Egyptian Journal of Ophthalmology (MOC) 2022;*2:65-74*

Outcome of Infectious Keratitis

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Received: 5-8-2021, Accepted: 13-3-2022, Published online:15-6-2022

EJO(MOC) 2022;2:65-74.

Running title: Infectious Keratitis.

ABSTRACT

Aim: The aim of the study is to evaluate the role of risk factors, clinical presentation and microbial profile on the outcome of infectious keratitis.

Methods: This prospective study of 40 eyes of 40 patients admitted for microbial keratitis in Mansoura ophthalmic center during the period from august 2019 to march 2020. The study focuses on risk factors, clinical course, and prognosis of infectious keratitis. Patients were not included in this study if they had concomitant endomphthalimitis, corneal perforation and descemetocele or Noninfectious keratitis as chemical, thermal or autoimmune keratitis.

Results: There is no statistically significant association between presence of ocular and systemic risk factors and outcome of treatment among studied cases, however; Exposure keratopathy illustrates a statistically significant higher frequency among cases with bad outcome (28.6%) versus no cases with good outcome.

Conclusion: Risk factors in ocular history had no significant effect on the treatment outcome of microbial keratitis except for exposure Keratopathy which showed the worst effect on the outcome of treatment. Clinical picture of microbial keratitis had no significant effect on the treatment outcome of microbial keratitis except for the depth of infiltration which showed a highly significant effect on the outcome of treatment.

Key word: Infectious, Keratitis, microbial keratitis risk factors.

INTRODUCTION:

Infectious keratitis is a critical reason for ocular morbidity and visual disability particularly in vulnerable groups, for example, the elderly, Infectious keratitis mostly has a poor visual outcome. Being oriented to differences in risk factors, clinical course, and prognosis between elderly and younger patients could lead to further prevention and treatment of all age groups[1]. Adequate management of microbial keratitis requires information on the most common causative organisms of corneal infections in a given area. Geographic and clinical factors affect the spectrum of infectious keratitis[2]. Microbiological cultures play as important epidemiologic cultures on treatment decision is not always obvious[3-4].

Among younger patients, contact lens wear remains the most common risk factor. Trauma is also frequently mentioned as a risk factor. Alcohol abuse and neglect were additional risk factors among younger population. Among the elderly, the most prevalent predisposing factors were previous ocular surgery, use of topical steroids, systemic disorders, recurrent HED, and blepharitis. Prior studies also found previous ocular disease and surgery, systemic conditions, and use of topical steroids to be leading risk factors among the elderly. These risk factors decrease the efficacy of the local immune response, increasing patients' susceptibility to microbial keratitis. Patients with an underlying, often long-standing autoimmune disorder (e.g. Rheumatoid Arthritis) may develop an autoimmune keratitis with a superimposed or accompanying corneal infection[5].

Bacterial keratitis is characterized as an epithelial defect overlying an area of stromal infiltration seen on slit-lamp biomicroscopy which led to extreme visual and ocular disability. Bacteria are identified on corneal Scrapings and show antibiotic sensitivity on culture media[6].

Serrated edges, raised slough and color other than yellow were found to be independently associated with fungal keratitis in a logistic regression model. The likelihood of fungal infection was 63% if one clinical feature was present, expanding to 83% if all three features were present[7].

The course of amoebic keratitis is depicted by remissions and exacerbations; the cornea shows enormous variety of epithelial and stromal lesions, patchy or diffuse, central or peripheral infiltrations affecting part or the whole layers of stroma. Erosion, ulcers, even abscess or perforation can occur. An immune ring is also very common[8-9].

Broad spectrum antibiotics showing adequate coverage against Gram-positive and Gram-negative pathogens should be initiated as the first line of treatment[10].

