ORIGINAL ARTICLE

DOI: 10.4274/hamidiyemedj.galenos.2023.77487

Hamidiye Med J 2023;4(3):184-190

Epidemiological Characteristics and Microbiological Profile of Infectious Keratitis in the Last Decade at a Tertiary Care Center in İstanbul: A Retrospective Study

Enfeksiyöz Keratitlerin Epidemiyolojik Özellikleri ve Mikrobiyolojik Profili: İstanbul'da Bir Üçüncü Basamak Merkezde On Yıllık Retrospektif Analiz

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ABSTRACT

Background: Regional epidemiological studies are needed for the management of microbial keratitis. The aim of this study was to analyze the epidemiological features, risk factors, causative microorganisms, and antibiotic susceptibility patterns in microbial keratitis in the last decade.

Materials and Methods: Medical and laboratory records of patients with microbial keratitis who underwent corneal scrapings between 2013 and 2023 were reviewed. Risk factors, culture results, and antibiotic sensitivity of the microorganisms were evaluated. **Results:** We obtained a 45.0% culture-positive rate (90/200). The mean age of the patients was 64±19 years (range: 18-94) (45 female, 45 male). The most common risk factor was corneal transplantation (42.2%). Of all positive cultures, 75 (83.3%) were bacterial and 15 (16.7%) were fungal keratitis. Polymicrobial growth was detected in 13 cultures. In total, 87 bacteria and 16 fungi were isolated. The 103 isolated microorganisms consisted of 46 gram-positive bacteria (44.7%), 41 gram-negative bacteria (39.8%), and 16 fungi. The most frequent microorganisms in bacterial keratitis were *Pseudomonas aeruginosa* (16.5%), *Staphylococcus aureus* (13.6%), and *Candida* species (8.7%) in fungal keratitis. The gentamicin and vancomycin susceptibilities of gram-positive bacteria were 100%. The susceptibility of gram-negative bacteria to various aminoglycosides ranged from 76.5% to 87.0%, which was comparable to that of ceftazidime (81.8%). The susceptibility of all bacterial species to various fluoroquinolones ranged from 77.8% to 100% **Conclusion:** Bacteria are the most common causative agent of microbial keratitis. The most frequent microorganisms were *Pseudomonas aeruginosa* and *Staphylococcus aureus*. According to our results, empirical treatment of bacterial keratitis may be initiated with a combination of vancomycin and cephalosporin or aminoglycoside. Early treatment modification may be considered when a clinical response is not achieved.

Keywords: Microbial keratitis, epidemiology, etiology, antibiotic resistance

ÖZ

Amaç: Mikrobiyal keratitlerin yönetimi için bölgesel epidemiyolojik çalışmalara ihtiyaç vardır. Çalışmamızda, kliniğimizde son on yılda görülen mikrobiyal keratit hastalarının epidemiyolojik özelliklerini, predispozan risk faktörlerini, kornea kültürlerinden izole edilen mikroorganizmaları ve antibiyotik duyarlılığını analiz etmek amaçlanmıştır. **Gereç ve Yöntemler:** Kliniğimizde 2013-2023 yılları arasında keratit tanısı ile kültür örneği alınmış hastaların dosyaları retrospektif olarak tarandı. Hastalar risk faktörlerinin varlığı, kültür sonuçları ve antibiyotik duyarlılığı açısından değerlendirildi. **Bulgular:** Mikrobiyal keratit tanısı ile kültür alınan 200 hastanın, 90'ında kültür pozitifliği elde edildi (%45,0). Hastaların yaş ortalaması 64±19 (18-94) olup 45'i kadın 45'i erkekti. En yaygın görülen risk faktörü korneal transplant (%42,2) idi. Pozitif kültürlerin 75'inden (%83,3) bakteriyel, 15'inden fungal keratit sorumlu idi (%16,7). On üç kültürde polimikrobiyal üreme oldu. Toplamda 87 bakteri ve 16 mantar izole edildi. İzole edilen 103 mikroorganizmanın 46'sı gram-pozitif bakteri (%44,7), 41'i gram-negatif bakteri (%39,8) ve 16'sı mantar (%15,5) idi. Bakteriyel keratitlerde en yaygın mikroorganizmalar *Pseudomonas aeruginosa* (%16,5), *Staphylococcus*

