Clinical Profile and Outcomes of Central Microbial Keratitis in the Philippines

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ABSTRACT

Objective: Despite being a preventable and treatable condition, central microbial keratitis (CMK) and its complications remain to be a significant cause of vision loss in our country. This study presents the demographic profile, risk factors, etiologies, treatments, and outcomes of CMK in the Philippines.

Methods: The study was a two-center, prospective, non-randomized clinical study involving the patients of the External Disease and Cornea Clinics of two tertiary eye referral centers in the Philippines. It was conducted as the Philippine leg of the Asia Cornea Society Infectious Keratitis Study (ASCIKS).[1] Patients with a clinical diagnosis of CMK rendered by a cornea specialist, and who signed the consent form, were recruited into the study. They underwent uniform sample collection and culture techniques as described in the ACSIKS. All patients were followed-up for 6 months. Data collected included demographics, risk factors, culture results, management, and treatment outcomes. Descriptive statistics and frequency were used to analyze the data.

Results: A total of 348 patients diagnosed with CMK were included. Trauma (65.5%) among the middle-aged (42.9 ± 17.9 years) male population was the most significant risk factor for development of CMK, followed by contact lens wear (12.9%), prior ocular surgery (6.0%), and ocular surface diseases (3.4%). Bacterial keratitis (53.2%) was still the most common etiology of CMK, followed by fungal keratitis (27.0%), *Acanthamoeba* keratitis (5.7%), and viral keratitis (2.0%). *Aspergillus* species (18.3%) were the most common microbial isolates. *Pseudomonas* species (13.9%) were the most common bacterial isolates. The median time from onset of symptoms to consultation with the study centers was 2 weeks. Medical treatment was enough to treat the infection in 34.8% of cases. Surgical intervention was necessitated in 22.6% with evisceration/enucleation done in 1 out of 3 patients who had surgery.

Conclusion: Bacterial infection remains the most common cause of CMK in the Philippines, followed by fungal infection. Significant risk factors include trauma and contact lens wear. *Aspergillus* species and *Pseudomonas* species were the most common fungal and bacterial isolates, respectively. Despite medical treatment, almost a quarter of the cases still required surgical intervention.

Keywords: Central microbial keratitis, profile, outcomes, Philippines

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Central microbial keratitis (CMK) is clinically diagnosed by the presence of corneal ulceration with or without stromal infiltration and hypopyon. It can be caused by bacteria, fungi, viruses, or parasites. CMK should be treated as an emergency, since complications from this potentially vision-threatening condition may lead to blindness and even loss of the eyeball.[2]

Based on the data of the World Health Organization (WHO), corneal blindness is a significant cause of vision loss after cataract and glaucoma. Among the top ten main causes of bilateral blindness reported in the Third Philippine National Survey on Blindness, corneal blindness ranked sixth, accounting for 3.5% of cases.[3,4] CMK ranked first as the most common condition referred to the Philippine General Hospital (PGH) in the twenty-year survey of cornea and external eye disease problems by Valenton in 2000.[5] In a study on indications of penetrating keratoplasty (PKP) in the Philippines, CMK with its complications was the third most common reason for PKP.[6.] The economic burden of corneal blindness is highly related to reduction in vision-related quality of life that can limit daily activities and productivity among affected individuals, and is difficult to ascertain as there are only limited data available.[2,7]

Despite being a preventable and treatable condition, the authors have observed a constant number of patients with CMK in our clinics. It was still the second most common diagnosis by new consultations at the External Disease and Cornea Clinic of the Department of Ophthalmology and Visual Sciences at the PGH in 2022. The most extensive study on CMK published locally in 2000 described the etiology, epidemiology, clinical features, and treatment of CMK cases over a 20-year period at the PGH.[8] The authors deemed it necessary to present the Philippine data of the ACSIKS separately and further analyze the data in order to present a more recent picture of the demographic profile, risk factors, etiologies, treatments, and outcomes of CMK from two major public tertiary eye referral centers in Metro Manila, Philippines. By doing so, we will have more accurate and updated data regarding this potentially blinding disease, which will enable us to better understand and manage the same.

This research was a two-center, prospective, non-randomized clinical study involving the patients of the External Disease and Cornea Clinics of two tertiary eye referral centers (PGH and East Avenue Medical Center/EAMC) conducted from April 2012 to November 2014. The study was conducted as the Philippine leg of the multicenter ACSIKS involving 8 Asian countries.[1] The study protocol was approved by the Institutional Review Board of the two institutions. Informed written consent was obtained from each patient prior to enrollment into the study.

