



## Case report

## Rapid and progressive decline despite early intervention in a case of bilateral hemorrhagic occlusive retinal vasculitis



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## ABSTRACT

**Purpose:** To present a case of severe bilateral hemorrhagic occlusive retinal vasculitis (HORV) after uncomplicated cataract surgery with intracameral vancomycin. We present a report of a single patient with bilateral presentation of HORV that demonstrated classic features of the disease and progressed to profound vision loss despite early and aggressive intervention.

**Observations:** On initial presentation, the patient had good Snellen visual acuity of 20/25 PH 20/20 OD and 20/60 PH 20/30 OS with retinal hemorrhages in both eyes and sub-hyaloid hemorrhage in the left eye. Early therapeutic intervention with intravitreal corticosteroids, anti-vascular endothelial growth factor (anti-VEGF) agents and oral steroids was pursued. Even with treatment, the clinical picture rapidly deteriorated with progression of occlusive and hemorrhagic complications in both eyes resulting in bilateral ischemic retinopathy and breakthrough vitreous hemorrhage. After a prolonged course of treatment including the aforementioned along with panretinal photocoagulation (PRP) in both eyes and vitreoretinal surgery in the left eye, the final visual acuity was light perception (LP) OD and 20/100 OS.

**Conclusions and importance:** Hemorrhagic occlusive retinal vasculitis remains a feared complication of uncomplicated cataract surgery utilizing intracameral vancomycin. Despite early recognition and appropriate intervention, our patient still had a poor visual outcome with significant ischemic damage.

## 1. Introduction

Cataract surgery is one of the most common surgical procedures in the world and is the most commonly performed ophthalmologic surgery.<sup>1</sup> Post-operative bacterial endophthalmitis is one of the most serious potential complications of this procedure and significant effort has been made to reduce the incidence of its occurrence. The incidence of postoperative endophthalmitis has been reported to occur in 0.04%–0.2% of all cataract surgery cases.<sup>2</sup> The standard of care for many years in the United States has been the use of pre- and post-operative topical antibiotics to prevent this complication. In 2007, the European Society of Cataract & Refractive Surgery (ESCRS) reported five-fold reduction in post-operative endophthalmitis with use of intracameral cefuroxime in a randomized clinical trial.<sup>3</sup> Surgeons in the United States have been slower to adopt intracameral use of antibiotics primarily due to the lack of commercially available Food and Drug Administration (FDA) approved antibiotics for intracameral use. In addition to this, there is concern surrounding the complex two-step dilution process required to prepare off-label cefuroxime, which was the antibiotic of choice validated in the ESCRS trial.<sup>3</sup> Dilution errors

with intracameral cefuroxime have resulted in toxic anterior segment syndrome (TASS) and ocular toxic effects,<sup>4–7</sup> which has led to the utilization of moxifloxacin and vancomycin for intracameral formulations in the United States. Unfortunately, over the last several years, reports have surfaced in which the use of intracameral vancomycin for prophylaxis of endophthalmitis was associated with the development of hemorrhagic occlusive retinal vasculitis (HORV).<sup>1,8,9</sup>

HORV is characterized by severe hemorrhagic vascular occlusion and resulting ischemic manifestations that carries a devastating visual prognosis. In 2016, the American Society of Retina Specialists (ASRS) and the American Society of Cataract & Refractive Surgery (ASCRS) formed a joint HORV Task Force to address this seemingly new entity. The joint Task Force defined key features of HORV based on characteristics of fourteen eyes of nine patients that were previously reported and twenty-two eyes of fourteen patients that were newly reported by the Task Force. Salient findings included use of intraocular vancomycin, delayed onset of rapid loss of vision, mild anterior chamber reaction with no hypopyon, sectoral retinal hemorrhage along the venules, peripheral involvement in all cases with macular ischemia in advanced cases and sectoral retinal vasculitis and occlusion in areas

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of retinal hemorrhage.<sup>8</sup> Other important associations identified included progression to neovascular glaucoma, especially poor outcome with additional vancomycin injections that occurred in cases thought to represent acute post-operative endophthalmitis and when both eyes involved, second eye has faster course and more severe complications.<sup>8</sup> Treatment recommendations made by the HORV Task Force included consideration of the use of systemic, topical, periocular and intravitreal steroids, early anti-VEGF therapy and early PRP.

