Respiratory Flora May Contribute Significantly to Endophthalmitis After Anti-VEGF Injection

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Introduction
The prevalence of intraocular infections of anti-VEGF medications has increased substantially over the past several years, and with it, so has the incidence of endophthalmitis cases.

Previous studies have reported rates of endophthalmitis after injection of anti-VEGF medications ranging from 0.13% to 0.54%.

The study of such cases of endophthalmitis will determine the best methods of prevention and to optimize management of this rare but potentially visually-devastating ocular complication.

There is no uniformly agreed upon optimal management strategy and treatment paradigm for endophthalmitis treatment.

In this study, we report the rate of post anti-VEGF injection endophthalmitis at a large academic institution within our academic institution.

To determine the rate of endophthalmitis after anti-VEGF injection, we determined the number of injections at our institution and the number of endophthalmitis cases secondary to these injections. During the same time period, the Retina Division Infusion Center was responsible for 7146 total anti-VEGF injections, comprised of 6133 ranibizumab, and 1133 bevacizumab.

We also scrutinized each case of these cases of endophthalmitis, including those referred from community physicians, to elucidate if there were any associations with sources of infection or better outcomes in visual acuity.

Methods
To determine the prevalence of endophthalmitis among patients treated in the Retina Division Infusion Center, after obtaining Institutional Review Board approval (JHR study# 10–005312), we collected all cases of endophthalmitis in the department by interrogating the billing data base for ICD-9 codes 360.01 (endophthalmitis), 360.03 (chronic endophthalmitis), and 360.1 (other endophthalmitis). The billing records were available from November 2008 through March 2011 inclusive.

All cases of endophthalmitis yielded by the search were evaluated for association with recent anti-VEGF injection prior to the onset of symptoms. The total number of endophthalmitis cases reported during this time period was obtained from the Retina Division Infusion Center records, which were obtained biweekly from each provider on a monthly basis.

A retrospective chart review was performed on the patients who had been diagnosed with endophthalmitis following anti-VEGF injection. Data collected included the pre-endophthalmitis best corrected visual acuity (BCVA), BCVA at the time of endophthalmitis presentation, the timing of endophthalmitis symptom onset, the type of intervention performed (e.g., vitreous sampling, intravitreal antibiotic injection, vitrectomy, and culture result) type of anti-VEGF drug injected, and length of follow up.

Other patients outside the time period of the billing department search were also included based on the records of the retina providers from 2004 through 2011.

The total number of anti-VEGF injections for each fiscal year from 2004 through 2011 was obtained from the Retina Division Infusion Center records.

Results
The search of ICD-9 codes yielded 115 patients with endophthalmitis of various etiologies from November 2008 through March 2011. All cases associated with anti-VEGF injection (both after ranibizumab) at the retina infusion center were identified. A third case was identified (after bevacizumab) who had previous injections at the retina infusion division center, and was referred to our center for management from an outside injecting physician. Therefore, we estimate anti-VEGF injections account for a relatively small proportion of endophthalmitis cases (3115, 1.5%) at our academic institution.

To determine the rate of endophthalmitis after anti-VEGF injection, we defined the number of injections at our infusion center and the number of endophthalmitis cases secondary to these injections. During the same time period above, the Retina Division Infusion Center was responsible for 7146 total anti-VEGF injections, comprised of 6133 ranibizumab, and 1133 bevacizumab. Therefore, we estimate the endophthalmitis rate associated with anti-VEGF injection is 0.028% (2/7146). The risk associated with ranibizumab alone was 0.033% (2/6013). The risk associated with bevacizumab is undetermined, but is presumably less than 0.008% (1/123).

To estimate the rate of endophthalmitis after anti-VEGF injection another way, we explored our search beyond the dates available in the billing data base. We collected all cases of endophthalmitis associated with anti-VEGF injections from retina providers in our department. We also determined the number of injections given in the history of the Retina Division Infusion Center from the time close records had been kept. We found that from January 1, 2007 through December 31, 2011, 141-141 ranibizumab, and 2152 bevacizumab were given, totaling 1426 anti-VEGF injections. No patients were infected.