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Received: 26.02.2023 **Accepted:** 31.10.2023

ÖZ

aureus (%13,6), iken fungal keratitlerde *Candida* türleri (%8,7) idi. Gram pozitif bakterilerin Gentamisin ve Vankomisin duyarlılığı %100 idi. Gram-negatif bakterilerin çeşitli aminoglokozidlere duyarlıkları %76,5 ile %87,0 arasında olup Seftazidim (%81,8) ile karşılaştırılabilir düzeydeydi. Tüm bakteri türleri için çeşitli florokinolonlara duyarlılık %77,8 ile %100 arasında değişmekteydi. **Sonuç:** Kliniğimizdeki mikrobiyal keratitlerin en yaygın etkeni bakterilerdi. En yaygın mikroorganizmalar *Pseudomonas aeruginosa* ve *Staphylococcus aureus* idi. Sonuçlarımıza göre bakteriyel keratit ampirik tedavisine vankomisin ile bir sefalosporin veya aminoglikozid kombinasyonu ile başlanabilir. Yakın takip ile kültür sonuçlanana kadar ya da kültür negatif olgularda yanıt alınamaması durumunda erken tedavi modifikasyonunu düşünülebilir.

Anahtar Kelimeler: Mikrobiyal keratit, epidemiyoloji, etiyoloji, antibiyotik direnci

Introduction

Microbial keratitis is a corneal infection caused by bacteria, fungi, parasites, or viruses. Keratit is an important cause of ocular morbidity, which can cause corneal scarring, corneal perforation, and endophthalmitis and is associated with a risk of severe vision loss. It is one of the most important causes of visual impairment worldwide (1,2).

Keratitis is an ophthalmic emergency that can progress rapidly and requires effective treatment. Successful treatment of patients depends on early diagnosis, appropriate antibiotic selection, and close follow-up (2). In the management of microbial keratitis, culturing with corneal swab or scraping is necessary to identify the organism responsible for the infection and to determine the appropriate antimicrobial therapy (3). Broad-spectrum antibiotics are used as empirical therapy until the corneal culture results are obtained. Empirical treatment selection is based on epidemiological data. The etiology of infectious keratitis varies depending on demographic characteristics, risk factors, geography, and climate (4,5). For empirical treatment selection, careful evaluation of the patient's history and clinical signs and knowledge of regional microbial profiles and antibiotic susceptibility patterns are important. Therefore, current local epidemiological studies are required.

The aim of this study was to analyze the epidemiological features and predisposing risk factors of patients with microbial keratitis, microorganisms isolated from corneal cultures, and antibiotic susceptibility patterns of the pathogens in our tertiary care center in the last decade.

Materials and Methods

This cross-sectional descriptive study was conducted by examining the clinical records and microbiological reports of patients diagnosed with microbial keratitis in the ophthalmology clinic of our hospital, which is a tertiary care institution. The study was approved by the local ethics committee (approval number: HNEAH-KAEK 2022/218), and the results were consistent with the tenets of the Declaration of Helsinki. Informed consent was not required as the design of the study was retrospective.

The medical records of all inpatients diagnosed with keratitis between 2013 and 2023 were retrospectively reviewed. Eyes without culture samples or negative cultures were excluded. Patients with typical viral keratitis findings were excluded because the protocols required to analyze these microorganisms were not available in our laboratory. Interstitial keratitis, marginal keratitis, peripheral ulcerative keratitis associated with autoimmune diseases, Mooren's ulcer, and neurotrophic keratopathy were also excluded from the study.