We present a case with bilateral involvement and typical features of HORV that was diagnosed early and treated immediately in accordance with known guidelines. However, this case importantly highlights the progressive nature of this disease even with early intervention. To the best of our knowledge, the clinical features and course identified in this case are similar to other severe HORV cases in the literature. However, this case highlights a particularly severe clinical course that progressed despite early aggressive treatment with anti-VEGF and corticosteroid treatment.

## 2. Case report

A 71-year-old female was referred for evaluation after complaining of vision loss in the left eye following uncomplicated cataract extraction with posterior chamber intraocular lens implantation in that eye performed two weeks earlier. She also recently underwent cataract surgery in the fellow eye, the right eye, the day before presentation. During each surgery, a standardized formulation of intracameral vancomycin/moxifloxacin/triamcinolone (Imprimis Pharmaceuticals Inc., San Diego, California, USA) was injected for prevention of post-operative endophthalmitis. On initial assessment, Snellen visual acuity of the right eye was 20/25 PH 20/20 and 20/60 PH 20/30 in the left eye. Intraocular pressures were 16 mmHg in the right eye and 18 mmHg in the left eye by Tonopen. Slit lamp examination revealed 1 + cell and 2 + flare in anterior segment of the right eye and 1 + cell in the anterior segment of the left eye. Posterior examination revealed disc hemorrhage and mild disc edema in both eyes. There was venous dilation and mild tortuosity in both eyes, with the left eye affected worse than the right eye. In the right eye, there was visible triamcinolone in the vitreous from cataract surgery the previous day. In the left eye, there was evidence of sub-hyaloid hemorrhage nasal to the optic nerve. Optical coherence tomography (OCT) revealed minimal retinal thickening and normal retinal contour with preservation of the foveal contour in both eyes. Fluorescein angiography (FA) revealed mild vascular leakage in both eyes and only a small area of hypofluorescence consistent with capillary nonperfusion in the superotemporal periphery of the left eye. These initial findings are seen in Fig. 1 and are comparable to HORV described in previous cases.<sup>1,8</sup>

Based on the clinical exam, diagnostic studies and temporal relationship with administration of intracameral vancomycin, the diagnosis of bilateral HORV was suspected. Differential diagnosis considered included bilateral central retinal vein occlusion and hypercoagulable retinopathy. A thorough systemic workup was all negative or non-contributory to the acute process. This included inflammatory markers of C-reactive protein and erythrocyte sedimentation rate; hypercoagulability workup including Protein C and S, Factor V Leiden, antithrombin, homocysteine, prothrombin, lupus anticoagulant, anticardiolipin and Russell viper venom time; imaging including lower extremity duplex ultrasound, magnetic resonance imaging (MRI) of the head and orbit, echocardiogram, chest x-ray and magnetic resonance angiogram (MRA) of the head and neck; autoimmune workup including antinuclear antibodies and antineutrophil cytoplasmic antibodies; immunologic serum workup for cytomegalovirus, syphilis, herpes simple×1 and 2, varicella and serum protein electrophoresis; and finally, routine laboratory workup including comprehensive metabolic panel and complete blood count with differential.

