

# Effect of intravitreal antibiotic injections on culture-negative keratitis-induced endophthalmitis

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## Original research

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## Abstract

**Background:** This study aimed to evaluate treatment outcomes of culture-negative keratitis-induced endophthalmitis (CNKE) .

**Methods:** We reviewed the medical records of 13 patients with CNKE, who underwent treated from January 2011 to December 2017. All patients were referred from the emergency room or outpatient department of local clinics. Outcome evaluation included the assessment of visual acuity and any requirements of evisceration/enucleation.

**Results:** Thirteen eyes of 13 patients were included in this study. The mean age of the patients was  $75.0 \pm 13.3$  years. All patients used antibiotic eye drops before the initial visit. Visual acuity values at the initial visit ranged from no light perception to 2/100, while final visual acuity values ranged from no light perception to 2/100. All patients underwent a vitreous tap and intravitreal ceftazidime/vancomycin injection. Two eyes underwent evisceration after intravitreal injection.

**Conclusions:** Intravitreal antibiotic injections demonstrated favorable results for the treatment of patients with CNKE .

## Background

Infectious endophthalmitis is a rare and vision-threatening ocular infection, involving the anterior and posterior chambers of the eye.<sup>1</sup> Endophthalmitis is classified into two categories: exogenous and endogenous, based on the route of infection. Exogenous endophthalmitis occurs when microbial pathogens enter the eye after intraocular surgery or trauma and spread from adjacent tissues or infiltrate through the corneal surface. Endogenous endophthalmitis is caused by the hematogenous spread of infectious organisms from an infection at a distant location into the eye. Microbial keratitis-associated endophthalmitis is uncommon, with a reported incidence of 6–10% of cases of exogenous endophthalmitis.<sup>2</sup> An earlier study revealed that 1.8% of patients with severe microbial keratitis required evisceration or enucleation, due to uncontrolled infection.<sup>3</sup>

The most common treatment modalities include antibiotics, corneal scraping, vitrectomy,<sup>4,5</sup> and intravitreal injections of ceftazidime (2.25 mg/0.01 mL)/amikacin (400 µg/0.01 mL) and vancomycin (1 mg/0.01 mL). Vitreous and anterior chamber taps should be performed for microbiological analysis during intravitreal injections, to facilitate appropriate antibiotic selection, since identifying the causative organism is one of the most important aspects of treating patients with endophthalmitis.<sup>6</sup> O'Neill et al. (2014) reported that 83.8% of patients with microbial keratitis-associated endophthalmitis were culture-positive.<sup>7</sup> Broad-spectrum intravitreal antibiotics are used empirically in patients with culture-negative keratitis-induced endophthalmitis (CNKE). Vancomycin is the first-line treatment for gram-positive bacterial endophthalmitis. However, vancomycin has a limited effect on gram-negative bacteria. On the other hand, ceftazidime/amikacin are effective against gram-negative organisms.<sup>8</sup>

To date, few studies have investigated the treatment outcomes of CNKE. This retrospective study reported the clinical manifestations and prognoses of 13 eyes with CNKE, and the clinical outcomes after treatment with intravitreal injection of ceftazidime/vancomycin.

## Methods

This retrospective study was conducted at the Department of Ophthalmology at Sanggye Paik Hospital of Inje University, Seoul, South Korea. The study protocol was approved by the institutional review board of Sanggye Paik Hospital and was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The medical records of all patients diagnosed with CNKE at Sanggye Paik Hospital from January 2011 to December 2017 were retrospectively reviewed. The need for informed patient consent was waived, owing to the retrospective nature of this study.

Data on demographic information, past medical history, and clinical presentation were collected. Ophthalmologic examinations included slit-lamp assessment, initial and final best corrected visual acuity (BCVA) measurements, Goldmann applanation tonometry, and anterior segment photography.

## Results

A total of 13 eyes of 13 patients were included in this study. All patients were referred from local clinics, via the emergency room (ER) or outpatient department (OPD). All patients had been using the following antibiotic eye drops before their initial visit: 0.5% levofloxacin (Cravit, Santen, Japan), 0.3% gatifloxacin ophthalmic solution [Gatiflo, Handok, Chungbuk, Korea (preservative-free)], 0.5% moxifloxacin hydrochloride ophthalmic solution [Vigamox, Alcon Laboratories, Inc, Fort Worth, TX, USA (preservative-free)], and 0.5% tobramycin

(Tobra, Samil, Korea). The mean age of the patients was  $75.0 \pm 13.3$  years (range, 50 – 89 years). Five patients were men and 8 were women. The diagnosis of CNKE was based on slit-lamp examination: corneal ulcers were diagnosed upon determining a loss of corneal epithelium, accompanied by underlying infiltration of the corneal stroma. Endophthalmitis was defined as hypopyon with vitreous inflammation.