Fungal infections including deeper parts of the stroma are not exposed to topical antimicrobial therapy. Furthermore; the diffusion of many antifungal drugs into the cornea is substandard, which makes it hard to treat cases of deep fungal keratitis. To defeat these issues, investigators have tested other routes such as intracameral and intrastromal injections of Amphotericin or Voriconazole to treat fungal keratitis[7].

The majority of bacterial infections of the anterior segment are treated by topically administered anti-microbial drugs except for gonococcal and chlamydial conjunctivitis, which are regarded as systemic infections[11].

Empiric antibiotics should be promptly given in extensively two options available; Fluoroquinolone monotherapy (commercially available) or a duo therapy of fortified antibiotics (Cefazolin 5% and Tobramycin or Gentamicin 1.4%), (Ceftazadime (2.25 mg/0.1 ml) and Vancomycin (1 mg/0.1 ml)). The frequency of drops relies upon the severity, but it is normal to start half-hourly drops all through 24 h for most patients. A starting dose with a drop every 5 minutes for one hour is utilized in severe cases. Then decline the frequency according to the clinical response. Fortified Aminoglycoside drops such as Gentamicin and Tobramycin can have a supreme coverage against Gram- negative bacteria, staphylococci and some streptococci as well but not against pneumococci[12].

Topical antifungal drugs provide the best opportunity for achieving therapeutic corneal levels. Subconjunctival injection of Amphotericin-b and Natamycin and the azoles aside from Itraconazole isn't valuable. Systemic antifungal therapy may be essential for resistant fungal ulcers[13].

The most specific agents for treating amoebic keratitis are Polyhexamethylene biguanide and Chlorhexidine and when combined they cover both cysts and trophozoites. Their action is mediated by enhancing cytoplasmic membrane permeability, so they cover large spectrum of pathogens[8].

Penetrating keratoplasty is one of the most common and successful tissue transplants worldwide, with the major indications including: (1) optical purpose for improving vision; (2) therapeutic purpose for controlling medical refractory disease; and (3) tectonic purpose for reestablishing the structural integrity of the eye[14].

The combination of riboflavin and ultraviolet A light (UVA) exposure has been extensively used in collagen cross-linking (CXL) for the treatment of ectatic disorders of the cornea.[1] The antimicrobial effect of a similar photochemical reaction using riboflavin and UVA has been successfully exploited in the field of transfusion medicine for inactivation of various microorganisms in blood products[15].

Despite effective antimicrobial therapy, the tissue damage initiated by inflammatory cells and microorganisms continues long after the control of infection. Therefore, in addition to antimicrobial therapy, there has always been a search for safe anti-inflammatory as well as anti-collagenolytic therapy in the management protocols of corneal infections. Based on the existing evidences, CXL can provide antimicrobial properties or synergizes actions of currently used antimicrobial agents and simultaneously makes corneal collagen resistant to the action of collagenolytic enzymes[16].

PATIENTS AND METHODS:

This study was carried out on patients admitted for microbial keratitis in Mansoura ophthalmic center over a six-month during the period from august 2019 to march 2020. The study included 40 eyes of 40 patients with microbial keratitis. The following categories were excluded: Corneal perforation and descemetocele, Concomitant endophthalmitis and Non-infectious keratitis as chemical, thermal or autoimmune keratitis.

A written informed consent was obtained from all participants before inclusion in the study, explaining the value of the study, plus the procedure that will be commenced.

The whole study design was approved by the institutional review board (IRB), Faculty OF medicine, Mansoura University (MS/17.10.110). Confidentiality and personal privacy were taken in all levels of the study. Patients feel free to withdraw from the study at any time without any consequences. Collected data will not be used for any other purpose.

History taking: For each patient, a proper history was taken regarding the age, sex, visual acuity on admission, duration of symptoms and predisposing factors (e.g. trauma, contact lens usage, and usage of topical steroids). Ocular and systemic history was also taken and Patients' medications before and after admission were recorded.

