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Title: Management outcomes of microbial keratitis at a tertiary hospital: a review of 10 years records.

Running title: Management outcomes of microbial keratitis

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Abstract:

Background: Microbial keratitis (MK) is a potentially sight-threatening condition with an annual incidence of 2 million cases globally. The present study is aimed at reviewing the treatment options and outcomes for MK in 10 years at the ophthalmic unit of a tertiary hospital in central Saudi Arabia.

Methods: This retrospective review of the health records was conducted in 2020 reviewing the records from 2010 to 2019. Microbial profile and treatment outcomes were analyzed. Persons with the Best-corrected visual acuity (BCVA) at last follow-up, as well as eyes eviscerated, were estimated.

Results: A total of 181 MK cases were considered for the study. Among which culture was positive in 98 (54.1%) patients. Gram-positive and Gram-negative bacteria were in 50 (49%) and 35 (35.7%) cases respectively. Fungus MK was in 13 (13.3%) cases. Fusarium (6) and Aspergillosis (4) were main fungus identified. Topical antibiotic included Ceftazidim+cefazolin (113; 62.4%), Cefazolin+gentamycin (45; 24.8%) and Ceftazidim+ vancomycin (23; 12.7%). Antifungals included amphoterecin (13) and Natamycin (13) cases. Among the 181 eyes treated, 75 [41.2%(95% Confidence interval 34.3, 48.6)] eyes had regained vision better than 20/60 (normal functional vision) at six months after completion of treatment. The rate of anatomic failure (removal of eyeball) was 2.2% (95% CI 0.1, 4.4). Final BCVA was <20/200 in 47 (26%) eyes. Infection due to Staphylococcus and Streptococcus had poor visual recovery. The eyes with MK due to Pseudomonas had remarkable visual gain after treatment.

Conclusion: Management of MK at a tertiary hospital had good outcomes, and underlying causes like late presentation and uncontrolled diabetes need to be addressed concurrently.

Keywords: Microbial Keratitis, antibiotics, anti-fungal, ocular infection, vision restoration.

Introduction:

MK is a potentially sight-threatening condition with an annual incidence of 2 million cases globally. With incriminate usage of antibiotics, the risk of resistance cannot be ruled out, resulting in corneal blindness that can be avoided by early detection, identification of causative organisms, and appropriate treatment[1]. The risk has increased in the younger generation due to the rampant usage of contact lenses for
cosmetics [2]. In adults, the rising prevalence of diabetes and dry eye syndrome adds to the risk of MK[3]. Different ophthalmic professional bodies have proposed management protocols for early detection and standard treatment and have periodically revised them [4,5]. Treatment modalities like collagen cross-linkage and therapeutic keratoplasty are recommended in conjunction with antibiotic therapy [6,7]. Organism profile and antibiotic sensitivity profile to MK were studied in a tertiary eye hospital in Saudi Arabia. Oxacillin treatment resistance was rising among S aureus organisms. At the same time, it remained the same with S epidermis[8]. in another university-affiliated hospital, it was noted that all gram-positive organisms of MK were sensitive to Vancomycin. At the same time, S pneumonia was resistant to gentamycin[9]. A review highlighted an issue of keratitis due to acanthamoeba related to contact lens abuse in the Middle East countries and Iran, along with limitations of treatment outcomes [10]. To the best of our knowledge, the long-term study of organism profile and antibiotic pattern and treatment outcomes on vision and corneal status in Saudi Arabia is not documented in detail. We present ten years of data on microorganism profile, antibiotic sensitivity, and anatomic and functional outcomes of the MK treatment at a tertiary level eye hospital over ten years.

