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# Endophthalmitis after Intravitreal Injection of Vascular Endothelial Growth Factor Inhibitors

## *Management and Visual Outcomes*

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***Purpose:*** We describe the presentation of patients developing endophthalmitis after intravitreal injection with vascular endothelial growth factor (VEGF) inhibitors. Moreover, we evaluate the management by comparing the outcomes of immediate tap and injection of intravitreal antibiotics (TAI) versus initial surgical pars plana vitrectomy (PPV). Finally, we analyze the predictive factors of visual outcomes at 6-month follow-up.

***Design:*** Retrospective, single-center, nonrandomized interventional study.

***Participants:*** Patients developing endophthalmitis after receiving an intravitreal injection of anti-VEGF agent between 2006 and 2016.

***Methods:*** All patients received a vitreous biopsy sent for cultures before the initiation of treatment: TAI group versus PPV with intravitreal antibiotics (PPV group).

***Main Outcome Measures:*** Best-corrected visual acuity (BCVA) at 6-month follow-up after treatment for endophthalmitis.

***Results:*** A total of 258 357 intravitreal injections occurred over the course of the 10-year period, of which 40 patients (0.016%) had endophthalmitis within 3 weeks after injection. In total, 34 patients (85.0%) had pain and 25 patients (62.5%) had hypopyon on initial examination. Among 24 culture-positive cases, 66.7% of the causative organisms were coagulase-negative *Staphylococcus*, followed by *Streptococcus* species (10.0%). The best-corrected visual acuity (BCVA) (logarithm of the minimum angle of resolution [logMAR]) at 6-month follow-up was significantly worse for patients who had a positive culture for *Streptococcus* species (4.0; standard deviation [SD], 0.8) (approximately light perception) compared with those who had a positive culture for coagulase-negative *Staphylococcus* (0.4; SD, 0.3) (~20/50) ($P < 0.0001$). Compared with the TAI group, a higher proportion of samples were culture-positive in the PPV group (90.9% vs. 48.3%, $P = 0.03$). There was no statistically significant difference in BCVA at 6-month follow-up between the TAI and PPV groups. Younger age (<85 years) and lower intraocular pressure (IOP) at presentation were predictive of achieving a BCVA of 20/400 or better at 6-month follow-up after treatment. Initial management (TAI vs. PPV), duration of symptoms, presence of pain, presence of hypopyon, presenting BCVA, and culture status (positive vs. negative) were not found to be predictive of visual outcomes at 6-month follow-up.

***Conclusions:*** No significant difference in BCVA at 6-month follow-up was detected between the TAI and PPV groups. Younger age and lower IOP at presentation were associated with better visual outcomes at 6-month follow-up. *Ophthalmology 2018;■:1–8 © 2018 by the American Academy of Ophthalmology*

Intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors is commonly used for exudative age-related macular degeneration (AMD), diabetic macular edema, and retinal vein occlusion. It was projected that more than 6 million anti-VEGF injections would be performed in 2016.[1] The most feared complication of anti-VEGF injections is endophthalmitis, which has an occurrence or incidence ranging from 1 case in 1000 to 1 case in 5000.[2–5] Although endophthalmitis after anti-VEGF injection is uncommon, it can have devastating visual outcomes.

The Endophthalmitis Vitrectomy Study (EVS) has provided us with treatment guidelines for acute endophthalmitis after cataract surgery or secondary intraocular implantation[6]; however, it is unclear how these guidelines can be used for cases after anti-VEGF injection because of differing inoculation pathogenesis and modern vitrectomy techniques.



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To our knowledge, limited studies exist investigating the predictive factors for visual outcomes among patients with endophthalmitis after anti-VEGF injection. Likewise, it is unclear which initial treatment (i.e., vitreous biopsy with intravitreal injection of antibiotics [IIA] vs. pars plana vitrectomy [PPV] with IIA) offers optimal long-term visual outcomes. In our study, we describe the incidence, clinical presentation, and culture status for patients developing endophthalmitis after intravitreal injection. We also compare the visual outcomes of immediate tap and injection of intravitreal antibiotics (TAI) versus PPV as the initial treatment of choice. Finally, we analyze the predictive factors of visual outcome for this challenging group of patients.

## Methods

### Study Design

A retrospective study was conducted adhering to the tenets of the Declaration of Helsinki with Salus institutional review board approval. This study is HIPPA compliant. The study sample is composed of all patients with endophthalmitis after anti-VEGF injections at a multicentered single subspecialty (retina only) private practice institution (VitreoRetinal Surgery, PA, Minneapolis, MN) over a 10-year period between 2006 and 2016.

