

10-1-2011

Outcomes and risk factors associated with endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents.

Chirag P Shah

Ophthalmic Consultants of Boston, Boston, MA, United States

Sunir J Garg

Retina Service of Wills Eye Institute, Thomas Jefferson University, sunirgarg@yahoo.com

James F Vander

Retina Service of Wills Eye Institute, Thomas Jefferson University

Gary C Brown

Retina Service of Wills Eye Institute, Thomas Jefferson University

Richard S Kaiser

*Retina Service of Wills Eye Institute, Thomas Jefferson University**See next page for additional authors*

[Let us know how access to this document benefits you](#)

Follow this and additional works at: <http://jdc.jefferson.edu/willsfp> Part of the [Ophthalmology Commons](#)

Recommended Citation

Shah, Chirag P; Garg, Sunir J; Vander, James F; Brown, Gary C; Kaiser, Richard S; Haller, Julia A; and The Post-Injection Endophthalmitis (PIE) Study Team, "Outcomes and risk factors associated with endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents." (2011). *Wills Eye Institute Papers*. Paper 10.
<http://jdc.jefferson.edu/willsfp/10>

Authors

Chirag P Shah, Sunir J Garg, James F Vander, Gary C Brown, Richard S Kaiser, Julia A Haller, and The Post-Injection Endophthalmitis (PIE) Study Team

1 **As submitted to:**

2
3 *Ophthalmology*

4
5 **And later published as:**

6
7 **Outcomes and Risk Factors Associated with**
8 **Endophthalmitis**
9 **after Intravitreal Injection of Anti-Vascular Endothelial**
10 **Growth Factor Agents**

11
12
13 **Volume 118, Issue 10, October 2011, Pages 2028-2034**

14
15 **DOI: 10.1016/j.opthta.2011.02.034**

16
17 Chirag P. Shah, MD, MPH^{1,2}, Sunir J. Garg, MD², James F. Vander, MD², Gary C.
18 Brown, MD, MBA², Richard S. Kaiser, MD², Julia A. Haller, MD², for The Post-
19 Injection Endophthalmitis (PIE) Study Team*

20
21 ¹ Ophthalmic Consultants of Boston, Boston, MA

22 ² Wills Eye Institute, Retina Service, Philadelphia, PA

23
24 *Darrell E. Baskin, MD², Jeremy D. Wolfe, MD², Paul Baker, MD², Allen Chiang, MD²,
25 Eugene Milder, MD², William Benson, MD², Jay Federman, MD², David Fischer, MD²,
26 Allen C. Ho, MD², Jason Hsu, MD², Alfred Lucier, MD², Joseph I. Maguire, MD², J.
27 Arch McNamara, MD², Carl D. Regillo, MD², Lov Sarin, MD², Arunan Sivalingam, MD²

28
29 Proprietary interests: none

30
31 Running head: Post-injection Endophthalmitis

32
33 Correspondence to: Sunir J. Garg, MD
34 sunirgarg@yahoo.com

35
36 Financial support: none

37
38 Online only materials: This article contains online-only material. The following should
39 appear online-only: Table 1

40
41 Video: no

1
2 Key Words: endophthalmitis, anti-VEGF injection, bevacizumab, ranibizumab, AMD,
3 risk factor

1 **Objective:** Describe outcomes of and risk factors for endophthalmitis following
2 intravitreal anti-VEGF injection.

3
4 **Design:** Single-center, consecutive, case series and retrospective case-control study

5
6 **Participants:** Between 1/1/09 and 5/31/10, 16 vitreoretinal surgeons administered a total
7 of 27,736 injections. During this period, twenty-three cases of presumed infectious
8 endophthalmitis occurred. Each surgeon used their own preferred injection technique.

9
10 **Intervention:**

11 Vitreous and/or aqueous tap with intravitreal antibiotic injection and subsequent topical
12 antibiotic and steroid drops.

13
14 **Main Outcome Measures:** Visual acuity, bladed lid speculum use, conjunctival
15 displacement, hemisphere of injection, bevacizumab vs. ranibizumab, and infectious
16 organism.

17
18 **Results:** Seven of 23 cases were culture-positive; three grew coagulase negative
19 Staphylococcus. All cases presented with pain and vitritis on average 3.4 days (range 1 –
20 6) after injection, with no difference between culture-positive and culture-negative
21 groups. Eighteen of 23 cases (78%) had a hypopyon. 16 of 23 cases returned to baseline
22 vision (+/- 2 lines) within three months. Neither lid speculum use (0.10% vs. 0.066% in
23 the no use group, $p = 0.27$), conjunctival displacement (0.11% vs. 0.076% no
24 displacement, $p = 0.43$), hemisphere of injection (0.11% superior vs. 0.079% inferior, $p =$
25 0.56), or bevacizumab vs. ranibizumab (0.11% vs 0.066%, $p = 0.21$) affected risk.
26 Analysis of only culture positive results yielded similar results. There was no statistically
27 significant difference between the proportion of culture-negative cases after bevacizumab
28 (83%) versus ranibizumab injection (55%, $p = 0.13$).