**Subjects and methods:**

The ethical committee of our hospital approved this retrospective cohort study. The study was held in 2020, and cases of MK from January 2010 to December 2019 that were managed at our hospital were included. This being the retrospective nature of the health record review, the patient's consent was waived. All the tenets of the Helsinki declaration were strictly adhered to during different stages of the research. We assumed that the moderate to severe visual impairment after the management of MK
would be in 22% of the treated cases [11]. To achieve a 95% confidence interval and 80% power to the study, we need 168 cases to be studied before and after MK treatment. To compensate for the loss of data, we increased the sample by 10%. Thus, we needed at least 185 MK cases to be reviewed. We used the sample size calculation method in the Open Epi software[12].

One cornea surgeon and two general ophthalmologists were the study investigators. Routinely, the patients visiting either the emergency unit or consultant office with signs and symptoms suggestive of MK were investigated for the underlying causes like abuse of contact lens, uncontrolled diabetes, ocular trauma, and past treatment by family physician and referring ophthalmologist, especially with the topical steroid and antibiotic medications. The slit-lamp biomicroscopic examination (Topcon, USA) is carried out after instilling topical anesthesia. If perforation is not suspected, applanation tonometry is also performed to measure the intraocular pressure. By using a fluoresceine sterile strip, we study the extent of the ulcer and the presence of overhanging edges. The sample is collected under the overhanging edge. It is transferred into a sterile swab containing a tube to the laboratory to review the culture of organisms and sensitivity to standard antibiotics. The sample is also subjected to fungal culture and anti-fungal medication sensitivity based on the clinical presentation and absence of bacterial growth. The initial treatment protocol included an hourly installation of a broad-spectrum topical antibiotic (Cephazolin and Ceftazidime) until the results of the culture and sensitivity are available. Topical steroids are used in accordance with the preference of senior ophthalmology consultants guidance.

Patients remain in hospital till the corneal infiltrate is resolved and corneal epithelium covers the ulcer. The regimen was subsequently modified based on the evolving clinical course and the results of microbiological cultures and sensitivities. If clinical
evidence of a favorable clinical response was present, topical steroid therapy was initiated after 48 hours in cases of confirmed Gram-positive keratitis and after 72 hours in cases of confirmed mixed Gram-positive and Gram-negative keratitis. Prednisolone acetate 1.0% or fluorometholone 0.1% were introduced twice daily in the absence of progressive corneal ulceration and thinning. In all cases, an epithelial defect was still present at the introduction of the topical steroids. If the opening of the topical steroid was not associated with an adverse response (increase in the size of the infiltrate or corneal thinning), the frequency was progressively increased over several days, up to a maximum frequency every 2 hours. The frequency of topical steroids never exceeded the frequency of topical antibiotics. If significant stromal ulceration or thinning was present without evidence of progression, systemic doxycycline 100 mg twice daily was. If progressive stromal ulceration and thinning were documented, topical corticosteroids were withheld or discontinued, and efforts to control inflammation and collagenolysis were restricted to the use of systemic doxycycline. Topical steroid therapy was sometimes not initiated (at the discretion of the attending physicians) for treatment of small peripheral infiltrates without significant inflammation or threat to the visual axis.

The systemic ailment like diabetes was judiciously treated. The presence of other immuno-compromising systemic ailments was also inquired and investigated, and treatment was given simultaneously.

The outcome like microbiological cure (medical or medical plus surgical) and the distance visual acuity after six months of healing was used to define the success. A microbiological cure was defined as eradicating the infection without the requirement to perform evisceration or enucleation. A medical cure was defined as the eradication of all clinical evidence of disease with medications only. A surgical cure
was defined as eradicating all clinical evidence of infection but with the requirement to provide tectonic support with cyanoacrylate glue or keratoplasty. Treatment failure was defined as the need to perform evisceration or enucleation for any reason. Visual acuity was recorded at the most recent outpatient follow-up examination. If the best-corrected visual acuity (BCVA) was not available, the uncorrected visual acuity (UCVA) was documented.

The demographic information included age, gender, and eye involved. The data was collected on a pretested data collection form and then transferred into a spreadsheet of Microsoft XL®. After consistency and frequency check, it was transferred to Statistical Package for Social Sciences (SPSS 25) (IBM, NY USA) for analysis. Univariate analysis was carried out by using the parametric method. For qualitative variables, we calculated frequency and percentage. For the quantitative variable, we reviewed the distribution curve. If it was expected, we presented their mean and standard deviation. If not having normal distribution, we presented their median and interquartile range (IQR).