### Injection Technique

All eyes were injected with an anti-VEGF agent (bevacizumab [Genentech, South San Francisco, CA], ranibizumab [Genentech], or aflibercept [Regeneron, Tarrytown, NY]) in an outpatient clinic setting. Facemasks were not used during the injections; however, talking during the injection by the physician and patient was kept to a minimum. Topical anesthetic drops (proparacaine 0.5%), viscous anesthetic (tetracaine 0.5%), or subconjunctival lidocaine was used to anesthetize the eye before intravitreal injection. Topical 5% povidone-iodine (Betadine) was used to prep the eye by swabbing the eyelashes, caruncle, and upper and lower eyelids followed by the instillation of 1 or 2 drops of topical povidone-iodine solution into the conjunctival cul-de-sac. All anti-VEGF agents were injected through the pars plana using a 30-gauge needle. Variation in the injection technique included differences in injection location (the majority being in the superotemporal quadrant and the minority in the inferotemporal or superonasal quadrants). Another variation of injection technique involved using Betadine liberally on the conjunctiva while the lids were held open with a speculum. Eyelashes were kept out of the field, and no blink was allowed after the last drop of Betadine right before the injection. No topical antibiotic eyedrops were prescribed to the patient after the injection.

### Inclusion and Exclusion Criteria

Patient charts were retrospectively reviewed. Only cases with presumptive endophthalmitis after anti-VEGF injections were included, and the endophthalmitis had to have occurred within 3 weeks of intravitreal injection. All patients received vitreous biopsy ("tap") before the initiation of the treatment, and the collected sample was sent for microbial culture. All patients received treatments the same day when they presented to the clinic with presumed endophthalmitis.

This study is a nonrandomized interventional study. The treatment decisions (IIA vs. PPV with IIA) were based on the clinical judgment of the treating physicians. This retrospective study was based on the initial treatment that patients received, and patients were categorized into the TAI group (received IIA only) or the PPV group (first received PPV with intraocular antibiotics).

Patients who had intravitreal injection of medications other than anti-VEGF agent, such as triamcinolone, were excluded. Those who had a history of any intraocular or extraocular surgery within 1 year of receiving the last intravitreal injection of anti-VEGF agent were excluded. Cases were excluded if endophthalmitis developed after a history of trauma.

### Tap and Injection of Intravitreal Antibiotics Group

All eyes in this group received immediate diagnostic vitreous biopsy ("tap") through the pars plana followed by injection of intravitreal antibiotics. The vitreous biopsy consisted of insertion of a short 25- or 27-gauge needle into the vitreous cavity to aspirate a vitreous sample. If an adequate vitreous sample could not be obtained, an aqueous tap was then performed via a short 30-gauge needle at the corneal limbus. All collected specimens were sent for gram stain, cultures, and sensitivities. Patients were given intravitreal injections of vancomycin (1 mg/0.1 ml) and ceftazidime (2.25 mg/0.1 ml). Intravitreal dexamethasone was not administered any cases. Topical steroid and antibiotic drops were also prescribed at the discretion of the treating physician, and patients were followed daily until they improved clinically. The drops were tapered as deemed necessary, and examination intervals were extended.

### Pars Plana Vitrectomy Group

Patients in this group were transferred to the operating room on the same day of diagnosis. A retrobulbar block was placed in the periorbital space for anesthesia. The eye was then prepped and draped in usual sterile fashion, and a lid speculum was inserted.

Pars plana vitrectomy (23- or 25-gauge) was performed, and all unopacified vitreous and any vitreous membranes present were removed with the vitreous cutter. A vitreous sample with the infusion line turned off was sent for culture at the start of the surgery. Peripheral vitreous was then removed with the vitreous cutter and with aid of scleral indentation.

Inspection was performed, and any retinal breaks (if present) were demarcated with laser retinopexy. A partial or complete air−fluid exchange was performed at the discretion of the attending surgeon. Any leaking sclerotomy sites were sutured. At the conclusion of the case, 0.1 ml of vancomycin (1.0 mg/0.1 ml) and 0.1 ml of ceftazidime (2.25 mg/0.1 ml) were injected through the pars plana with a short 30-gauge needle.

### Variables of Interest

Patient characteristics included age, sex, cigarette smoking status (past or present), and clinical diagnosis (indication for injection). Signs, symptoms, and clinical findings on presentation included pain, hypopyon, Snellen best-corrected visual acuity (BCVA) on presentation using logarithm of the minimum angle of resolution (logMAR) visual acuity, intraocular pressure (IOP), duration of endophthalmitis symptoms (e.g., pain, redness, vision loss, or floaters) before presentation, and the time between last injection of anti-VEGF agent and symptoms.

In addition, information about the anti-VEGF agents that the patient last received (bevacizumab, ranibizumab, or aflibercept), total number of injections received for each patient, culture growth results, initial treatment (IIA vs. PPV with intraocular antibiotics), and follow-up time were also collected. The difference of BCVA