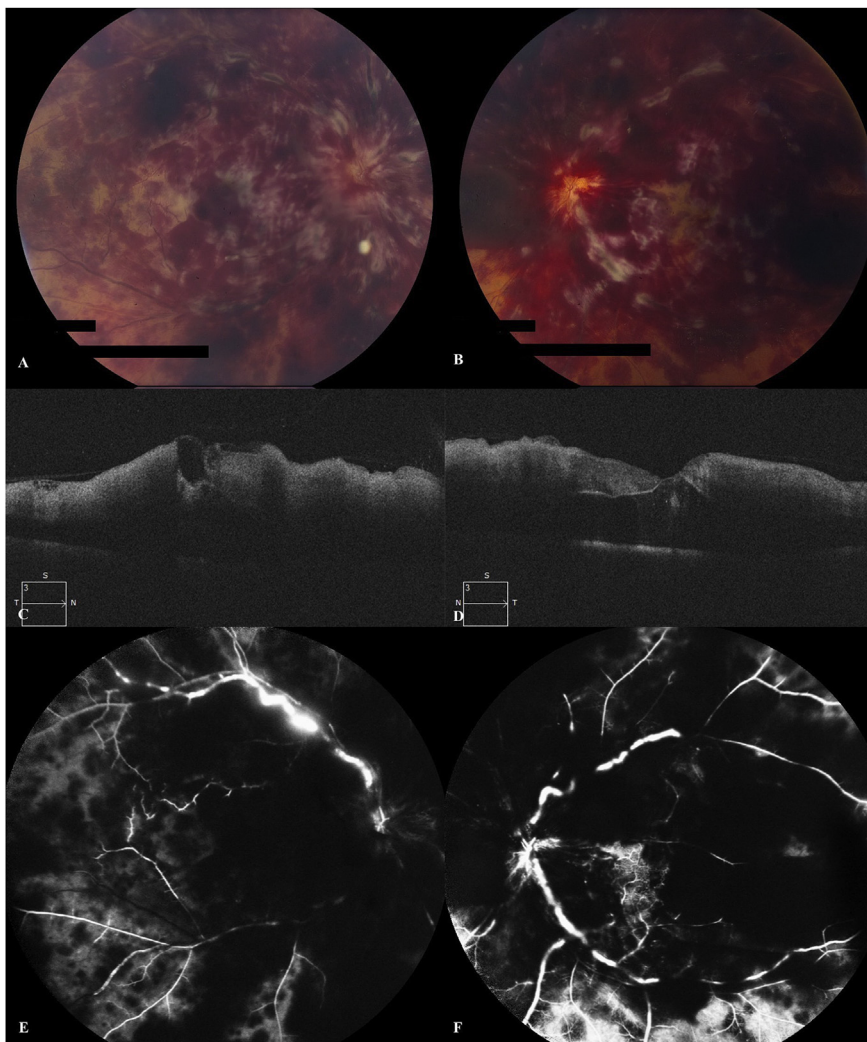
There was an opportunity to initiate treatment in the setting of



**Fig. 1.** Initial presentation. (A) Fundus photograph of the right retina demonstrates scattered retinal hemorrhage, venous tortuosity, and mild venous engorgement. Triamcinolone from cataract surgery the day prior is still visible. (B) Fundus photograph of the left retina demonstrates scattered retinal hemorrhage in addition to sub-hyaloid hemorrhage. (C) Optical coherence tomography (OCT) of the right eye showed a normal contour. (D) OCT of the left eye showed trace retinal thickening. (E) Fluorescein angiography (FA) of the right eye demonstrates mild vascular leakage consistent with blockage from retinal hemorrhages. (F) FA of the left eye demonstrates mild vascular leakage, blockage from retinal hemorrhages and sub-hyaloid hemorrhage, and an area of hypofluorescence that is consistent with peripheral capillary nonperfusion in the far temporal periphery.

preserved visual acuity. The patient was given an intravitreal triamcinolone acetonide (4.0mg/0.05ml) injection in the left eye on the day of presentation. It was felt that the steroid depot from the standardized formulation given the day earlier in the right eye would be protective. Despite promising results from the use of early and aggressive intraocular steroids in previously reported cases,<sup>1,8</sup> the clinical course in our patient continued to deteriorate. In fact, the following day, visual acuity had worsened to count finger (CF) OD and 20/40 OS. The decision was then made to proceed with triamcinolone acetonide (4.0mg/0.05ml) in the right eye. Three days after initial presentation, the patient returned with worsening symptoms and visual acuity of CF OD and 20/70 OS. At this point, the judgement to initiate anti-VEGF therapy was made and the patient received bilateral ranibizumab (0.5mg/0.05ml). Five days after initial presentation, the patient once again returned to clinic complaining of worsening symptoms. During this follow-up visit her visual acuity was limited to hand motion (HM) in the right eye and 20/100-2 in the left eye. PRP was added to the right eye due to worsening peripheral ischemia. The severity of the progression is evident in multimodal imaging only ten days after presentation as seen in Fig. 2. A month after initial evaluation, there was continued decline with the development of profound macular ischemia, macular edema, peripheral ischemia and breakthrough vitreous hemorrhage. Multimodal imaging including fundus photos and FA revealed worsening of disease as seen in Fig. 3.