Microbiological Examination

Samples for culture were obtained from patients with central, large, deep, chronic, antibiotic-resistant, or atypical infiltrates. All samples were collected under topical anesthesia. Samples from the infiltrate were obtained using a sterile cotton-tipped applicator or a sterile scalpel. The corneal samples were sent to the Microbiology Laboratory for culture and antibiotic susceptibility testing with transport medium within 2 h. Samples were inoculated on MacConkey, blood agar, chocolate agar, and Sabouraud dextrose agar and incubated for 48 h at the appropriate temperature. Selective media for the anaerobic bacteria Mycobacterium and Acanthamoeba were used in clinically suspicious cases. The causative microorganisms were identified using VITEX® 2 (BioMérieux, France) and MALDI-TOF MS (bioMerieux, France), and antibiotic susceptibility was determined using an automated antimicrobial identification and sensitivity system (VITEX® 2). Antibiotic susceptibility test results were evaluated according to the Clinical and Laboratory Standards Institute) criteria until 2018 and according to theEuropean Committee on Antimicrobial Susceptibility Testing) criteria after 2018.

Patients were treated with hourly empirical topical fortified ceftazidime (50 mg/mL) and vancomycin (50 mg/mL) or moxifloxacin hydrochloride 0.5% monotherapy until culture results were available. Topical fortified antifungals were added to the treatment regimen if there was a suspected fungal etiology (soil contamination or

vegetative trauma) or if clinical features of fungal keratitis were present. The treatment was then adjusted according to the culture and antibiotic susceptibility results.

The patients were evaluated in terms of demographic characteristics, presence of risk factors (ocular surface diseases, previous ocular surgery, ocular trauma, using contact lenses, systemic diseases, corticosteroid use), culture results, and antibiotic susceptibility of pathogens.

Statistical Analysis

Data were analyzed using Microsoft Excel and SPSS version 22 (Package for the Social Sciences). Descriptive statistical methods (mean, standard deviation, frequency, ratio, minimum, maximum) were used to evaluate the study data. The chi-square test was used for the comparison of the two proportions. P<0.05 was considered statistically significant

Results

Corneal samples were taken from 200 patients diagnosed with microbial keratitis between 2013 and 2023, and pathogens were recovered in 90 of these patients (45.0%). Of the patients with a positive culture, 45 were female and 45 were male. The mean age of the patients was 64±19 years and ranged from 18 to 94 years.

Risk Factors

Eighty-one patients (90%) had identifiable risk factors, whereas nine (10%s) did not have a predisposing factor. The most common risk factor was corneal transplantation (42.2%). Among the corneal transplant patients, 16 had graft failure, two had suture keratitis, five had topical antiglaucomatous use and ocular surface disease, and one had herpetic keratitis superinfection. Ocular surface disease (13.3%) and topical medication (13.3%) were other common risk factors. The other risk factors are shown in Table 1.

Microbiology Spectrum

Of 90 patients with positive cultures, 75 (83.3%) had bacterial and 15 (16.7%) had fungal keratitis. Thirteen cultures showed polymicrobial growth (12 bacterial, one fungal). In total, 87 bacteria and 16 fungi were isolated. Of the 103 isolated microorganisms, 46 were gram-positive bacteria (44.7%), 41 were gram-negative bacteria (39.8%), and 16 were fungi (15.5%). The most common microorganisms in bacterial keratitis are *Pseudomonas aeruginosa* (16.5%), *Staphylococcus aureus* (13.6%), coagulase-negative *staphylococci* (10.7%), and *Streptococcus pneumoniae* (10.7%), whereas *Candida species* (8.7%) are the most common in fungal keratitis. Table 2 shows all the isolated microorganisms.

Patients who underwent corneal transplantation were compared with patients with other risk factors. Bacteria were the causative agent in 86.8% of patients with corneal transplantation and in 80.8% of patients with other risk factors (p=0.445). Of the bacteria isolated in patients with corneal transplant, 57.6% were gram-positive bacteria, compared with 45.2% in patients with other risk factors (p=0.289). The two groups differed in terms of bacterial spectrum (p=0.026).The most common bacteria recovered in patients with corneal transplantation was *Staphylococcus aureus* (33.3%), whereas in other patients it was *Pseudomonas aeruginosa* (25.6%).

