

Epidemiological, clinical and laboratory findings of infectious keratitis at Mansoura Ophthalmic Center, Egypt

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Abstract

• **AIM:** To analyze the epidemiological, clinical and laboratory findings of infectious keratitis.

• **METHODS:** A retrospective study on cases of infective keratitis, attended our institution from Mar. 2013 to Feb. 2015, was done at Mansoura Ophthalmic Center, Egypt. Corneal scrapings were performed and processed for direct microscopy and culture in appropriate media using standard laboratory protocols.

• **RESULTS:** Out of 245 patients enrolled for study, 247 corneal scrapings were obtained. Ocular trauma was the most common predisposing factor (51.4%), followed by diabetes mellitus (15.1%). Cultures were positive in 110 scraping samples (44.5%): 45.5% samples had pure fungal infection, 40% had pure bacterial infections and 10% had mixed fungal and bacterial growths. *Acanthamoeba* was detected in 5 (4.5%) samples. The most common fungal pathogen was *Aspergillus* spp. (41%). The most common bacterial isolates were *Staphylococcus aureus* (38.2%) and *Pseudomonas aeruginosa* (21.8%).

• **CONCLUSION:** Incidence of fungal keratitis is high in our region. Therapeutic approach can initially be based on clinical features and sensitivity/resistance patterns. Microbiological research should direct the antimicrobial treatment. Antibiotic resistance to fluoroquinolones and aminoglycosides is an important consideration.

• **KEYWORDS:** infectious keratitis; bacterial; fungal; parasitic; predisposing factors; antibiotic resistance

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INTRODUCTION

Infectious keratitis is an important preventable cause of monocular blindness worldwide. It is considered an ocular emergency that requires prompt and appropriate management to ensure the best visual outcome for the patient^[1]. Several studies have evaluated the etiology, management, and outcome of microbial infectious^[2]. However, there are regional variations in the prevalence, risk factors, and outcome in corneal ulcers^[3-4]. For example, infective corneal ulcers appear to be occurring in epidemic pattern and being 10 times more common in the developing world than in the developed countries^[5]. The clinical diagnosis of infective keratitis does not give an unequivocal indication of the causative organisms because a wide range of organisms can produce a similar clinical picture^[6]. Culture and direct microscopic detection of causative organisms are the two important microbiological investigations that are widely used. To minimize ocular morbidity, timely antimicrobial treatment must be initiated on the basis of clinical and microbiological evaluation^[7]. A significant percentage of patients with infectious keratitis are referring to our ophthalmic center (Mansoura Ophthalmic Center, Mansoura University, Egypt) as it is considered a large tertiary hospital. However there is lack of published literature on the epidemiology and microbiological spectrum of corneal ulcer cases from Egypt. The purpose of this study was to identify the risk factors, laboratory findings and clinical outcomes of patients presenting with infectious keratitis at Mansoura Ophthalmic Center.

SUBJECTS AND METHODS

Subjects A retrospective study was performed for all patients with clinically diagnosed infective keratitis presenting to Mansoura Ophthalmic Center, Egypt, from Mar. 2013 to Feb. 2015. The following categories of ulcers were excluded: suspected viral ulcers, Mooren's ulcer, marginal keratitis and atheromatous ulcers. A proper history regarding the age, sex, occupation, duration of symptoms, predisposing factors (e.g. presence and nature of trauma, contact lens usage, previous history of ocular surgeries, history of diabetes, and usage of topical or systemic steroids) and therapy received were recorded for all the patients. Also, given treatment, response to treatment

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during follow up and the clinical outcome were recorded. All cases were submitted to complete ophthalmologic examination by the slit lamp, visual acuity at the time of presentation. Corneal staining with fluorescein 2% was done and recorded using digital camera (Canon PowerShot A480) attached to the slit-lamp biomicroscope. This study was conducted with approval from the Medical Research Ethics Committee, Mansoura University.

Sample Collection Corneal scrapings were obtained under aseptic conditions from the patients with surface anesthesia, the active edge and the bed of ulcer were scraped using platinum spatula or sterile surgical blade (number 15) with the aid of surgical microscope to avoid corneal perforation. Several scrapings had been performed to obtain adequate material for direct microscopy and culture.