Ophthalmic examination: For each patient, a proper ophthalmic examination was performed. First, visual acuity was assessed and charted. Then slit lamp biomicroscopy was utilized to assess the size of epithelial defect with the use of fluorescein stain, the size of stromal infiltration and anterior chamber reaction (cells, flare, and hypopyon). Finally, the Posterior segment was evaluated to exclude concomitant Endophthalmitis. The lesion was photographed by a Nikon camera and a photo slit lamp for documentation.

Corneal scraping: For each patient, corneal scraping was done. First, topical and systemic medical treatment was discontinued for 24 hours then corneal scraping was performed using a disposable blade under topical anesthesia using Benoxinate hydrochloride 0.4%. After the topical anesthetic was applied, the back of surgical blade no 15 was used to scrape the lesion under magnification of operating microscopy. The ulcer base and edges were both scraped. Several scrapings had been performed to obtain adequate material for direct microscopy and culture.

Sample processing: Corneal scrapings for each patient were sent to Microbiology and Parasitology department Laboratories, Faculty of Medicine, Mansoura University, Egypt. The obtained material was smeared on clean sterile slide and subjected to direct microscopic examination for the presence of bacteria, fungi using Gram stain, 10% Potassium Hydroxide (KOH), KOH with Calcofluor white preparation and Giemsa stain. The other corneal scrapings were transferred directly from spatula to agar media that support the growth of bacteria and fungi by two rows of C-shaped cuts on the media. Three different media were utilized: blood agar, chocolate agar and Sabouraud's dextrose agar (SDA). The blood and chocolate agar plates were incubated at 37°C for 24-48h. The SDA plates were incubated at 27°C and were examined daily for three weeks. The inoculated non nutrient agar plates were incubated at 30°C after overlaying with Escherichia coli, and were examined daily for the presence of Acanthamoeba species by inverted phase contrast microscopy, and discarded at 3wk if there were no signs of growth.

Isolation and identification of causative pathogens: Identification of causative organism by colonial morphology, Gram-stained films, biochemical reactions: oxidase, triple sugar iron (TSI), sulfide indole motility (SIM), urease, citrate test, VP and Methyl red test (for Gram negative organisms), catalase reaction, coagulase test, DNase test and bile esculin test (for Gram positive organisms).

Antibiotic susceptibility testing: The drug sensitivity was determined by the Kirby-Baüer method, carried out on a Muller-Hinton agar board, as recommended by CLSI M100-S26, using the following antibiotic disks: Vancomycin (30 µg), Cefoxitin (30µg), Amikacin (30µg), gentamicin (10µg), Cefotaxime (30µg), Chloramphenicol (30µg), Ciprofloxacin (5µg), Ofloxacin (5µg), Gatifloxacin (5µg), Oxifloxacin (5µg) and

Tobramycin (10µg). Bacterial isolates were classified as sensitive or resistant to the tested antibiotics.

Treatment Protocol:

Initial empirical therapy was administered until the results of culture and sensitivity results are available within 48 to 72hours. Topical broad-spectrum antibiotic was given in the form of (Moxifloxacin 0.5%) eye drops then it was modulated according to the clinical course and the results of lab. (Moxifloxacin 0.5%) was chosen for broad spectrum, preservative free solution and less toxicity to the cornea. It was used at frequency of each hour **q.h.** in the first three days during the wakeup time then every two hours **q.2.h.** in the next few days .this empirical regime was started in every case except in those with suspected fungal keratitis. (Moxifloxacin 0.5%) was discontinued or changed for the following cause: healed lesion fungal cultures, in vitro resistance to Moxifloxacin and lack of improvement or worsening of conditions. Chloramphenicol (0.5%) drops was applied to four cases of suspected staph keratitis at the first day of admission. Natamycin (0.5%) was used as a potent broad-spectrum antifungal in all infectious keratitis caused by vegetative matter ocular traumas and in suspected fungal keratitis.