The patient continued to receive monthly bilateral anti-VEGF therapy with ranibizumab. Over the ensuing months, there was dissipation of the retinal hemorrhage, attenuation and sclerosis of the



**Fig. 2.** Ten days after initial presentation. (A) Fundus photograph of the right retina demonstrates worsening of disease, increased vitreous hemorrhage and vascular sheathing. (B) Fundus photograph of the left retina similarly demonstrates worsening of disease and vascular sheathing. (C) Optical coherence tomography (OCT) of the right eye increased hyperreflectivity of the inner retina. (D) OCT of the left eye showed increased retinal thickening consistent with macular edema in addition to increased hyperreflectivity. (E) Fluorescein angiography (FA) of the right eye demonstrates increased retinal hemorrhage, staining of venous vasculature, and delayed filling. (F) FA of the left eye demonstrates similar findings to the right eye.

retinal vasculature and oxidation of the vitreous hemorrhage. The patient elected to proceed with vitreoretinal surgery in the left eye to clear the vitreous hemorrhage and address mild vitreomacular traction from elevation of the hyaloid. PRP was performed at the time of surgery and the surgery did result in visual improvement from HM to 20/100 OS. A well-known sequela of HORV is neovascular glaucoma. Fortunately, our patient has avoided this complication due to the serial anti-VEGF therapy and PRP. Post-surgical images approximately eleven months after initial presentation are seen in Fig. 4.

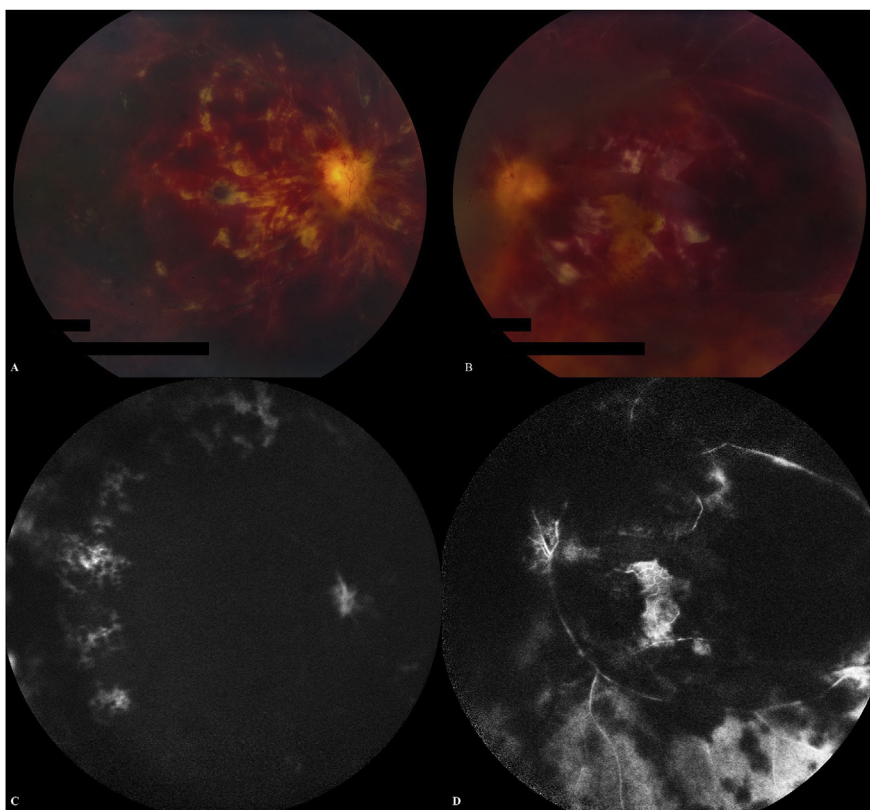
### 3. Discussion

Pre, peri- and post-operative antibiotic prophylaxis in cataract surgery remains the topic of ongoing debate. Recent meta-analysis of the literature showed no difference in efficacy of intracameral antibiotics alone versus intracameral antibiotics plus topical antibiotics for prophylaxis of post-operative endophthalmitis.<sup>10,11</sup> Moxifloxacin exhibited the best safety profile due to risk of dilution error with cefuroxime and toxic retinal events with vancomycin.<sup>10</sup> The joint HORV Task Force did not recommend discontinued use of intraocular vancomycin, based on its popularity of use and limitations of study power.<sup>8</sup> Since then the FDA, however, released a warning regarding the risk associated with intracameral vancomycin use.<sup>12</sup> Even so, the reality remains that the use of intraocular vancomycin for endophthalmitis prophylaxis is largely at the discretion of the individual surgeon. While there is compelling support for the efficacy of intracameral antibiotics, there are