29
30 **Conclusion:** Most patients who develop presumed infectious endophthalmitis after anti-
31 VEGF injection regained baseline vision after treatment. Bladed lid speculum use,
32 conjunctival displacement, hemisphere of injection, and type of anti-VEGF agent did not
33 affect risk. We did not detect a difference in culture-negative endophthalmitis rates after
34 bevacizumab versus ranibizumab injection. Neither the presence of pain, vitritis,
35 decreased vision, or hypopyon, nor the interval between injection and development of
36 symptoms, differentiated culture-positive from culture-negative cases. As a subgroup of
37 patients have poor outcomes, a low threshold for vitreous tap with intravitreal antibiotic
38 injection may be warranted.

Introduction:

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents have revolutionized the treatment of neovascular age-related macular degeneration (AMD). The use of these medications continues to increase as their indications expand, including for diseases such as retinal vein occlusions^{1,2}, neovascular glaucoma³, and diabetic macular edema⁴.

Infectious endophthalmitis remains one of the most feared complications of intravitreal injections. Endophthalmitis can lead to apoptosis of ganglion cells, bipolar cells, and photoreceptors⁵, or to retinal detachment, which can all lead to significant vision loss or to loss of the eye.

Few clinical studies describe visual outcomes after post-injection endophthalmitis⁶⁻⁸ or identify modifiable risk factors to prevent infection. Further, there is debate regarding the clinical distinction between infectious and non-infectious endophthalmitis, with some authors positing that absence of pain supports a non-infectious etiology^{9,10}. This study evaluates a large series of endophthalmitis cases developing after anti-VEGF injection and assesses outcomes and risk factors.

Patients and Methods**Overview:**

Institutional Review Board approval was obtained from Wills Eye Institute. During an infection surveillance program, the authors prospectively recorded cases of endophthalmitis occurring after intravitreal injection of bevacizumab or ranibizumab between January 1, 2009 and May 31, 2010. Charts from these cases were retrospectively reviewed at the conclusion of the surveillance period. All injections were performed at a single, retina-only practice by 16 different vitreoretinal specialists with 16 different offices. The total number of intravitreal bevacizumab and ranibizumab injections was determined using billing data, allowing a retrospective case-control analysis for risk factors.

Injection technique:

All eyes were prepped in a standardized fashion. Briefly, eyes were anesthetized with topical drops (e.g., proparacaine 0.5% [Ophthetic, Allergan, Inc.]), a topical antibiotic (e.g., ofloxacin 0.3% [Ocuflox, Allergan, Inc.]), topical 5% povidone-iodine (Betadyne, Alcon Labs), viscous anesthetic (e.g., tetracaine solution 0.5% [TetraVisc, OCuSoft, Inc.]), and another drop of topical 5% povidone-iodine prior to injection. Rarely, subconjunctival lidocaine 2% was substituted for viscous anesthesia. The eyelashes were not prepped and a sterile drape was not used. Pre-injection antibiotics were not used.

Each vitreoretinal specialist administered anti-VEGF injections through the pars plana, 3.5 – 4.0 mm from the limbus with a 30- or 31-gauge needle using his or her preferred technique. Physicians were asked to consistently use his or her preferred injection technique for the duration of the infection surveillance period, and periodic monitoring was performed to ascertain whether there was identifiable change in technique. Variables included bladed lid speculum use, conjunctival displacement with a sterile cotton tip applicator prior to injection, and superior versus inferior hemisphere of injection. Physicians not using a lid speculum employed variable techniques to expose

1 the globe, including gloved or ungloved fingers to open the lids, an assistant's gloved or
2 ungloved fingers, or simply instructed patients to open their eyelids widely. Those not
3 displacing conjunctiva with a cotton tip applicator injected straight through conjunctiva
4 and sclera into the vitreous. Patients were prescribed a topical antibiotic to use four times
5 a day for four days post-injection. The specific antibiotic was per the preference of the
6 injecting physician.

7
8 ***Tap and inject protocol:***

9 All eyes that developed presumed infectious endophthalmitis were sent to Wills
10 Eye Institute for immediate tap of the vitreous through the pars plana with injection of
11 intravitreal antibiotics (tap and inject). No patients were treated at satellite offices. The
12 vitreous tap consisted of insertion of a 25-gauge needle into the vitreous cavity with
13 attempted aspiration of vitreous in all patients. If adequate vitreous fluid was unable to
14 be obtained, an aqueous tap was performed. All samples were sent to the department of
15 microbiology at Thomas Jefferson University Hospital, Philadelphia, PA, for gram stain,
16 cultures, and sensitivities. Patients then received intravitreal vancomycin (1 mg/0.1 mL)
17 and intravitreal ceftazidime (2 mg/0.1 mL). Penicillin allergic patients received
18 intravitreal amikacin (400 mcg/0.1 mL) instead of intravitreal ceftazidime. All patients
19 were then placed on fortified vancomycin (25 mg/mL), fortified tobramycin (15 mg/mL),
20 and prednisolone acetate 1% drops every hour, as well as atropine sulfate 1% drops twice
21 a day. Patients were followed daily until they had evidence of clinical improvement, at
22 which time the drops were slowly tapered and examination intervals were gradually
23 extended. Antibiotic drops also were modified based on culture sensitivity data.

