

## Management and visual outcomes of twenty-four cases of culture-proven acute bacterial endophthalmitis following intravitreal injection of contaminated bevacizumab in a single day.

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### Abstract

**Purpose:** Bevacizumab requires compounding for off-label intravitreal injection and thus there is a risk of possible contamination during preparation. Here we describe the visual outcomes and management for a case series of culture-proven acute bacterial endophthalmitis following contaminated bevacizumab intravitreal injection performed in a single day.

**Design:** Retrospective consecutive case series from a single site.

**Subjects:** Patients who developed culture-proven acute endophthalmitis after receiving intravitreal injection with contaminated bevacizumab.

**Methods:** All patients suspected of endophthalmitis had vitreous biopsy and microbial cultures prior to initiation of treatment. All patients were managed with immediate tap and injection of antibiotics (TAI) followed early by pars plana vitrectomy (PPV).

**Main outcome measures:** Best-corrected visual acuity (BCVA) at three-month follow-up after treatment.

**Results:** Twenty-four patients developed acute bacterial endophthalmitis following intravitreal injection of 24 contaminated bevacizumab single-dose syringes in a single day. All cases had culture-positive microbiology; 23 (95.8%) grew *Streptococcus* species and one (4.2%) grew *Enterococcus* species. Six cases (25.0%) had optic nerve atrophy, 3 (12.5%) developed retinal detachment (RD), one (4.2%) had vitreous hemorrhage and one (4.2%) had band keratopathy. At three-month follow-up, compared to BCVA at the time of initial presentation, 11 (45.8%) patients had improved vision; 8 patients (33.3%) had unchanged BCVA and 5 patients (20.8%) had worse BCVA. However, at three month follow-up, when compared to BCVA prior to endophthalmitis (baseline), 22 cases (91.7%) had significantly worse BCVA.

**Conclusion:** Contamination of off-label bevacizumab poses devastating risk of endophthalmitis following intravitreal injection. The most common virulent pathogen was *Streptococcus* which portends poor visual prognosis and requires immediate aggressive management. Vigilance needs to continue to ensure that all possible safeguards are in place to prevent contamination during preparation of off-label bevacizumab for intravitreal injection.

**Keywords:** Bevacizumab, Endophthalmitis, Keratopathy, Intravitreal injection.

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### Introduction

Biologic vascular endothelial growth factor (VEGF) antagonists, such as bevacizumab, ranibizumab and aflibercept, are mainstays in the treatment for common vitreoretinal disorders such as diabetic macular edema, exudative age-related macular degeneration and edema associated with retinal vein occlusions. Although the incidence of endophthalmitis following anti-VEGF injections is low, this is still the most devastating and challenging complication faced by retina specialists [1-5].

Worldwide, bevacizumab is routinely used as an effective off-label intravitreal anti-VEGF agent; however, because a single 100 mg bevacizumab vial can be aliquoted into multiple individual 1.25 mg (0.05 mL) intravitreal vial preparations via a compounding pharmacy, there is risk for contamination and loss of sterility which can produce unfortunate clusters of complications such as endophthalmitis.

Our case series is an unfortunate example of a cohort of patients who were affected by a contaminated batch of bevacizumab vials that resulted in severe endophthalmitis. Although we routinely extrapolate management of

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endophthalmitis following cataract surgery as suggested in the Endophthalmitis Vitrectomy Study (EVS) [6], this study is both dated and inadequate when faced with atypical occurrences such as contamination from compounding. The purpose of our case series is to evaluate the microbiology results, management and visual outcomes of endophthalmitis following intravitreal injection secondary to contaminated bevacizumab in order to mitigate the knowledge gap present in these inherently rare circumstances.

## Methods

### Study design

This case series was conducted adhering to the tenets of the Declaration of Helsinki with Institutional Ethics Review Board approval. This study is HIPPA-compliant. The study sample is composed of all patients with culture-proven acute bacterial endophthalmitis following intravitreal injection of bevacizumab (Genentech, South San Francisco, CA) injections at the International Eye Centre (Palestinian Authority, Gaza). All patients received intravitreal injection on June 13, 2019. All patients injected developed endophthalmitis (100% rate of endophthalmitis). Once risk of possible contamination was identified, no other patients were treated with the same bevacizumab lot. No other cases of endophthalmitis occurred during the study period.

