Corneal Ulcer Leading to Evisceration or Enucleation in a Tertiary Eye Care Center in Thailand: Clinical and Microbiological Characteristics

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Background: *Very severe corneal infection can lead to permanent visual loss, and there is still inadequate knowledge about these severe cases.*
Objective: *To identify clinical and microbiological characteristics of corneal ulcers resulting in evisceration or enucleation in a tertiary eye care center in Thailand.*
Material and Method: *A retrospective chart review was performed of all patients who required evisceration or enucleation due to corneal ulcer at Rajavithi Hospital, Bangkok, Thailand between October 2008 and September 2013.*
Results: *One hundred patients who underwent evisceration or enucleation as a result of corneal ulcer were included in the study. The mean age of the patients was 56.5±12 years, most cases were referred from other hospitals (93%), and 13% of patients were diabetic. At presentation, visual acuity was worse than 5/200 in almost all cases (98%), and trauma (66%), especially by organic substances (36%), was the most common cause. Most cases had full thickness infiltration (81%) with mean size of 6.6±2 mm. Corneal perforation was found in 18% of patients at presentation, and 60% of corneal scraping cultures were positive. Bacteria were the most common pathogens (65%), leading by Pseudomonas aeruginosa (10 cases), and the most common fungus was Fusarium spp. (7 cases). Secondary glaucoma (39%) and corneal perforation (25%) were the main ocular complications. Over half of the patients (52%) needed therapeutic or tectonic surgical intervention during admission. Following evisceration (94%) or enucleation (6%), 23 cases had wound complications that required further surgical treatment. Bacterial infection was found to increase the risk of wound complications more than infection by other pathogen groups (40.9%, p = 0.013).*
Conclusion: *Despite aggressive medical and surgical treatments, very severe corneal ulcers at referral can lead to loss of an eye. Bacterial infection, especially by Pseudomonas aeruginosa, following eye trauma was the most common cause. Evisceration in bacterial corneal ulcers had greater wound complications than ulcers infected by other pathogens.*

Keywords: *Corneal ulcer, Infectious keratitis, Microbial keratitis, Bacteria, Fungus, Evisceration, Enucleation, Blindness*

J Med Assoc Thai 2016; 99 (Suppl. 2): S116-S122
Full text. e-Journal: *http://www.jmatonline.com*

Corneal ulcers are among the leading causes of corneal blindness, which is responsible for 1.5-2.0 million annual new cases of monocular blindness globally[1]. In some cases, corneal ulcers may result in the loss of the eye[2-9].

The severity of microbial keratitis depends on many factors such as virulence of the organism, antibiotic resistance and duration from onset of disease to proper evaluation and prompt treatment [10,11].

The pathogens of microbial keratitis can be bacteria, fungi, viruses, or protozoa. A study in Thailand by Tananuvat el al[10] found that the most common causative pathogens were bacteria (49.3%) and fungi (46.3%) , and *Pseudomonas aeruginosa* (14.90%) and *Fusarium* spp. (26.90%) were the most common bacterial and fungal pathogens. Type of pathogen can vary with geographic location, and in Nepal, fungi (*Aspergillus spp.* and *Fusarium spp.*) were the most common causative pathogens followed by bacteria (*Staphylococcus aureus*)[13,14].

In very severe microbial keratitis, evisceration or enucleation can sometimes be the treatment necessary to prevent spread of infection to nearby structures[3]. The indications of evisceration or enucleation from microbial keratitis are non-healing

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microbial keratitis in a blind eye, corneal perforation that cannot be treated with corneal gluing, or tectonic keratoplasty, endophthalmitis, and panophthalmitis[2-4].

To the best of our knowledge, there has been no review in Thailand of these severe corneal ulcers, which can lead to the loss of an eye. This study aimed to identify the clinical presentation and causative pathogens of very severe microbial keratitis that necessitates evisceration or enucleation. We hope that the results can be used to improve treatment and prevent loss of eyes.

Material and Method

The study included all patients who underwent evisceration or enucleation resulting from corneal ulcers at Rajavithi Hospital, Bangkok, Thailand, between October 2008 and September 2013. Following approval from the Ethics Committee, medical records were reviewed. Data were collected relating to patients' demographic profiles as follows; the duration from onset of symptoms to getting treatment with a primary doctor; the duration from onset of symptoms to getting treatment at Rajavithi Hospital; the admission duration; the time from admission to evisceration or enucleation; underlying disease; underlying ocular disease; presenting visual acuity; lesion characteristics; culture results and drug sensitivity; histology result; treatment; surgical type; complications after surgery; and follow-up duration.