Amphotericin was given to three cases of fungal candida infections in the form of Photericin-b fortified drops. Fortified antibiotics (Vancomycin and Fortum) were given in only one case resistant to Moxifloxacin. Systemic antibiotics (Ciprocin) were given to 15 patients with peripheral infiltration and corneal vascularization. Subconjunctival injection was of limited use due to its associations of severe pain, intolerance by the patient, high risk of globe perforation. Cycloplegic agents were used for all patients to relieve ciliary spasm incited by corneal inflammation and to reduce the risk of post synechia. Antiglucomatous drugs were used in 10 patients due associated elevation of intraocular pressure.

Good outcome when the cornea healed with the same or better visual acuity, corneal scar or corneal vascularization. Bad outcome when the cornea healed with worse visual acuity, complicated corneal perforation, anterior Staphyloma, Endophthalmitis and other complications.

Statistical Analysis:

Data were fed to the computer and analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics are for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-parametric data and mean, standard deviation for parametric data after testing normality using Shapiro–Wilk test. Significance of the obtained results was judged at the (0.05) level.

RESULTS:

The study included 40 eyes of 40 patients with microbial keratitis in the period between August 2019 and March 2020 with mean age of 48.15±17.73 years and age range between 4 and 76 years. There were 26 males (65%) and 14 females (35%). 42.5% from urban residence while (57.5%) from rural residence. (75%) were workers, (17.5%) were non-workers and (7.5%) were students.

According to the culture and sensitivity test results, 11 cases (27.5%) showed no growth, 13 cases (32.5%) had positive culture of Staph aureus and 16 cases (40%) had positive culture for Aspergillus.

The study reveals that the most common predisposing factor is Ocular trauma 13 cases (32.5%), blepharitis & dry eye was the second most common relevant history in 10 cases (25%) followed by use of topical steroids in 4 cases (10%), followed by recurrent corneal ulcers in 3 cases (7.5%), exposure keratopathy in 2 cases (5%). The following were reported in 1 case for each; LASIK, entropion, and CL wearing (2.5 %).

The most common predisposing factor in systemic history was DM and combined HTN & DM 5 cases for each (12.5%) of the cases, followed by Rheumatoid Arthritis in 2 cases (5%) and drug addict in only one case (2.5%).

The study showed that the VA of the included cases at time of admission and follow-up was illustrated in table (2). Mean VA changed from 0.316±0.23 at the first day of the study to

0.357±0.23 after three days to 0.392±0.22 after one week, 0.423±0.20 after two weeks and 0.450±0.20 at three weeks. There was a significant change in the mean VA from the first week to the sixth month in the follow up period as compared with the first day (Table 1).

The study showed that there is a significant difference in the mean width and length of the infiltration at Day 3, at Week 1, at Week 2, at Week 3 and at Week 4 from starting the treatment as compared with the first day of treatment. There was a significant decrease in the length and width of ulcers among the included cases. At the 1st week, 24 cases showed significant improvement in regard to the size of ulcer, 19 cases at the 2nd week, 11 cases at the 3rd weeks, 8 cases at the 4th weeks, 3 cases at the 3rd months and at last all ulcers had healed by the 6th month of treatment (Table 2).

There was a significant decrease in the amount of hypopyon among the included cases at the third week, the fourth week and after 3 months as compared with the first day of the study. At the 3rd month there was only 1 case with hypopyon and it completely recovered at the 6th month.

Among the included cases, complications were detected only in 7 cases and it was classified as leucoma adherent in 1 case, endophthalmitis in 2 cases and anterior Staphyloma in 4 cases.

In this study, out of 40 patients who were followed up for 6 months, 33 (82.5%) patients achieved good outcome in the form of complete healing regarding improved visual acuity, cornea scar and vascularization, while 7(17.5%) patients had bad outcome in the form of worsening visual acuity or healed with severe complications e.g., leucoma adherent, endophthalmitis, anterior staphyloma and corneal perforation. Among cases with bad outcome, 57.1% were Aspergillus and 28.6% were Staph aureus without statistically significant association between them.