24
25 ***Inclusion and exclusion criteria:***

26 All eyes with presumed infectious endophthalmitis warranting tap and inject were
27 included in this case series. The criteria for tap and inject were dependent on the
28 judgment of individual vitreoretinal specialists, but universally included decreased visual
29 acuity, the presence of pain, and the presence of vitritis within one week of intravitreal
30 anti-VEGF injection. Patients not included in this case series were those with mild post-
31 injection anterior chamber inflammation (1+ or less), who improved on topical
32 corticosteroid and antibiotic drops without undergoing tap and inject.

33
34 ***Endophthalmitis surveillance log:***

35 One researcher (CPS) recorded data for all patients undergoing tap and inject in
36 an infection surveillance log. These data included the presence of pain, vitritis, and/or
37 hypopyon, visual acuity before the causative injection and at time of tap and inject
38 (Snellen acuity, not best corrected), date of causative anti-VEGF injection, date of tap
39 and inject, office location, injecting vitreoretinal surgeon, type of anti-VEGF injection
40 (bevacizumab versus ranibizumab), lot number, underlying retinal diagnosis, number of
41 prior anti-VEGF injections, lens status, source of tap (vitreous or aqueous), identified
42 organism, and antibiotic specificities. At the end of the surveillance period, charts were
43 retrospectively reviewed to collect follow-up data.

44
45 ***Analysis of case series and case-control study:***

1 Clinical variables of presumed infectious endophthalmitis were analyzed using
2 Excel (Microsoft, Redmond, WA). These features included the presence of pain,
3 hypopyon, vitritis, decreased vision, and duration between causative anti-VEGF injection
4 and tap and inject. Outcome data included return of baseline visual acuity (plus or minus
5 two lines of Snellen acuity, not best-corrected) and need for pars plana vitrectomy.

6 To evaluate risk factors for developing endophthalmitis, the authors conducted a
7 retrospective case-control analysis. The total number of bevacizumab and ranibizumab
8 injections administered was determined using billing data. The number of anti-VEGF
9 injections was also stratified by office location and injecting vitreoretinal surgeon.
10 Several risk factors for presumed infectious endophthalmitis after anti-VEGF injection
11 were examined. These included bladed lid speculum use, conjunctival displacement with
12 a sterile cotton tip applicator prior to injection, superior versus inferior hemisphere of
13 injection, the use of bevicizumab versus ranibizumab, office location, injecting
14 vitreoretinal specialist, and lot number of the specific anti-VEGF agent. A two-sample
15 test of proportion was performed using Stata 9 (College Park, TX). Analysis was done
16 for all cases of presumed infectious endophthamitis and further stratified for culture-
17 positive and culture-negative cases.

18 **Results**

19 **Clinical Features**

20
21 During the 17-month study period, a total of 27,736 consecutive intravitreal anti-
22 VEGF injections were administered, including 10,958 bevacizumab and 16,778
23 ranibizumab injections. Twenty-three of these cases underwent emergent tap and inject
24 for presumed infectious endophthalmitis (0.083%, 95% confidence interval 0.049% to
25 0.12%). Twenty-one of these eyes received anti-VEGF injection for neovascular AMD,
26 while two were treated for macular edema secondary to branch retinal vein occlusion.
27

28 All cases of presumed infectious endophthalmitis presented with pain, vitritis, and
29 decreased visual acuity. Most cases had a hypopyon at time of tap and inject (18 of 23
30 eyes, 78%). Five of seven culture-positive cases presented with hypopyon (71%,
31 $p=XXX$).

32 There was an average of 3.4 days (range 1 to 6 days) between administration of
33 anti-VEGF injection and emergent tap and inject. This average was similar between
34 culture-negative (3.5 days, range 1 to 6 days) and culture-positive cases (3.1 days, range
35 1 to 5 days, $p = 0.54$). One culture-negative case presenting 17 days after injection was
36 excluded from this analysis because the patient's nursing home delayed seeking medical
37 attention.

38 Vitreous tap was performed in all cases, and an adequate specimen was obtained
39 in 14 of 23 cases. When the vitreous tap was unsuccessful, an aqueous tap was performed
40 successfully in the remaining 9 of 23 cases. An infectious organism was identified from
41 vitreous and/or aqueous biopsy in 30.4% of patients (7 of 23), for a culture-positive
42 endophthalmitis rate of 0.025% per injection. Causative organisms included three cases
43 of coagulase negative staphylococci, and one case of each *Staphylococcus aureus*,
44 *Streptococcus viridans*, *Streptococcus mitis*, and *Enterococcus faecalis*.