As described in the ACSIKS, the study consisted of a clinical protocol and a microbiological protocol. Patients with a clinical diagnosis of CMK confirmed by a designated cornea specialist were recruited into the study. All patients were followed-up for 6 months, but the patients could be discharged prior to the 6th month if no further management was necessary. The inclusion criteria were: a diagnosis of CMK, with or without prior treatment, in one or both eyes; and signed informed consent. For minors under 21 years of age, consent was provided by a parent or guardian. Patients who were unable to follow up, were uncooperative, or who could not follow instructions were excluded from the study.

CMK was clinically diagnosed based on the presence of an ulcer, infiltrates, and/or abscess, believed to be of infectious etiology. Corneal scraping or biopsy specimens collected from each patient were sent for standard microbial culture for identification of the etiologic microorganism. However, specimens from cases of suspected viral keratitis were not sent for culture, as cell cultures and polymerase chain reaction testing were not included in the microbiological protocol.[1] The clinical data gathered from the patients included age in years, sex, laterality of CMK, duration of symptoms in weeks, prior treatment with medications, risk factors for CMK (trauma, contact lens wear, prior ocular surgery, and presence of ocular surface disease), final diagnosis (bacterial, fungal, viral, parasitic, not specified), outcomes of medical treatment, and types of surgery performed. All fungal and bacterial organisms isolated from study patients were sub-cultured and transferred into Microbank vials (Pro-Lab Diagnostics, Round Rock, Texas, USA) for storage in dedicated ultra-

low deep freezers (–80 °C) at each study center. At least two samples of each isolate were preserved, ensuring that by the end of the study, each center would retain one sample for its own research, while the second sample would be sent to the ACSIKS Central Repositories.

The clinical data were manually entered into an electronic spreadsheet file. The subsequent data processing and analysis were carried out using the Microsoft Excel software (Microsoft Corporation, Washington, USA). The patient's identity was not included in the electronic spreadsheet and was replaced by a sequence number to ensure privacy and confidentiality. The authors adhered to the tenets of the Declaration of Helsinki, the Philippine Data Privacy Act of 2012, and the regulations of local Institutional Review Boards. The privacy and confidentiality of each subject were upheld.

Total sampling of consecutive patients who met the inclusion and exclusion criteria was used in this study. Descriptive statistics such as mean, median, standard deviation, and range were used for describing the age of participants in years and duration of symptoms, while frequency and percentage were used for the categorical data variables such as sex, laterality, prior treatment with medications, risk factors for CMK, final diagnosis, outcomes of medical treatment, and types of surgery performed.

RESULTS

A total of 348 patients were recruited during the nearly two-year study period. More than two-thirds (67.8%) were males, as shown in Table 1. All patients had unilateral CMK. About half of the patients (57.5%) presented within two weeks from the onset of symptoms, and most had prior treatment (73.6%) with a topical and/or systemic medication. The median duration of symptoms prior to consultation was 2 weeks. Twenty-one patients (6%) were on topical steroids with or without antimicrobial coverage. Trauma was the most common risk factor followed by contact lens wear at 65.5% and 12.9%, respectively. More than two-thirds of patients with trauma suffered trauma from non-vegetative material. Almost all who were contact lens wearers wore them for refractive or cosmetic purposes.

Table 1. Baseline Characteristics of the Study Population (*n*: 348)

Characteristic	Number (Percentage)
Average age (years)	42.9 ± 17.9
Sex	
Male	236 (67.8%)
Female	112 (32.2)
Laterality of involvement	
Unilateral	348 (100%)
Bilateral	0 (0%)
Duration of symptoms	
≤2 weeks	200 (57.5%)
>2 weeks	148 (42.5%)
Median duration of symptoms	2 weeks
Prior treatment with medications	
Yes	256 (73.6%)
No	92 (26.4%)
Risk factor	
Trauma	228 (65.5%)
Vegetative	80 (23.0%)
Non-vegetative	148 (42.5%)
Contact Lens Wear	45 (12.9%)
Refractive/Cosmetic	44 (12.6%)
Therapeutic	1 (0.3%)
Prior Ocular Surgery	21 (6.0%)
Ocular Surface Diseases	12 (3.4%)