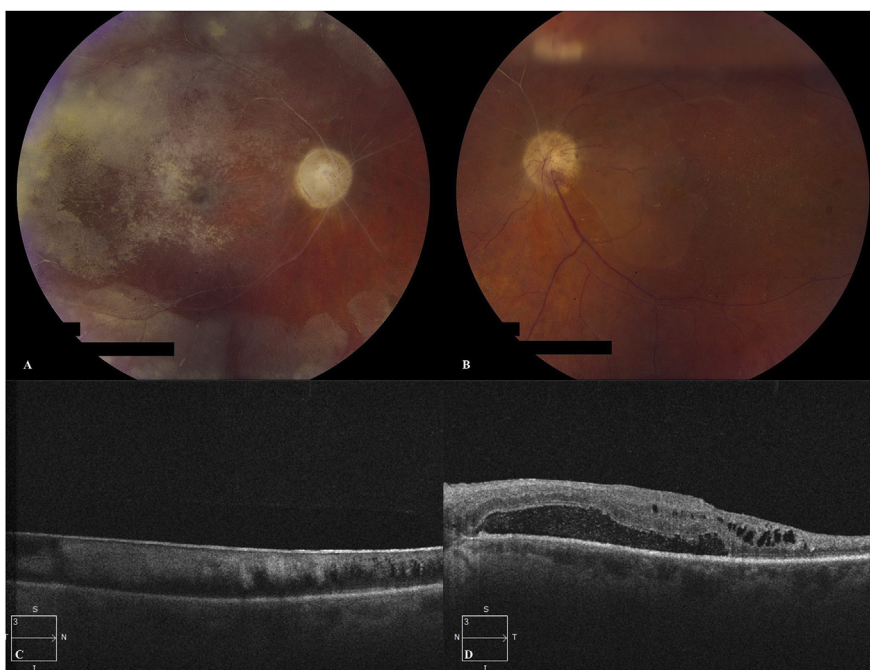
also recent studies that call into question the baseline rates of post-operative endophthalmitis and demonstrate lower rates without use of intracameral antibiotics altogether.<sup>13,14</sup>

The compounding pharmacy Imprimis has discontinued offering the standardized formulation used in our patient and does not currently market any intracameral formulations with vancomycin. In Europe and Canada there is a commercially available formulation of single-dose cefuroxime sold under the brand name Aprokam (Théa Laboratory, Clermont-Ferrand, France).<sup>15</sup> Perhaps if this became available for use in the United States, it would be utilized over formulations prepared by compounding pharmacies. In fact, while 54% respondents of the 2007 ASCRS survey stated that commercially available intracameral antibiotics should be FDA approved in the United States, this number has since increased to 75% in the 2014 survey.<sup>16,17</sup>

Originally, the pathophysiological mechanism of HORV was postulated to be an immune-mediated type III hypersensitivity reaction to the injected vancomycin that resulted in immune complex deposition within retinal vessels.<sup>1</sup> This hypothesis is supported by the fact that there is often a delayed presentation of HORV, especially regarding involvement of the second eye even though the surgery of the first eye may have occurred years earlier. In our patient, the second eye injected with vancomycin ended up with worse visual acuity, which fits the pattern of HORV suggestive of an immune-mediated, sensitization phenomenon. However, more recently, histopathologic evidence from an enucleated eye with HORV revealed an absence of immune complexes in retinal vessels.<sup>1</sup> Instead, predominantly T-cell lymphocytes



**Fig. 3.** One month after initial presentation. (A) Fundus photograph of the right eye showed progression of disease with worsening of hemorrhagic component and constriction of the vasculature. (B) Fundus photograph of the left eye was similar to the right eye. (C) Fluorescein angiography (FA) of the right eye was revealing for blockage from retinal hemorrhage. (D) FA of the left eye was similar to that of the right eye.



