away from the injection site, and avoiding treatment of eyes with active surface or eyelid disease all appear to be straightforward measures to limit the likelihood of IRE.
- Current evidence comparing tap and inject or early vitrectomy is inadequate to determine an optimal treatment strategy.

Keywords Antivascular endothelial growth factor · Corticosteroids · Injection-related endophthalmitis · Intravitreal injection

Extended author information available on the last page of the article

Introduction

Intravitreal injections (IVI) are one of the most common treatment modalities in modern retina practice globally. Strong clinical studies have demonstrated that treatment of chorioretinal vascular diseases including neovascular age-related macular degeneration (ARMD), diabetic retinopathy (DR), and retinal vein occlusion (RVO) with antivascular endothelial growth factor medications (anti-VEGF) such as bevacizumab, ranibizumab, aflibercept, and brolucizumab results in dramatic improvements in visual acuity results [1–4]. Intravitreal corticosteroids such as triamcinolone (IVTA) and dexamethasone are effective for the treatment of non-infectious uveitis as well as macular edema of multiple etiologies [5, 6]. Over the past decade, based on both their efficacy and relative safety, these drugs have supplanted laser therapies and surgeries as the mainstay of treatment for various retinal disorders.

However, intravitreal injections are associated with potential complications such as cataract, intraocular pressure elevation, retinal vascular occlusion, ocular hemorrhages and inflammation, retinal vasculitis, and infection [7]. Injection-related endophthalmitis (IRE) is one of the most devastating and feared complications. Although it is a rare event, due to the high volume of intravitreal injections performed, IRE represents 8.5–11% of endophthalmitis cases in tertiary referral centers [8, 9]. As the number of intravitreal injections performed yearly continues to increase, retinal specialists are ever-more likely to encounter this complication. Thus, the purpose of this article is to review the various factors that could potentially influence the risk of IRE and discuss evidence-based strategies for management.

Methods

A PubMed database query was performed using search terms “intravitreal injection” and “endophthalmitis” from the period of 1995–2021. Relevant articles were reviewed and their references served as a further source of additional studies. Selected articles were analyzed with respect to the incidence, potential preventive factors, clinical presentation, microbial profile, management, and outcomes for IRE.

Results

Clinical characteristics

Broadly, IRE associated with either anti-VEGF or steroid injections can present as a noninfectious/sterile inflammation

or a vision threatening infectious endophthalmitis. Infectious endophthalmitis is characterized by pronounced anterior and posterior chamber inflammation with pain (74%), hypopyon (86%), conjunctival injection (82%), and decreased vision (94–100%) present in the majority of cases (Fig. 1) [8, 11, 12]. Symptom onset is between 1 and 6 days after injection with patient presentation at a mean of 3–4 days [8, 11–13]. While 80% of patients present with vision worse than 20/100, presenting visual acuities in one large study varied between 2080 to hand motion [8]. Intravitreal antibiotics remain the mainstay of treatment for infectious endophthalmitis, although, as will be discussed later, some cases may warrant vitrectomy surgery.

While some cases of sterile endophthalmitis may mimic infectious IRE, others are characterized by a milder intraocular inflammation and relatively preserved vision. Symptoms present 1–7 days after the injection with the mean time to presentation in a multi-center study at 2.6 days [11, 14–16]. Common symptoms include floaters (60%) and blurred vision (93%) with hypopyon (4%), conjunctival injection (10%), and fibrin (3%) occurring significantly less often than in infectious endophthalmitis (Fig. 2) [15, 17]. Pain was reported in 44% of cases but was characterized as severe pain in only 6%, usually in cases associated with a more vigorous anterior chamber inflammation and vitritis [15, 17, 18]. Sterile endophthalmitis can often be treated with topical steroids alone with relatively good visual acuity results [15, 17, 19]. In a prospective study, 73% of sterile IRE cases returned within 2 lines of baseline visual acuity (VA), in comparison to 53% of infectious cases [20].

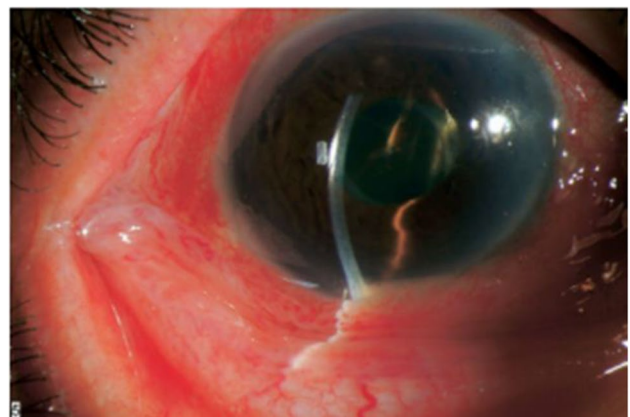


Fig. 1 Eye with infectious endophthalmitis after intravitreal triamcinolone acetonide (IVTA) injection. Note the hyperemia and chemosis of the conjunctiva. The anterior chamber (AC) is hazy attributable to inflammatory cells with associated fibrin and a yellow-white hypopyon. Reprinted from Roth and Flynn [10], Copyright (2008), with permission from Elsevier



Fig. 2 Eye with noninfectious endophthalmitis after IVTA injection. Note the yellow-white nature of the hypopyon with some associated hemorrhage in the inferior angle. Some conjunctival hyperemia is present, but this may often be absent. Reprinted from Roth and Flynn [10], Copyright (2008), with permission from Elsevier

An additional entity, termed pseudo-endophthalmitis, has been described following intravitreal triamcinolone injections. In pseudo-endophthalmitis, chalky white crystals of triamcinolone acetonide accumulate as a pseudo-hypopyon in the anterior chamber (Fig. 3). Pseudo-hypopyon occurs commonly in association with posterior capsule defects but can be differentiated from a true hypopyon by its white color (in contrast to off white in infectious cases) and shifting location with head tilt [21]. Pseudo-endophthalmitis usually presents within a few hours to 3 days following injection, generally is not associated with pain or other signs of intraocular inflammation, and tends to resolve within a few days to weeks without active intervention [21–23].



Fig. 3 Eye with pseudoendophthalmitis after IVTA injection. Note the chalk-white pseudohypopyon attributable to the collection of triamcinolone crystals in the AC. A dusting of the crystals on the corneal endothelium in the absence of fibrin can often be seen. Reprinted from Roth and Flynn [10], Copyright (2008), with permission from Elsevier

Given the considerable overlap of features, relying purely on clinical exam to distinguish infectious versus sterile IRE can be difficult [11, 24]. Nelson et al. have reported atypical cases of infectious bacterial IRE presenting as late as 2 weeks after injection without pain or conjunctival injection as well as noninfectious cases presenting with significant pain and vision loss [25]. It should be noted that even in cases of clinically suspected infectious IRE, aqueous and vitreous sampling isolates a causative organism in only 30–60% of cases [11, 13, 24, 26]. Thus it seems prudent to approach every case of IRE with a high level of suspicion and low threshold for intervention.

Incidence of IRE

With anti-VEGF agents

The reported per-procedure incidence of endophthalmitis following intravitreal injection of anti-VEGF agents varies from 0.016 to 0.083% [20, 24, 26–34]. Meta-analyses by Fileta et al. and McCannel et al. have reported incidences of 0.056% (197 in 350,535) and 0.049% (52 in 105,536), respectively [29, 30]. While the per-procedure IRE rate is low, it is important to remember that most patients require repeated treatments each of which carries a risk. In one study, the cumulative per-patient risk increased from 0.0055 to 0.843% as the injection number grew from 10 to 60 [20].

Most studies have found no difference in the rate of IRE when comparing individual anti-VEGF agents. A retrospective cohort study by Rayess et al. reported a similar low rate of endophthalmitis with bevacizumab (0.039%), ranibizumab (0.035%), and aflibercept (0.035%) [26]. A recent database compiled from Jan 1, 2006, to Nov 30, 2016, by Fight Retinal Blindness (FRB) estimated an incidence of 0.020% per injection (1/4897) and reported no difference in infectious endophthalmitis rates between each of the 3 commonly used agents (bevacizumab 0.020%, ranibizumab 0.021%, aflibercept 0.020%) [20]. However, this study revealed a higher rate of noninfectious endophthalmitis with bevacizumab compared to ranibizumab and aflibercept, a finding they attributed to irregularities in bevacizumab preparation by compounding pharmacies.

Conversely, a recent retrospective cohort study of over 800,000 anti-VEGF injections reporting an overall low incidence rate for IRE (0.061%) found a significantly increased rate associated with aflibercept (0.1%) when compared to bevacizumab (0.056%) and ranibizumab (0.047%) [34]. It is important to highlight that this retrospective study did not distinguish between infectious and non-infectious endophthalmitis. Of 498 subjects diagnosed with endophthalmitis in this study, only 192 were treated with intravitreal antibiotics within the first 2 weeks, suggesting that the majority of reported cases were felt to be sterile or non-infectious. No

differences in initial anti-VEGF treatment medication were found amongst the subjects treated with intravitreal antibiotics, suggesting that infectious cases were relatively equally distributed between agents. Another large retrospective case series reported a significant difference in sterile IRE rates between medications (bevacizumab 0.10%, ranibizumab 0.02%, aflibercept 0.16%) [27]. Sterile endophthalmitis with anti-VEGF medications can occur in eyes that have

previously tolerated injections, and in one report, eyes suffering sterile IRE with bevacizumab were unlikely to have a recurrence with subsequent injections [19].

The recently approved anti-VEGF medication brolucizumab has been associated with post-injection intraocular inflammation (IOI) including potentially severe occlusive retinal vasculitis (Fig. 4). Post-hoc review of 2 large phase 3 studies of patients treated for ARMD revealed “definite/