As shown in Table 2, the most common microorganisms that grew on cultures were fungi (43.3%). Molds (29.8%) were more common than yeasts (13.5%). *Aspergillus* species were the most common fungi as well as the most common microorganisms identified by culture. Bacteria (23.6%) were the second most common microorganisms identified. Gram-negative bacteria (15.9%) were the more common bacterial isolates as compared to Gram-positive bacteria (7.7%). The most common Gram-negative bacterial isolates were *Pseudomonas* species, while the most common Gram-positive isolates were *Bacillus* species. Parasitic organisms were seen in only 2 eyes, and *Acanthamoeba* species (1%) were the only parasitic microorganisms identified. Sixty-seven (32.2%) eyes had some growth on the culture medium, but these were not identifiable. This study had a positive culture rate of 61%.

The final diagnosis was made based on a positive microbiological culture result, except for suspected viral keratitis. In the absence of culture results, the final diagnosis was made based on the clinical characteristics and the response to treatment. At the conclusion of the study, half or 53.2% of the eyes were diagnosed with bacterial keratitis (Table 3). Twenty-seven percent (27%) had a final diagnosis of fungal keratitis. Almost 6% had a final diagnosis of parasitic (*Acanthamoeba*) keratitis. Only 2% of eyes were suspected to have viral keratitis. In 42 (12.1%) eyes, the cause of infection remained undetermined.

Table 2. Microbiologic Growth Patterns of the Corneal Samples (*n*: 208)

Microorganism Isolated	Number (Percentage)
Bacterial	49 (23.6%)
Gram-positive	16 (7.7%)
Bacillus species	10 (4.8%)
Streptococcus species	3 (1.4%)
Enterococcus faecium	1 (0.5%)
Staphylococcus aureus	1 (0.5%)
Leuconostoc species	1 (0.5%)
Gram-negative	33 (15.9%)
Pseudomonas species	29 (13.9%)
Acinetobacter baumannii	2 (1.0%)
Enterobacter species	1 (0.5%)
Burkholderia cepacia	1 (0.5%)
Fungal	90 (43.3%)
Yeast	28 (13.5%)
Candida species	28 (13.5%)
Molds	62 (29.8%)
Aspergillus species	38 (18.3%)
Fusarium species	24 (11.5%)
Parasitic	2 (1.0%)
Acanthamoeba species	2 (1.0%)
Undetermined	67 (32.2%)

Table 3. Final Diagnosis of Etiologic Cause of Central Microbial Keratitis (*n*: 348)

Etiologic Cause	Number (Percentage)
Bacterial	185 (53.2%)
Fungal	94 (27.0%)
Parasitic	20 (5.7%)
Viral	7 (2.0%)
Not specified	42 (12.1%)

Medical treatment alone was enough to treat the infection in almost one-third (34.8%) of the eyes, as shown in Table 4. Eight eyes (2.3%) had persistent infection on the last documented follow-up, but no surgical intervention was needed. Surgical intervention was necessary in 22.6% at initial presentation or during the course of the follow-up period. A large number of eyes (40.3%) were lost to follow-up. Data regarding outcomes were unavailable for 3 eyes.

Table 4. Outcomes of Medical Treatment (*n*: 345)

Outcome	Number (Percentage)
Infection resolved on last follow-up	120 (34.8%)
Infection not resolved on last follow-up	8 (2.3%)
Surgical intervention required	78 (22.6%)
Lost to follow-up	139 (40.3%)

The types of surgery performed are listed in Table 5. Penetrating keratoplasty (PKP) was performed in two-thirds (66.7%) of the eyes that required surgery, with the numbers of tectonic and therapeutic indications being almost equal. Nearly one-third (29.5%) of eyes that required surgery underwent enucleation or evisceration for uncontrollable or severe infection with corneal melt or perforation.