Hypopyon was observed in every patient with endophthalmitis. B-scan ultrasonography revealed vitreous inflammation in all patients. All 13 eyes were diagnosed with exogenous endophthalmitis. Of the 13 eyes with exogenous endophthalmitis, 2 eyes had secondary keratitis, which was caused by previous trauma, while the remaining 11 eyes had primary keratitis, without clear etiologies for the inflammation. All 13 patients diagnosed with exogenous endophthalmitis underwent corneal biopsy. Among the risk factors for poor visual outcomes, 10 eyes had visual acuity of light perception or worse, 9 patients were older than 65 years, and 5 patients had diabetes mellitus.

All patients received intravitreal injections of ceftazidime (2.25 mg/0.01 mL) and vancomycin (1 mg/0.01 mL), with vitreous and anterior chamber taps on the day of diagnosis. The mean number of intravitreal injections was  $1.23 \pm 0.4$  (range, 1 – 2) and none of the patients underwent vitrectomy. All patients were simultaneously treated with systemic intravenous and topical antibiotics. Seven eyes were prescribed moxifloxacin, 2 eyes were prescribed levofloxacin, 2 eyes were prescribed gatifloxacin, 1 eye was prescribed levofloxacin and tobramycin, and 1 eye was prescribed moxifloxacin and tobramycin.

The initial visual acuity ranged from no light perception (NLP) to 2/100 and the final visual acuity ranged from NLP to 2/100. Two patients underwent evisceration about 1 week after the intravitreal injection (Table 1). The visual acuity of 3 of the 13 eyes improved compared with the initial visual acuity after treatment. Table 1 summarizes the patients' clinical information.

[Table 1 near here]

### ***Patient 1***

A 58-year-old man presented to the ER of the local ophthalmology clinic with decreased visual acuity and pain on injection in the left eye, about 1 week after symptom onset. However, the symptoms aggravated, and he was referred to our clinic. Ocular examination revealed a BCVA of NLP in the left eye. The intraocular pressure (IOP) was 12 mmHg in the left eye, as measured with a noncontact tonometer. Slit-lamp examination revealed a corneal ulcer with hypopyon and ciliary injection (Figure 1a). We administered an intravitreal injection of ceftazidime and vancomycin and performed a vitreous tap on the day of diagnosis. A second intravitreal injection was administered 1 week later. The inflammation improved after the second injection. However, the final BCVA of the left eye was still categorized as "NLP," 4 months after the second injection.

[Figure 1 near here]

### ***Patient 2***

An 84-year-old woman was referred to our clinic by the ER of a local clinic for the treatment of a corneal ulcer with endophthalmitis in the left eye. Ocular examination revealed a visual acuity of "NLP" and an IOP of 21.0 mmHg in the left eye. Slit-lamp examination revealed corneal infiltration with hypopyon, ciliary injection, and an edematous cornea (Figure 1b). We administered an intravitreal ceftazidime and vancomycin injection and performed a vitreous tap on the day of diagnosis. The inflammation improved after the injection. However, the final BCVA for the right eye was still "NLP" 3 months after the second injection.

### ***Patient 3***

A 60-year-old man was referred to the ophthalmology department by a local clinic for ocular pain and ciliary injection in the right eye. Ocular examination revealed a visual acuity of "hand motion" and an IOP of 15 mmHg in the right eye. Slit-lamp examination revealed ciliary injection with corneal infiltration and hypopyon (Figure 1c). We administered an intravitreal injection of ceftazidime and vancomycin and performed a vitreous tap on the day of diagnosis. The inflammation improved after the intravitreal injection. The final BCVA for the right eye was "NLP" 2 months after the injection.

#### ***Patient 4***

A 50-year-old woman, who wore soft contact lens ordinals, was referred to our clinic for the treatment of endophthalmitis by the local clinic. Ocular examination revealed a BCVA of “hand movement” and an IOP of 23 mmHg in the left eye. Slit-lamp examination revealed ciliary injection, corneal infiltration, and hypopyon in the left eye (Figure 1d). We administered an intravitreal injection of ceftazidime and vancomycin and performed a vitreous tap on the day of diagnosis. A second injection was administered 1 week after the first injection. The inflammation improved after the second injection, but the visual acuity of the left eye was “NLP” 3 months after injection.