Results:

We treated 181 eyes of 179 patients of MK. Their mean age was 40.1 ± 20.7 years (range 1 to 100), and there were 95 males (52.7%) and 86 (47.3%) females. As many as 55 (30.4%) contacted lens-induced while 30 (16.6%) followed ocular trauma. The interval between symptom onset and patient coming to our institution was 7.9 ± 3.6 days (range 1 to 60 days). Diabetes was noted in 102 (57%) patients, and 76(75%) of them had poor glycemic control (HbA1C >10). The microbial profile is represented in Table 1. Nearly half of them had no organism isolated. Gram-positive bacteria were in more than half of the positive sample. The fungus was isolated in 13 (13.2%)
samples. During treatment, endophthalmitis developed in eight (4.4%) eyes. Four eyes were eviscerated due to endophthalmitis not responding to the treatment for one week. There was a risk of spreading infection, and the eyes had poor visual potential. Corneal scarring developed as a sequel in 76 (42%) eyes. Of the 181 eyes treated, 75 [41.2%(95% Confidence interval 34.3, 48.6)] eyes had regained vision better than 20/60 (normal functional vision) at six months after completion of treatment. The rate of anatomic failure (removal of eyeball) was 2.2% (95% CI 0.1, 4.4) Among 13 eyes having fungal keratitis, Seven patients underwent a therapeutic keratoplasty (53.8%). Overall, this group's success rate of treating the infection (medical and surgical) and preventing endophthalmitis was 92%. For one case, did not complete six months follow up and was lost to follow up. The visual recovery was associated with the type of organism Table: 2. MK associated with Pseudomonas has superior visual outcomes after treatment. While MK with Staphylococcus and Streptococcus had poor visual effects. Those without organisms detected visual gain was promising. Although Fungal MK did not result in blindness, the vision did not improve significantly following treatment.

Discussion:

Management of MK is a challenge due to changing organisms, predisposing factors, and antibiotic resistance. The client and corneal sub-specialists desire the goal of avoiding eye amputation and restoring normal functional vision. In the present study, one in forty MK treated failed to reach anatomical success while less than half of eyes could regain normally available vision. Late presentation and uncontrolled diabetes could be the reason for the delay in healing and compromised outcomes.
The national prevention of blindness committee of Saudi Arabia has existed since the beginning of 2000. The expansion of secondary and tertiary eye care occurred in 13 administrative regions in the last two decades[13,14]. This resulted in a decline in infectious diseases related to visual impairment[14]. However, there seems to be a need for integrating primary eye care within primary health care as per the recommendation of the World Health Organization[15]. This will enable the early diagnosis of sight-threatening eye conditions like MK and prompt and standard management protocol through public health approach.

In our study, one in four eyes after the management of MK had severe visual impairment (SVI). Chidembaran et al. [16] reported a 34% rate of SVI in severe MK cases managed in South India. However, in the latter study, the majority were fungal keratitis. A study on MK of the pediatric age group of Australia noted one in ten with SVI after management[17]. Poor outcomes in African countries than that reported in the present study were attributed to traditional healers' late presentation and initial treatment [18].

In our study, the success of anatomical and functional recovery post MK management was better in MK by Pseudomonas but worse in Staphylococcus and streptococcus MK. This could be the resistance of later organisms to conventional antibiotics like Gentamycin, Penicillin, and Chloremphenicol[9]. Pseudomonas infection is more common in contact lens-induced MK and is usually in young patients with fewer commonalities resulting in better response to treatment[19, 20].