Data was retrospectively collected from clinical records included: age, sex, clinical diagnosis, number of days from inciting event to presentation, number of days from presentation to undergoing tap and injections of antibiotics (TAI), number of days from TAI to pars plana vitrectomy (PPV), number of days from presentation to undergoing PPV. Snellen best-corrected visual acuity (BCVA) at the time of receiving bevacizumab injections, at presentation of infection, and three-month post-management of the endophthalmitis were collected. In addition, microbiology culture results and complications were also recorded.

### Anti-VEGF agent and injection technique

All of the eyes with acute endophthalmitis were previously injected with bevacizumab [Genentech, South San Francisco, CA] 1.25 mg/0.05 mL in an outpatient clinic setting. The single dose syringes of bevacizumab were provided by Concept Pharmacy (Tel Aviv), a compounding company located in Gaza. After identifying the cluster of endophthalmitis cases, it was discovered that sterility had not been ensured during transportation of single dose bevacizumab syringes likely resulting in contaminated anti-VEGF agent.

Facemasks were utilized during intravitreal injections and talking was minimized during injection by physician and patient. Topical anesthetic drops (proparacaine 0.5%) and gel anesthetic (tetracaine 0.5%) were used to anesthetize the eye prior to 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 two to three drops of this solution into the

conjunctival cul-de-sac prior to injection. The lids were held open with a sterile eyelid speculum to keep the eyelids and eyelashes out of the field. Bevacizumab was injected into the vitreous cavity via the pars plana (3-4 mm from the limbus) using a short 30-gauge needle for all patients by 2 different retina specialists. All injections were performed in the inferotemporal location. No post-operative eye drops (e.g. antibiotics) were prescribed to the patient after the injection.

### Endophthalmitis management

Once the clinical diagnosis of endophthalmitis was made, all eyes received immediate diagnostic vitreous biopsy followed by injection of intravitreal antibiotics on the same day. Diagnostic vitreous tap was performed through the pars plana. The vitreous biopsy was performed with insertion of a short 25-gauge needle into the vitreous cavity to aspirate a vitreous sample. A 0.1 to 0.3 mL vitreous sample was taken for microbiological assessment. All collected specimens were sent for gram stain, cultures, and sensitivities. Patients were then given intravitreal injections of vancomycin (1 mg/0.1 mL), ceftazidime (2.25 mg/0.1 mL) and dexamethasone (0.4 mg/0.1 mL). Topical steroid (1% prednisolone acetate) and fortified antibiotic drops (vancomycin and ceftazidime) were also prescribed and the patients were followed daily.

Following initial TAI, all twenty-four patients underwent PPV within 72 hours of presentation. 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. PPV (20-gauge) was performed and all opacified vitreous were removed with the vitreous cutter. Limited core vitrectomies were performed and peripheral shaving was not performed. When required, the corneal epithelium was debrided and pars plana lensectomy was performed.

Inspection was performed and any retinal breaks (if present) were demarcated with laser retinopexy. A partial or complete air-fluid exchange was performed. All sclerotomy sites were sutured. Silicone oil was used for severe cases. At the conclusion of the case, intravitreal injection of 0.1 mL of vancomycin (1.0 mg/0.1 mL) and 0.1 mL of ceftazidime (2.25 mg/0.1 mL) were performed through the pars plana with a short 30-gauge needle.

### Statistical analysis

Descriptive analysis was used to describe the sample characteristics. Continuous variables were described by using means and standard deviations (SD). Categorical variables were described by using frequencies and percentages (%). All statistical analyses were performed using the SAS, Version 9.3 (SAS, Institute, Cary, NC).

## Results

Twenty-four patients with culture-proven acute bacterial endophthalmitis following bevacizumab intravitreal injection related to contaminated lots were identified. Patient mean age was 59.3 (SD=8.7) years and 58.3% of the patients were male.

Majority of patients received bevacizumab for proliferative diabetic retinopathy (PDR) (66.7%) and diabetic macular edema (DME) (62.5%) (Table 1).

**Table 1.** Study sample (n=24).

Variables	Mean	(SD)	Frequency	(%)
Age	59.3	8.7		
Sex				
Male			14	58.3
Female			10	41.7
Diagnosis (treatment indications)				
PDR			16	66.7
DME			15	62.5
PDR with DME			9	37.5
PDR with VH			5	20.8
Exudative AMD			2	8.3
CSCR			1	4.2
Time from bevacizumab injection to presentation (days)	2.29	0.69		
Time from bevacizumab injection to TAI (days)	2.33	0.7		
Time from TAI to PPV (days)	2.04	0.81		
Culture				
Streptococcus species			23	95.8
Enterococcus species			1	4.2

\*Note: PDR: Proliferative Diabetic Retinopathy; DME: Diabetic Macular Edema; VH: Vitreous Hemorrhage; AMD: Age-Related Macular Degeneration; CSCR: Central Serous Chorioretinopathy; TAI: Tap and Injection of Antibiotics; PPV: Pars Plana Vitrectomy

Before developing endophthalmitis, six (25.0%) patients had a baseline vision better than 20/40, four (16.7%) had 20/40 to 20/80 vision, eleven (45.8%) had 20/100 to 20/400 vision, two (8.3%) had counting figures (CF) vision, and one (4.2%) had hand motion (HM) vision (Table 2).