There is no statistically significant association between presence of ocular and systemic risk factors and outcome of treatment among studied cases except for exposure keratopathy illustrates a statistically significant association with bad outcome (P=0.027), the two cases were bad outcome versus no cases with good outcome (table 3). There is no statistically significant association between clinical picture and treatment outcome except for the depth of infiltration which showed a statistically significant association with the outcome of treatment (p=0.006) among studied cases (Table 4).

Table (1): Visual acuity during follow up among studied cases (n=40).

Visual acuity	Day 1	Day 3	Week 1	Week 2	Week 3	Week 4	3 months	6 months
HM No(%)	27 (67.5)	25 (62.5)	22 (55.0)	20 (50.0)	14 (35.0)	12 (30.0)	12 (30.0)	7 (17.5)
mean VA	0.316±0.23	0.357±0.23	0.392±0.22	0.423±0.20	0.450±0.20	0.461±0.16	0.467±0.18	0.468±0.16
Comparison of mean VA every follow up with 1st day	p=0.205	p=0.046*	p=0.001*	p≤0.001	p≤0.001	p≤0.001	p≤0.001	

Table (2): infiltration and ulcer during follow up among studied cases (n=40).

Ulcer	Day 1	Day 3	Week 1	Week 2	Week 3	Week 4	3 months	6 months
No (%)	30 (75.0%)	30 (75.0%)	24 (60.0%)	19 (47.5%)	11 (27.5%)	8 (20%)	3 (7.5%)	0 (0%)
Mean ± SD	11.21±10.58	9.23±9.79	9.04±12.45	8.0±12.24	6.10±10.67	4.54±10.61	0.50±1.4	-
Median (range)	8.8 (0.2-46.8)	7.5 (0.12-46.8)	3.77 (0-46.8)	1.5 (0-46.8)	0 (0-43.20)	0 (0-43.20)	0 (0-5.0)	
Difference from day1		p=0.002*	p=0.001*	p≤0.001*	p≤0.001*	p≤0.001*	p≤0.001*	-
Ulcer site and depth			**no**		**%**			-
Ulcer site								-
Central			21		55.0			
paracentral			6		15.0			
peripheral			3		7.5			
Ulcer size								-
<1/3 cornea			3		10.0			
1/3 cornea			19		63.3			
2/3 cornea			7		23.3			
>2/3 cornea			1		3.3			

Table (3): Association between risk factors and outcome among studied cases.

	Bad outcome n=7	**Good outcome n=33**	**P value**
Systemic factors			
Yes	2 (28.6)	11(33.3)	FET 1.0
No	5 (71.4)	22 (66.7)	
Local factors			
No	0 (0)	5 (15.1)	P=0.565
Ocular trauma	3 (42.9)	10 (30.3)	P=0.662
Blepharitis&dry eye	1 (14.3)	9 (27.3)	P=0.656
Topical steroids	0 (0)	4 (12.1)	P=1.0
Recurrent corneal ulcers	0 (0)	3 (9.1)	P=1.0
Exposure keratopathy	2 (28.6)	0 (0)	P=0.027*
Lasik	1 (14.3)	0 (0)	P=0.175
Contact lens wear	0 (0)	1 (3.0)	P=1.0
Entropion	0 (0)	1 (3.0)	P=1.0

Table (4): Association between Clinical picture and Outcome among studied cases.