Laboratory Methods

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 and protozoa 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, fungi, and *Acanthamoeba* 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). In addition, non nutrient agar seeded with *Escherichia coli* overlay had been used for clinically-suspected *Acanthamoeba* ulcers. 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). Optochin sensitivity test was also performed to identify *Streptococcus pneumoniae*^[8].

Antibiotic susceptibility testing The drug sensitivity was determined by the Kirby-Bauer method, carried out on a Muller-Hinton agar board, as recommended by CLSI M100-S26^[9], using the following antibiotic disks: vancomycin (30 µg), cefoxitin (30 µg), amikacin (30 µg), gentamicin (10 µg), ceftaxime (30 µg), chloramphenicol (30 µg), ciprofloxacin (5 µg),

ofloxacin (5 µg), gatifloxacin (5 µg), oxifloxacin (5 µg) and tobramycin (10 µg). Bacterial isolates were classified as sensitive or resistant to the tested antibiotics.

The Initial Treatment

Bacterial keratitis Initial treatment was according to a standard protocol with a broad spectrum antibiotic to cover both Gram positive and Gram negative pathogens. All patients with bacterial keratitis received monotherapy with topical fluoroquinolones (e.g. gatifloxacin ophthalmic solution 0.3%), which was effective and well tolerated. A loading dose of a drop every 5-15min for the first hour in moderate-severe ulcers, followed by frequent applications every hour for the first few days to achieve therapeutic tissue concentrations and rapid control of the infection, then the frequency was reduced later based on the clinical response. Topical steroid was not usually part of an initial treatment. Oral or parenteral antibiotics were used only in ulcers with perforation, scleral involvement, endophthalmitis or Gonococcal infections. Modification of treatment was done according to culture sensitivity test in some cases.

Fungal keratitis Antifungal topical therapy with combination of 0.15% amphotericin B and 5% natamycin was started for all cases immediately on receiving a positive report of fungal examination of the corneal scraping. One hourly topical drops were applied for first three days followed by two hourly drops during waking hours and then continued on a tapering basis depending on the activity of keratitis till resolution of the ulcers. Systemic ketoconazole 200 mg were given twice daily for 7d in addition to the combination drop in patients with severe stromal infiltrate and corneal thinning. Treatment was continued for a minimum period of 3wk and maximum 3mo.

***Acanthamoeba* keratitis** Patients with *Acanthamoeba* keratitis were treated by Brolene 0.1% (propamidine) drops every hour around the clock for the first few days of treatment. Medications have to be used for a long time after clinical resolution of infection to prevent relapses. This is because of the drugs being less effective against the cystic forms. All patients require several (3-5) months of treatment prior to resolution.

All infectious keratitis patients received 1% atropine sulphate drops 3 times/d, tobramycin ointment at bedtime, eye lubricants as adjuvant therapies. The majority of patients were treated on an outpatient basis. Hospitalization was only in severe keratitis, vision-threatening, or poor compliance. Patients lost to follow-up before complete healing were excluded from further analysis.

RESULTS

A total of 247 eyes of 245 patients clinically diagnosed to have infectious keratitis were include in this study of which a single eye was infected in 243 patients and both eyes were infected in 2 patients.

Epidemiological Results The study results showed a male preponderance with 162 (66.1%) patients. Agricultural workers were mostly affected 108 (44.1%); followed by housewives 65 (26.5%), outdoor manual occupation 51 (20.8%), professionals 18 (7.3%) and students 3 (1.2%). The Demographic data of patients are given in Table 1, about 70 cases (28.6%) of total keratitis number were at the age of less than 40y, 118 cases (48.2%) were at 40-59y and 57 cases (23.3%) were at 60y or older. As shown in Table 2, the most common predisposing factor was trauma (51.4%), followed by diabetes mellitus (15.1%), impact foreign body (5.7%), topical steroid use (5.3%), local ocular pathology and postoperative related keratitis (4.5% for each), and lastly contact lens related ulcer was only (2.4%). No apparent cause was observed in 17 cases (6.9%).

Laboratory Results

Results of direct microscopic examination Positive smears were found in 75 scrapping samples (30.4%). Positive bacterial smears were detected in 30 samples, positive fungal smears in 41 samples. *Acanthamoeba* was positive in 3 stained samples by Giemsa and Calcofluor and 1 stained sample by Calcofluor only, with no positive Microsporidia stained samples.