**Table 2.** Visual acuity prior to endophthalmitis, at presentation, and at 3-month follow-up after treatments (n=24).

Variables	Mean	(SD)	Frequency	(%)
<b>BCVA at the time receiving bevacizumab injection</b>				
Better than 20/40			6	25
20/40 to 20/80			4	16.7
20/100 to 20/400			11	45.8
CF			2	8.3
HM			1	4.2
LP			0	0

NLP			0	0
<b>BCVA at presentation</b>	2.7	0.72	-	-
Better than 20/40			0	0
20/40 to 20/80			0	0
20/100 to 20/400			2	8.3
CF			4	16.7
HM			17	70.8
LP			1	4.2
NLP			0	0
<b>BCVA at 3-month follow-up</b>	2.4	1.2	-	-
Better than 20/40			0	0
20/40 to 20/80			0	0
20/100 to 20/400			6	25
CF			8	33.3
HM			5	20.8
LP			4	16.7
NLP			1	4.2

\*BCVA: Best-Corrected Visual Acuity; CF: Counting Finger; HM: Hand Motion; LP: Light Perception; NLP: No Light Perception

The mean time between bevacizumab injection and the initial presentation was 2.3 days (SD=0.7). All of patients received TAI same day of initial presentation. At presentation, two (8.3%) patients had a BCVA of 20/100 to 20/400, four (16.7%) patients had a vision of CF, seventeen (70.8%) had HM vision, and one (4.2%) had LP vision. On presentation, nineteen (79.1%) patients had severe inflammation, four (16.7%) had moderate inflammation, and one (4.2%) had mild inflammation.

All patients had a culture-positive vitreous biopsy result. Out of 24 patients, 23 (95.8%) grew Streptococcus species and one (4.2%) grew Enterococcus species. Following initial TAI, all patients underwent PPV and the mean time between TAI and PPV was 2.0 days (SD=0.81). During PPV, 1 (4.2%) patient had pars plana lensectomy and 2 (8.3%) patients had SO tamponade. One patient needed repeat PPV with intravitreal injection of antibiotics at the surgeon's discretion.

**Table 3.** Complications following endophthalmitis and treatments (n=24).

Complications	Frequency	(%)
Optic nerve atrophy	6	25
Retinal detachment	3	12.5
Vitreous hemorrhage	1	4.2
Band Keratopathy	1	4.2

At three-month follow-up, six (25.0%) patients had a BCVA of 20/100 to 20/400, eight (33.3%) had a vision of CF, five (20.8%) had HM vision, and four (16.7%) had LP vision, and

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one (4.2%) had no light perception vision. At three-month follow-up, compared to the BCVA before patients developed endophthalmitis, one patient (4.2%) had improved BCVA, one (4.2%) had same BCVA but 22 (91.7%) had worse BCVA. When comparing BCVA at three-month follow-up to the BCVA at the initial endophthalmitis presentation, eleven (45.8%) patients had improved BCVA, eight patients (33.3%) had unchanged BCVA and five (20.8%) had worse BCVA.

## Discussion

Although rare, acute bacterial endophthalmitis following intravitreal injection of contaminated bevacizumab has been reported worldwide [7]. Our case series is one of the largest and consists of predominantly *Streptococcus* species. Previously, it was suggested that the positive culture of *Streptococcus* in post-injection endophthalmitis might reflect on the possibility of aerosol contamination of the surgical field by respiratory flora [8]. In our case series, the cluster feature of the affected cases was a result from contamination occurring by loss of sterility during transportation of single use bevacizumab syringes (facemask was used by treating physician in all cases).