	Bad outcome n=7	**Good outcome n=33**	**P value**
Infiltration			
Infiltration size			0.062
Mean± SD	25.61 ± 16.41	14.90±12.08	
Median (range)	24.0 (4.4-44.1)	15.5 (1-46.8)	
Infiltration site			0.689
Central	6 (85.7)	20 (60.6)	
Paracentral	1 (14.3)	8 (24.2)	
Peripheral	0 (0)	3 (9.1)	
Infiltration depth			0.006*
<1/3	0 (0)	3 (9.7)	
1/3	1 (14.3)	20 (64.5)	
2/3	4 (57.1)	8 (25.8)	
>2/3	2 (28.6)	0 (0)	
Ulcer			
Ulcer size			0.07
Mean± SD	16.34 ±8.14	10.19±10.84	
Median (range)	18 (6.25-24)	5.25 (0.2-46.8)	
Ulcer site			0.80
central	5 (71.4)	16 (48.5)	
paracentral	1 (14.3)	5 (15.2)	
peripheral	0 (0)	3 (9.1)	
Ulcer depth			0.133
<1/3	0 (0)	3 (12)	
1/3	2 (33.3)	17 (68)	
2/3	2 (33.3)	5 (20)	
>2/3	2 (33.3)	0 (0)	
Hypopyon			
Hypopyon			
Mean± SD	2.67±1.15	1.68±0.71	0.118
Median (range)	2 (2-4)	1.65 (1-3)	

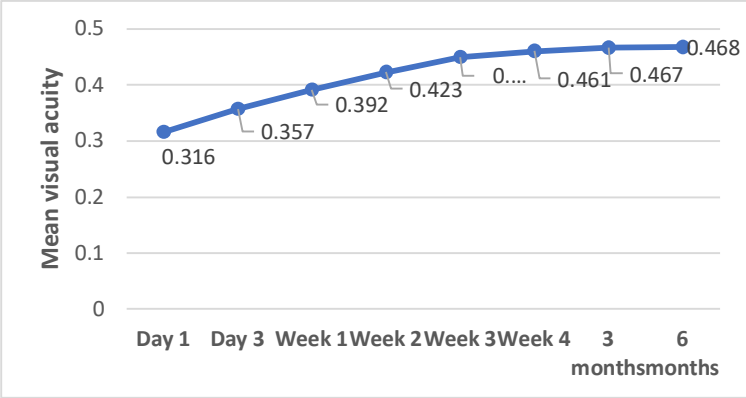

Figure (1): Visual acuity during follow up among studied cases (n=40).

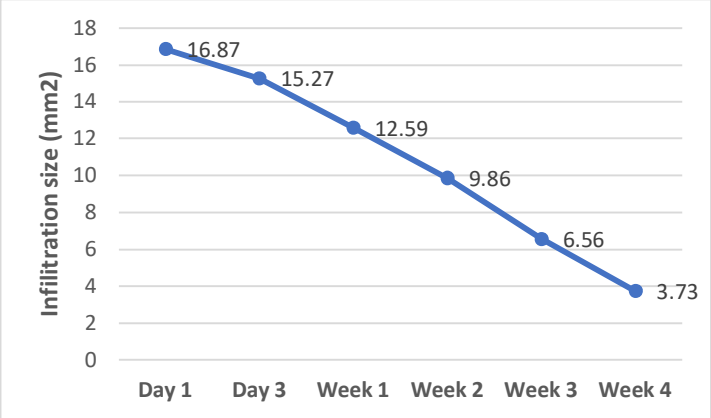

Figure (2): infiltration and ulcer during follow up among studied cases (n=40).

Discussion:

Corneal illness is the main cause of ocular blindness worldwide, particularly harming poor populations. Corneal scars due to infectious keratitis are the fourth cause of blindness worldwide. 10% of evitable visual disability are caused directly by infectious keratitis in developing countries[17].

Infectious keratitis is one of the prevalent causes of corneal blindness all over the world[18]. Prompt diagnosis of keratitis is necessary in deciding treatment and promoting healing and recovery. Gram stain and culture of corneal samples are the gold standard techniques in diagnosing microbial keratitis, despite poor sensitivity[19].

Antibiotic regime should be determined before the culture and sensitivity results are available, depending on demographics, risk factors, clinical picture and microbial pattern[20]. The etiological and epidemiological style differs from country to country, region to region within the same country and over the time in the same region. Therapeutic challenges and bad outcomes make it difficult to handle[21].