45 **Visual Outcomes**

1 Most cases (16 of 23, 70%) returned to baseline vision (+/- 2 lines) within three
2 months (see Table 1, available at <http://aaojournal.org>). Four more cases returned to
3 baseline vision at six months; a total of 83% of cases had recovery of baseline vision.
4 Specifically, the three eyes that did not return to baseline were as follows: the vision of
5 one patient dropped from 20/300 to no light perception after retinal detachment with
6 subsequent retinal detachment repair, one from 20/40 to counting fingers after retinal
7 detachment repair, one from 20/400 to counting fingers, and one from 20/50 to 20/100.
8 Four of 23 cases (17%) underwent pars plana vitrectomy three days to 3 weeks after
9 initial tap and inject for retinal detachment, vitreous hemorrhage, or worsening
10 endophthalmitis.

11 Of the seven culture-positive cases, four returned to baseline vision by three
12 months and an additional case returned by six months (71%). Of the two culture-positive
13 eyes not returning to baseline vision, both underwent subsequent pars plana vitrectomy
14 for retinal detachment. These eyes grew *Streptococcus viridans* and *Streptococcus mitis*,
15 respectively.

16 Of the 16 culture-negative cases, 13 returned to baseline vision by three months
17 with another two returning by six months (94%). There was no significant difference in
18 the visual recovery rate between culture positive and culture-negative cases ($p = 0.14$). Of
19 note, one patient developed pain, decreased vision, and hypopyon twice after sequential
20 bevacizumab injection (patient's third and fourth injections). During the first episode, the
21 patient underwent tap and inject three days after causative bevacizumab injection and
22 improved to baseline visual acuity at six weeks. During the second episode, the patient
23 was treated initially with hourly prednisolone acetate drops and had continued worsening
24 of inflammation. The patient underwent tap and inject three days after causative
25 bevacizumab injection, and did not regain baseline visual acuity at six months. This eye
26 was counted twice, once for each episode.

27 28 **Risk Factors**

29 Cases of endophthalmitis occurred in nine of 16 offices by nine of 16 injecting
30 vitreoretinal surgeons. There were no clusters of endophthalmitis with any individual
31 treating physician or in any particular office location. There were no trends associated
32 with lot numbers of bevacizumab or ranibizumab injections.

33 No modifiable risk factors were identified (see Table 2). Neither lid speculum use
34 [0.10% (13 of 12,500) vs. 0.066% (10 of 15,236) in the no use group, $p = 0.27$, 95%
35 confidence interval of the difference -0.031 to 0.11%], conjunctival displacement [0.11%
36 (6 of 5,421) vs. 0.076% (17 of 22,315) no displacement, $p = 0.43$, 95% confidence
37 interval of the difference -0.061 to 0.13%], hemisphere of injection [0.11% (4 of 3,683)
38 superior vs. 0.079% (19 of 24,053) inferior, $p = 0.56$, 95% confidence interval of the
39 difference -0.082 to 0.14%], or bevacizumab (0.11%, 12 of 10,958) vs. ranibizumab
40 (0.066%, 11 of 16,778, $p = 0.21$, 95% confidence interval of the difference -0.030 to
41 0.12%), affected risk. Results were similar with analysis of only culture-positive cases
42 [0.032% (4 of 12,500) vs. 0.020% (3 of 15,236) in the no speculum group ($p = 0.52$),
43 0.018% (1 of 5,421) vs. 0.027% (6 of 22,315) in the no conjunctival displacement group
44 ($p = 0.73$), 0.054% (2 of 3,683) superior vs. 0.021% (5 of 24,053) inferior hemisphere of
45 injection ($p = 0.23$), and 0.018% (2 of 10,958) post-bevacizumab vs. 0.030% (5 of
46 16,778) post-ranibizumab ($p = 0.55$)]. The proportion of culture-negative cases was

1 similar after bevacizumab (83%, 10 of 12) and ranibizumab injection (55%, 6 of 11, $p =$
2 0.13).

3 Power calculations revealed that 101,958 injections evenly split between two
4 groups would be needed to detect a difference between 0.05% and 0.10% with an alpha
5 of 0.05 and a beta of 0.20.

6 7 **Discussion**

8 This large, single-center cases series and case-control study evaluated cases with
9 presumed infectious endophthalmitis occurring after intravitreal anti-VEGF injection.
10 Overall, we detected 23 cases of endophthalmitis after 27,736 injections for an incidence
11 of 0.083%. All cases presented with pain, decreased visual acuity, and vitritis three to
12 four days after intravitreal anti-VEGF injection; most eyes had hypopyon. These features
13 did not help distinguish between culture-positive and culture-negative cases. Most cases
14 returned to baseline visual acuity within three to six months, though some suffered
15 significant visual loss. There were no modifiable risk factors for post-injection
16 endophthalmitis, including the use of a bladed lid speculum, conjunctival displacement
17 with a sterile cotton tip applicator, superior versus inferior hemisphere of injection, and
18 the use of bevacizumab versus ranibizumab.