Table 5. Types of Surgery Performed to Control Infection (*n*: 78)

Type of Surgery	Number (Percentage)
Penetrating keratoplasty	52 (66.7%)
Tectonic penetrating keratoplasty	25 (32.0%)
Therapeutic penetrating keratoplasty	27 (34.6%)
Conjunctival flap	1 (1.3%)
Evisceration/enucleation	23 (29.5%)
Others	2 (2.6%)

DISCUSSION

The mean age of this cohort of patients was 43 years, which falls within what is considered the most productive age group (40-49 years) in occupational settings.[9,10] The preponderance of males in this study reflected a greater risk among males for traumatic eye injury. In developing countries, the male dominated occupations involving manual labor, such as construction work and farming, have a higher risk for eye trauma.[11] On the other hand, a study on contact-lens associated keratitis noted a greater proportion of female patients.[12] This is consistent with the findings of this study. In 2000, Valenton reported that among his cohort of Filipino patients, trauma was a risk factor for CMK in 77% of eyes, contact lens usage in 1.9%, prior ocular surgery in 0.97%, and ocular surface diseases in 1.4%.[8] Comparing the previous results to this study, trauma (65.5%) decreased as a risk factor for CMK, while contact lens wear (12.9%), prior ocular surgery (6.0%), and ocular surface diseases (3.4%) increased as risk factors. This may reflect the changing behavior of Filipinos and greater accessibility to ocular surgery. The authors believe that the increase in prior ocular surgery as a risk for CMK may be due to the increased accessibility of surgery brought about by the broadening financial coverage of various eye surgeries by the Philippine Health Insurance Corporation (PhilHealth) since Republic Act 7879 (or the PhilHealth Act) was passed in 1995.[13] Even among the population that seeks treatment at government institutions, there are now also more individuals, mainly females, using contact lenses, as compared to decades ago. This behavior is influenced by societal expectations, increased availability of fairly inexpensive contact lenses, and the internet. It may also be possible that more safety measures at industrial workplaces, such as the use of protective goggles, as well as first aid with antimicrobials, are now more in place than in the

past. The Department of Labor and Employment (DOLE) has set safety guidelines, and a study on the compliance with safety policies for workplaces would be helpful.[14] While corneal trauma was still the number one reason for consults in PGH up to 2022, these factors may account for the comparative decrease in the percentage of trauma as a risk factor for CMK.

The findings of risk factors in our study are similar to those of developing countries such as India, but differ from those of developed countries in general.[1] In a cohort of 94 patients with CMK in a developed country, the most common risk factor identified was contact lens usage (73%), while trauma (3.1%), ocular surface disease (11.7%), and prior ocular surgery (4.3%) accounted for only 19% of the cases.[15]

Valenton reported bacteria as the most common microorganism (48.1%) isolated by culture with *Moraxella* species (13.3%) and *Pseudomonas* species (13.3%) as the most common bacterial organisms from 2,064 eyes. Fungi grew on culture only in 16.9%. *Aspergillus* species were identified in 6.1%, while *Fusarium* species were identified in 5.1%. *Candida* was only identified in 2 eyes.[8] The results of the current study showed fungi as the most common organism identified at 43% and bacterial organism at only 23% which is the opposite of the data collected prior to 2000. This reversal is probably due to the availability and wider usage of the newer generation topical fluoroquinolones such as gatifloxacin, moxifloxacin, levofloxacin after traumatic eye injury in this cohort of patients. The prior use of these antibiotic eye drops in 73% of cases may have drastically lessened the yield on microbiologic culture. This study has a culture positive rate of 61%.

The most common bacteria identified in this study was *Pseudomonas* species (13.9%) which is consistent with the proportion of patients wearing contact lenses. Contact lens wear is still the most common risk factor in developing *Pseudomonas* keratitis. *Pseudomonas* possess virulence factors that promote macromolecular deposition or biofilm formation on contact lenses which resist disinfection.[16] In a similar study done in Thailand of 292 CMK cases, *Pseudomonas* was the most common bacterial isolate (15.29%).[17]

The most common fungal isolate in our study was *Aspergillus*, and the percentage of fungal keratitis in our series is as high as those of China and India.[1] This similarity can be explained by the fact that all three countries have a significant agricultural sector and trauma by vegetative matter is a known risk factor for fungal CMK.[18,19,20] However, *Fusarium* was the most common fungal isolate equivalent to 14.42% of the 3,183 CMK cases in India.[18] In a study of 654 fungal keratitis in China, *Fusarium* grew in 73.3% of the cases and *Aspergillus* only in 12.1% of the cases.[21]

As with the study of Valenton, bacterial keratitis remained to be the most common final diagnosis (56.6% versus 53.2%). A decrease in the incidence of viral keratitis was seen in this study (22.6% versus 2.0%); however, there was doubling of the incidence of fungal keratitis in this study compared to the previous study (12.5% versus 27.0%).[8] PGH and EAMC both being tertiary eye referral centers, this increase may be explained by the higher number of fungal keratitis referred for management. It is common knowledge that fungal keratitis is more difficult to treat than bacterial keratitis. It may also reflect the greater access to broad spectrum antibiotics that can effectively treat bacterial keratitis while access to topical anti-fungal remains challenging. These noted changes highlight the importance of gathering and analyzing new data regularly since these findings are affected by changes in diagnostic tests, practice patterns, socio-economic status, drug availability, and health seeking behaviors to name a few.