All data were recorded and analyzed using SPSS program (version 16.0, IBM, NY, USA). Post-surgical results and complications were compared between causative organism groups using Fisher's exact test, and a *p*-value of less than 0.05 was considered statistically significant.

Results

One hundred patients were included in the study, composed of 57 males and 43 females, whose mean age was 56.53±12.7 (range 25-86) years. Right (50%) and left eye (50%) were equally affected. Ninety-three percent of the cases were referred from other hospitals. Most patients (69%) worked outdoors or had agriculture-related jobs (69%) while some were retired (28%) or had an office/indoor job (3%). The average duration of onset of symptoms to treatment by a primary doctor was 8.46±12.35 (0-90) days, and the average duration of onset of symptoms to admission to Rajavithi Hospital was 19.22±20.27 (range 2-120) days. The average time from admission to evisceration or enucleation was 19.26±18.15 (0-100) days. Most of the patients had no underlying systemic disease (66%). Hypertension (17%) and diabetes mellitus (13%) were the most common associated systemic conditions (Table 1), and glaucoma was the most common associated ocular disease (6%).

Seventeen patients (17%) had a history of self-medication. The most common cause of ulcer was ocular trauma at 66%; organic objects (36%) were the most common cause of this problem. Interestingly, there was no case of contact lens-associated corneal ulcer in our study (Fig. 1).

At presentation, almost all patients (98%) had visual acuity worse than 5/200 as shown in Fig. 2.

Most ulcers were full-thickness infiltration

Table 1. Systemic and ocular underlying diseases (n = 100 patients)

Systemic underlying disease	No. (%)	Ocular underlying disease	No. (%)
None	66	No	87
Hypertension	17	Glaucoma	6
Diabetes	13	Exposure keratitis	3
Gout	3	Retinal detachment	2
HIV	2	Peripheral ulcerative keratitis	1
Alcoholism	2	Bullous keratopathy	1
Asthma	2		
Chronic kidney disease	2		
Delirium	1		
Parkinsons	1		
Thyroid	1		
Bell palsy	1		
Brain tumor	1		
Total	100		100

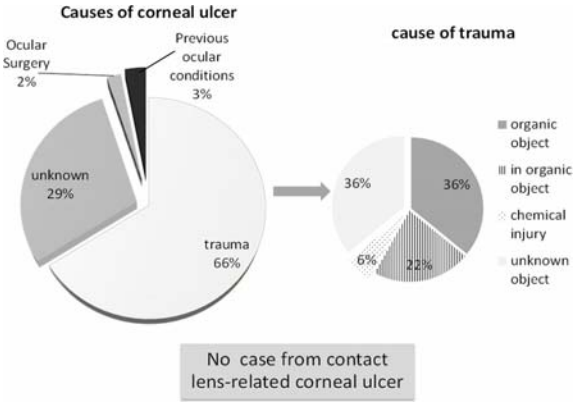

Fig. 1 Causes of corneal ulcer.

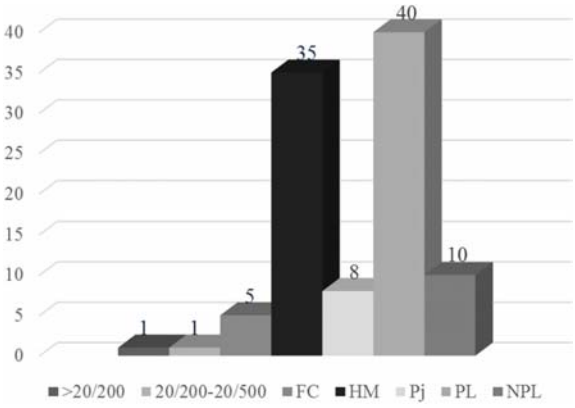

Fig. 2 Presenting visual acuity at Rajavithi Hospital.

Table 2. Culture results from corneal scraping

Pathogens	Number of cases
Gram positive bacteria	
Coagulase negative *Staphylococci* (cMLSB Resistant Strain)	5
Coagulase negative *Staphylococci*	4
Coagulase negative *Staphylococci* (MRCoNS)	2
Corynebacterium spp.	4
Staphylococcus epidermidis	2
Staphylococcus saprophyticus	1
Staphylococcus warneri	1
None-hemolytic *Streptococcus*	1
Bacillus cereus	1
Gram negative bacteria	
Pseudomonas aeruginosa	10
Acinetobacter baumannii	1
Acinetobacter schindleri	1
Achromobacter xylosoxidans	1
Anaerobic Gram Positive Bacilli	1
Anaerobic Gram Positive Cocci	1
Fungus	
Fusarium spp.	7
Fungus	4
Fungus: Black Mold	1
Fungus: Mold	1
Scedosporium apiospermum	1
Yeast (not Albican)	1
Pythium spp.	1

(81%) with mean size 6.6±2.07 mm x 6.6±2.09 (1.5-10) mm. Corneal perforations were found in 18% of cases at presentation.