During this time period, five cases of endophthalmitis were seen, four ranibizumab, and one bevacizumab. The rate of endophthalmitis, therefore, 0.028% (1/141) for ranibizumab, 0.083% (2/2152) for bevacizumab, and 0.005% (5/100) overall.

The injecting physicians followed a variety of injection protocols, with respect to whether or not a surgical face mask was utilized, the type of anesthetic (subcutaneous vs. topical), and use of post-injection antibiotics.

All injecting physicians were, however, consistent in that they all wore gloves (some wore sterile gloves and some wore non-sterile gloves during the injection, and all used providone-iodine ocular surface preparation, and a lid speculum.

Four patients eventually had therapeutic vitrectomy to clear the source of injection contamination.

Conclusions
1. Post-injection inflammation with decreased vision, pain, and vitritis should be treated as endophthalmitis.
2. Our post-injection endophthalmitis rate is 0.033%.038%
3. The decision to proceed with and timing of vitrectomy should be made on a case by case basis.
4. Respiratory droplets may be a significant source of injection contamination.
5. Avoiding speaking and/or wearing a mask is logical. However, these measures remain an unproven means of decreasing the rate of post-injection endophthalmitis.

Table
Age Sex Location Diagnosis Drug Days to Presentation Hypopyon Tap & Inject Days to PPV Cultures weeks follow up pre VA final VA

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>Diagnosis</th>
<th>Drug</th>
<th>Days to PPV</th>
<th>Hypopyon</th>
<th>Tap &amp; Inject</th>
<th>Days to PPV</th>
<th>Cultures</th>
<th>weeks follow up</th>
<th>pre VA</th>
<th>final VA</th>
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<tbody>
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<td>AMD</td>
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<td>17</td>
<td>20/100</td>
<td>20/50</td>
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Disclosures
The authors have no financial disclosures.

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Literature cited
Methods

To determine the prevalence of endophthalmitis among patients treated in the Retina Division Infusion Center, after obtaining Institutional Review Board approval (JHH study# NA_00043312), we collected all cases of endophthalmitis in the department by interrogating the billing database for ICD-9 codes 360.0 (purulent endophthalmitis), 360.01 (acute endophthalmitis), 360.03 (chronic endophthalmitis), and 360.1 (other endophthalmitis). The billing records were available from November 2008 through March 2011 inclusive. All cases of endophthalmitis yielded by the search were evaluated for association with recent anti-VEGF injection prior to the onset of symptoms. The total number of anti-VEGF injections given during this time period was obtained from the Retina Division Infusion Center records, which are meticulously kept for each provider on a monthly basis. A retrospective chart review was performed on the patients who had been diagnosed with endophthalmitis following anti-VEGF injection. Data collected included the pre-endophthalmitis best corrected visual acuity (BCVA), BCVA at the time of endophthalmitis presentation, the timing of endophthalmitis symptom onset, the type of intervention performed (for example, vitreous sampling, intravitreal antibiotic injection, vitrectomy, and culture results) type of anti-VEGF drug injected, and length of follow-up. Other patients outside the time period of the billing department search were also included based on the records of the retina providers from 2004 through 2011. The total number of anti-VEGF injections for each fiscal year from 2004 through 2011 was obtained from the Retina Division Infusion Center records.
Results

- The search of ICD-9 codes yielded 115 patients with endophthalmitis of various etiologies from November 2008 through March 2011. Two cases associated with anti-VEGF injection (both after ranibizumab) at the retina infusion center were identified. A third case was identified (after bevacizumab) who had not been injected at the retina division infusion center, and was referred to our center for management from an outside injecting physician. Therefore, we estimate anti-VEGF injections account for a relatively small proportion of endophthalmitis cases (3/115, 2.6%) at our academic institution.