19 The reported rates of endophthalmitis after intravitreal anti-VEGF injection vary
20 between institutions, study designs, and definitions of endophthalmitis. Our rate is
21 consistent with other large prospective trials. The Minimally Classic/Occult Trial of the
22 Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA)
23 study reported an endophthalmitis incidence of 0.05% (5 cases per 10,443 injections)¹¹,
24 identical to the rate reported in the Anti-VEGF Antibody for the Treatment of
25 Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) study^{12, 13} (3
26 cases per 5,921 injections). However, 14 patients in the MARINA trial and 10 patients in
27 the ANCHOR trial experienced 2+ to 4+ inflammation on slit-lamp examination and
28 were not treated for presumed endophthalmitis. In contrast, at our institution, nearly all
29 patients who develop vitritis, or who develop significant anterior chamber cellular
30 reaction, would be given intravitreal antibiotics. Including these untreated patients, the
31 clinically presumed endophthalmitis rate increases to 0.18% in the MARINA trial and
32 0.22% in the ANCHOR trial. It is possible that our study includes eyes with post-
33 injection inflammation that would have been observed in the MARINA and ANCHOR
34 trials.

35 Endophthalmitis rates in retrospective studies vary tremendously. Fintak and
36 colleagues¹⁴ identified cases of endophthalmitis from billing records at four institutions,
37 reporting a rate of 0.02% (6 of 26,905 injections). All injecting physicians used a lid
38 speculum and 5% to 10% topical povidone-iodine drops to disinfect the ocular surface;
39 some physicians used 10% povidone-iodine soaked swabs to clean the eyelid skin,
40 eyelashes, and lid margin. Pilli and colleagues⁸ also reported a similarly low rate of post-
41 injection endophthalmitis in an office setting (0.029%, 3 of 10,254 injections). In this
42 study, the authors retrospectively collected endophthalmitis cases by reviewing case
43 notes and from conversations with referral sources and other vitreoretinal groups in the
44 area. Patients were prepped with 5% povidone-iodine drops. A lid speculum was used
45 based on the surgeon's discretion. In both of these studies, the retrospective study design
46 could have missed endophthalmitis cases, underestimating the incidence of this rare

1 complication. At the other end of the spectrum, Fong and colleagues¹⁵ reported a 10-fold
2 higher rate of endophthalmitis in a retrospective study of intravitreal bevacizumab and
3 ranibizumab injections (0.26%, 4 of 1,553 total injections), collecting cases from an AMD
4 registry amassed from injection logs. Details were not given regarding the injection
5 technique.

6 Non-infectious endophthalmitis, or uveitis, has been reported after intravitreal
7 anti-VEGF injection, particularly after bevacizumab injection^{9, 10, 16, 17}. In our study,
8 however, the proportion of culture-negative—and possibly non-infectious—
9 endophthalmitis cases was similar after bevacizumab and ranibizumab injections.

10 Prior studies have offered clinical criteria to distinguish between culture-positive
11 and culture-negative endophthalmitis. Ness and colleagues⁹ reported 10 cases of uveitis,
12 termed toxic vitritis, after bevacizumab injection. They felt the timing and severity of
13 pain helped distinguish it from infectious endophthalmitis. All toxic vitritis cases
14 presented within 48 hours with mild to no pain. A hypopyon was not a distinguishing
15 feature; six cases of toxic vitritis presented with hypopyon. The authors attributed these
16 cases to a toxic reaction from the brand of syringe used for injection. Georgopoulos and
17 colleagues¹⁰ reported eight cases of non-infectious endophthalmitis after bevacizumab.
18 All cases presented within two days of injection without hypopyon. Only one patient had
19 pain. Mezd-Koursh and colleagues found that later presentation, pain, keratic
20 precipitates, fibrin, hypopyon, and anterior synechiae were more typical of culture
21 positive endophthalmitis¹⁸.

22 In contrast, our study suggests that one cannot clinically distinguish between
23 culture-positive and culture-negative endophthalmitis after anti-VEGF injection. All
24 cases in our series had pain, decreased vision, and vitritis. Both culture-positive and
25 culture-negative cases presented an average of three to four days after injection. Most
26 patients in both groups had a hypopyon. Anecdotally, one case of endophthalmitis due to
27 *Streptococcus viridans* with a final visual acuity of no light perception initially presented
28 two days after injection with 3+ cell and no hypopyon. Another patient presented with
29 sequential hypopyon endophthalmitis after bevacizumab. The first episode resolved to
30 baseline visual acuity six weeks after tap and inject. The second episode did not improve
31 with hourly topical prednisolone acetate, and required tap and inject to control the
32 inflammation; the vision never returned to baseline visual acuity at six months. We
33 suggest that presumed infectious endophthalmitis should be considered in all instances
34 with post-injection inflammation in the vitreous cavity greater than 1+ cell, and strong
35 consideration should be given to treating these cases with emergent tap and injection of
36 intravitreal antibiotics.

37 Although most cases with endophthalmitis after intravitreal anti-VEGF injection
38 returned to baseline visual acuity within three to six months, 17% lost more than two
39 lines at final follow-up. These outcomes are similar to those reported by Klein and
40 colleagues⁶, and worse than those in other smaller studies^{8, 19}. There was no significant
41 difference in rates of visual recovery between culture-positive and culture-negative cases.
42 Only a small percentage of cases (17%) required pars plana vitrectomy.