#### ***Patient 5***

A 57-year-old man was referred to our clinic for the treatment of endophthalmitis by the local clinic, via the OPD. Ocular examination revealed a BCVA of “light perception” (LP) and IOP of 19 mmHg in the left eye. Slit-lamp examination revealed corneal infiltration, ciliary injection, and hypopyon in the anterior chamber (Figure 1e). We administered an intravitreal injection of ceftazidime and vancomycin and performed a vitreous tap on the day of diagnosis. The BCVA of the left eye was “hand movement” 1 month after intravitreal injection.

#### ***Patient 6***

An 87-year-old man was referred to our clinic for the treatment of endophthalmitis, via the OPD of the local ophthalmology clinic. Ocular examination revealed that visual acuity was “NLP” and the IOP was 10 mmHg in the right eye. Slit-lamp examination revealed ciliary injection, corneal ulceration, and hypopyon. We administered an intravitreal injection of ceftazidime and vancomycin and performed a vitreous tap for the right eye on the day of diagnosis. The BCVA of the right eye was “NLP”, and the inflammation in the anterior chamber resolved 1 month after the intravitreal injection.

#### ***Patient 7***

An 89-year-old man, who was referred to our clinic via the OPD of the local ophthalmology clinic, presented with pain on injection in the right eye. Ocular examination revealed a BCVA of “NLP” in the right eye. Noncontact tonometry revealed an IOP of 5 mmHg in the right eye. Slit-lamp examination revealed a corneal ulcer, hypopyon, and ciliary injection (Figure 1f). We administered intravitreal injection of ceftazidime and vancomycin and performed a vitreous tap on the day of diagnosis. The inflammation improved 3 months after the injection. Moreover, the final BCVA for the right left eye improved to “hand movement” 3 months after the intravitreal injection.

#### ***Patient 8***

A 74-year-old woman was referred to our clinic by the local clinic, via the OPD, for the treatment of a corneal ulcer with endophthalmitis in the right eye. Ocular examination revealed a visual acuity of “NLP” and an IOP of 5 mmHg in the right eye. Slit-lamp examination revealed corneal infiltration, hypopyon, and ciliary injection (Figure 1g). We administered intravitreal injection of ceftazidime and vancomycin and performed a vitreous tap on the day of diagnosis, Another intravitreal injection was administered 1 week later. The inflammation improved after the second injection. The final BCVA of the right eye was “hand movement” 2 months after the second injection .

#### ***Patient 9***

An 82-year-old Korean woman was referred to the ophthalmology department, via the ER of the local clinic, for ocular pain and ciliary injection in the right eye. Ocular examination revealed a visual acuity of “LP” and an IOP of 46 mmHg in the right eye. Slit-lamp examination revealed ciliary injection, corneal infiltration, and hypopyon (Figure 1h). We administered intravitreal injection of ceftazidime

and vancomycin and performed a vitreous tap on the day of diagnosis. The inflammation improved after the intravitreal injection. The final BCVA for the right eye was “NLP” and the IOP was 34 mmHg, 3 months after the injection.

### ***Patient 10***

An 88-year-old woman was referred to our clinic for the treatment of endophthalmitis by the local clinic. Ocular examination revealed a BCVA of “NLP” and an IOP of 27 mmHg in the left eye. Slit-lamp examination revealed ciliary injection, corneal infiltration, and hypopyon in the left eye. We administered intravitreal injection of ceftazidime and vancomycin and performed a vitreous tap on the day of diagnosis. The inflammation improved after the intravitreal injection, but the visual acuity in the left eye was “NLP” 3 months after treatment.

### ***Patient 11***

An 83-year-old woman was referred to our clinic for the treatment of endophthalmitis by the local clinic, via the OPD. Ocular examination revealed a BCVA of “NLP” and an IOP of 28 mmHg in the right eye. Slit-lamp examination revealed a corneal ulcer, ciliary injection, and hypopyon in the anterior chamber. We administered intravitreal injection of ceftazidime and vancomycin and performed a vitreous tap on the day of diagnosis. Subsequently, the patient underwent evisceration 5 days after the injection, due to disease exacerbation.