Results of culture methods The distribution of microbial isolates was shown in Tables 3 and 4. Culture positive ulcers were found in 110 scraping samples (44.5%). Among which, pure fungal growth was present in 50 (45.5%) samples, pure bacterial growth in 44 (40%) samples, mixed fungal and bacterial infections in 11 (10%) samples and *Acanthamoeba* in 5 (4.5%) samples. *Aspergillus* spp. was most commonly isolated (41%), followed by *Fusarium* spp. (26.2%) among the fungal isolates. Among bacterial cultures, 34 (61.8%) samples grew Gram positive, with increased incidence of *Staphylococcus aureus* (*S. aureus*) (38.2%), followed by *Pseudomonas aeruginosa* (*P. aeruginosa*) (21.8%). There was no organism isolated in rest of the 137 samples.

Antibiotic resistance Table 5 shows susceptibility profile of bacterial isolates recovered. Among 21 cases of *S. aureus*, there was 3 (14.3%) cases of methicillin resistant *S. aureus* (MRSA) and all were vancomycin sensitive. *S. aureus* showed high rate of susceptibility to gatifloxacin (95%), amikacin (95%), gentamicin (81%) and ofloxacin (81%). About 92% of *P. aeruginosa* isolates were susceptible to amikacin and gentamicin, while 83% were susceptible to ciprofloxacin and moxifloxacin. However, they showed a high resistance rate towards ceftriaxone (67%) and chloramphenicol (42%). Interestingly, one isolate of *P. aeruginosa* was resistant to all the tested antibacterials.

Clinical Results

Time between the onset of complaints and examination In bacterial keratitis the majority (32/55; 58.2%) came within the first week of complaints and no one came after 30d, it was

Table 1 Demographic data of 245 patients with infectious keratitis n (%)

Age (a)	Sex		Total
	M	F	
0-9	3 (1.2)	0 (0)	3 (1.2)
10-19	4 (1.6)	4 (1.6)	8 (3.3)
20-29	6 (2.4)	10 (4.1)	16 (6.5)
30-39	28 (11.4)	15 (6.1)	43 (17.6)
40-49	37 (15.1)	13 (5.3)	50 (20.4)
50-59	47 (19.2)	21 (8.6)	68 (27.8)
60 and above	37 (15.1)	20 (8.2)	57 (23.3)
Total	162 (66.1)	83 (33.9)	245 (100)

Table 2 Predisposing factors for infectious keratitis n (%)

Predisposing factors	Total
Ocular trauma	126 (51.4)
Systemic factors	
Diabetes mellitus	37 (15.1)
Rheumatoid disease	7 (2.9)
Ocular factors	
Impact foreign body	14 (5.7)
Steroid uses	13 (5.3)
Postoperative	11 (4.5)
Post viral hypoesthesia	3 (1.2)
Contact lens users	6 (2.4)
Local eye disease (blephritis, dry eye)	11 (4.5)
No apparent cause	17 (6.9)

found that about 46 (75.4%) patients among the mycotic group came for ocular examination from 14d up to 30d and all cases of *Acanthamoeba* keratitis had delayed referral (4 -12wk). Before their initial presentation, most patients (more than 60%) had received previous treatment from general practitioners or through self-medication. They were using either antibiotics or a combination of antibiotics and steroid eye drops.

Characteristic clinical findings The site, size as well as the severity of the ulcer were recorded. All lesions were determined as central (involving the central 4-mm diameter of the cornea) and peripheral ulcers. As regard the ulcer size, all lesions at initial presentation, were classified as small (<2 mm), moderate (2-4 mm) or large (>4 mm). In this study, we found central ulceration in 193 (78.1%) cases, 132 (53.4%) eyes had large ulcers, 83 (33.6%) eyes had moderate ulcers and 32 (13%) had small ones. Clinical features at presentation included conjunctival injection (100%), hypopyon in 177 (71.7%) and moderate to severe pain in 196 (79.4%) eyes. Special corneal features according to the causative organism are shown in Figure 1.

Follow up period The follow up period of the patients with bacterial keratitis ranged from 21-60d, from 45-90d in fungal patients and from 90-150d in *Acanthamoeba* group, to reach the clinical outcome of healed scar.