**Fig. 4.** Eleven months after initial presentation. (A) Fundus photograph of the right eye showed severe vascular attenuation and optic nerve pallor. (B) Fundus photos of the left eye revealed some preservation of the retinal vasculature inferiorly. Gas bubble is present. (C) Optical coherence tomography (OCT) of the right eye displayed persistent hyperreflectivity of the inner retina. (D) OCT of the left eye was again similar to that of the right eye.

with other inflammatory cells including mast cells and eosinophils were found in the choroid layer and there was overlying necrosis of the neurosensory retina, which is consistent with leukocytoclastic vasculitis. *Todorich et al.* hypothesized that HORV is primarily a choroidal driven process and perhaps should be renamed hemorrhagic occlusive choroidal and retinal vasculopathy (HOCR/V).<sup>1</sup> The findings were more consistent with drug-mediated process similar to Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Both of these follow type IV hypersensitivity mechanisms and are known to occur

with systemic administration of vancomycin. Moreover, if the pathogenic mechanism of HORV is in fact mediated by a type IV hypersensitivity reaction, then theoretically any antibiotic could induce a HORV-type reaction, not just vancomycin. The treatment of these type IV reactions is mainly supportive although intravenous immunoglobulins may alter the course of disease. This treatment option, however, has not thus far been proposed by the HORV task force, possibly in part due to an unclear understanding of the exact underlying pathophysiology.

In the paper by Witkin et al., it was demonstrated that use of intravitreal corticosteroids may result in a better prognosis.<sup>8</sup> Unfortunately, in our patient the condition continued to deteriorate despite early intravitreal injection of triamcinolone in both eyes. This underscores that HORV may not be an immune-mediated disease. The clinical course was marked by worsening retinal hemorrhage leading to breakthrough vitreous hemorrhage within the first month. The vitreous hemorrhage was not a neovascular complication in this case and fortunately the patient has not developed neovascular glaucoma due to serial anti-VEGF therapy in combination with PRP. Even if intervention with PRP does not improve the long-term visual acuity, the application is warranted to eliminate the ischemic drive necessary for neovascularization.

As with previously described cases of HORV, we present this case to raise awareness for the risk of intracameral vancomycin use. Despite the feared sequelae of post-operative endophthalmitis, the devastating visual outcome associated with HORV must be considered. Some recent cases of HORV have documented better visual prognosis and potential variants of HORV, which may indicate that there is a spectrum of hypersensitivity reactions related to intracameral vancomycin use.<sup>9,18,19</sup> If this is the case, there is a possibility that HORV is underreported across the country. Regardless, the best form of treatment for HORV should be considered prevention. Eliminating the use of intracameral vancomycin is the best approach to this, but deconstructing routine practice is difficult for many surgeons. Looking ahead, we must also consider the rising rates of antibiotic resistance when using intraocular antibiotics in ophthalmic procedures. Practicing antimicrobial stewardship is yet another reason to eliminate the use of intracameral vancomycin. Each surgeon should carefully consider the risk of HORV prior to its administration and be well-versed on recognition of HORV in the clinical setting. We present a unique case of HORV that epitomizes the devastating visual outcome associated with this entity even with early recognition and immediate treatment with the various recommended therapies.

#### Patient consent

Written informed consent was not obtained for this case as the report does not contain any personal or identifiable information that could lead to identification of this patient.

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#### Authorship

All authors attest that they meet the current ICMJE criteria for Authorship. All work was completed at the University of Arizona, Department of Ophthalmology.