Microbiological investigations, including corneal scrape for gram-stain, KOH, culture, corneal tissue culture, and histology, returned positive results for fungus (26%), bacteria (22%), and mixed organism (19%). No identifiable organism accounted for 26% of cases. Corneal scraping revealed that 21 cases were KOH positive for fungus (septate hyphae 15%, non-septate hyphae 1%, and yeast 5%). Nine cases were gram-stain positive from corneal scraping followed by gram negative bacilli (7 cases), gram-positive cocci (1 case), and gram-positive bacilli (1 case). Corneal histopathology found fungus in 14 cases, while corneal scraping cultures were positive in 60% of cases. Bacteria were the most common pathogens (65%), followed by *Pseudomonas aeruginosa* (10 cases). The most common fungus was *Fusarium spp.* (7 cases, Table 2).

Thirty-nine corneal tissue cultures were positive, followed by gram-positive bacteria (31%) and mold (36%). Similar from corneal scraping results, the most common gram-negative bacteria was *Pseudomonas aeruginosa* (8 cases) and coagulase-negative *Staphylococci* (four cases) was the most common gram-positive bacteria. *Fusarium spp.* was the most common fungus found (Table 3).

Most of the *Pseudomonas aeruginosa* were sensitive to ceftazidime, gentamicin, amikacin, and levofloxacin, while most coagulase-negative Staphylococci demonstrated resistance to the medication (Table 4, 5).

The list of drugs used and number of cases in which each one was used are shown in Table 6. Most of the cases were treated by a combination of more than two drugs (Fig. 3).

Secondary ocular hypertension (39%) and corneal perforation (25%) were the main ocular complications (Fig. 4). Just over half of the patients (52%) needed therapeutic or tectonic surgical

Table 3. Culture results from corneal tissue

Pathogens	No. cases
Gram positive bacteria	
Coagulase negative Staphylococci (cMLSB Resistant Strain)	3
Coagulase negative Staphylococci (MRCoNS)	1
Staphylococcus saprophyticus	2
Enterococcus spp.	2
Staphylococcus epidermidis	1
Viridans Group Streptococci	1
Bacillus cereus	1
Corynebacterium spp.	1
Gram negative bacteria	
Pseudomonas aeruginosa	8
Klebsilla pneumoniae (ESBL)	1
Achromobacter xylosoxidans	1
Fungus	
Fusarium spp.	5
Aspergillus spp.	4
Fungus	3
Pythium insidiosum	2
Fungus: Mold	1
Acremonium spp.	1
Scedosporiumapiospermum	1
Yeast (not Albican)	1

Table 4. Drug sensitivity for *Pseudomonas aeruginosa* (10 cases)

Drug	Sensitive (%)	Resistant (%)
Ceftazidime	90	10
Gentamicin	80	20
Amikacin	80	20
Levofloxacin	90	10

Table 5. Drug sensitivity for *Coagulase-Negative Staphylococci* (11 cases)

Drug	Sensitive (%)	Resistant (%)
Erythromycin	18	82
Gentamicin	63	27

interventions such as corneal gluing or keratoplasty during admission.

Evisceration was performed in 94 cases and enucleation in six cases. After evisceration or enucleation, 23 cases had wound complications (e.g. glass ball exposition) that needed further surgical treatment. Bacterial infection was found to increase the risk of wound complications (40.9%, $p = 0.013$) more than fungal (3.8%) or mixed organism (21.1%) infections.

Table 6. Antimicrobials used in corneal ulcer cases

Drugs	Number of cases
Antibiotic eye drops (ed)	
Vancomycin	62
Cefazolin	20
Ceftazidime	42
Amikacin	35
Gentamicin	7
Moxifloxacin	19
Levofloxacin	2
Antifungal medications	
Amphotericin B (ed)	53
Fluconazole (ed)	50
Natamycin (ed)	37
Variconazole (ed)	2
Ketoconazole (per oral)	40
Itraconazole (per oral)	18

Discussion

In this study, *Pseudomonas spp.* was the most common causative pathogen. This result is similar to the findings of previous studies by Cruz CS et al[2] and Constantinou M et al[3]: in both of these studies, *Pseudomonas spp.* was also the most common causative pathogen, which led to loss of eyes. The reasons for this could be the virulence of *Pseudomonas spp.* which has *Pseudomonas aeruginosa* small protease (PASP)[15,16], or its commonness. It has been found to be a common cause of corneal ulcers in many prior studies[3,12,17-19].