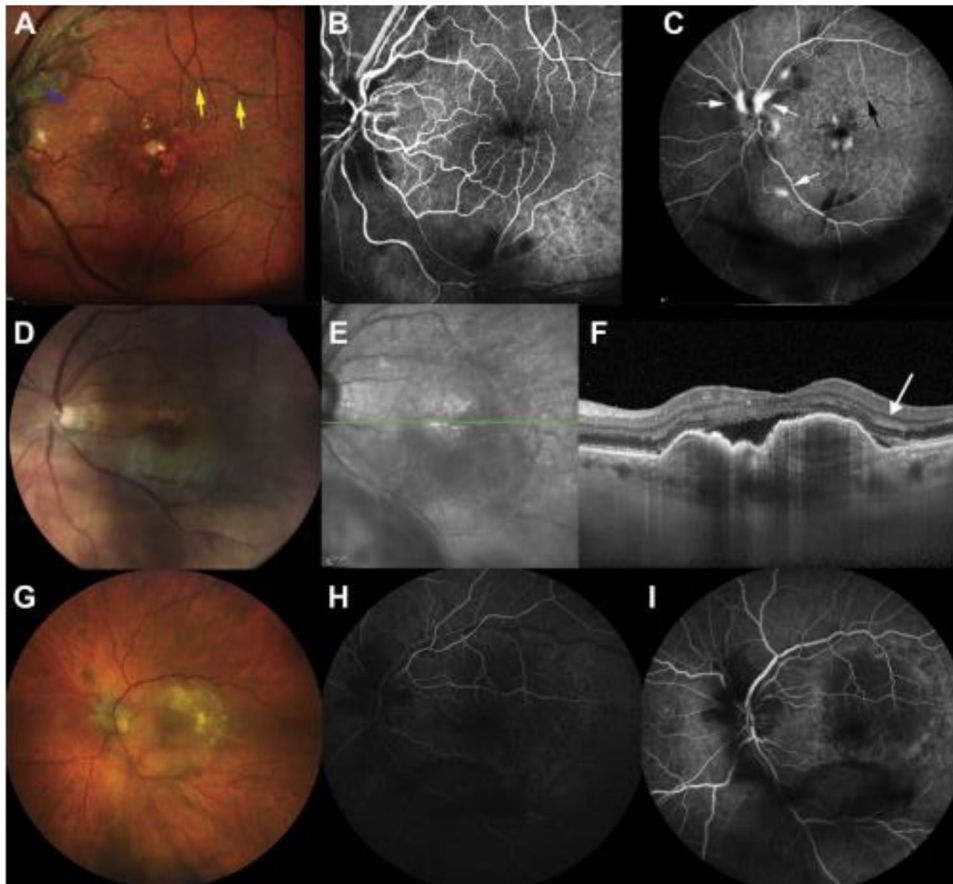


Fig. 4 Three representative cases demonstrating the spectrum of ocular findings related to IOI and occlusive retinal vasculitis. Case 1 (A–C): An 88-year old woman was diagnosed with retinal vasculitis in her left eye at 6 weeks after bilateral intravitreal brolucizumab injection. Color fundus photograph (A) reveals multiple intra-arterial foci of gray material (yellow arrow) and retinal whitening extending from the optic nerve along the superotemporal arcade (blue arrow). Fluorescein angiography (B early, C late) shows delayed flow along the inferotemporal arcade, with late focal staining of the retinal arteries (white arrow). A region of nonperfusion is noted superior to the fovea (black arrow) corresponding to the foci of intra-arterial gray material in 2A. Case 2 (D–F): An 80-year-old woman presented with reduced vision and a superior scotoma at 7 days after her second brolucizumab injection. Fundus photograph (D) shows retinal whitening involving the inferior macula, arterial sheathing, and focal interruptions of the blood column within an inferotemporal macular branch retinal artery. Near-infrared (E) and OCT (F) show subretinal fluid that was improved from prior OCT evaluations and intraretinal

foci of hyperreflectivity (white arrow). Case 3 (G–I): A 75-year-old woman had persistent subretinal fluid despite 18 previous anti-VEGF injections (14 aflibercept/4 ranibizumab), comprising the reason to switch to brolucizumab. She presented with floaters and reduced vision and was diagnosed with IOI and occlusive retinal vasculitis 30 days after her first brolucizumab injection. Fundus photograph (G) shows multiple cotton wool spots around the optic nerve and perimacular and subtle periarterial whitening. There is some vitreous opacity along the inferotemporal arcade. Fluorescein angiography (H, early 28 s) shows globally delayed retinal arterial filling, notable around the optic nerve. At 68 s (I), there remains delayed arterial filling around the optic nerve and inferiorly, and blockage from vitreous opacity. A to C courtesy of Haug et al. and D to G courtesy of Bauman et al. Reprinted from *Ophthalmology Retina*, 5(6), Bauman CR, Bodaghi B, Singer M et al. Expert Opinion on the Management of Intraocular Inflammation, Retinal Vasculitis, and Vascular Occlusion after Brolucizumab Treatment, 519–527, Copyright (2021), with permission from Elsevier

probable drug related” IOI in 50 of 1088 (4.6%) brolicuzumab-treated patients as compared to 1.1% of aflibercept-treated patients [35]. In 8 of 1088 (0.74%) brolicuzumab patients, IOI and retinal vasculitis resulted in moderate vision loss of greater than 15 ETDRS letters. Older patient age, female gender, and history of diabetes have been identified as potential risk factors for brolicuzumab-related IOI [36]. Mean time to diagnosis in a retrospective analysis of 15 eyes of 12 patients was 30.3 days (range 7–56 days) after injection [37]. An expert panel recommended discussion of this possible risk with patients prior to treatment with brolicuzumab and clinical exam with widefield photography and angiography where available of any patient with floaters or eye pain lasting more than 2 days after injection or with vision loss or photophobia at any point post-treatment [38]. Patients in whom clinical exam reveals sterile IOI should be immediately started on topical corticosteroids that can be supplemented with subtenons, intravitreal, or systemic corticosteroids based on the severity of inflammation and treatment response.

Various factors have been suggested to explain sterile IRE post anti-VEGF injection including patient specific (development of antibodies after repeated exposure, retinal disease related compromise of the blood-retinal barrier, and history of intraocular or systemic inflammatory disease), delivery specific (silicone oil in syringes, syringe agitation, inconsistencies in medication handling), and medication specific (contamination with bacterial endotoxin, medication impurities, formulation, and presence of potentially pro-inflammatory Fc portion of antibody) [14, 16]. Clusters of sterile IRE related to breakdowns of the manufacturing process, as was the case in an outbreak due to bacterial endotoxin contamination, have been reported [39]. Melo et al. suggested a potential role for silicone oxide used in medication syringes, and improper medication storage and handling have also been implicated [40]. As per the manufacturer’s guidelines, anti-VEGF medications should be stored between 2 and 8 °C, protected from light, stored in original cartons, and used within 8 h [14]. Any variation from the above could provoke an immunological reaction. Finally, it has been suggested that immunogenicity of the Fc portion of bevacizumab and aflibercept may account for higher rates of sterile IRE with these medications than ranibizumab [16, 17, 27, 41].

With corticosteroid agents

Several studies may lend support to the concern that the anti-inflammatory and immune-suppressive properties of corticosteroids may result in a higher risk of infectious endophthalmitis with intravitreal steroids in comparison to anti-VEGF medications. Bhavsar et al. reported an IRE

incidence of 0.05% using triamcinolone in the DRCR.net and SCORE clinical trials [42]. A medical claims database review by Vanderbeek et al. found an IRE odds ratio 6.92 times higher in the triamcinolone group than the anti-VEGF group [43]. The definition used for IRE in this study (a clinical diagnosis of IRE and subsequent treatment with intravitreal antibiotics and/or vitrectomy) suggests that many cases were severe enough to warrant concern for infectious IRE. The authors also proposed that in addition to their immunosuppressive qualities, the larger needle gauge used for steroid injections could contribute to a greater risk of infectious endophthalmitis, as a larger penetration size offers more chance of infiltration by microorganisms.

Sterile IRE also may be a more common complication of steroids than anti-VEGF medications. Fong et al. reported sterile IRE in 10 of 81 (12.3%) eyes treated with intravitreal triamcinolone [44], whereas Maia et al. found a non-infectious IRE rate of 1.2% with preservative free triamcinolone and 7.3% with preserved medication [45]. While some authors have postulated benzyl alcohol preservatives as the etiology of sterile post steroid IRE [46], an interventional case series by Dodwell et al. showed a higher endophthalmitis rate with Triesence® (preservative free triamcinolone acetate) than Kenalog® (preserved triamcinolone) thus calling into question this supposition [47]. This study instead suggested smaller particle size and higher particle load as contributors to steroid-related sterile endophthalmitis. On a similar note, Lorenzo et al. reported sterile endophthalmitis with preservative free triamcinolone [48].

Based upon condition being treated

As both diabetes and advanced age are conditions associated with relative immunosuppression, there has been concern whether patients with these characteristics may be at higher risk of IRE. A multicenter, retrospective case–control study comparing patients treated for neovascular AMD, diabetic eye disease, and RVO reported a statistically significantly lower rate of IRE in RVO (0.012%) than AMD and diabetic eye disease (0.040% vs. 0.049%) [49]. Similarly, a recent case–control study indicated diabetes as a significant risk factor for post vitrectomy endophthalmitis [50].

Microbiologic spectrum

Differences when compare to post-surgical endophthalmitis

Similar to post-cataract surgery infection, the most common microorganism isolated in culture proven IRE is coagulase-negative *Staphylococcus* [30, 51]. Other less common organisms including *Streptococcus species*, *Staphylococcus*

aureus, *Haemophilus influenzae*, *Enterococcus faecalis*, and *Bacillus* species have been reported [52]. In 2016, a retrospective analysis reported isolated rare microorganisms like *Corynebacterium*, *Escherichia coli*, *Neisseria*, *Enterobacter cloacae*, and *Lactococcus garvieae* as causes [8].

The incidence of *Streptococcus* species is three times higher in IRE than in post-surgical infection [30, 51–53]. Various studies have found that IRE cases associated with *Streptococcal* species found in oropharyngeal flora (*S. viridans* and *S. pyogenes*) present earlier, follow a more aggressive course, and are associated with worse visual outcomes [51, 53, 54] (Table 1). In line with this association, a retrospective analysis conducted over a period of 10 years demonstrated that due to the severity of clinical presentation, patients with endophthalmitis due to *Streptococcus* species were more likely to require vitrectomy surgery as part of their management and had worse visual outcomes [52]. In a retrospective case series conducted by Goldberg et al., an outbreak of infection caused by *Streptococcus mitis/oralis* resulted in 7 of 12 patients (58%) requiring enucleation or evisceration by 1 year follow-up [55]. A multicenter, retrospective study of 56 IRE cases from 168,247 anti-VEGF injections revealed that patients with infections related to *Streptococcus* species were significantly less likely to return to baseline visual acuity than culture-negative or *Staphylococcus*-related cases [56].

Review of preventive strategies (Table 2)

Antisepsis with betadine versus chlorhexidine

The use of 5% povidone iodine (betadine) applied directly to the conjunctival surface and lid margins is the most established strategy to prevent ophthalmic procedure-related infections [57]. One study showed that 30 s of contact time is sufficient to significantly reduce the conjunctival bacterial load [58], and others have established betadine's effectiveness against gram-positive and gram-negative bacteria as

well as viruses and fungi [59]. As betadine does not alter the ocular flora even with repeated exposure, the incidence of bacterial resistance is minimal [60]. While topical irritation from betadine is common, true allergy to povidone iodine is quite rare. Anaphylactic reactions to povidone following exposure to open wounds or mucous membranes have been described, but never in association with an ophthalmic procedure [61]. In a survey of injection practice patterns, almost 60% of retinal specialists used betadine even in patients with self-reported allergy [63].

Since betadine use is associated with post-procedure conjunctival irritation, corneal epitheliopathy, and pain, clinicians have investigated alternative antiseptic treatments. A retrospective study of chlorhexidine 0.1% reported a similar (0.023%) IRE incidence as povidone iodine, with a decrease in average procedure-related pain score (3 of 10 vs. 8 of 10) [62]. A retrospective, multicenter case series comparing 0.05% or 0.1% chlorhexidine reported a very low rate of endophthalmitis of 0.0074% [63]. Though chlorhexidine is an effective potential alternative to povidone iodine, due to concerns over possible reduced susceptibility of methicillin-resistant *Staphylococcus aureus* (MRSA) and potential for development of resistance to chlorhexidine, povidone iodine remains the antiseptic of choice in ocular practice [64]. Based on our clinical experience and patient feedback, a saline rinse of excess betadine from the ocular surface and fornices after the injection results in decreased post-procedure irritation and discomfort, although this finding was not verified in a small trial of 21 patients [65].