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Table 3 Isolated bacterial pathogens from culture-positive keratitis n (%)

Bacterial type	Pure growth	Mixed with fungi	Total
Gram-positive	27	7	34 (61.8)
<i>Staphylococcus aureus</i>	18	3	21 (38.2)
<i>Staphylococcus epidermidis</i>	6	2	8 (14.5)
<i>Streptococcus pneumoniae</i>	3	0	3 (5.5)
<i>Streptococcus viridans</i>	0	2	2 (3.6)
Gram-negative	17	4	21 (38.2)
<i>Pseudomonas aeruginosa</i>	9	3	12 (21.8)
<i>Klebsiella pneumoniae</i>	4	1	5 (9.1)
<i>Enterobacter</i> spp.	2	0	2 (3.6)
<i>Proteus</i> spp.	1	0	1 (1.8)
<i>Moraxella</i> spp.	1	0	1 (1.8)
Total	44	11	55 (100)

Table 4 Isolated fungal pathogens from culture-positive keratitis n (%)

Fungus type	Pure growth	Mixed with bacteria	Total
<i>Aspergillus</i> spp.	21	4	25 (41.0)
<i>Fusarium</i> spp.	13	3	16 (26.2)
<i>Candida</i> spp.	8	4	12 (19.7)
<i>Alternaria</i> spp.	5	0	5 (8.2)
<i>Penicillium</i> spp.	3	0	3 (4.9)
Total	50	11	61 (100)

Table 5 Frequencies of antibiotic efficacy in relation to the type of organism n (%)

Organism (No. of isolates)	Antibacterial agents									
	VA	AK	GEN	C	CIP	OFX	GF	MO	TB	CTX
<i>S. aureus</i> (21)	21 (100)	20 (95)	17 (81)	17 (81)	16 (76)	17 (81)	20 (95)	15 (71)	18 (86)	17 (81)
<i>S. epidermidis</i> (8)	8 (100)	7 (88)	7 (88)	6 (75)	6 (75)	7 (88)	8 (100)	5 (63)	6 (75)	7 (88)
<i>Streptococcus</i> spp.(5)	5 (100)	2 (40)	2 (40)	4 (80)	3 (60)	4 (80)	5 (100)	4 (80)	2 (40)	5 (100)
<i>P. aeruginosa</i> (12)	-	11 (92)	11 (92)	5 (42)	10 (83)	9 (75)	9 (75)	10 (83)	9 (75)	8 (67)
<i>K. pneumoniae</i> (5)	-	5 (100)	5 (100)	4 (80)	4 (80)	4 (80)	5 (100)	5 (100)	3 (60)	3 (60)

n: Number of isolates susceptible to the antibiotic. VA: Vancomycin; AK: Amikacin; GEN: Gentamicin; C: Chloramphenicol; CIP: Ciprofloxacin; OFX: Ofloxacin; GF: Gatifloxacin; MO: Moxifloxacin; TB: Tobramycin; CTX: Cefotaxime.

Fate and complications At the end of the treatment 222 (89.9%) eyes responded well to this regimen and the healed scar without perforation or endophthalmitis was achieved. However, in bacterial keratitis, the initial treatment was needed to modify after culture sensitivity tests in 12 (21.8%) cases. Visual acuity improved in 113 (45.7%) eyes, while it remained the same in 57 (23.1%) eyes and worsen in 77 (31.2%) eyes. Seventeen (6.9%) patients had progressive corneal thinning and corneal perforation, and 8 (3.2%) cases ended by endophthalmitis based on clinical exam and/or echography.

DISCUSSION

In our study, the predominance of infectious keratitis was in the middle age group (40-59 years old) and among males, which could be attributed to their greater involvement in outdoor activities, thus more prone to corneal injury with external agents. Similar observations were reported by other studies^[10-11]. In the current study, risk factors for infectious keratitis were identified in most patients (91.8%). Acute corneal trauma was the most

common predisposing factor (51%). Ocular trauma was reported a common predisposing factor in rural areas or low income countries were it accounts for up to 77.5% of cases^[12]. The systemic risk factors were diabetes mellitus and rheumatoid disease, which had been implicated as risk factors for microbial keratitis^[10,13]. Ocular risk factors included impact foreign body, topical steroid use, local ocular pathology, postoperative related keratitis and contact lens wear. The association of microbial keratitis with compromised corneas (local eye disease and postoperative) is common, also it introduces the possibility of eye drop contamination during long term use and microbial resistance resulting from antibiotic use^[14]. The use of topical steroids was observed in 13 (5.3%) of our patients. Steroids may affect the healing mechanisms of the epithelium^[15], but is not directly implicated in causing microbial keratitis. Contact lens wear was noted in only 2.4% of patients with microbial keratitis, however, contact lens wear was reportedly one of the major associated conditions in other studies^[13,16], due to contact