### ***Patient 12***

A 76-year-old woman was referred to our clinic for the treatment of endophthalmitis, via the OPD of the local ophthalmology clinic. Ocular examination revealed a visual acuity of “NLP” and an IOP of 21 mmHg in the right eye. Slit-lamp examination revealed ciliary injection, corneal infiltration, and hypopyon. We performed an intravitreal ceftazidime and vancomycin injection and a vitreous tap on the day of diagnosis. Subsequently, the patient underwent evisceration 1 week after the injection, due to disease exacerbation.

### ***Patient 13***

An 86-year-old woman was referred to our clinic by the local clinic via the OPD for the treatment of a corneal ulcer with endophthalmitis in the right eye. Ocular examination revealed a visual acuity of 2/100 and an IOP of 16 mmHg in the right eye. Slit-lamp examination revealed ciliary injection with corneal infiltration, and hypopyon. We performed an intravitreal injection of ceftazidime and vancomycin and a vitreous tap on the day of diagnosis. The inflammation improved after intravitreal injection. The final BCVA of the right eye was 2/100, 6 months after injection.

## **Conclusions**

Endophthalmitis is a rare, but severe, vision-threatening ocular infection of the intraocular cavity. The disease can be exogenous or endogenous in origin: exogenous endophthalmitis occurs when infectious organisms gain direct entry into the eye, while endogenous endophthalmitis occurs by the hematogenous spread of infectious organisms into the eye, from an infection at a distant location.<sup>9</sup> Microbial keratitis-associated endophthalmitis is an uncommon disease. Ramakrishnan et al. reported that the incidence of microbial keratitis-associated endophthalmitis was 6–10% of cases of exogenous endophthalmitis.<sup>2</sup> Endophthalmitis secondary to keratitis is a predominantly bacterial infection.<sup>2,10</sup> *Staphylococcus aureus*, *Streptococcal* species, and *Pseudomonas aeruginosa* are the common causative pathogens of keratitis-induced endophthalmitis.<sup>11,12,13</sup> *Aspergillus* species and *Fusarium* species are common causes of fungal infections.<sup>10,14</sup>

O'Neill et al. demonstrated that the rate of culture-positivity of keratitis-induced endophthalmitis was 83.8%.<sup>7</sup> Polymerase chain reaction (PCR) analyses have recently demonstrated a significant increase in the percentage of bacterial and fungal detection in clinical samples of the aqueous and vitreous humors.<sup>15,16</sup> However, PCR was not performed in this study, which may be responsible for the negative culture results. Moreover, another cause for the negative culture results could be that all patients underwent antibiotic eye drop-

instillation treatment (3–14 days) before the initial visit. Wykoff et al. (2008) reported that 85% of patients with fungal endophthalmitis received topical corticosteroids before the diagnosis of fungal endophthalmitis.<sup>17</sup> However, no patient received topical corticosteroids in our case series.

Urgent ophthalmologic treatment is required for treating endophthalmitis. The most commonly used methods include the administration of an intravitreal tap and broad-spectrum antibiotics, and intravenous administration of antibiotics with intravitreal injections of ceftazidime (2.25 mg/0.01 mL) or amikacin (400 µg/0.01 mL) and vancomycin (1 mg/0.01 mL).<sup>18</sup> Vancomycin constitutes the first-line treatment for gram-positive bacterial endophthalmitis. On the other hand, ceftazidime and amikacin are effective against gram-negative organisms.<sup>19</sup> Ceftazidime is used more frequently for intravitreal antibiotic injections than amikacin, owing to the decreased risk of retinal toxicity<sup>8,20</sup> and superior efficacy in acidic and hypoxic environments (such as that of endophthalmitis), compared with amikacin.<sup>21</sup>

Lifschitz et al. reported precipitation after intravitreal injections of vancomycin and ceftazidime in patients with endophthalmitis.<sup>21</sup> This may be attributed to the alkaline pH of vancomycin (pH 5–7.5), compared with that of ceftazidime (pH 2.5–4.5).<sup>21</sup> However, the combination of vancomycin and ceftazidime is a widely accepted treatment for endophthalmitis.<sup>22</sup> Park et al. reported that low temperatures (4°C) and small media volumes increased the frequency of precipitation.<sup>23</sup> In this study, we administered intravitreal vancomycin and ceftazidime injections for all patients on the day of diagnosis. Vancomycin is the drug of choice for gram-positive bacteria, and ceftazidime is preferred for gram-negative organisms.