Existing ocular conditions

Treatment of pre-existing eye conditions such as blepharitis that could lead to contamination of the injection site is recommended prior to injection [66]. A case control study from 2012 identified blepharitis as a significant risk factor for IRE [13]. When preparing the eye for injections, topical antiseptic should be applied to the conjunctiva, eyelids, and lashes, but scrubbing of the lids should be avoided due to the

Table 1 Vision outcomes based on organism in selected studies

Organism	Final VA \geq 20/40	Final vision \leq 20/200	Final vision within 2 lines of baseline
Coagulase negative staphylococcus	7/50 (14%)	23/50 (46%)	18/38 (47%)
Other staphylococcus species	4/14 (29%)	7/14 (50%)	8/13 (62%)
Streptococcus species	1/11 (9%)	8/11 (88%)	1/9 (11%)
Other*	0/7 (0%)	4/7 (57%)	3/4 (75%)
Negative culture	3/52 (6%)	18/52 (37%)	22/38 (58%)
Total	15/134 (11%)	60/134 (45%)	52/102 (51%)

*Other—*Enterococcus faecalis* (2), *Corynebacterium* (2), *Serratia marcescens* (1), *Acinetobacter calcoaceticus* (1), *Pseudomonas* (1)

Data included from Mezd-Koursch 2010 [12], Chaudhary 2013 [125], Mithal 2013 [136], Meredith 2015 [28], Cunningham 2017 [137], Raman 2016 [137], Sachdeva 2016 [8], Mishra 2018 [139], Dar 2020 [141]

Table 2 Intravitreal injection procedure recommendations from (a) 2014 US and (b) 2018 European expert panels

a.

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

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b.

Subject	Recommendations
Clinical setting for IVI	Operating theater, adequate room or in-office setting
Anesthetics	Topical anesthesia No recommendation for a specific substance or technique
Topical antiseptics	Topical administrations of 5% povidone-iodine over at least 30 s into the conjunctival sac. Chlorhexidine for patients with local irritation due to povidone-iodine
Perioperative antibiotics	Not recommended
Pupil dilation	No concluding recommendation, but it might be advisable for beginners in order to be able to immediately examine the retinal vessel perfusion after IVI
Globe softening	No recommendation Might be considered in vulnerable eyes
Lid speculum	Sterile speculum is recommended
Needle gauge and length	30-gauge or thinner needles are recommended for liquid injections whereas larger needles should be used when necessary
Injection location	Inject through the pars plana, between 3.5 and 4 mm from the limbus Switch injection sites if patients receive repeated IVI
Feasibility of bilateral injections	Handle each injection as separate procedure
Gloves/draping	Gloves are recommended Draping may not be essential
Use of facial masks	Face masks recommended

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risk of expression of potentially infectious materials from the meibomian glands.

Lid speculum vs. eyelid retraction

A variety of methods can be used in order to retract the eyelids and potentially decrease the risk of lid and lash flora contaminating the injection site. According to a 2019 survey of US retina specialists, the majority favor the use of a lid speculum [67], although patient discomfort associated with metal lid speculums potentially explains a recently reported trend toward other lid retraction techniques [68, 69]. Alternative methods for lid retraction include unimanual or bimanual two-person techniques, use of cotton tipped applicators, and Desmarres lid retractors [70–73]. Fineman et al. found no difference in the infection rate using a bimanual lid retraction method in comparison to a conventional lid speculum [71]. In light of these findings, physician and patient preference should dictate the choice of lid retraction techniques.

Antibiotic prophylaxis

Numerous studies have concluded that topical antibiotic prophylaxis is not only ineffective in preventing IRE but may actually increase the incidence of post injection infection [74–76]. A meta-analysis by Rebaldi et al. reported an incidence of IRE 3 times higher with post injection topical antibiotic prophylaxis and postulated that the emergence of resistant bacterial strains may contribute to higher infection rates [76]. Repeated short courses of topical antibiotics such as would be used following intravitreal injections have been demonstrated to alter the antibiotic resistance patterns of conjunctival flora [77]. In a randomized study of eyes treated with topical antibiotics following repeated injections, resistance to fluoroquinolones reached 67–85% by the end of 1 year [78]. Based on this data, retinal specialists have changed their practice, with a recent survey revealing that only 10.9% use pre-injection antibiotics and 16.6% use antibiotics post-injection, a substantial decline from the findings of a similar 2011 survey [69, 79].

Office vs Operating Room (OR) setting

Surveys have revealed geographic differences in preferred injection setting, with an OR setting predominant in most of Europe versus primarily an office-based setting in the USA [80]. Theoretical advantages of an OR setting for intravitreal injections include superior air circulation potentially resulting in better sterility. A large multicenter study from Europe reported a very low rate of endophthalmitis (0.0074%) in an OR setting [81]. A comparative study by Tabandeh et al. reported similar low rates of endophthalmitis in an OR (0.065%) and office-based (0.035%) setting [80]. A meta-analysis of 31 studies including 1,275,815 anti-VEGF injections found no difference in IRE rates between the 2 settings (0.03% office vs. 0.02% OR), although there was a higher rate of culture-positive IRE in the office than OR [82]. In consideration of the potential additional time, administrative effort, and cost associated with OR-based procedures, office-based injections appear to be safe and may be logistically simpler in light of the growing number of intravitreal injections performed every year.

Hand hygiene, antisepsis, and use of gloves

Hand hygiene and antisepsis are a prerequisite before any surgical procedure. As per the guidelines of an expert retina panel, gloves and hand hygiene should constitute essentials of retina practice [66]. While alcohol-based antiseptics have better antimicrobial efficacy than aqueous based products [83, 84], to our knowledge no study has identified hand antisepsis as an independent risk factor for post-injection infection. While a recent US survey reported that the majority of surgeons use gloves every time they inject [67], there is no clear consensus as to the necessity of sterile gloves or if clean gloves suffice. Bhavsar et al. reported a low rate of endophthalmitis even with gloves that were not sterile [42]. As long as the hand does not contact the needle or the ocular surface injection site, we suggest that clean, non-sterile gloves are adequate.

Masks

There is no uniform consensus among retina specialist regarding the use of face masks during intravitreal injection procedures in an office-based setting. A recent survey reported 32.9% of retina specialist wear a mask and two-thirds of those who do not wear a mask follow a “no-talking” policy [69]. Expert panels from both the USA and Europe have recommended the use of surgical masks or a “no-talking” policy to minimize the risk of IRE [66, 85].

Due to the association of oral flora pathogens with IRE, several studies have analyzed the role of face masks or a “no-talking” policy as preventive measures [30, 86–90]. A recent

retrospective cohort study found similar low rates of IRE whether face masks (9/30,162, 0.0298%) or “no-talking” (168/453,460 0.0371%) were employed [89]. While there were fewer cases of oral-flora associated IRE in the face mask group, this finding failed to meet statistical significance ($p=0.302$). A large study investigating the changes in IRE incidence over a 9-year period indicated that adoption of a “no-talking” policy resulted in a trend towards decreased IRE incidence [90].

Other studies, however, have postulated that surgical masks may represent a possible source of bacterial shedding with the potential to increase infections [91]. The universal face mask policies instituted during the COVID-19 pandemic have offered a real-world scenario to test this hypothesis. Several recent studies demonstrated an increase in bacterial dispersion from the superior edge of a patient’s mask towards the injection field, potentially increasing the incidence of IRE [92, 93]. However, a multicenter retrospective study of over 210,000 injections performed with both physician and patient masked revealed an IRE rate (0.0213%) comparable to that of the no face mask control group (0.0289%) [94]. A lower incidence of culture positive endophthalmitis was reported in “universal face mask group” compared to “no mask group” ($p=0.041$). In a subset of patients amounting to 9% of total injections, adhesive tape applied to the superior portion of the mask did not significantly alter the endophthalmitis risk but was associated with no cases of oral pathogen-related endophthalmitis.

Based on this data, we feel that both physician masking and the use of a “no-talking” policy are effective preventive strategies to decrease the risk of IRE. Patient masking does not appear to influence the rate of IRE, and as the COVID-19 pandemic continues, we would advocate for the continued use of face masks to decrease the spread of disease.

Prefilled syringes

The US Food and Drug Administration (FDA) has approved prefilled syringes (PFS) of both ranibizumab and aflibercept for intravitreal use. Prefilled syringes are packaged in a single use, sterile sealed tray with a sterile cap, eliminating several steps in drug preparation. These measures not only reduce injection procedure time but also potentially allow for more precise drug dosing [95, 96]. PFS may reduce the chance of air or silicone oil bubble injection into the vitreous cavity, diminishing the likelihood of visually troubling floaters [97].

The prefilled sterile drug delivery system decreases the likelihood of contamination during preparation, thereby decreasing the risk of IRE. In a recent multicenter retrospective cohort study, the use of the ranibizumab PFS resulted in a statistically significant decrease in culture-positive endophthalmitis rates compared to conventional preparation (odds

ratio 0.19; 95% confidence interval 0.045–0.82; $p = 0.025$) [98]. This study found no cases of oral flora-associated endophthalmitis when using the ranibizumab PFS in over 78,000 injections.

Same day, bilateral injection

ARMD and DR are commonly bilateral diseases with many patients requiring injections in both eyes. In many cases, in order to reduce both the patient and physician visit burden, one can consider same day, bilateral injections. According to a survey conducted in 2019, 45% of US retinal physicians “always perform bilateral injections the same day if necessary” [67]. A retrospective study of almost 5000 same day, bilateral injections reported a low rate (0.01%) of endophthalmitis with no cases of bilateral infection [99]. A larger retrospective cohort study of over 50,000 same day, bilateral injections demonstrated a low incidence of unilateral endophthalmitis (0.027%) comparable to previous studies reporting unilateral injections, no cases of bilateral endophthalmitis, and no patient with more than one episode of endophthalmitis [100]. We recommend that when performing same day bilateral injections, each eye should be treated as a separate procedure, with no instruments or materials reused, and whenever possible, separate drug lots for each eye.

Anesthesia

A recent systematic review found no gold standard for anesthesia with respect to patient comfort during the intravitreal injection procedure [101]. A second systematic review of 847 patients in 8 studies described pain associated with intravitreal injections as “mild” (visual analog scale rating 5–44 mm). While a single included study found a significant pain reduction using subconjunctival lidocaine vs. topical proparacaine or lidocaine gel, the authors stated that no single method of anesthesia could be considered superior [102]. Both topical and subconjunctival anesthetics offer effective pain control, and the choice of anesthetic used is largely made by physician or patient preference. Commonly used topical anesthetics include lidocaine, proparacaine, and tetracaine which can be used in both drop and gel forms. Lidocaine can also be used as subconjunctival injection.

Topical gel anesthetics have been hypothesized to serve as a barrier to penetration of topical antiseptics, potentially interfering with the antibacterial effect of betadine [103]. A retrospective cohort study concluded the use of topical gel anesthesia as an independent risk factor for IRE [104]. Inman et al. proposed application of povidone iodine before and after gel anesthesia in order to reduce the incidence of endophthalmitis [105]. While one report demonstrated that the pre-application of povidone iodine before gel anesthesia did not impact endophthalmitis rates, this study included

only 8802 injections and thus likely was underpowered to reveal a true effect [106]. A recent survey reported application of povidone iodine both before and after gel anesthesia by half of topical gel users [69]. Beyond its anesthetic effect, lidocaine may offer the additional benefit of antibacterial activity, as a study by Tustin et al. demonstrated the potential antimicrobial activity of 2% lidocaine against common endophthalmitis organisms including *S. aureus*, *S. epidermidis*, and *S. viridans* [107].