Antibiotic Susceptibility

Antibiotic susceptibility patterns of gram-positive and gram-negative microorganisms are shown in Table 3. The susceptibilities to some antibiotics commonly used for treating bacterial keratitis were as follows:

The susceptibility of gram-positive bacteria to both gentamicin and vancomycin was 100%. Ciprofloxacin, moxifloxacin, and levofloxacin susceptibilities were 77.8%, 83.3%, and 86.4%, respectively. Three of the *Staphylococcus aureus* species (21.4%) were methicillin-resistant *Staphylococcus aureus*, and one of the coagulase-negative *staphylococci* was methicillin-resistant coagulase-negative *Staphylococcus aureus* (9.1%).

Table 1. Predisposing risk factors

Risk factors	n	%
Trauma	5	5.6
Ocular surface disease	12	13.3
• Bullous keratopathy	6	6.7
• Meibomian gland dysfunction	1	1.1
• Dry eye	3	3.3
• Eyelid disorder	2	2.2
Corneal transplant	38	42.2
• Graft failure	16	17.8
• Suture keratitis	2	2.2
• Medications (anti-glaucomatous)	5	5.6
• Herpetic keratitis (superinfection)	1	1.1
Contact lens wear	6	6.7
Medications (systemic/topical steroid, antiglaucomatous)	12	13.3
Ocular surgeries	3	3.3
Herpetic keratitis (superinfection)	2	2.2
Systemic diseases (diabetes mellitus, autoimmune disease under immunosuppressant)	24	26.7
Unknown	9	10

The susceptibilities of gram-negative bacteria to amikacin, netilmicin, tobramycin, and gentamicin were 87.0%, 76.5%, 81.3%, and 84.6%, respectively. Ceftazidime and ceftriaxone sensitivity was 81.8% and 100%, respectively. The sensitivity to ciprofloxacin, moxifloxacin and levofloxacin was 81.8%, 100% and 85.7%, respectively.

Antifungal susceptibility was evaluated in seven cultures of *Candida* species. Of these, sensitivity was reported to amphotericin B in seven cultures, voriconazole in five cultures, fluconazole in six cultures, caspofungin in six cultures, and micafungin in six cultures. Antifungal susceptibility could not be evaluated for filamentous fungi.

Table 2. Microorganisms isolated from microbial keratitis

	n	%
G (+) cocci	40	38.8
Coagulase-negative staphylococci (*CNS*)	11	10.7
• *Staphylococcus epidermidis*	5	4.9
• *Staphylococcus capitis*	1	1
• *Staphylococcus hominis*	3	2.9
• *Staphylococcus saprophyticus*	2	1,9
• *Methicillin-resistant coagulase-negative staphylococci* (*MRCNS*)	1	1
Staphylococcus aureus	14	13.6
Streptococcus pneumoniae	11	10.7
Streptococcus parasanguinis	1	1
Streptococcus mitis/oralis	1	1
G (+) bacilli	6	5.8
Corynobacterium turneri	5	4.9
Bacillus cereus	1	1
G (-) cocci	9	8.7
Moraxella turneri	8	7.8
E. coli	1	1
G (-) bacilli	32	31.1
Pseudomonas aeruginosa	17	16.5
Serratia marcescens	7	6.8
Klebsiella turneri	4	3.9
Acinetobacter lwoffii	1	1
Burkhelderia	1	1
Eikenella corrodens	1	1
Sphingomonas paucimobilis	1	1
Yeast-like fungi	9	8.7
Candida parapsilosis	4	3.9
Candida albicans	4	3.9
Candida ferri	1	1
Filamentous fungi	7	6.8
Fusarium solani	2	1.9
Aspergillus terreus	1	1
Aspergillus niger	1	1
Paecilomyces spp.	1	1
Penicillium	1	1
Acrenomium	1	1