Previously, we have shown that there is no significant difference in BCVA at six-month follow-up between TAI and PPV with intravitreal injection of antibiotics as the initial management for patients with endophthalmitis following anti-VEGF injections [5]. Although we know visual outcomes are significantly worse for patients with *Streptococcus* species (mean final visual acuity is LP), when approaching atypical and rare occurrences such as contamination, no suitable evidence-based literature exists. Our case series demonstrates that when the causative pathogen is *Streptococcus* species, aggressive management with prompt TAI followed by early PPV may be essential to improve or preserve any meaningful vision. In our current analysis, earlier vitrectomy done within 72 hours of endophthalmitis diagnosis might be beneficial as it not only allows for removal of bacteria, inflammatory cells or membranes, and toxic debris from the vitreous cavity but also promotes better diffusion of antibiotics.

Retinal detachment (RD) is a known complication of endophthalmitis, TAI and PPV. In 1983, Olson et al., reported an overall rate of 10% for RD following treatment of post-surgical endophthalmitis (14% for eyes with PPV) [9]. In 1985, Nelsen et al., reported an overall rate of 16% for RD after endophthalmitis (21% for eyes treated with PPV and 9% for eyes not treated with PPV) [10]. In 2000, based on the data collected for the EVS, Doft and colleagues reported an incidence of 8.3% for RD after treatment of post-cataract endophthalmitis, and there was no difference in incidence based on whether initial management was PPV (7.8%) or TAI (9.0%) [11].

In the same study, the authors also reported that the rates were relatively low among eyes with no growth (5%) or Gram-positive coagulase-negative growth (5%) [11]. Higher rates were reported for more virulent organisms, at 12% for Gram-negative organisms and 23% for "other" Gram-positive

organisms (the term used in the EVS to describe all Gram-positive organisms that were not coagulase-negative micrococci) [11]. In our case series, 3 (12.5%) patients developed RD after TAI plus PPV for the treatment for endophthalmitis following bevacizumab injections.

Compared to the rates of RD following PPV previously reported [9,10], a lower rate was reported in our study, which might suggest the significant advancements in vitreoretinal surgery technology and this might have allowed surgeons to perform a more thorough vitrectomy while reducing the risk of inducing iatrogenic retinal injury and subsequent RD. Compared to the rate of RD following treatment for endophthalmitis reported in Doft's study, our case series reported a higher rate of RD.

One of the explanations for this might be associated with less virulent organisms in the EVS. For example, the rate of *Streptococcus* associated post-operative endophthalmitis was 9.0% among culture-positive endophthalmitis cases in the EVS (EVS 1995), while 95.8% patients in our case series had a positive culture of *Streptococcus* species [12].

In a previous study, we found that the mean time between last anti-VEGF injection and the symptoms of endophthalmitis was 3.6 (SD=1.7) for patients with a positive culture (66.7% grew coagulase-negative *Staphylococcus*, followed by *Streptococcus* species (16.7%), *Haemophilus influenzae* (4.2%), *Erysipelothrix rhusiopathiae* (4.2%), *Serratia marcescens* (4.2%), and *Enterococcus faecalis* (4.2%)) [5]. In our current case series, the time between bevacizumab injection and start of symptoms could not accurately be determined; nonetheless, mean time between bevacizumab injection and presentation was 2.29 days (SD=0.69). This suggests a long held belief that virulent pathogens, like *Streptococcus*, which are capable of producing severe endophthalmitis, have earlier presentation times. Similar to previous studies, we see very poor visual outcomes after *Streptococcus* endophthalmitis and 91.6% of patients had worse BCVA at three-month follow-up compared to baseline vision prior to developing endophthalmitis [13].

There are several limitations in this case series. Firstly, the data was collected retrospectively; therefore, there might be biases inherent in the data

collection. Secondly, we compared the BCVA at three-month follow-up with the BCVA when the patient received the bevacizumab injection as well as the BCVA at the presentation. This could be problematic since many patients had worsening cataract after vitrectomy which will undoubtedly adversely affect BCVA. Thirdly, although our 24 cases is one of the largest in the literature for a series of endophthalmitis due to contamination, the sample size is still relatively small.

## Conclusion

In conclusion, we describe culture results, management, complications, and visual outcomes for patients with acute endophthalmitis after intravitreal injection secondary to contaminated bevacizumab. Although rare, contamination of off-label bevacizumab poses a devastating risk of endophthalmitis following intravitreal injection, and remains a

risk whenever handling of medication is performed by multiple sites as is typical for compounding pharmacies. The likelihood of virulent pathogens like *Streptococcus* species is associated with very poor visual prognosis and immediate aggressive management is necessary in the hopes of minimizes vision loss.

## Acknowledgements

### Conflicts of interest

None of the authors have any proprietary interests.

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