Apart from the need to eviscerate in eyes with bacterial keratitis that led to endophthalmitis and painful blind eyes removed, our study showed poor visual outcomes of eyes with fungal keratitis than bacterial keratitis following management. This confirmed an earlier observation noted by Austin et al. [21].
In our study, less than 5% of eyes with MK needed therapeutic full-thickness keratoplasty. Only 2 eyes had undergone collagen cross-linkage. Newer ancillary techniques are found helpful to the medical treatment of MK[22]. They include topical corticosteroids, corneal collagen cross-linking, intrastromal antimicrobials, amniotic membrane transplantation, and others. Limited application of such technique in university hospital; the present study site of an industrialized country is challenging to explain. Perhaps the nonavailability of donor material, both cornea and an amniotic membrane in university hospitals could be the reason for this observation.

There were few limitations in the present study. Photographic evidence of success was not collected due to the retrospective nature of the study. The duration of follow-up varied widely, and few patients had irregular follow-ups. Thus, internal comparison of patients with varying follow-up periods should be noted before concluding. Ten year period of MK care in a university is a unique issue, especially when there is one major specialist hospital in the same city.

**Conclusion:**

Management of MK at a tertiary hospital had good outcomes, and underlying causes like late presentation and uncontrolled diabetes need to be addressed concurrently. Early diagnosis and standard management protocol through a program approach could further improve eye care of patients with MK in the Kingdom.

**List of Abbreviations:**

MK Microbial keratitis
SPSS: Statistical Package for the Social Sciences
Conflict of Interests:
The authors declare that there is no conflict of interest regarding the publication of this article.

Funding:
None.

Consent to Participate:
Informed consent was obtained from all the participants.

Ethical Approval:
Please provide ethical approval: For example Ethical approval was granted by Internal Review Board (IRB) at Institution name, Address, Ethical approval No. a and date of approval
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<th></th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture positive</td>
<td>98</td>
<td>54.1</td>
</tr>
<tr>
<td>Culture negative</td>
<td>83</td>
<td>45.9</td>
</tr>
<tr>
<td><strong>Bacterial isolate</strong></td>
<td>85</td>
<td>86.7</td>
</tr>
<tr>
<td>Gram-positive</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>Corynebacterium</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Gram-negative</td>
<td>35</td>
<td>35.7</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>28</td>
<td>80</td>
</tr>
<tr>
<td>Serratia spp.</td>
<td>3</td>
<td>8.5</td>
</tr>
<tr>
<td>Moraxella</td>
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<td>5.7</td>
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<tr>
<td>Klebsiella</td>
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<td>5.7</td>
</tr>
<tr>
<td><strong>Fungus</strong></td>
<td>13</td>
<td>13.2</td>
</tr>
<tr>
<td>Fusarium</td>
<td>6</td>
<td>46.1</td>
</tr>
<tr>
<td>Aspergillus</td>
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<td>23</td>
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<tr>
<td>Cryptococcus</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Candida</td>
<td>2</td>
<td>15.3</td>
</tr>
</tbody>
</table>
Table 2: Visual impairment status six months after treatment of microbial keratitis by type of organisms

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Eyes with MK</th>
<th>20/20 to 20/50</th>
<th>20/60 to 20/200</th>
<th>&lt;20/200 to 20/400</th>
<th>&lt;20/400 or eye removed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
<td>%</td>
<td>Number</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>28</td>
<td>18</td>
<td>6</td>
<td>21.4</td>
<td>3</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>25</td>
<td>8</td>
<td>3</td>
<td>12.0</td>
<td>5</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>21</td>
<td>1</td>
<td>8</td>
<td>38.1</td>
<td>2</td>
</tr>
<tr>
<td>Fungal</td>
<td>13</td>
<td>0</td>
<td>6</td>
<td>46.2</td>
<td>4</td>
</tr>
<tr>
<td>Culture negative</td>
<td>83</td>
<td>48</td>
<td>15</td>
<td>18.1</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>181</td>
<td>75</td>
<td>38</td>
<td>21.0</td>
<td>23</td>
</tr>
</tbody>
</table>

Information of vision was missing in 10 eyes, of whom six were culture negatives.