Use of compounded medicines

Bevacizumab is not FDA approved for use in the eye and is used as an off-label drug in treatment of chorioretinal vascular disease. It undergoes an extra step of compounding in pharmacies where it is repackaged into syringes for individual use. As discussed before, extra steps during medication preparation allow for potential contamination and hence pose a threat for endophthalmitis. Of particular concern is the potential for endophthalmitis “outbreaks” associated with contaminated compounded medication lots. Xu et al. have reported one such case, where 24 patients injected on a single day with contaminated bevacizumab developed *Streptococcal* endophthalmitis, with over 90% losing significant vision at the end of 3 months follow-up [108]. In another case series described by Goldberg et al., multiple violations of sterile technique were found in a subsequent FDA investigation of the compounding pharmacy supplying the medication [55]. Small et al. reported cases of fungal endophthalmitis caused by *Bipolaris hawaiiensis*, a dematiaceous fungus, in 23 of 25 (92%) eyes following injection with triamcinolone derived from a compounding pharmacy [109]. While such clusters are certainly frightening, there remains good evidence that compounded drugs, when made using appropriate technique, can be injected safely. Forooghian et al. used compounded preparations of bevacizumab, ranibizumab, and aflibercept for over 50,000 injections and reported low endophthalmitis rates (0.041%) with no significant difference between the three drugs [110]. While compounded anti-VEGF and steroids prepared in a sterile, aseptic manner appear safe for intravitreal injections, we would encourage the use of separate drug lots whenever possible for same day bilateral injections in order to minimize the already tiny risk of a devastating bilateral infection.

Management

Though the prevalence of IRE remains low, its potentially devastating effects require optimal management in order to achieve the best possible visual outcomes. This section summarizes the literature on management of IRE.

Lessons from the Endophthalmitis Vitrectomy Study

Currently there are no specific evidence-based protocols or prospective, controlled studies for the management of IRE. While it may be tempting to apply the results of the Endophthalmitis Vitrectomy Study (EVS), a multicenter randomized trial comparing tap and inject to immediate vitrectomy in the management of endophthalmitis post-cataract surgery and secondary IOL implantation, several key differences prevent this generalization [111]. The EVS demonstrated an advantage to early vitrectomy in post-cataract surgery endophthalmitis patients presenting with vision of LP or worse but similar results for both tap and inject and vitrectomy in patients with vision of HM or better. However, the EVS excluded patients with significant vision limiting eye disease that is common in patients requiring intravitreal injections. Additionally, vitrectomy techniques with small gauge instruments and widefield viewing systems have advanced significantly since the publication of the EVS in 1995. Finally, in cases of IRE due to *Streptococcus* species associated with a recognized more aggressive clinical course, early incorporation of vitrectomy with the potential to remove bacterial toxins and inflammatory debris has been postulated to potentially offer better outcomes. Thus, we cannot strictly extrapolate the EVS results to cases of IRE.

The EVS used empiric treatment with intravitreal vancomycin (1 mg/0.1 ml) and amikacin (0.4 mg/0.1 ml) for optimal coverage of both gram-positive and gram-negative bacteria and found no additional benefit to the use of systemic antibiotics. Given that gram-positive cocci, particularly coagulase negative *Staphylococci*, are the most frequent cause of post-procedure endophthalmitis, the use of vancomycin remains appropriate. A 2016 review study described only 27 cases over 25 years of culture-positive endophthalmitis caused by vancomycin-resistant bacteria including *Enterococcus*, coagulase negative *Staphylococcus*, *Staphylococcus aureus*, *Bacillus*, and *Streptococcus* [112]. A retrospective case series (2006–2016) reported all endophthalmitis-related isolates of *Staphylococcus epidermidis* to be sensitive to vancomycin [113]. Based on the results of retrospective studies, 93–95% of gram negative endophthalmitis isolates remain sensitive to amikacin. However, due to concerns regarding the possibility of macular infarction associated with intravitreal aminoglycosides, ceftazidime has largely supplanted the use of amikacin in the treatment of post-procedure endophthalmitis [114–116].

Although the EVS did not find a benefit associated with additional systemic ceftazidime and amikacin, the superior intraocular penetration of some new systemic antibiotics potentially calls this finding into question. A recent review article found that meropenem, linezolid, and high dose moxifloxacin all reach therapeutic levels in the vitreous after systemic administration and states that an empiric

combination of meropenem and linezolid would offer the bacterial spectrum to cover the majority of endophthalmitis pathogens [117]. Fluoroquinolone resistance rates as high as 40–60% for coagulase-negative *Staphylococcus* make moxifloxacin a less attractive systemic candidate in spite of good vitreous penetration [118]. Although there is no current randomized clinical trial evidence supporting the use of systemic antibiotics in post procedure endophthalmitis, it does appear to be a common practice, especially in Europe, where a 2019 retrospective study of practice patterns revealed that systemic antibiotics were employed as part of the treatment plan in two-thirds of cases of acute postsurgical and post-injection endophthalmitis [119].

In addition to systemic antibiotics, patients in the EVS also received systemic corticosteroids. Given the highly inflammatory nature of IRE, aggressive steroid therapy seems logical. In a retrospective review of 133 eyes treated for endophthalmitis, subjects receiving systemic corticosteroids were significantly more likely to regain 3 or more lines of vision [120]. In a second study, the use of systemic steroids as part of the treatment regimen in post-procedure endophthalmitis eliminated the need for eventual enucleation in severe cases [121]. However, in patients with IRE, many of whom are of advanced age or have comorbidities including diabetes, the health risks of systemic steroids must also be considered. The use of intravitreal steroids may limit these potential risks, although studies to date have been inconclusive about their benefits. A Cochrane review failed to find evidence favoring intravitreal corticosteroids for post-surgical endophthalmitis [122], and one randomized trial of 57 patients with post-cataract surgery endophthalmitis found worse visual outcomes in those receiving intravitreal steroids [123].

Review of available evidence (Table 3)

There are no prospective, controlled studies investigating management of IRE. In a retrospective study of 23 patients with presumed infectious post-injection endophthalmitis, treatment with immediate tap and inject resulted in a return to within 2 lines of baseline vision in 15 patients (78%) within 6 months [11]. Immediate vitrectomy of 30 eyes with IRE (within 6 h of diagnosis) resulted in excellent vision outcomes at 1 year (logMAR 0.63), approaching pre-infection levels (logMAR 0.55) [124]. Thus, both treatment options appear to offer the potential for visual recovery.

Studies comparing tap and inject to PPV are limited by small subject numbers and the potential for selection bias, whereby patients with a more aggressive clinical course may be more likely to undergo vitrectomy. Chaudhary et al.

Table 3 Outcomes of selected studies of TAI and PPV for treatment of IRE

Study	Treatment	Mean pre-injection VA (LogMAR)*	Mean presenting VA (LogMAR)*	Mean final VA (LogMAR)*	Complications	Other
Mezad-Koursch 2010 [12]	TAI: 5 PPV: 4	TAI: 0.63 PPV: 0.47	TAI: 1.8 PPV: 2.5	TAI: 1.0 PPV: 1.48	RD 2/4 (50%) PPV, 1/5 (20%) TAI Phacolytic glaucoma 1/4 (25%) PPV Recurrent endophthalmitis 1/4 (25%) PPV	3/5 (60%) TAI required secondary PPV All subjects culture-positive
Irigoyen 2012 [135]	TAI: 19	TAI: 0.79	TAI: 1.84	TAI: 1.04	RD 4/19 (21%) TAI	All initially treated with TAI 5/19 (26%) TAI had secondary PPV
Chaudhary 2013 [125]	TAI: 10 PPV: 13	TAI: 0.82 PPV: 0.65	TAI: 1.53 PPV: 2.33	TAI: 0.79 PPV: 1.28	RD 1/13 (8%) PPV	All patients initially treated with TAI PPVs performed 1–21 days post TAI due to worsening pain, vision, or inflammation, or for dense vitreous opacities Culture positive 1/10 (10%) TAI vs. 8/13 (62%) PPV
Mithal 2013 [136]	TAI: 1 PPV: 7	TAI: 0.6 PPV: 0.99	TAI: 1.0 PPV: 2.07	TAI: 0.5 PPV: 1.6	RD 1/7 (14%) PPV	Repeat vitrectomy in 2/7 (28%) PPV
Meredith 2015 [28]	TAI: 7 PPV: 4	TAI: 0.24 PPV: 0.2	Not reported	TAI: 0.86 PPV: 0.55	Not reported	Final acuity within 2 lines of pre-endophthalmitis acuity in 5/11 (55%) Timing of PPV (immediate vs. delayed) not reported
Raman 2016 [138]	TAI: 5 PPV: 8	TAI: 0.35 PPV: 0.85	TAI: 2.46 PPV: 2.45	TAI: 0.53 PPV: 1.1	Hypotony and cataract in 1/8 (13%) PPV	No statistical difference in change from pre-injection to final BCVA when comparing treatment groups
Cunningham 2017 [137]	TAI: 15 PPV: 6	N/A	TAI: 1.12 PPV: 1.24	TAI: 0.65 PPV: 1.05	1/6 (17%) PPV required enucleation due to <i>Serratia marcescens</i> 2 subjects (10%) with final vision NLP	4/15 (27%) TAI had secondary PPV No statistical difference in change from pre-injection to final BCVA when comparing treatment groups
Sachdeva 2016 [8]	TAI: 15 PPV: 1	TAI: 0.73 (N/A in 3) PPV: 0.3	TAI: 2.04 PPV: 1.9	TAI: 0.84 PPV: 2.3	Not reported	6/15 (40%) TAI had secondary PPV
Mishra 2018 [139]	TAI: 20 PPV: 7	TAI: 0.65 PPV: 0.64	TAI: 1.76 PPV: 1.80	TAI: 1.11 PPV: 1.18	RD 1/20 (5%) TAI NVG 1/20 (5%) TAI and 1/7 (14%) PPV	17/20 (85%) TAI had secondary PPV after mean 2 days (range 1–6 days)

Table 3 (continued)

Study	Treatment	Mean pre-injection VA (LogMAR)*	Mean presenting VA (LogMAR)*	Mean final VA (LogMAR)*	Complications	Other
Xu 2018 [32]	TAI: 29 PPV: 11	TAI: 0.5 PPV: 0.4	TAI: 2.2 PPV: 2.9	TAI: 0.9 PPV: 1.7	Not reported	No significant difference in BCVA at 6 months detected between TAI and PPV groups ($p=0.06$) Younger age and lower presenting IOP associated with better vision outcomes
Ho 2019 [140]	23 subjects Initial TAI followed by PPV within 72 h	N/A	3.07	1.42	Not reported	Inclusion criteria CF or worse vision at time of endophthalmitis diagnosis
Dar 2020 [141]	TAI: 2 PPV: 10	TAI: N/A PPV: 0.76 (N/A in 3)	TAI: 2.3 PPV: 2.11	TAI: 1.65 PPV: 1.80	Not reported	No statistically significant improvement in vision following treatment
Januschowski 2021 [124]	PPV: 30	PPV: 0.55	PPV: 1.66	PPV: 0.63	RD 1/30 (3%) PPV ERM 1/30 (3%) PPV	All subjects treated with PPV within 6 h of diagnosis No statistically significant difference between pre-injection and final BCVA

Abbreviations: VA visual acuity, TAI vitreous tap and injection of antibiotics, PPV pars plana vitrectomy, RD retinal detachment, NLP no light perception, BCVA bet corrected visual acuity, NVG neovascular glaucoma, IOP intraocular pressure, CF counting fingers, ERM epiretinal membrane

*When necessary, Snellen visual acuities (VA) were converted to logarithm of the minimum angle of resolution (LogMAR) scale, with “counting fingers” converted to 1.9, “hand motions” converted to 2.3, “light perception” converted to 2.7, and “no light perception” converted to 3

reported that 9 of 10 (90%) patients in their tap and inject group regained visual acuity within 1 line of baseline compared to only 6 of 13 (46%) in the vitrectomy group [125]. Of note, all patients in this study underwent initial tap and inject alone with the decision for subsequent vitrectomy made primarily on the basis of worsening vision, inflammation, or pain in spite of previous intravitreal antibiotic treatment. The authors admit the inherent selection bias of this retrospective study as well as the small subject number and make clear that their results do not support an assertion that tap and inject is superior to vitrectomy in disease management.