#### Declaration of competing interest

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#### References

- Todorich B, Faia LJ, Thanos A, et al. Vancomycin-associated hemorrhagic occlusive retinal vasculitis: a clinical-pathophysiological analysis. *Am J Ophthalmol*. 2018;188:131–140. <https://doi.org/10.1016/j.ajo.2018.01.030>.
- Miller JJ, Scott IU, Flynn HWJ, Smiddy WE, Newton J, Miller D. Acute-onset endophthalmitis after cataract surgery (2000-2004): incidence, clinical settings, and visual acuity outcomes after treatment. *Am J Ophthalmol*. 2005;139(6):983–987. <https://doi.org/10.1016/j.ajo.2005.01.025>.
- Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. *J Cataract Refract Surg*. 2007;33(6):978–988. <https://doi.org/10.1016/j.jcrs.2007.02.032>.
- Olavi P. Ocular toxicity in cataract surgery because of inaccurate preparation and erroneous use of 50mg/ml intracameral cefuroxime. *Acta Ophthalmol*. 2012. <https://doi.org/10.1111/j.1755-3768.2010.02103.x>.
- Qureshi F, Clark D. Macular infarction after inadvertent intracameral cefuroxime. *J Cataract Refract Surg*. 2011. <https://doi.org/10.1016/j.jcrs.2011.03.032>.
- Delyfer MN, Rougier MB, Leoni S, et al. Ocular toxicity after intracameral injection of very high doses of cefuroxime during cataract surgery. *J Cataract Refract Surg*. 2011. <https://doi.org/10.1016/j.jcrs.2010.08.047>.
- Braga-Mele R, Chang DF, Henderson BA, Mamalis N, Talley-Rostov A, Vasavada A. Intracameral antibiotics: safety, efficacy, and preparation. *J Cataract Refract Surg*. 2014. <https://doi.org/10.1016/j.jcrs.2014.10.010>.
- Witkin AJ, Chang DF, Jumper JM, et al. Vancomycin-associated hemorrhagic occlusive retinal vasculitis: clinical characteristics of 36 eyes. *Ophthalmology*. 2017;124(5):583–595. <https://doi.org/10.1016/j.ophtha.2016.11.042>.
- Miller MA, Lenci LT, Reddy CV, Russell SR. Postoperative hemorrhagic occlusive retinal vasculitis associated with intracameral vancomycin prophylaxis during cataract surgery. *J Cataract Refract Surg*. 2016;42(11):1676–1680. <https://doi.org/10.1016/j.jcrs.2016.09.013>.
- Bowen RC, Zhou AX, Bondalapati S, et al. Comparative analysis of the safety and efficacy of intracameral cefuroxime, moxifloxacin and vancomycin at the end of cataract surgery: a meta-analysis. *Br J Ophthalmol*. 2018. <https://doi.org/10.1136/bjophthalmol-2017-311051>.
- Beselga D, Campos A, Castro M, et al. Postcataract surgery endophthalmitis after introduction of the ESCRS protocol: a 5-year study. *Eur J Ophthalmol*. 2013. <https://doi.org/10.5301/ejo.5000417>.
- U.S. Food and Drug Administration. A case of hemorrhagic occlusive retinal vasculitis (HORV) following intraocular injections of a compounded triamcinolone, moxifloxacin, and vancomycin formulation. <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm578514.htm>; 2017 Published.
- Moshirfar M, Feiz V, Vitale AT, Wegelin JA, Basavanthappa S, Wolsey DH. Endophthalmitis after uncomplicated cataract surgery with the use of fourth-generation fluoroquinolones. A retrospective observational case series. *Ophthalmology*. 2007. <https://doi.org/10.1016/j.ophtha.2006.08.038>.
- Lalitha P, Rajagopalan J, Prakash K, Ramasamy K, Prajna NV, Srinivasan M. Postcataract endophthalmitis in south India: incidence and outcome. *Ophthalmology*. 2005. <https://doi.org/10.1016/j.ophtha.2005.05.020>.
- Rhee MK, Mah FS. Factors influencing adoption: intracameral antibiotics and steroids. *Cataract Refract Surg Today Eur*. 2016(July/August):22–29.
- Chang DF, Braga-Mele R, Mamalis N, et al. Prophylaxis of postoperative endophthalmitis after cataract surgery. Results of the 2007 ASCRS member survey. *J Cataract Refract Surg*. 2007. <https://doi.org/10.1016/j.jcrs.2007.07.009>.
- Chang DF, Braga-Mele R, Henderson BA, Mamalis N, Vasavada A. Antibiotic prophylaxis of postoperative endophthalmitis after cataract surgery: results of the 2014 ASCRS member survey. *J Cataract Refract Surg*. 2015. <https://doi.org/10.1016/j.jcrs.2015.01.014>.
- Goldberg RA, Crawford C, Heier JS. Postoperative hemorrhagic occlusive retinal vasculitis: a forme fruste variant? *Retin Cases Brief Rep*. 2018;12(4):305–306. <https://doi.org/10.1097/ICB.0000000000000514>.
- Arepalli S, Modi YS, Deasy R, Srivastava SK. Mild bilateral hemorrhagic occlusive retinal vasculitis following intracameral vancomycin administration in cataract surgery. *Ophthalmic Surg Lasers Imaging Retina*. 2018;49(5):369–373. <https://doi.org/10.3928/23258160-20180501-12>.