In our study, the most common cause of corneal ulcer was trauma caused by organic substances. This may be a result of the occupations of our patients, as they were mainly agricultural or other out-doors workers. Interestingly, there was no case of contact lens- related corneal ulcer in our study. Possible reasons were the low rate of contact lens usage in our study population; they were mainly employed in agriculture-related or other outdoor jobs in rural parts of Thailand, and contact lens users tend to live in big cities and seek earlier care from corneal specialists. The organisms

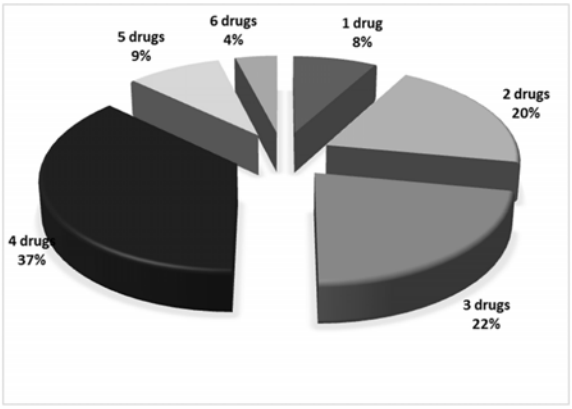

Fig. 3 Number of antibiotics eye drops used.

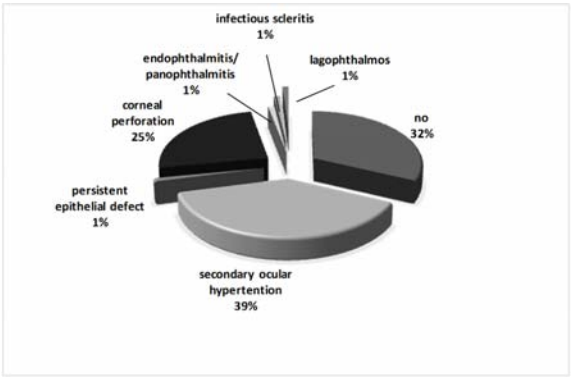

Fig. 4 Ocular complications (n = 100).

responsible for contact lens-related keratitis may also be less aggressive and more responsive to medication than post-traumatic corneal ulcers.

This study discovered that bacterial infection caused higher rates of wound complication after evisceration and enucleation than infection by other pathogens. This finding may be because bacteria are more virulent than other pathogens, especially *Pseudomonas aeruginosa* that has PASP as a virulence-promoting factor[15,16]. The interrelationship between bacterial keratitis and wound complication after evisceration or enucleation had not been previously established.

Due to the retrospective nature of chart reviews, there were some limitations in this study such as missing data regarding drug sensitivity. Our referral cases were also unusual; for instance, there was no case of contact lens-related corneal ulcer, and this is unlike other studies, so that other populations in primary or secondary eye care centers or other regions may be different. The yield of positive cultures may also be lower than initial cultures in primary eye care service because when they arrived at the tertiary hospital, almost all patients received topical antibiotics immediately, and this may have retarded growth of microorganisms in culture media. Our laboratory setting still lacks anti-fungal drug sensitivity study, so it would be difficult to know if there were any drug-resistant fungal infections in our study patients.

Most of the cases were referred from rural areas, which led to delayed treatment (average duration of symptoms to treatment by primary doctor was 8.46 days), with severe clinical presentations, combined with a shortage of corneal donors in our country. There is a 3-5 year wait for optical corneal transplantation and up to 1-3 months for tectonic or therapeutic corneal transplantation. These factors were the main reasons for loss of eyes.

Especially in settings in Thailand, the authors suggest the following strategies to minimize avoidable blindness resulting from corneal ulcers:

1) Encouraging the general public to wear protective eye wear when doing out-door/agricultural work, or other tasks which carry a high-risk of eye injury.

2) Educating patients about corneal infection and the importance of seeking early professional care to minimize ocular damage.

3) Encouraging primary ophthalmologists to do early corneal scraping culture to detect the responsible organisms, perform partial debridement, and prescribe early appropriate intensive treatment with fortified antibiotics or anti-fungal.

4) Monitoring disease and making prompt referrals to a corneal specialist in Thailand Service Plan when corneal ulcers continue to progress despite treatment with the most appropriate available medications.

5) Promoting corneal donations in Thailand to supply eye-saving therapeutic or tectonic corneal transplantation when necessary.