Similarly, Xu et al. detected no significant difference in vision results at the end of 6 months between their tap and inject and immediate (same day) PPV groups [32]. There was a trend towards both worse entering acuity (logMAR 2.9 vs. 2.2, $p=0.06$) and worse final acuity (logMAR 1.7 vs. 0.9, $p=0.06$) in the vitrectomy group, again indicating a potential selection bias. In this study, younger subject age and lower presenting intraocular pressure (IOP) were associated

with a better visual prognosis. Even in cases of Streptococcal post-injection or post-surgical endophthalmitis, a study failed to show benefit of early vitrectomy done within 48 h of presentation compared to tap and inject, with almost 25% of eyes requiring enucleation or evisceration [126]. It should be noted, though, that only 15 of 101 patients (14.9%) were treated with early vitrectomy in this retrospective study. A recent meta-analysis including IRE subjects from 5 retrospective case-series showed no difference in the likelihood of vision improvement with tap and inject versus PPV [127].

Recommendations

Prompt management of all patients with presumed endophthalmitis is mandatory. Patients presenting with any intraocular inflammation following an intravitreal injection should undergo a detailed eye examination to differentiate between infectious and sterile endophthalmitis. Cases clearly consistent with sterile inflammation based on clinical exam could be treated with steroids alone under close clinical

observation. In the absence of a robust clinical response, and certainly in the case of declining vision or worsening exam, the treatment plan should be adjusted to tap and inject or vitrectomy. In cases with an ambiguous clinical picture, we would recommend treatment for a presumptive diagnosis of infectious endophthalmitis.

Patients presenting with presumed IRE must undergo either tap and inject or PPV with intravitreal antibiotics as soon as possible. As currently available data does not indicate the superiority of either treatment modality, clinical judgement based on disease severity and timing should guide the treatment choice. One advantage of vitrectomy surgery is the consistent ability to obtain a vitreous specimen for culture and testing of antibiotic susceptibilities. In cases of tap and inject where a vitreous specimen cannot be obtained, an anterior chamber (AC) paracentesis may substitute, although the microbiologic yield is less reliable. In a UK study of post-cataract surgery endophthalmitis in which both vitreous and aqueous fluid were obtained, 53.4% of vitreous samples grew bacteria as opposed to only 25.7% of AC samples [128].

A recent study, however, raises questions regarding the utility of intraocular fluid culture results. Patel et al. reported that of 60 patients treated for IRE, in no case did culture results lead to change in the clinical management [129]. Rather, of the 6 patients requiring a change in clinical management (additional intravitreal antibiotics or progression to vitrectomy) within 2 weeks of initial treatment, all new treatment decisions were made on the basis of deteriorating clinical exam or vision. The study did report that vitreous culture results may serve as a prognostic factor, as culture-positive cases (especially those with oral flora) had significantly worse visual results than culture negative cases.

In cases that worsen in spite of initial treatment with tap and inject, the value of additional antibiotic injections is unclear. Vancomycin is known to maintain therapeutic levels in the vitreous for at least 3–4 days after initial injection, and additional injections may come with the risk of retinal toxicity [130]. We believe it is prudent to consider vitrectomy in cases that do not show significant improvement after initial antibiotic injection since the limited studies done to date have not proven an optimal treatment in this circumstance. Certainly, a frank discussion with the patient regarding the likely poor visual prognosis would be part of any treatment plan.

Need for continued injections post-IRE

After successful management of IRE in patients with AMD, studies report potential reductions in activity of the exudative disease process. In a retrospective report, 14% of eyes had no fluid recurrence post-endophthalmitis and 48% achieved a greater than 12-week recurrence free interval (as

opposed to only 8.3% prior to endophthalmitis) [131]. In a case series of 7 AMD patients, Kokame et al. reported that 5 of 7 had resolution of subretinal and sub-RPE fluid without the need for additional anti-VEGF injections post-infection [132].

Several theories have been proposed to explain the decreased exudative activity following endophthalmitis but the exact pathophysiology behind this phenomenon is still not clear. A shift in the inflammatory cytokine profile during infection may result in a more antiangiogenic vitreous environment with resulting regression of neovascular membranes [132]. In cases treated surgically, removal of the vitreous may reduce vitreomacular traction that has been linked to persistent CNV activity or may increase vitreous oxygen levels subsequently reducing ischemia-induced neovascularization [133].

Conclusion

In a 2012 editorial, Schachat et al. wrote that endophthalmitis following intravitreal injections should not be considered a “never event” [134]. They argued that to deem it as such would imply that cases of IRE are caused by substandard care. In fact, most recommendations regarding the safe performance of intravitreal injections are based at best on retrospective studies with their tendencies towards bias and more often on consensus reports from leaders in the retinal community. Given the rarity of IRE, designing adequately powered prospective trials to define “optimal” procedures would require huge and unrealistic sample sizes.

A review of the literature reveals consensus on several logical steps to ensure that IRE is at least a “seldom event.” The use of povidone iodine topical antiseptic, eyelid retraction away from the injection site, and avoiding treatment of eyes with active surface or eyelid disease all appear to be straightforward measures to limit the likelihood of IRE. Less consensus exists, however, on several other issues, including the use of face masks versus “no-talking” policies and optimal anesthetic technique, and there remains inadequate evidence comparing tap and inject or early vitrectomy as an optimal treatment strategy. Recognizing that it is likely impossible to fully eliminate IRE, one certain way to minimize its prevalence is to limit the number of intravitreal injections performed. In the future, more durable medications, depot systems, or even non-injection methods of medication administration may accomplish this goal. In the meanwhile, in light of the sight-saving nature of intravitreal injections, physicians and patients must strive to limit but also accept the small but real risk of infectious injection-related complications.

Declarations

Consent for publication This submission has not been published anywhere previously and is not simultaneously being considered for any other publication. This review article has not been presented at any meetings.

Conflict of interest The authors declare no competing interests.

References

- CATT Research Group TCR, Martin DF, Maguire MG et al (2011) Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 364:1897–1908. <https://doi.org/10.1056/NEJMoa1102673>
- Elman MJ, Qin H, Aiello LP et al (2012) Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: Three-year randomized trial results. *Ophthalmology* 119:2312–2318. <https://doi.org/10.1016/j.ophtha.2012.08.022>
- Nguyen QD, Brown DM, Marcus DM et al (2012) Ranibizumab for diabetic macular edema: Results from 2 phase iii randomized trials: RISE and RIDE. *Ophthalmology* 119:789–801. <https://doi.org/10.1016/j.ophtha.2011.12.039>
- Ogura Y, Roeder J, Korobelnik JF et al (2014) Intravitreal aflibercept for macular edema secondary to central retinal vein occlusion: 18-month results of the phase 3 GALILEO study. *Am J Ophthalmol* 158:1032–1038.e2. <https://doi.org/10.1016/j.ajo.2014.07.027>
- Jonas JB (2005) Intravitreal triamcinolone acetonide for treatment of intraocular oedematous and neovascular diseases. *Acta Ophthalmol Scand* 83:645–663
- Couch SM, Bakri SJ (2009) Intravitreal triamcinolone for intraocular inflammation and associated macular edema. *Clin Ophthalmol* 3:41–47. <https://doi.org/10.2147/OPHTH.S4477>
- Cox JT, Elliott D, Sobrin L (2021) Inflammatory complications of intravitreal anti-vegf injections. *J Clin Med* 10:1–16. <https://doi.org/10.3390/jcm10050981>
- Sachdeva MM, Moshiri A, Leder HA, Scott AW (2016) Endophthalmitis following intravitreal injection of anti-VEGF agents: long-term outcomes and the identification of unusual microorganisms. *J Ophthalmic Inflamm Infect* 6:1–7. <https://doi.org/10.1186/s12348-015-0069-5>
- Gupta A, Orlans HO, Hornby SJ, Bowler ICJW (2014) Microbiology and visual outcomes of culture-positive bacterial endophthalmitis in Oxford, UK. *Graefes Arch Clin Exp Ophthalmol* 252:1825–1830. <https://doi.org/10.1007/s00417-014-2658-7>
- Roth DB, Flynn HW Jr (2008) Distinguishing Between Infectious and Noninfectious Endophthalmitis After Triamcinolone Acetonide Injection. *Am J Ophthalmol* 146:346–347. <https://doi.org/10.1016/j.ajo.2008.04.037>
- Shah CP, Garg SJ, Vander JF et al (2011) Outcomes and risk factors associated with endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. *Ophthalmology* 118:2028–2034. <https://doi.org/10.1016/j.ophtha.2011.02.034>
- Mezad-Koursh D, Goldstein M, Heilwail G et al (2010) Clinical characteristics of endophthalmitis after an injection of intravitreal antivascular endothelial growth factor. *Retina* 30:1051–1057. <https://doi.org/10.1097/IAE.0b013e3181cd47ed>
- Lyall DAM, Tey A, Foot B et al (2012) Post-intravitreal anti-VEGF endophthalmitis in the United Kingdom: Incidence, features, risk factors, and outcomes. *Eye* 26:1517–1526. <https://doi.org/10.1038/eye.2012.199>
- Wickremasinghe SS, Michalova K, Gilhotra J et al (2008) Acute Intraocular Inflammation after Intravitreal Injections of Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration. *Ophthalmology* 115:1911–1915. <https://doi.org/10.1016/j.ophtha.2008.05.007>
- Greenberg JP, Belin P, Butler J et al (2019) Aflibercept-Related Sterile Intraocular Inflammation Outcomes. *Ophthalmol Retin* 3:753–759. <https://doi.org/10.1016/j.oret.2019.04.006>
- Anderson WJ, da Cruz NFS, Lima LH et al (2021) Mechanisms of sterile inflammation after intravitreal injection of antiangiogenic drugs: a narrative review. *Int J Retin Vitre* 7:37. <https://doi.org/10.1186/s40942-021-00307-7>
- Hahn P, Chung MM, Flynn HW et al (2015) Postmarketing analysis of aflibercept-related sterile intraocular inflammation. *JAMA Ophthalmol* 133:421–426. <https://doi.org/10.1001/JAMAOPHTHALMOL.2014.5650>
- Agrawal S, Joshi M, Christoforidis JB (2013) Vitreous inflammation associated with intravitreal anti-VEGF pharmacotherapy. *Mediators Inflamm* 2013:94309. <https://doi.org/10.1155/2013/943409>
- Chong DY, Anand R, Williams PD et al (2010) Characterization of sterile intraocular inflammatory responses after intravitreal bevacizumab injection. *Retina* 30:1432–1440. <https://doi.org/10.1097/IAE.0b013e3181dc04da>
- Daien V, Nguyen V, Essex R et al (2018) Incidence and Outcomes of Infectious and Noninfectious Endophthalmitis after Intravitreal Injections for Age-Related Macular Degeneration. *Ophthalmology* 125:66–74. <https://doi.org/10.1016/j.ophtha.2017.07.005>
- Moshfeghi AA, Scott IU, Flynn HW, Puliafito CA (2004) Pseudohypopyon after intravitreal triamcinolone acetonide injection for cystoid macular edema. *Am J Ophthalmol* 138:489–492. <https://doi.org/10.1016/j.ajo.2004.03.025>
- Mason RH, Ballios BG, Yan P (2020) Noninfectious endophthalmitis following intravitreal triamcinolone acetonide: clinical case and literature review. *Can J Ophthalmol* 55:471–479
- Chen SDM, Lochhead J, McDonald B, Patel CK (2004) Pseudohypopyon after intravitreal triamcinolone injection for the treatment of pseudophakic cystoid macular oedema [13]. *Br J Ophthalmol* 88:843–844
- Dossarps D, Bron AM, Koehrer P et al (2015) Endophthalmitis after intravitreal injections: Incidence, presentation, management, and visual outcome. *Am J Ophthalmol* 160:17–25.e1
- Nelson ML, Tennant MTS, Sivalingam A et al (2003) Infectious and presumed noninfectious endophthalmitis after intravitreal triamcinolone acetonide injection. *Retina* 23:686–691. <https://doi.org/10.1097/00006982-200310000-00014>
- Rayess N, Rahimy E, Storey P et al (2016) Postinjection Endophthalmitis Rates and Characteristics Following Intravitreal Bevacizumab, Ranibizumab, and Aflibercept. *Am J Ophthalmol* 165:88–93. <https://doi.org/10.1016/j.ajo.2016.02.028>
- Williams PD, Chong D, Fuller T, Callanan D (2016) Noninfectious vitritis after intravitreal injection of anti-vegf agents. *Retina* 36:909–913. <https://doi.org/10.1097/IAE.0000000000000801>
- Meredith TA, McCannel CA, Barr C et al (2015) Postinjection endophthalmitis in the comparison of Age-Related Macular Degeneration Treatments Trials (CATT). *Ophthalmology* 122:817–821. <https://doi.org/10.1016/j.ophtha.2014.10.027>
- Fileta JB, Scott IU, Flynn HW (2014) Meta-analysis of infectious endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. *Ophthalmic Surg Lasers Imagin Retin* 45:143–149. <https://doi.org/10.3928/23258160-20140306-08>
- McCannel CA (2011) Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents: Causative organisms and possible prevention strategies.