43 Several authors have emphasized the role of specific aspects of prepping
44 technique to prevent endophthalmitis after intravitreal injection. The only proven
45 endophthalmitis prophylaxis remains topical povidone-iodine to sterilize the ocular
46 surface^{20, 21}. It is important to sterilize the ocular surface with povidone-iodine before

1 applying a viscous anesthetic; viscous gel can form a barrier preventing povidone-iodine
2 from coming in contact with conjunctival bacteria^{22, 23}. Further, physicians and patients
3 should avoid talking, coughing, and sneezing during anti-VEGF injection administration
4 to prevent contamination with oral flora^{24, 25}. Streptococcus species isolates, bacteria
5 commonly found in oral flora and isolated in two of our cases, occur three to four times
6 more frequent in endophthalmitis after intravitreal injection than after intraocular
7 surgery^{24, 25}.

8 The VEGF Inhibition Study in Ocular Neovascularization (VISION) trial²⁶
9 investigators felt the risk of post-injection endophthalmitis could be modified by
10 vigilance to an aseptic injection technique. Their initial endophthalmitis rate was 0.18%
11 per injection (13 cases in 7,171 injections). After amending the injection protocol to
12 include a sterile drape and an additional pre-injection antibiotic or povidone-iodine flush,
13 rates decreased to 0.04% (2 of 4,465) at centers adopting the amended protocol. They
14 attributed 75% of cases (9 of 12) to the failure of using a lid speculum. Many authors
15 recommend use of a bladed lid speculum²⁷⁻³⁰, though this recommendation is based on
16 the theoretical benefit of covering the eyelashes and eyelids from touching the needles
17 and injection site, and not on empiric evidence. Others argue that insertion of a lid
18 speculum can massage secretions from meibomian glands, thus contaminating the ocular
19 surface³⁰. Mason and colleagues³¹ recently reported in a prospective masked randomized
20 trial of 174 patients undergoing intravitreal injection that lid speculum use did not result
21 in an increase in conjunctival bacterial counts (paired t-test, p=0.9455). Our study found
22 no difference in endophthalmitis rates when comparing injections administered with and
23 without a bladed lid speculum. All of the studies to date, including ours with a relatively
24 large sample size, are underpowered to detect smaller differences in the rate of
25 endophthalmitis due to the low incidence of endophthalmitis. Over 100,000 injections
26 would need to be administered in order to find a difference in endophthalmitis rate of
27 0.05% and 0.10%.

28 There is some debate as to the whether hemisphere or quadrant of injection affects
29 endophthalmitis rates. Superior hemisphere injections tend to be covered by the upper
30 eyelid, away from a potentially contaminated lid margin and meibomian glands.
31 Additionally, this location allows masking of incidental subconjunctival hemorrhage by
32 the upper eyelid. The disadvantage of superior hemisphere injections is the difficulty of
33 administering the injection when patients attempt to squeeze their eyes with resultant
34 Bell's reflex and supraduction. Those who inject in the inferior hemisphere often find
35 good exposure. Further, the upward gaze required by inferior hemisphere injection thins
36 the inferior tear film, theoretically decreasing the concentration of bacteria⁸. On the other
37 hand, other ocular surgeries, such as inferiorly placed trabeculectomies, carry an
38 increased risk of endophthalmitis compared to those placed superiorly^{32, 33}, a finding
39 attributed to the bacteria-rich tear film³⁴. Roth and colleagues³⁵ reported a greater risk of
40 endophthalmitis after inferior hemisphere injection compared to those in the superior
41 hemisphere among 10,834 consecutive injections. Our study found no difference in
42 endophthalmitis risk between superior and inferior hemisphere injections, suggesting
43 either hemisphere is acceptable.

44 Some vitreoretinal specialists displace the conjunctiva with a sterile cotton tip
45 applicator when injecting through the pars plana in an effort to avoid a straight tract for
46 bacteria to enter through the conjunctiva and sclera into the vitreous cavity³⁶. Others

1 argue it is best to minimize manipulation of the ocular surface to decrease risk of
2 potential contamination. In our study, there was no difference in endophthalmitis risk
3 between those who do and do not displace conjunctiva while injecting.

4 There was no difference in endophthalmitis risk after bevacizumab or
5 ranibizumab injection in our study, similar to the findings of other studies^{6,8}. Given the
6 wide confidence intervals, however, we cannot draw strong conclusions from this result.