Alternately, vitrectomy can reduce the inflammation and bacterial count, and ensure greater antibiotic penetration.<sup>24</sup> However, no patient underwent vitrectomy in this study, which distinguished it from earlier studies on postoperative, post-traumatic endophthalmitis.<sup>1,25</sup> This may be attributed to several factors including the lack of a surgical view because of the corneal lesions and the severity of the disease at the initial visit.

Latency to diagnosis of keratitis-induced endophthalmitis is expected to be higher than that for other types of endophthalmitis.<sup>26</sup> This might be attributed to pre-existing ocular pain and decreased visual acuity caused by keratitis.<sup>27</sup> Final BCVA outcomes ranged from “NLP” to 2/100; visual acuity improved in 3 eyes (patients 5, 7, and 8), decreased in 3 eyes (patients 3, 4, and 9), and 2 eyes ultimately underwent evisceration. Ormerod et al. found that 6% of elderly patients with bacterial keratitis developed endophthalmitis, while 7% required evisceration/enucleation.<sup>28</sup> Another study reported that 62.2% of patients underwent primary or secondary evisceration/enucleation for keratitis-induced endophthalmitis.<sup>7</sup> In our study, 15.3% (2/13) of patients underwent evisceration; these results were favorable compared with those of previous studies.

Moreover, the visual acuity did not improve more than 20/100 in the 13 eyes with endophthalmitis treated in our study. However, the visual acuity of 3 eyes improved (compared with the initial visual acuity). This result is comparable to the study by Zapp et al.,<sup>27</sup> which found that 90.9% (10 of 11 eyes) of patients became legally blind and only 1 of the 11 eyes retained visual function. Meanwhile, the Endophthalmitis Vitrectomy Study reported that 33% of the patients with initial “light perception-only” vision, who underwent vitrectomy demonstrated visual acuity that was better than 20/40.<sup>29</sup> These results suggest that surgery may be a superior treatment modality, but the disadvantages of surgical treatment should be considered.

On the other hand, the use of intravitreal steroids for treating endophthalmitis is controversial. A retrospective analysis reported the detrimental effect of adjunctive intravitreal steroid treatment.<sup>30</sup> Patients who received adjunctive intravitreal steroids were significantly less likely to achieve a 3-line improvement in visual acuity than patients who only received intravitreal antibiotics. However, another study found similar visual outcomes for patients treated with or without adjunctive intravitreal steroids.<sup>31</sup> A third prospective study suggested a trend towards improved vision with intravitreal steroids, although the results were not statistically significant.<sup>32</sup> Therefore, intravitreal steroid injection is not recognized as standard treatment for endophthalmitis, and the authors did not administer this treatment to the patients enrolled in this study.

The present study is subject to two limitations: the small sample size precluded statistical analysis, and all patients had undergone antibiotic eye drop-instillation treatment before the initial visit. This treatment may have affected the patients’ prognoses.

In conclusion, intravitreal ceftazidime and vancomycin injections showed favorable results in patients with CNKE.

## Declarations

## **Ethics Approval and Consent to Participate**

The study protocol was approved by the institutional review board of Sanggye Paik Hospital (IRB Number: 2019-03-13) and was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

## **Consent to Publication**

Not applicable

## **Availability of Data and Material**

Not applicable

## **Competing Interest**

The authors declare that they have no competing interests

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## **Authors' Contributions**

S.H.E and H.J.H participated in the design of the study

K.M.J and S.H.E wrote most of paper

P.J.Y and K.J.S performed data collection and interpretation

All authors read and approved the final manuscript.