- Retina 31:654–661. <https://doi.org/10.1097/IAE.0B013E31820A67E4>
31. Englander M, Chen TC, Paschalis EI et al (2013) Intravitreal injections at the Massachusetts Eye and Ear Infirmary: Analysis of treatment indications and postinjection endophthalmitis rates. *Br J Ophthalmol* 97:460–465. <https://doi.org/10.1136/bjophthalmol-2012-302435>
 32. Xu K, Chin EK, Bennett SR et al (2018) Endophthalmitis after Intravitreal Injection of Vascular Endothelial Growth Factor Inhibitors: Management and Visual Outcomes. *Ophthalmology* 125:1279–1286. <https://doi.org/10.1016/j.ophtha.2018.01.022>
 33. Yannuzzi NA, Gregori NZ, Rosenfeld PJ et al (2018) Endophthalmitis associated with intravitreal injections of Anti-VEGF agents at a tertiary referral center: In-house and referred cases. *Ophthalmic Surg Lasers Imaging Retin* 49:313–319. <https://doi.org/10.3928/23258160-20180501-04>
 34. Kiss S, Dugel PU, Khanani AM et al (2018) Endophthalmitis rates among patients receiving intravitreal anti-VEGF injections: A USA claims analysis. *Clin Ophthalmol* 12:1625–1635. <https://doi.org/10.2147/OPHTH.S169143>
 35. Monés J, Srivastava SK, Jaffe GJ et al (2021) Risk of Inflammation, Retinal Vasculitis, and Retinal Occlusion-Related Events with Brolucizumab: Post Hoc Review of HAWK and HARRIER. *Ophthalmology* 128:1050–1059. <https://doi.org/10.1016/J.OPHTHA.2020.11.011>
 36. Mukai R, Matsumoto H, Akiyama H (2021) Risk factors for emerging intraocular inflammation after intravitreal brolucizumab injection for age-related macular degeneration. *PLoS ONE* 16:e0259879. <https://doi.org/10.1371/JOURNAL.PONE.0259879>
 37. Bauml CR, Spaide RF, Vajzovic L et al (2020) Retinal Vasculitis and Intraocular Inflammation after Intravitreal Injection of Brolucizumab. *Ophthalmology* 127:1345–1359. <https://doi.org/10.1016/J.OPHTHA.2020.04.017>
 38. Bauml CR, Bodaghi B, Singer M et al (2021) Expert Opinion on Management of Intraocular Inflammation, Retinal Vasculitis, and Vascular Occlusion after Brolucizumab Treatment. *Ophthalmol Retin* 5:519–527. <https://doi.org/10.1016/J.ORET.2020.09.020>
 39. Wang F, Yu S, Liu K et al (2013) Acute intraocular inflammation caused by endotoxin after intravitreal injection of counterfeit bevacizumab in Shanghai, China. *Ophthalmology* 120:355–361. <https://doi.org/10.1016/j.ophtha.2012.07.083>
 40. Melo GB, da Cruz NFS, Emerson GG et al (2021) Critical analysis of techniques and materials used in devices, syringes, and needles used for intravitreal injections. *Prog Retin Eye Res* 80:100862. <https://doi.org/10.1016/j.preteyeres.2020.100862>
 41. Souied EH, Dugel PU, Ferreira A et al (2016) Severe ocular inflammation following ranibizumab or aflibercept injections for age-related macular degeneration: A retrospective claims database analysis. *Ophthalmic Epidemiol* 23:71–79. <https://doi.org/10.3109/09286586.2015.1090004>
 42. Bhavsar AR, Googe JM, Stockdale CR et al (2009) Risk of endophthalmitis after intravitreal drug injection when topical antibiotics are not required: The diabetic retinopathy clinical research network laser-ranibizumab-triamcinolone clinical trials. *Arch Ophthalmol* 127:1581–1583. <https://doi.org/10.1001/archophthalmol.2009.304>
 43. VanderBeek BL, Bonaffini SG, Ma L (2015) The Association between Intravitreal Steroids and Post-Injection Endophthalmitis Rates. *Ophthalmology* 122:2311–2315.e1. <https://doi.org/10.1016/j.ophtha.2015.07.005>
 44. Fong AHC, Chan CKM (2017) Presumed sterile endophthalmitis after intravitreal triamcinolone (Kenalog)-more common and less benign than we thought? *Asia-Pacific J Ophthalmol* 6:45–49. <https://doi.org/10.1097/APO.0000000000000194>
 45. Maia M, Farah ME, Belfort RN et al (2007) Effects of intravitreal triamcinolone acetonide injection with and without preservative. *Br J Ophthalmol* 91:1122–1124. <https://doi.org/10.1136/bjo.2007.115386>
 46. Hoyt C, Dick A (2007) Another Anglo-American editorship. *Br J Ophthalmol* 91:1099
 47. Dodwell DG, Krimmel DA, de Fiebre CM (2015) Sterile endophthalmitis rates and particle size analyses of different formulations of triamcinolone acetonide. *Clin Ophthalmol* 9:1033–1040. <https://doi.org/10.2147/OPHTH.S82562>
 48. Carrero JL, Barcia MG, Flores IP (2008) Sterile endophthalmitis after benzyl alcohol-filtered triamcinolone acetonide injection [3]. *Arch Ophthalmol* 126:142–143
 49. Rayess N, Rahimy E, Shah CP et al (2016) Incidence and clinical features of post-injection endophthalmitis according to diagnosis. *Br J Ophthalmol* 100:1058–1061. <https://doi.org/10.1136/bjophthalmol-2015-307707>
 50. Bhende M, Raman R, Singh N et al (2018) Risk Factors for Endophthalmitis after Pars Plana Vitrectomies in a Tertiary Eye Institute in India. *Ophthalmol Retin* 2:779–784. <https://doi.org/10.1016/J.ORET.2018.01.001>
 51. Chen E, Lin MY, Cox J, Brown DM (2011) Endophthalmitis after intravitreal injection: The importance of viridans streptococci. *Retina* 31:1525–1533. <https://doi.org/10.1097/IAE.0B013E318221594A>
 52. Simonett JM, Igelman A, Taylor SC et al (2019) Culture-proven endophthalmitis after intravitreal injection: A 10-year analysis. *Ophthalmic Surg Lasers Imaging Retin* 50:33–38. <https://doi.org/10.3928/23258160-20181212-05>
 53. Simunovic MP, Rush RB, Hunyor AP, Chang AA (2012) Endophthalmitis following intravitreal injection versus endophthalmitis following cataract surgery: Clinical features, causative organisms and post-treatment outcomes. *Br J Ophthalmol* 96:862–866. <https://doi.org/10.1136/bjophthalmol-2011-301439>
 54. Garg SJ, Dollin M, Storey P et al (2016) Microbial spectrum and outcomes of endophthalmitis after intravitreal injection versus pars plana vitrectomy. *Retina* 36:351–359. <https://doi.org/10.1097/IAE.0000000000000694>
 55. Goldberg RA, Flynn HW, Miller D et al (2013) Streptococcus endophthalmitis outbreak after intravitreal injection of bevacizumab: One-year outcomes and investigative results. *Ophthalmology* 120:1448–1453. <https://doi.org/10.1016/j.ophtha.2012.12.009>
 56. Rayess N, Obeid A, Storey PP et al (2019) LONG-TERM VISUAL OUTCOMES and CLINICAL FEATURES after ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTION-RELATED ENDOPHTHALMITIS. *Retina* 39:2070–2076. <https://doi.org/10.1097/IAE.0000000000002300>
 57. Speaker MG, Menikoff JA (1991) Prophylaxis of Endophthalmitis with Topical Povidone-iodine. *Ophthalmology* 98:1769–1775. [https://doi.org/10.1016/S0161-6420\(91\)32052-9](https://doi.org/10.1016/S0161-6420(91)32052-9)
 58. Friedman DA, Mason JO, Emond T, McGwin G (2013) Povidone-iodine contact time and lid speculum use during intravitreal injection. *Retina* 33:975–981. <https://doi.org/10.1097/IAE.0b013e3182877585>
 59. Tan EL, Johari NH (2021) Comparative in vitro evaluation of the antimicrobial activities of povidone-iodine and other commercially available antiseptics against clinically relevant pathogens. *GMS Hyg Infect Control* 16:Doc05. <https://doi.org/10.3205/dgkh000376>
 60. Eggers M (2019) Infectious Disease Management and Control with Povidone Iodine. *Infect Dis Ther* 8:581–593. <https://doi.org/10.1007/S40121-019-00260-X>
 61. Wykoff CC, Flynn HW, Han DP (2011) Allergy to povidone-iodine and cephalosporins: the clinical dilemma in ophthalmic