Table 3. Antibiotic susceptibility patterns of microorganisms isolated from microbial keratitis

Antibiotic	Gram-positive		Gram-negative	
Ampicillin sulbactam	100%	5/5	0%	0/12
Amoxicillin clavulanate	100%	1/1	41.7%	5/12
Penicillin	40.9%	9/22	100%	3/3
Oxacillin	60%	3/5		
Ceftazidime			81.8%	18/22
Sefepim			82.6%	19/23
Cefoxitin	80%	4/5	0 %	0/5
Cefoxitin	100%	6/6	80%	4/5
Cefazolin			11.1%	1/9
Cefuroxime			45.5%	5/11
Ceftriaxone	100%	9/9	100%	7/7
Meropenem			84.2%	16/19
Imipenem			69.2%	9/13
Piperacillin			72.2%	13/18
Piperacillin tazobactam			85.7%	24/28
Ciprofloxacin	77.8%	14/18	81.8%	27/33
Moxifloxacin	83.3%	5/6	100%	2/2
Levofloxacin	86.4%	19/22	85.7%	18/21
Amikacin			87.0%	20/23
Netilmicin			76.5%	13/17
Tobramicin			81.3%	13/16
Gentamicin	100%	15/15	84.6%	22/26
Eritromicin	65.5%	19/29	100%	7/7
Clindamycin	73.3%	22/30		
Trimethoprim-sulfamethoxazole	84%	21/25	76.2%	16/21
Fusidic acid	76.5%	13/17		
Tetracycline	59.1%	13/22	57.1%	4/7
Colistin			45.5%	6/11
Chloramphenicol	100%	3/3	100%	1/1
Tigecycline	100%	6/6	50%	3/6
Vancomycin	100%	10/10		
Teicoplanin	100%	4/4		
Daptomycin	100%	7/7		
Linezolid	100%	4/4		

Discussion

The distribution and resistance patterns of isolates from microbial keratitis vary with geography and change over time. Therefore, it is important to analyze regional microbial profiles and antibiotic susceptibility of pathogens for evidence-based selection of empirical treatment regimens. In our study, the demographic characteristics and microbiological profile of patients with microbial keratitis and antibiotic susceptibility of the responsible pathogens are presented. To the best of our knowledge, this is the first study in Turkey in which antibiotic susceptibility of keratitis cases has been reported.

In our study, positive culture was observed in 90 of 200 patients who underwent corneal cultures with the diagnosis of microbial keratitis. We obtained a 45.0% culture-positive rate. In current reports in the literature, culture positivity rates range from 35.1% to 71.6% (6-14). These rates are affected by antibiotic therapy before culture, inadequate sampling, limited culture media, or sensitive microorganisms. Most of our cases were consulted in our clinic, and culture results may have been affected by antibiotic treatment that began in the center they were first referred to.

The cornea has a natural resistance to infections, with its healthy epithelium acting as a protective barrier against pathogens. Microbial keratitis rarely affects healthy eyes (3). Predisposing factors such as trauma, wearing of contact lenses, previous corneal surgery, and long-term use of corticosteroids weaken the defense mechanisms of the ocular surface and facilitate the invasion of the cornea by microorganisms (3). While the leading risk factors are using contact lenses and ocular surface disease in developed countries (10,12,15), trauma is more prevalent in developing countries (6,8,14). The most common local risk factors in our study were corneal graft and ocular surface disease. The high rate of corneal grafts in our study may be related to frequent keratoplasty surgery and follow-up of patients with keratoplasty because of the presence of an eye bank in our clinic.