- To determine the rate of endophthalmitis after anti-VEGF injection, we determined the number of injections at our infusion center and the number of endophthalmitis cases secondary to these injections. During the same time period above, the Retina Division Infusion Center was responsible for 7146 total anti-VEGF injections, comprised of 6013 ranibizumab, and 1133 bevacizumab. Therefore, we estimate the endophthalmitis risk associated with anti-VEGF injection is 0.028% (2/7146). The risk associated with ranibizumab alone was 0.033% (2/6013). The risk associated with bevacizumab is undetermined, but is presumably less than 0.088% (1/1133).

- To estimate the rate of endophthalmitis after anti-VEGF injection another way, we expanded our search beyond the dates available in the billing data base. We collected all cases of endophthalmitis associated with anti-VEGF injections from retina providers in our department. We also determined the number of injections given in the history of the Retina Division Infusion Center from the time close records had been kept. We found that from January 1, 2007 through December 31, 2011, 11491 ranibizumab, and 2635 bevacizumab were given, totaling 14126 anti-VEGF injections. No pegaptanib was injected. During this time period, five cases of endophthalmitis were seen, four ranibizumab, and one bevacizumab. The rate of endophthalmitis was, therefore, 0.035% (4/11491) for ranibizumab, 0.038% (1/2635) for bevacizumab, and 0.035% (5/14126) overall.
Results

The injecting physicians followed a variety of injection protocols, with respect to whether or not a surgical face mask was utilized, the type of anesthesia (subconjunctival vs. topical), and use of post-injection antibiotics. All injecting physicians were, however, consistent in that they all wore gloves (some wore sterile gloves and some wore non-sterile gloves) during the injection, and all used povidone-iodine ocular surface preparation, and a lid speculum.

Table 1 shows the list of eight patients with post-injection endophthalmitis. Four occurred after ranibizumab injection, and four followed bevacizumab injection. All of the cases had decreased vision, pain, and vitritis. Patients presented for treatment 3 to 4 days after injection, and all received intravitreal injection of vancomycin and ceftazidime and vitreous sampling at the time of presentation.

Four patients had positive cultures, and the other four had negative cultures. Of the four patients with positive vitreous cultures, two cases were associated with ubiquitous ocular surface flora (coag. Neg. Staphylococcus, P. Acnes). The other two cases were associated with bacteria which dominate the oral and upper respiratory flora (Corynebacterium, Neisseria spp. and Strep. viridans) (Ross, 1971).

Four patients eventually had therapeutic vitrectomy to clear the vitreous debris to improve media opacity. Each of our reported cases has a minimum follow up period of twelve weeks. Four patients of the eight had substantial vision loss. All but one patient presented with hypopyon.

No parameters, including signs and symptoms on presentation, type of anti-VEGF therapy, culture positive or negative status, type of microbiologic isolate cultured, etiologic condition (neovascular age-related macular degeneration, retinal vein occlusion, etc.), performance of vitrectomy, or timing of vitrectomy, correlated significantly with final visual outcome.
## Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>Diagnosis</th>
<th>Drug</th>
<th>Days to Presentation</th>
<th>Hypopyon</th>
<th>Tap &amp; Inject</th>
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JHH = Johns Hopkins Hospital, SC = satellite clinic, AMD = age-related macular degeneration, RVO = retinal vein occlusion, CNV = choroidal neovascularization, CME = cystoid macular edema, PPV = pars plana vitrectomy
Conclusions

• Post-injection inflammation with decreased vision, pain, and vitritis should be treated as endophthalmitis.

• Our post-injection endophthalmitis rate is 0.033-0.038%.

• The decision to proceed with and timing of vitrectomy should be made on a case by case basis.

• Respiratory droplets may be a significant source of contamination.

• Avoiding speaking and/or wearing a mask is logical. However, these measures remain an unproven means of decreasing the rate of post-injection endophthalmitis.