- use. *Am J Ophthalmol* 151:4–6. <https://doi.org/10.1016/J.AJO.2010.08.044>
62. Oakley CL, Vote BJ (2016) Aqueous chlorhexidine (0.1%) is an effective alternative to povidone–iodine for intravitreal injection prophylaxis. *Acta Ophthalmol* 94:e808–e809
 63. Merani R, McPherson ZE, Luckie AP et al (2016) Aqueous Chlorhexidine for Intravitreal Injection Antisepsis: A Case Series and Review of the Literature. *Ophthalmology* 123:2588–2594. <https://doi.org/10.1016/j.ophtha.2016.08.022>
 64. Grzybowski A, Brona P (2017) Povidone-iodine is still a premium antiseptic measure in ocular surgery. *Acta Ophthalmol* 95:e253–e254
 65. Jandorf S, Krogh Nielsen M, Sørensen TL (2019) Irrigating the eye after intravitreal injection reduces epithelial damage but not patient discomfort. *Acta Ophthalmol* 97:e670–e671. <https://doi.org/10.1111/AOS.14014>
 66. Avery RL, Bakri SJ, Blumenkranz MS et al (2014) Intravitreal injection technique and monitoring: Updated guidelines of an expert panel. *Retina* 34:S1–S18
 67. Chaturvedi R, Wannamaker KW, Riviere PJ et al (2019) Real-World Trends in Intravitreal Injection Practices among American Retina Specialists. *Ophthalmol Retin* 3:656–662. <https://doi.org/10.1016/j.oret.2019.03.023>
 68. Raevis J, Karl M, Parendo A et al (2020) Eyelid retraction discomfort with cotton-tipped applicator, unimanual and speculum intravitreal injection techniques: Eyelid retraction technique randomized comparison trial (Eyelid RETRACT). *Indian J Ophthalmol* 68:1593–1595. https://doi.org/10.4103/ijo.IJO_2043_19
 69. Uhr JH, Xu D, Rahimy E, Hsu J (2019) Current Practice Preferences and Safety Protocols for Intravitreal Injection of Anti-Vascular Endothelial Growth Factor Agents. *Ophthalmol Retin* 3:649–655. <https://doi.org/10.1016/j.oret.2019.03.013>
 70. Dudani AI, Dudani AA, Dudani KA, Dudani AA (2021) Unimanual upper and lower eyelid retraction for intravitreal injections. *Indian J Ophthalmol* 69:781–782
 71. Fineman MS, Hsu J, Spirn MJ, Kaiser RS (2013) Bimanual assisted eyelid retraction technique for intravitreal injections. *Retina* 33:1968–1970. <https://doi.org/10.1097/IAE.0b013e318287da92>
 72. Shrier EM (2014) Cotton-tip applicator lid retraction technique for controlled intravitreal injection. *Retina* 34:1244–1246. <https://doi.org/10.1097/IAE.0000000000000219>
 73. Mason RWH (2013) Use of a desmarres retractor for upper lid and lash isolation during intravitreal injections. *Retina* 33:2175–2176. <https://doi.org/10.1097/IAE.0b013e3182999a1b>
 74. Menchini F, Toneatto G, Miele A et al (2018) Antibiotic prophylaxis for preventing endophthalmitis after intravitreal injection: a systematic review. *Eye* 32:1423–1431
 75. Torres-Costa S, Ramos D, Brandão E et al (2021) Incidence of endophthalmitis after intravitreal injection with and without topical antibiotic prophylaxis. *Eur J Ophthalmol* 31:600–606. <https://doi.org/10.1177/1120672120902028>
 76. Reibaldi M, Pulvirenti A, Avitabile T et al (2018) Pooled estimates of incidence of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents with and without topical antibiotic prophylaxis. *Retina* 38:1–11. <https://doi.org/10.1097/IAE.0000000000001583>
 77. Milder E, Vander J, Shah C, Garg S (2012) Changes in antibiotic resistance patterns of conjunctival flora due to repeated use of topical antibiotics after intravitreal injection. *Ophthalmology* 119:1420–1424. <https://doi.org/10.1016/j.ophtha.2012.01.016>
 78. Kim SJ, Toma HS (2011) Ophthalmic antibiotics and antimicrobial resistance: A randomized, controlled study of patients undergoing intravitreal injections. *Ophthalmology* 118:1358–1363. <https://doi.org/10.1016/j.ophtha.2010.12.014>
 79. Green-Simms AE, Ekdawi NS, Bakri SJ (2011) Survey of intravitreal injection techniques among retinal specialists in the United States. *Am J Ophthalmol* 151:329–332. <https://doi.org/10.1016/j.ajo.2010.08.039>
 80. Tabandeh H, Boscia F, Sborgia A et al (2014) Endophthalmitis associated with intravitreal injections: Office-based setting and operating room setting. *Retina* 34:18–23. <https://doi.org/10.1097/IAE.0000000000000008>
 81. Freiberg FJ, Brynskov T, Munk MR et al (2017) Low endophthalmitis rates after intravitreal anti-vascular endothelial growth factor injections in an operation room a retrospective multicenter study. *Retina* 37:2341–2346
 82. Li T, Sun J, Min J et al (2021) Safety of Receiving Anti-Vascular Endothelial Growth Factor Intravitreal Injection in Office-Based vs Operating Room Settings: A Meta-analysis. *JAMA Ophthalmol* 139:1080–1088. <https://doi.org/10.1001/jamaophthalmol.2021.3096>
 83. Shen NJ, Pan SC, Sheng WH et al (2015) Comparative antimicrobial efficacy of alcohol-based hand rub and conventional surgical scrub in a medical center. *J Microbiol Immunol Infect* 48:322–328. <https://doi.org/10.1016/j.jmii.2013.08.005>
 84. Lai KW, Foo TL, Low W, Naidu G (2012) Surgical hand antisepsis—a pilot study comparing povidone iodine hand scrub and alcohol-based chlorhexidine gluconate hand rub. *Ann Acad Med Singap* 41:12–16. <https://pubmed.ncbi.nlm.nih.gov/22499475/>
 85. Grzybowski A, Told R, Sacu S et al (2018) Update on Intravitreal Injections: Euretina Expert Consensus Recommendations. *Ophthalmologica* 239:181–193. <https://doi.org/10.1159/000486145>
 86. Doshi RR, Leng T, Fung AE (2012) Reducing oral flora contamination of intravitreal injections with face mask or silence. *Retina* 32:473–476. <https://doi.org/10.1097/IAE.0b013e31822c2958>
 87. Wen JC, McCannel CA, Mochon AB, Garner OB (2011) Bacterial dispersal associated with speech in the setting of intravitreal injections. *Arch Ophthalmol* 129:1551–1554. <https://doi.org/10.1001/ARCHOPHTHALMOL.2011.227>
 88. Garg SJ, Dollin M, Hsu J et al (2015) Effect of a strict “no-talking” policy during intravitreal injection on post-injection endophthalmitis. *Ophthalmic Surg Lasers Imaging Retin* 46:1028–1034. <https://doi.org/10.3928/23258160-20151027-07>
 89. Patel SN, Hsu J, Sivalingam MD et al (2021) The Impact of Physician Face Mask Use on Endophthalmitis After Intravitreal Anti-Vascular Endothelial Growth Factor Injections. *Am J Ophthalmol* 222:194–201. <https://doi.org/10.1016/J.AJO.2020.08.013>
 90. Pancholy M, Storey PP, Levin HJ et al (2021) Endophthalmitis following Intravitreal Anti-Vascular Endothelial Growth Factor Therapy: Changes in Incidence and Outcomes over a 9-Year Period. *Curr Eye Res* 46:1370–1377. <https://doi.org/10.1080/02713683.2021.1874023>
 91. Zhiqing L, Yongyun C, Wenxiang C et al (2018) Surgical masks as source of bacterial contamination during operative procedures. *J Orthop Transl* 14:57–62. <https://doi.org/10.1016/j.jot.2018.06.002>
 92. Patel SN, Mahmoudzadeh R, Salabati M et al (2021) Bacterial Dispersion Associated With Various Patient Face Mask Designs During Simulated Intravitreal Injections. *Am J Ophthalmol* 223:178–183. <https://doi.org/10.1016/j.ajo.2020.10.017>
 93. Hadayer A, Zahavi A, Livny E et al (2020) Patients Wearing Face Masks During Intravitreal Injections May Be at a Higher Risk of Endophthalmitis. *Retina* 40:1651–1656. <https://doi.org/10.1097/IAE.0000000000002919>
 94. Patel SN, Tang PH, Storey PP et al (2021) The Influence of Universal Face Mask Use on Endophthalmitis Risk after Intravitreal Anti-Vascular Endothelial Growth Factor Injections.