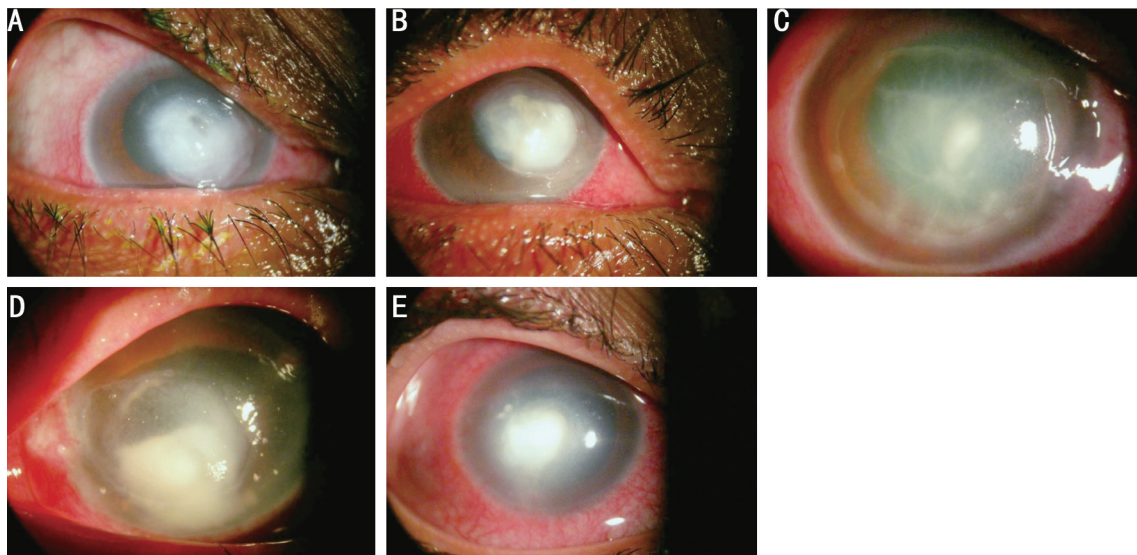


Figure 1 Special corneal features according to the causative organism A: Staphylococcal: central, oval, opaque, distinct margins, mild oedema of remaining cornea. B: Pseudomonas: rapidly spreading, extends peripheral & deep, stromal necrosis with shaggy surface, concentric ring ulcer with greenish-yellow discharge and hypopyon is present. C: Filamentous: dry infiltrate, irregular feathery edges and satellite lesions. D: Candida: focal, elevated and suppurative, resemble bacterial keratitis. E: Acanthamoeba: deep disciform infiltrate affecting the center and the intermediate portion of the cornea.

lens induced hypoxia and hypercapnia of the cornea^[17]. The lesser incidence in our study could be explained in view of the low socioeconomic level of the patients included. The analysis of the positive corneal scrapings through the study period showed a positive culture in 44.5% of the samples, showing lower diagnostic performance compared with other similar series, in which, Lichtinger *et al*^[18] reported 65% and Green *et al*^[19] reported 57.4%. However comparable results were reported by Shalchi *et al*^[20], where 34.2% of cultures were positive. One crucial factor that explains the variations between studies in the microorganism recovery rate is the use of antibiotics before the corneal scraping, in our study, more than 60% of the patients used antibiotics before sampling. In the current study, the most common causative organisms were fungi, followed by bacteria; gram positive bacteria were more common than gram negative bacteria, and *S. aureus* was the most commonly identified isolate, followed by *P. aeruginosa*. During our study period, 55.5% cases were diagnosed as having fungal keratitis. From reports available in the literature, the incidence of fungal keratitis range from 6% and 56%^[21]. A hot, humid climate and an agriculture-based occupation of a large population make fungal keratitis more frequent as in Egypt. *Aspergillus* species were the most common fungi, involved in 41% of the fungal cases, followed by *Fusarium* spp. (26.2%), which agree with previous comparable studies in Egypt^[22-23], Bangladesh^[24], and India^[25]. *S. aureus* were the most common bacteria (38.2%) isolated in our patients. The same finding has been observed by others^[22,26]. The spectrum of microorganisms accounting for microbial keratitis differ depending on geographic location, climate, and etiology^[27]. For example, gram positive bacteria are predominant in temperate climate regions, whereas