7 Our study has several limitations. Although we identified and recorded
8 endophthalmitis cases prospectively with an infection surveillance program, a method we
9 feel is more accurate than retrospective identification, it is possible that we
10 underestimated risk of endophthalmitis. We retrospectively reviewed charts at the end of
11 the surveillance period, which could have introduced certain biases and inaccuracies. For
12 example, our study utilized Snellen acuity, which is not as accurate as best-corrected
13 visual acuity. Also, we were unable to assess other relevant risk factors, such as degree of
14 blepharitis, because this was not systematically documented in the charts. Our culture-
15 positivity rate of 30.4% was lower compared to other studies. For example, the
16 Endophthalmitis Vitrectomy Study (EVS)³⁷ reported that 66% of cases (138 of 202)
17 undergoing tap and inject for endophthalmitis after cataract surgery were confirmed
18 culture-positive. Their higher rate of culture-positivity may be related to their
19 methodology; they collected vitreous samples by either single port vitrectomy or needle
20 aspiration whereas we only used needle aspiration. In our study, nine of 23 cases had an
21 unsuccessful vitreous biopsy and thus had aqueous biopsy alone, and in the EVS,
22 aqueous biopsy was associated with a lower confirmed laboratory infection rate (26.9%)
23 compared to undiluted vitreous (58.9%)³⁸.

24 Another possible reason our culture-positivity rate was low could be that we
25 included cases of presumed non-infectious endophthalmitis. Intraocular inflammation is
26 a known possible sequela of intravitreal anti-VEGF injection^{10,39}. Our standard practice
27 is to administer intravitreal antibiotics whenever the examining physician feels that the case
28 is more likely than non-infectious endophthalmitis.

29 Because of the low incidence of endophthalmitis, our risk factor analysis is
30 underpowered to find small differences. It is possible that our risk factor results are
31 subject to misclassification bias if the injecting vitreoretinal specialists deviated from
32 their preferred injection technique during some injections. Further, there may have been
33 undocumented variations in prepping technique in cases developing endophthalmitis.

34 In summary, the risk of endophthalmitis after intravitreal anti-VEGF injection is
35 low. The accuracy of reported rates in the literature, in part, depends on individual study
36 designs and the study's definition of "endophthalmitis". Visual outcomes are good for
37 most cases, with 83% to baseline visual acuity within three to six months. However, a
38 subgroup of infected eyes will have devastating visual outcomes. The presence or
39 absence of pain, vitritis, decreased vision, or hypopyon, and the interval between
40 injection and presentation, does not help distinguish culture-positive from culture-
41 negative cases. Thus, we recommend vitreoretinal specialists have a low threshold to
42 perform emergent tap and injection of intravitreal antibiotics. This study did not identify
43 any modifiable risk factors to prevent endophthalmitis. The incidence endophthalmitis
44 does not appear to be affected by use of a lid speculum, conjunctival displacement,
45 hemisphere of injection, or use bevacizumab or ranibizumab.

References

1. Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology* 2010;117:1124-33.
2. Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology* 2010;117:1102-12.
3. Gheith ME, Siam GA, de Barros DS, et al. Role of intravitreal bevacizumab in neovascular glaucoma. *J Ocul Pharmacol Ther* 2007;23:487-91.
4. Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010;117:1064-77 e35.
5. Pharmakakis NM, Petropoulos IK, Georgakopoulos CD, et al. Apoptotic mechanisms within the retina in *Staphylococcus epidermidis* experimental endophthalmitis. *Graefes Arch Clin Exp Ophthalmol* 2009;247:667-74.
6. Klein KS, Walsh MK, Hassan TS, et al. Endophthalmitis after anti-VEGF injections. *Ophthalmology* 2009;116:1225.
7. Diago T, McCannel CA, Bakri SJ, et al. Infectious endophthalmitis after intravitreal injection of antiangiogenic agents. *Retina* 2009;29:601-5.
8. Pilli S, Kotsolis A, Spaide RF, et al. Endophthalmitis associated with intravitreal anti-vascular endothelial growth factor therapy injections in an office setting. *Am J Ophthalmol* 2008;145:879-82.
9. Ness T, Feltgen N, Agostini H, et al. Toxic vitritis outbreak after intravitreal injection. *Retina*;30:332-8.
10. Georgopoulos M, Polak K, Prager F, et al. Characteristics of severe intraocular inflammation following intravitreal injection of bevacizumab (Avastin). *Br J Ophthalmol* 2009;93:457-62.
11. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419-31.
12. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. *Ophthalmology* 2009;116:57-65 e5.
13. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432-44.
14. Fintak DR, Shah GK, Blinder KJ, et al. Incidence of endophthalmitis related to intravitreal injection of bevacizumab and ranibizumab. *Retina* 2008;28:1395-9.
15. Fong DS, Custis P, Howes J, Hsu JW. Intravitreal bevacizumab and ranibizumab for age-related macular degeneration a multicenter, retrospective study. *Ophthalmology* 2010;117:298-302.
16. Yamashiro K, Tsujikawa A, Miyamoto K, et al. Sterile endophthalmitis after intravitreal injection of bevacizumab obtained from a single batch. *Retina* 2010;30:485-90.
17. Wickremasinghe SS, Michalova K, Gilhotra J, et al. Acute intraocular inflammation after intravitreal injections of bevacizumab for treatment of neovascular age-related macular degeneration. *Ophthalmology* 2008;115:1911-5.