- Ophthalmology 128:1620–1626. <https://doi.org/10.1016/j.ophtha.2021.05.010>
95. Subhi Y, Kjer B, Munch IC (2016) Prefilled syringes for intravitreal injection reduce preparation time. 63:A5214. <https://pubmed.ncbi.nlm.nih.gov/27034182/>.
 96. Souied E, Nghiem-Buffer S, Leteneux C et al (2015) Ranibizumab prefilled syringes: Benefits of reduced syringe preparation times and less complex preparation procedures. Eur J Ophthalmol 25:529–534. <https://doi.org/10.5301/EJO.5000629>
 97. Salsalos TM, Paulus YM (2019) Prefilled syringes for intravitreal drug delivery. Clin Ophthalmol 13:701–706
 98. Storey PP, Tauqeer Z, Yonekawa Y et al (2019) The Impact of Prefilled Syringes on Endophthalmitis Following Intravitreal Injection of Ranibizumab. Am J Ophthalmol 199:200–208. <https://doi.org/10.1016/j.ajo.2018.11.023>
 99. Juncal VR, Francisconi CLM, Altomare F et al (2019) Same-Day Bilateral Intravitreal Anti-Vascular Endothelial Growth Factor Injections: Experience of a Large Canadian Retina Center. Ophthalmologica 242:1–7
 100. Borkar DS, Obeid A, Su DC et al (2018) Endophthalmitis Rates after Bilateral Same-Day Intravitreal Anti-Vascular Endothelial Growth Factor Injections. Am J Ophthalmol 194:1–6. <https://doi.org/10.1016/j.ajo.2018.06.022>
 101. Han J, Rinella NT, Chao DL (2020) Anesthesia for intravitreal injection: A systematic review. Clin Ophthalmol 14:543–550
 102. Shiroma HF, Takaschima AKK, Farah ME et al (2017) Patient pain during intravitreal injections under topical anesthesia: a systematic review. Int J Retin Vitre 3:23. <https://doi.org/10.1186/S40942-017-0076-9>
 103. Doshi RR, Leng T, Fung AE (2011) Povidone-iodine before lidocaine gel anesthesia achieves surface antisepsis. Ophthalmic Surg Lasers Imaging 42:346–349. <https://doi.org/10.3928/15428877-20110210-02>
 104. Stem MS, Rao P, Lee IJ et al (2019) Predictors of Endophthalmitis after Intravitreal Injection: A Multivariable Analysis Based on Injection Protocol and Povidone Iodine Strength. Ophthalmol Retin 3:3–7. <https://doi.org/10.1016/j.oret.2018.09.013>
 105. Inman ZD, Anderson NG (2011) Incidence of endophthalmitis after intravitreal injection of antivascular endothelial growth factor medications using topical lidocaine gel anesthesia. Retina 31:669–672. <https://doi.org/10.1097/IAE.0b013e3181ef463d>
 106. Lad EM, Maltenfort MG, Leng T (2012) Effect of lidocaine gel anesthesia on endophthalmitis rates following intravitreal injection. Ophthalmic Surg Lasers Imaging 43:115–120. <https://doi.org/10.3928/15428877-20120119-01>
 107. Tustin A, Kim SJ, Chomsky A et al (2014) Antibacterial properties of 2% lidocaine and reduced rate of endophthalmitis after intravitreal injection. Retina 34:935–942. <https://doi.org/10.1097/IAE.0000000000000014>
 108. Xu K, Mousa R, Loewenstein A et al (2020) Management and visual outcomes of acute bacterial endophthalmitis following intravitreal injection of contaminated bevacizumab in a single day. Ophthalmic Surg Lasers Imaging Retin 51:346–352. <https://doi.org/10.3928/23258160-20200603-05>
 109. Small KW, Tran EM, Garabetian CA et al (2019) Fungal Endophthalmitis after Intravitreal Injections of Triamcinolone Contaminated by a Compounding Pharmacy: Five-Year Follow-up of 23 Patients. Ophthalmol Retin 3:133–139. <https://doi.org/10.1016/j.oret.2018.09.009>
 110. Forooghian F, Albani DA, Kirker AW, Merkur AB (2017) Comparison of endophthalmitis rates following intravitreal injection of compounded bevacizumab, ranibizumab, and aflibercept. Can J Ophthalmol 52:616–619. <https://doi.org/10.1016/j.cjco.2017.04.016>
 111. Endophthalmitis Vitrectomy Study Group (1995) Results of the endophthalmitis vitrectomy study. A randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. Arch Ophthalmol 113:147–1496. <https://pubmed.ncbi.nlm.nih.gov/7487614/>
 112. Relhan N, Albin TA, Pathengay A et al (2016) Endophthalmitis caused by Gram-positive organisms with reduced vancomycin susceptibility: Literature review and options for treatment. Br J Ophthalmol 100:446–452
 113. Yannuzzi NA, Patel NA, Relhan N et al (2018) Clinical Features, Antibiotic Susceptibilities, and Treatment Outcomes of Endophthalmitis Caused by Staphylococcus epidermidis. Ophthalmol Retin 2:396–400. <https://doi.org/10.1016/j.oret.2017.08.025>
 114. Kodati S, Eller AW, Kowalski RP (2017) The Susceptibility of Bacterial Endophthalmitis Isolates to Vancomycin, Cef-tazidime, and Amikacin: a 23 Year-Review. Ophthalmol Retin 1:206–209. <https://doi.org/10.1016/J.ORET.2016.11.010>
 115. Chen KJ, Sun MH, Hou CH et al (2021) Susceptibility of bacterial endophthalmitis isolates to vancomycin, ceftazidime, and amikacin. Sci Rep 11:15878. <https://doi.org/10.1038/S41598-021-95458-W>
 116. Galloway G, Ramsay A, Jordan K, Vivian A (2002) Macular infarction after intravitreal amikacin: mounting evidence against amikacin. Br J Ophthalmol 86:359–360. <https://doi.org/10.1136/BJO.86.3.359>
 117. Brockhaus L, Goldblum D, Eggenschwiler L et al (2019) Revisiting systemic treatment of bacterial endophthalmitis: a review of intravitreal penetration of systemic antibiotics. Clin Microbiol Infect 25:1364–1369. <https://doi.org/10.1016/J.CML.2019.01.017>
 118. Grzybowski A, Turczynowska M, Schwartz SG et al (2020) The Role of Systemic Antimicrobials in the Treatment of Endophthalmitis: A Review and an International Perspective. Ophthalmol Ther 9:485–498. <https://doi.org/10.1007/S40123-020-00270-W>
 119. Soliman MK, Gini G, Kuhn F et al (2019) International Practice Patterns for the Management of Acute Postsurgical and Postin-travitreal Injection Endophthalmitis: European Vitreo-Retinal Society Endophthalmitis Study Report 1. Ophthalmol Retin 3:461–467. <https://doi.org/10.1016/j.oret.2019.03.009>
 120. Robbins CB, Ma J, Feng HL, Fekrat S (2020) Clinical Decision Making and Visual Outcomes in Endophthalmitis Treated with Systemic Corticosteroids. Ophthalmol Retin 4:1103–1108. <https://doi.org/10.1016/J.ORET.2020.04.026>
 121. Conrady CD, Feist RM, Vitale AT, Shakoor A (2020) Long-term visual outcomes of endophthalmitis and the role of systemic steroids in addition to intravitreal dexamethasone. BMC Ophthalmol 20:181. <https://doi.org/10.1186/S12886-020-01449-2>
 122. Kim CH, Chen MF, Coleman AL (2017) Adjunctive steroid therapy versus antibiotics alone for acute endophthalmitis after intraocular procedure. Cochrane database Syst Rev 2:CD012131. <https://doi.org/10.1002/14651858.CD012131.PUB2>
 123. Shah GK, Stein JD, Sharma S et al (2000) Visual outcomes following the use of intravitreal steroids in the treatment of postoperative endophthalmitis. Ophthalmology 107:486–489. [https://doi.org/10.1016/S0161-6420\(99\)00139-6](https://doi.org/10.1016/S0161-6420(99)00139-6)
 124. Januschowski K, Boden KT, Szurman P et al (2021) Effectiveness of immediate vitrectomy and intravitreal antibiotics for post-injection endophthalmitis. Graefe's Arch Clin Exp Ophthalmol 259:1609–1615. <https://doi.org/10.1007/s00417-021-05071-w>
 125. Chaudhary KM, Romero JM, Ezon I et al (2013) Pars plana vitrectomy in the management of patients diagnosed with endophthalmitis following intravitreal anti-vascular endothelial growth factor injection. Retina 33:1407–1416. <https://doi.org/10.1097/IAE.0b013e3182807659>
 126. Kurniawan ED, Rocke JR, Sandhu SS, Allen PJ (2018) Predictors of visual outcome and the role of early vitrectomy in streptococcal endophthalmitis. Clin Exp Ophthalmol 46:424–431. <https://doi.org/10.1111/CEO.13077>

127. Far PM, Yeung SC, Farimani PL et al (2021) TAP AND INJECT VERSUS PARS PLANA VITRECTOMY FOR POSTPROCEDURAL ENDOPHTHALMITIS: A Meta-analysis. *Retina* 41:2009–2016. <https://doi.org/10.1097/IAE.0000000000003203>
128. Mollan SP, Gao A, Lockwood A et al (2007) Postcataract endophthalmitis: Incidence and microbial isolates in a United Kingdom region from 1996 through 2004. *J Cataract Refract Surg* 33:265–268. <https://doi.org/10.1016/j.jcrs.2006.10.022>
129. Patel SN, Storey PP, Pancholy M et al (2019) Changes in Management Based on Vitreous Culture in Endophthalmitis After Intravitreal Anti-vascular Endothelial Growth Factor Injection. *Am J Ophthalmol* 207:224–231. <https://doi.org/10.1016/j.ajo.2019.06.008>
130. Gan IM, Van Dissel JT, Beekhuis WH et al (2001) Intravitreal vancomycin and gentamicin concentrations in patients with postoperative endophthalmitis. *Br J Ophthalmol* 85:1289–1293. <https://doi.org/10.1136/bjo.85.11.1289>
131. Uhr JH, Storey PP, Kuley B et al (2021) The Effect Of Endophthalmitis On Recurrence Of Macular Edema In Eyes Receiving Intravitreal Anti-Vascular Endothelial Growth Factor. *Retina* 41:1470–1477. <https://doi.org/10.1097/IAE.0000000000003050>
132. Kokame GT, Yannuzzi NA, Shantha JG et al (2021) Involution Of Neovascular Age-Related Macular Degeneration After Endophthalmitis. *Retin Cases Brief Rep* 15:495–499. <https://doi.org/10.1097/ICB.0000000000000866>
133. Emoto H, Emoto Y, Lim JI et al (2010) Regression of choroidal neovascularization after vitrectomy for postinjection endophthalmitis. *Retin Cases Br Reports* 4:312–316. <https://doi.org/10.1097/ICB.0b013e3181d426e8>
134. Schachat AP, Rosenfeld PJ, Liesegang TJ, Stewart MW (2012) Endophthalmitis is not a “never event.” *Ophthalmology* 119:1507–1508
135. Irigoyen C, Ziahosseini K, Morphis G et al (2012) Endophthalmitis following intravitreal injections. *Graefes Arch Clin Exp Ophthalmol* 250:499–505. <https://doi.org/10.1007/s00417-011-1851-1>
136. Mithal K, Mathai A, Pathengay A et al (2013) Endophthalmitis following intravitreal anti-VEGF injections in ambulatory surgical centre facility: incidence, management and outcome. *Br J Ophthalmol* 97:1609–1612. <https://doi.org/10.1136/bjophthalmol-2013-303222>
137. Cunningham WJ, Michael E, Welch S et al (2017) The Auckland Endophthalmitis Study: The Incidence and Management of Endophthalmitis Following Intravitreal Bevacizumab. *J Vitreoretin Dis* 1:175–180
138. Raman R, Singh HS, Appanraj R et al (2016) Five-Year Incidence and Visual Outcomes in Postintravitreal Injection Endophthalmitis. *Ophthalmology* 123:1162–1164. <https://doi.org/10.1016/j.ophtha.2015.11.019>
139. Mishra C, Lalitha P, Rameshkumar G et al (2018) Incidence of Endophthalmitis after Intravitreal Injections: Risk Factors, Microbiology Profile, and Clinical Outcomes. *Ocul Immunol Inflamm* 26:559–568. <https://doi.org/10.1080/09273948.2018.1430238>
140. Ho IV, Fernandez-Sanz G, Levasseur S et al (2019) Early Pars Plana Vitrectomy for Treatment of Acute Infective Endophthalmitis. *Asia Pac J Ophthalmol (Phila)* 8:3–7. <https://doi.org/10.22608/APO.2018414>
141. Dar N, Pillar S, Friehmann A et al (2020) Endophthalmitis after intravitreal injections versus cataract surgery: a 15-year cohort. *Int Ophthalmol* 40:73–79. <https://doi.org/10.1007/s10792-019-01153-1>

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Authors and Affiliations

Rupali Singh¹ · Samaneh Davoudi² · Steven Ness² 

✉ Steven Ness
Steven.Ness@bmc.org

² Boston Medical Center, 85 East Concord Street, 8th Floor,
Boston, MA 02118, USA

¹ Boston, USA