In this study, the most common predisposing factor of microbial keratitis in previous ocular history was ocular trauma. Blepharitis & dry eye was the second most common relevant history in 10 cases (25%) followed by use of topical steroids in 4 cases (10%), Recurrent corneal ulcers in 3 cases (7.5%) and Exposure Keratopathy in 2 cases (5%). The following were reported in 1 case for each; LASIK, Entropion and CL wearing. In this study, DM and combined DM and HTN were present in 5 cases (12.5%) for each, followed by Rheumatoid Arthritis in 2 cases (5%) and drug addict in in one case (2.5%). In this study, the incidence of positive culture was 72.5% as 29 cases from the included 40 cases showed positive growth.

Regarding the visual outcomes in this study, the mean VA of the included cases changed from 0.316±0.23 at the first day of the study to 0.357±0.23 after three days, 0.392±0.22 after 1 week,

0.423±0.20 after 2 weeks, 0.450±0.20 at three weeks, 0.461±0.16 after 4 weeks, 0.467±0.18 after 3 months and 0.468±0.16 after 6 months of starting treatment. There was a significant change in the mean VA following treatment as compared with the first day of the study (Figure 1).

In this study, the mean size of infiltration changed significantly from 16.87±13.41 at the first day of the study, to 15.27±13.3 at the third day, to 12.59±13.9 after the first week, to 9.86±12.94 after the second week, to 3.73±10.5 after the first month from starting the treatment as compared with the first day of treatment (Figure 2). In regard to the size ulcer the 1st week, 24 cases showed improvement in regard to the size of ulcer, 19 cases at the 2nd weeks, 11 cases at the 3rd weeks, 8 cases at 4th weeks, 3 cases at the 3rd months and at last all ulcers had healed by the sixth month of treatment. All the values of infiltration and ulcer were decreased as compared with the first day of treatment (Figure 3).

Regarding the complications encountered in this study, complications were detected only in 7(17.5%) patients and it was classified as follow; (2.5%) leucoma adherent in 1 patient, (5%) endophthalmitis in 2 patients and (10%) anterior Staphyloma in 4 patients.

There was no statistically significant association between ocular and systemic risk factors and outcome of treatment among studied cases except for history of exposure keratopathy illustrates a statistically significant higher frequency among cases with bad outcome (28.6%) versus no cases with good outcome (p=0.027).

Regarding the microbiological profile in this study, there was no statistically significant association between culture result and outcome of treatment (p=0.548). Among cases with bad outcome, 57.1% were Aspergillus and 28.6% were Staph aureus without statistically significant association between them. Regarding the clinical picture at time of admission in this study, there was no statistically significant association with outcome of treatment except for the depth of inflammation which showed a statistically significant association with the outcome of treatment (p=0.006) among microbial keratitis cases.

Conclusion:

The most common predisposing factors for infectious keratitis were ocular trauma, blepharitis & dry eye. Exposure keratopathy had the worst effect on the outcome of microbial keratitis. Microbiological profile (microscopy and culture & sensitivity) had no significant effect on the treatment outcome of microbial keratitis. The depth of inflammation had significant effect on the treatment outcome of microbial keratitis.

DATA AVAILABILITY

All data are included in this article.

ACKNOWLEDGEMENT

None

Conflict of Interest

Authors declare no conflicts of interest.

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Ethics declarations

Conflict of interest

Ahmad E. Hassaan, Eman A. Abd El-Hamed, Sherief E. El-Khouly, Hosam M. Ali El-fallal all authors have no conflicts of interest that are directly relevant to the content of this review.

Funding: No sources of funding were used to conduct this review.

Reviewer disclosures: No relevant financial or other relationships to disclose.

Declaration of interest: No financial affiliations or financial involvement with any organization or entity with a financial competing with the subject matter or materials discussed in the review

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