- 1 18. Mezaad-Koursh D, Goldstein M, Heilwail G, et al. Clinical characteristics of
2 endophthalmitis after an injection of intravitreal anti-vascular endothelial growth factor.
3 *Retina* 2010;30:1051-7.
- 4 19. Mason JO, 3rd, White MF, Feist RM, et al. Incidence of acute onset
5 endophthalmitis following intravitreal bevacizumab (Avastin) injection. *Retina*
6 2008;28:564-7.
- 7 20. Speaker MG, Menikoff JA. Prophylaxis of endophthalmitis with topical
8 povidone-iodine. *Ophthalmology* 1991;98:1769-75.
- 9 21. Moss JM, Sanislo SR, Ta CN. A prospective randomized evaluation of topical
10 gatifloxacin on conjunctival flora in patients undergoing intravitreal injections.
11 *Ophthalmology* 2009;116:1498-501.
- 12 22. Boden JH, Myers ML, Lee T, et al. Effect of lidocaine gel on povidone-iodine
13 antisepsis and microbial survival. *J Cataract Refract Surg* 2008;34:1773-5.
- 14 23. Awotesu S, Eke T. Preoperative lidocaine gel. *Ophthalmology*;117:1049.
- 15 24. McCannel CA. Meta-analysis of endophthalmitis after intravitreal injection of
16 anti-VEGF agents: causative organisms and possible prevention strategies. Presented at
17 American Society of Retina Specialists, September 1, 2010, Vancouver, Canada.
- 18 25. Chen E LM, Cox J, Brown DM. Ten years of endophthalmitis at a single tertiary
19 retina practice: comparing intravitreal injection cases vs. post-anterior segment surgery
20 cases. Presented at American Society of Retina Specialists, September 1, 2010,
21 Vancouver, Canada.
- 22 26. D'Amico DJ, Masonson HN, Patel M, et al. Pegaptanib sodium for neovascular
23 age-related macular degeneration: two-year safety results of the two prospective,
24 multicenter, controlled clinical trials. *Ophthalmology* 2006;113:992-1001.
- 25 27. Ta CN. Minimizing the risk of endophthalmitis following intravitreal injections.
26 *Retina* 2004;24:699-705.
- 27 28. Scott IU, Flynn HW, Jr. Reducing the risk of endophthalmitis following
28 intravitreal injections. *Retina* 2007;27:10-2.
- 29 29. Bhavsar AR, Googe JM, Jr., Stockdale CR, et al. Risk of endophthalmitis after
30 intravitreal drug injection when topical antibiotics are not required: the diabetic
31 retinopathy clinical research network laser-ranibizumab-triamcinolone clinical trials.
32 *Arch Ophthalmol* 2009;127:1581-3.
- 33 30. Aiello LP, Brucker AJ, Chang S, et al. Evolving guidelines for intravitreal
34 injections. *Retina* 2004;24:S3-19.
- 35 31. Mason JO, 3rd, Friedman DA, Finley TA, et al. Timing of Povidone-Iodine
36 Prophylaxis for Intravitreal Injections. Presented at the American Academy of
37 Ophthalmology Annual Meeting, October 18, 2010, Chicago, Illinois.
- 38 32. Higginbotham EJ, Stevens RK, Musch DC, et al. Bleb-related endophthalmitis
39 after trabeculectomy with mitomycin C. *Ophthalmology* 1996;103:650-6.
- 40 33. Mac I, Soltau JB. Glaucoma-filtering bleb infections. *Curr Opin Ophthalmol*
41 2003;14:91-4.
- 42 34. Dunnington JH, Locatcher-Khorazo D. Value of cultures before operation for
43 cataract. *Arch Ophthalmol* 1945;34:215-9.
- 44 35. Roth D, Gowtham J, Kheterpal A, et al. Inferior Intravitreal Injection Site
45 Associated With Higher Incidence of Post-injection Endophthalmitis. Presented at

- 1 American Academy of Ophthalmology Annual Meeting, October 25, 2009, San
- 2 Francisco, CA.
- 3 36. Garg SJ, Recchia FM. Re: Evolving guidelines for intravitreal injections. *Retina*
- 4 2005;25:949-50.
- 5 37. Results of the Endophthalmitis Vitrectomy Study. A randomized trial of
- 6 immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative
- 7 bacterial endophthalmitis. Endophthalmitis Vitrectomy Study Group. *Arch Ophthalmol*
- 8 1995;113:1479-96.
- 9 38. Barza M, Pavan PR, Doft BH, et al. Evaluation of microbiological diagnostic
- 10 techniques in postoperative endophthalmitis in the Endophthalmitis Vitrectomy Study.
- 11 *Arch Ophthalmol* 1997;115:1142-50.
- 12 39. Bakri SJ, Larson TA, Edwards AO. Intraocular inflammation following
- 13 intravitreal injection of bevacizumab. *Graefes Arch Clin Exp Ophthalmol* 2008;246:779-
- 14 81.

Comment [SG1]: Hi C, citatin 23
needs year

15
16
17
18
19
20