Although fairly good health seeking behavior and practices amongst the subjects were observed in 57.5% of those who presented less than 2 weeks from the onset of the disease, there was still a large proportion (42.5%) who sought consultation only after 2 weeks of symptoms; while a considerable number (40.3%) were lost to follow-up. A large number of our patients were laborers who cannot afford a loss of daily income if they were not able to work for a day. This economic burden could have affected their health-seeking and follow-up behavior. One-third of the patients in this cohort of patients came from rural areas outside the metropolis where transportation costs and logistics would have likewise affected their capacity for follow-up visits.

This behavior among the study subjects is consistent with the findings of a study published in 2022 on catastrophic health expenditure in the Philippines. The study reported the lived realities of health financing through four domains that starts with "pagtitiis", or enduring the illness as long as they can, basically because of financial concerns and/or lack of access to healthcare.[22] Improved accessibility in terms of financing and proximity would improve health-seeking behavior and presumably improve outcomes of microbial keratitis as well as many other preventable and treatable illnesses.

The fairly high percentage of those who presented at our clinics after 2 weeks of the start of symptoms is in stark contrast to the findings in developed countries Taiwan, Singapore and Japan where median time of consultation after symptoms were 0.3, 0.4 and 0.6 weeks respectively.[1] These countries had better outcomes in terms of resolution of the infections and necessity for surgical intervention than the Philippines which had a median of 2 weeks before consultation. While outcomes of treatment are affected by many factors, the countries with shorter time prior to consultation had better outcomes.[1]

Nearly a quarter (22.6%) of the study population required surgical intervention. Aside from the 2-week median period for consultation, this might also be due to the high incidence of fungal keratitis where infections are usually advanced and deep in the cornea when referred, and recalcitrant to topical anti-fungal therapy.[23] For surgical interventions performed, tectonic and therapeutic PKP were most commonly done. Due to the relatively scarce donor corneal tissues locally, lower grade corneal tissues are commonly used for infectious and urgent cases, with the intention of performing an optical graft once the acute infection is controlled; thus, a higher rate of corneal graft failure is expected.

The rate of evisceration/enucleation was relatively high and similar to that of Thailand.[1] Again, this may have to do with the fairly high number of fungal infections that were brought for consultation more than 2 weeks from onset.

A limitation of this study is that it was conducted in two public tertiary eye referral centers thus the results are not completely generalizable to the entire Philippines. It is a fact that tertiary referral hospitals usually get cases with more serious and advanced disease. Moreover, the management of infectious keratitis in this study was not standardized. Medical and surgical treatments were determined by individual cornea specialist and by the availability of drugs and donor corneal tissues.

Despite the availability of a greater number of broad spectrum anti-microbials, CMK remains a formidable condition, especially in developing countries. This study showed that bacterial keratitis is still the most common etiologic diagnosis of CMK with fungal microorganisms coming in second. *Aspergillus* was the most common microbial isolate while *Pseudomonas* was the most common bacterial isolate. Eye trauma amongst the working male population was the most significant risk factor for the development of CMK followed by contact lens wear mainly among the female population. Median time from onset to consultation was 2 weeks; and despite medical treatment, almost a quarter of the eyes in the study required surgery. The findings of this study underscore the importance of timely detection and proper management of CMK to avoid permanent visual disability and blindness. It is hoped that the data presented may help ophthalmologists in the Philippines better understand and manage CMK.

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STATEMENT OF AUTHORSHIP

The current study is a sub-analysis of the already published Asia Cornea Society Infectious Keratitis Study (ASCIKS). The results presented were from the Philippine leg of the ASCIKS where one of the authors was primary investigator and another a co-

investigator. Acquisition of data was performed during the conduct of the ACSIKS.

All the current authors contributed to the conceptualization of this work; analysis of data; drafting and revision; and approval of the final version submitted.

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