Gram negative bacteria are prevalent in tropical regions^[13,18]. *Pseudomonas* spp. are associated with contact lens-related infections^[11], whereas fungi are related to trauma caused by plants^[28]. In our study, only 5 (4.5%) cases of *Acanthamoeba* keratitis were reported, which is consistent with other studies of microbial keratitis in which the incidence of *Acanthamoeba* ranged from (0-4.4%) of the culture-positive cases^[28-29]. However, it is much less than that was reported in a previous Scottish study (70%)^[30]. In the present series, more than 95% of Gram positive isolates were susceptible to gatifloxacin. However a lower percentage (71%-76%) were susceptible to ciprofloxacin and moxifloxacin, These data are consistent with those reported in earlier studies, in which, 80% of gram positive bacteria were susceptible to newer generation fluoroquinolone, gatifloxacin^[31-32]. Therefore, among the fluoroquinolones tested in our study, gatifloxacin and ofloxacin exhibited the lowest rates of resistance, and hence, can be recommended as first line therapy for bacterial keratitis due to gram positive organisms. Parmar *et al*^[33] reported that corneal ulcer healing rates with gatifloxacin were significantly higher in infections caused by gram positive pathogens than in those caused by gram negative pathogens. Newer fluoroquinolones, such as gatifloxacin and besifloxacin acts by inhibition of both DNA gyrase and topoisomerase IV of gram positive bacteria^[34], whereas ciprofloxacin and levofloxacin inhibit topoisomerase IV, thus gatifloxacin and besifloxacin are less prone to develop resistance from single-step mutations^[35]. On the other hand, high percentages of *P. aeruginosa* isolated in this study were susceptible to amikacin and gentamicin (91.7% each), ciprofloxacin and moxifloxacin (83.3% each) and lower percentages to gatifloxacin (75%). The percentage of ocular *P. aeruginosa*

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isolates resistant to gatifloxacin was reported to have increased to 13.2% in a European surveillance study conducted in 2001-2002^[36]. Also resistance of *P. aeruginosa* isolates to ciprofloxacin increased from less than 1.0% to 29% of those obtained from 2002 to 2003^[31]. The duration from the onset of symptoms to the presentation at our department ranged from 5 to 90 (mean 35)d. On the contrary, Xie *et al*^[37] reported the first visit of his patients between 16 and 30d. This delay presentation to our tertiary center might be due to the fact that the patient already received the therapy from their nearest ophthalmologists or through self-medication and were referred when the ulcers did not respond. In our series, the anterior chamber reaction associated with Gram negative rods were more severe compared to inflammation associated with Gram positive bacteria. This is due to the higher pathogenicity of the Gram negative compared to Gram positive bacteria. Therefore, the surface and depth of the infiltrate, corneal neovascularization and anterior chamber inflammation were significantly related to bacterial keratitis as previously reported^[38]. In the current study, medical treatment was successful in 89.9% of patients; however, the outcome in a high proportion of patients with fungal keratitis was not satisfactory. Medical treatment of fungal keratitis, is often unsatisfactory because of delayed diagnosis, inadequate drug penetration, and slow response to therapy^[39]. Interestingly, in our study, poor visual outcome was often associated with history of local eye disease and postoperative related keratitis. Moreover, we noticed that these patients with chronic symptoms had delayed referral. This finding agree with Musch *et al*^[40] who demonstrated that infectious ulcer patients with a history of previous ocular surgery, and pre-existing ocular disease were at higher risk for poor visual outcome.

Infectious keratitis is a serious ocular infectious disease that remains a therapeutic challenge and vision threatening ocular condition. Incidence of fungal keratitis is significantly high in our region. Clinical presentation of ocular infectious diseases vary considerably; therefore, clinical characteristics of infective keratitis alone are not conclusive of the causative organisms. The therapeutic approach can initially be based on clinical impression and evidence of the microbiologic trends of infectious keratitis and sensitivity/resistance patterns in our locality. Also exhaustive microbiological research should be done and direct the antimicrobial treatment to eliminate the corneal pathogens and decrease the risk of ocular comorbidities associated with keratitis. Antibiotic resistance to fluoroquinolones and aminoglycosides, though not common, is still an important consideration.

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