## **Acknowledgment**

None

## **List Of Abbreviations**

CNKE: Culture-Negative Keratitis-induced Endophthalmitis

BCVA: Best Corrected Visual Acuity

ER: Emergency Room

OPD: Outpatient Department

NLP: No Light Perception

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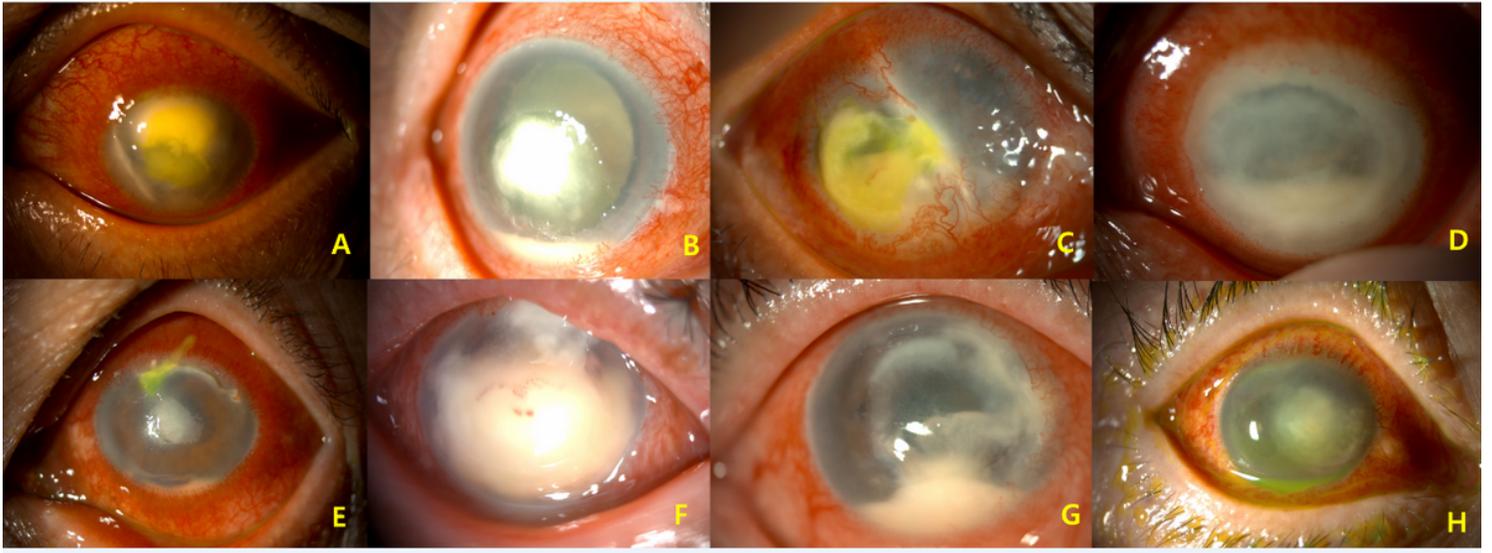
## Table

**Table 1. Clinical summary of the patients with culture negative keratitis-induced endophthalmitis**

Patient	Age/Sex	Eye affected	Initial VA	Types	Treatment	No. of injections	Referred	Systemic disease	Eye drops	Final VA
1	M/58	OS	NLP	Exogenous (Secondary after trauma)	IVCV	2	ER	DM/HTN	Levofloxacin, Tobramycin	NLP
2	F/85	OD	NLP	Exogenous (Primary)	IVCV	1	ER	None	Moxifloxacin	NLP
3	M/60	OD	HM	Exogenous (Primary)	IVCV	1	OPD	None	Moxifloxacin	NLP
4	F/50	OS	HM	Exogenous (Primary)	IVCV	2	OPD	None	Moxifloxacin	NLP
5	M/57	OS	LP	Exogenous (Primary)	IVCV	1	OPD	None	Levofloxacin	HM
6	M/87	OD	NLP	Exogenous (Primary)	IVCV	1	OPD	HTN	Gatifloxacin	NLP
7	M/89	OD	NLP	Exogenous (Primary)	IVCV	1	OPD	HTN	Moxifloxacin, Tobramycin	HM
8	F/74	OD	NLP	Exogenous (Primary)	IVCV	2	OPD	DM/HTN	Gatifloxacin	HM
9	F/82	OD	LP	Exogenous (Primary)	IVCV	1	ER	HTN	Moxifloxacin	NLP
10	F/88	OS	NLP	Exogenous (Primary)	IVCV	1	OPD	DM/HTN	Moxifloxacin	NLP
11	F/83	OD	NLP	Exogenous (Primary)	IVCV	1	OPD	None	Moxifloxacin	EV
12	F/76	OD	NLP	Exogenous (Primary)	IVCV	1	OPD	DM	Levofloxacin	EV
13	F/86	OD	2/100	Exogenous (Secondary after trauma) (Primary)	IVCV	1	OPD	DM	Moxifloxacin	2/100

DM, diabetes mellitus; ER, emergency room; EV, evisceration; F, female; FC, finger count; HM, hand movement; HTN, hypertension; IVCV, intravitreal ceftazidime/vancomycin injection; M, male; No, number; NLP, no light perception; OD, oculus dextrus; OPD, outpatient department; OS, oculus sinister; VA, visual acuity

## Figures



**Figure 1**

Anterior segment photography images at the initial examination for each patient a, patient 1 b, patient 2 c, patient 3 d, patient 4 e, patient 5 f, patient 7 g, patient 8 h, patient 9