Conclusion

Despite aggressive medical and surgical treatments, very severe corneal ulcers at referral can lead to the loss of an eye. Bacterial infection, especially *Pseudomonas aeruginosa*, following eye trauma was the most common cause. Evisceration of bacterial corneal ulcers had higher wound complications those infected by other pathogens.

What is already known on this topic ?

There is no known review clinical and

microbiological characteristics of such severe corneal ulcer that lead to loss of an eye.

What this study adds ?

Despite aggressive medical and surgical treatments, very severe corneal ulcer at referral can lead to loss of an eye.

Bacterial infection, especially *Pseudomonas aeruginosa*, following eye trauma was the most common cause.

Contact lens-related corneal ulcer is not found in this study. It maybe from less aggressive in nature or patient seeker earlier care with ophthalmologist.

Evisceration in bacterial corneal ulcer had higher wound complications when compared with other pathogens.

Acknowledgement

This study was supported by a Rajavithi Hospital research fund.

Potential conflicts of interest

None.

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Identification of a novel secreted protease from *Pseudomonas aeruginosa* that causes corneal erosions. Invest Ophthalmol Vis Sci 2005; 46: 3761-8.

โรคแผลที่กระจกตาที่นำไปสู่การผ่าตัดเอาดวงตาออกในโรงพยาบาลระดับตติยภูมิในประเทศไทย: อาการแสดงและเชื้อก่อโรค

ธีรวีร์ หงษ์หยก, วรภา ลีลาพฤทธิ์

วัตถุประสงค์: *เพื่อหาเชื้อก่อโรคและลักษณะอาการแสดงของคนไข้ที่มีกระจกตาติดเชื้อรุนแรงจะต้องเสียดวงตาในโรงพยาบาลระดับตติยภูมิในประเทศไทย*

วัสดุและวิธีการ: *ทบทวนเวชระเบียนผู้ป่วยทุกรายที่ต้องได้รับการผ่าตัดเอาตาออกหลังการติดเชื้อที่กระจกตาที่โรงพยาบาลราชวิถีระหว่าง เดือนตุลาคม พ.ศ. 2551 ถึง เดือนกันยายน พ.ศ. 2556*

ผลการศึกษา: *มีคนไข้ 100 คนที่เข้าเกณฑ์รวบรวมในการศึกษาอายุเฉลี่ยที่ 56.5 ปี กว่า 93% ส่งตัวมาจากโรงพยาบาลอื่น เบาหวานเป็นโรคประจำตัวที่พบบ่อย (13%) เกือบทุกคนการมองเห็นแย่กว่า 5/200 (98%) เมื่อมาถึงโรงพยาบาลราชวิถี แผลติดเชื้อที่กระจกตาตลอดทั้งความหนากระจกตา (81%) โดยมีขนาดเฉลี่ยที่ 6.6 มิลลิเมตร มีภาวะกระจกตาทะลุ 18% ตั้งแต่มาสาเหตุส่วนใหญ่เกิดจากอุบัติเหตุ (66%) โดยสารอินทรีย์ (36%) เพาะเชื้อขึ้นจากการขูดกระจกตา 60% โดยพบเชื้อแบคทีเรียมากที่สุด (65%) ตามมาด้วยเชื้อรา ระหว่างการรักษาพบต้อหินแทรกซ้อน 39% และกระจกตาทะลุ 25% กว่า 52% ของคนไข้ต้องได้รับการผ่าตัดรักษาเพื่อรักษาการติดเชื้อหรือกระจกตาทะลุ ที่สุดแล้วคนไข้ได้รับการผ่าตัดแบบ evisceration เป็นส่วนใหญ่ (94%) พบปัญหาแผลแยกถึง 23% การติดเชื้อแบคทีเรียเป็นปัจจัยหลักที่เพิ่มความเสี่ยงของแผลผ่าตัดเมื่อเทียบกับการติดเชื้อกลุ่มอื่นๆ (40.9%, p = 0.013)*

สรุป: *แม้ว่าจะได้รับการักษาอย่างเต็มที่ทั้งยาและการผ่าตัด แผลกระจกตาติดเชื้อที่รุนแรงอาจนำไปสู่การสูญเสียดวงตาอย่างถาวรได้ เชื้อแบซทีเรีย Pseudomonas aeruginosa หลังจากอุบัติเหตุทางตาเป็นสาเหตุที่พบบ่อยที่สุด การผ่าตัด evisceration จากแผลติดเชื้อที่กระจกตาจากแบคทีเรียจะมีปัญหาที่แผลผ่าตัดได้บ่อยกว่าเชื้ออื่น*