Consistent with the literature, bacterial keratitis (83.3%) was the most common type of infectious keratitis among culture-positive patients in our study, followed by fungal keratitis (16.7%) (6-15). Although there were cases that were cultured for suspected Acanthamoeba keratitis, the pathogen could not be isolated in our laboratory. While 44.7% of the isolated microorganisms were Gram-positive bacteria, 38.8% were gram-negative bacteria. Gram-positive bacteria dominance has been demonstrated in most of the studies in the literature (7-15). In a recent study reported in our country, *Pseudomonas aeruginosa* was reported as the most common pathogen with gram-negative bacteria dominance (16). In studies reported in different countries, coagulase-negative *Staphylococci* (10-12,15), *Staphylococcus aureus*, and *Streptococcus pneumoniae* (9,13) are the most frequently reported gram-positive agents. *Pseudomonas aeruginosa* is the most frequently isolated agent among gram-negative bacteria (9,12-15,17). The most common pathogens in our study were *Pseudomonas aeruginosa* (16.5%), *Staphylococcus aureus* (13.6%), coagulase-negative *Staphylococci* (10.7%), and *Streptococcus pneumoniae* (10.7%). *Pseudomonas aeruginosa* keratitis is more severe than keratitis caused by gram-positive bacteria (3). The frequency of need for treatments such as corneal transplantation and evisceration is higher in patients with a progressive clinical course. Therefore, the prevalence of *Pseudomonas aeruginosa* may have been high in patients referred to our clinic.

In this study, the rate of fungal keratitis was 16.7%, and *Candida* species (8.7%) were the most common agents. The rate of fungal keratitis varies between 2% and 46.6% in the current literature (6-14). Higher rates have been reported in studies conducted in developing countries with larger rural populations (6,7,9,16). Fungal keratitis is more common in tropical and subtropical regions than in temperate climates (6,9). In addition, while *Candida* species are the most frequently isolated fungi in temperate climates, filamentous fungi, particularly *Fusarium* species, are more frequently encountered in tropical regions (14). Because of the small number of patients referred to our clinic from rural areas, the rate of fungal keratitis may be small.

The World Health Organization has defined antimicrobial resistance as a growing public health threat (18,19). This is due to the prolonged and inappropriate use of antibiotics. To maintain the efficacy of empirical therapy, it is necessary to provide low rates of resistance to selected antibiotics. Here, the importance of antibiotic susceptibility reports is highlighted. Some studies in the literature have shown an increase in antibiotic resistance against fluoroquinolones, including the fourth generation (3,11,13,14,20). In the present study, the sensitivity of gram-positive bacteria to various fluoroquinolones was between 77.8% and 86.4%, and that of gram-negative bacteria was between 81.8% and 100%. The reason for the resistance to fluoroquinolones may be the widespread use of fluoroquinolones for the treatment of infections such as conjunctivitis and for postoperative prophylaxis. Considering the widespread use of fluoroquinolones in our country, their use for empirical monotherapy may not be a good option.

In our clinic, a combination of vancomycin and ceftazidime is often preferred for the empirical treatment of bacterial keratitis. In our antibiogram reports, vancomycin susceptibility was observed in cases after 2019, and all

of the gram-positive bacteria evaluated were susceptible to vancomycin. Vancomycin continues to be used as the first choice in the empirical treatment of gram-positive agents in our clinic. Our results, which are consistent with studies reporting high sensitivity to vancomycin, support this hypothesis (13,15,20-23). In our study, the sensitivity of gram-negative bacteria to ceftazidime was 81.8%. This rate was comparable to the sensitivity to aminoglycosides (76.5% to 87.0%). According to the antibiogram results, ceftazidime, which is frequently preferred in empirical treatment, was not superior to other agents. If there is no clinical response until culture results are obtained or in cases where culture positivity cannot be obtained, it may be beneficial to act early to choose an alternative treatment to empirical therapy.

Study Limitations

The main limitation was the retrospective design of the study. All the follow-up data of the patients could not be reached and their progression could not be determined. Antifungal susceptibility was not detected in filamentous fungal species. Our results may not reflect the microbial profile and antibiotic resistance pattern of the general population because of the referral of more complex cases caused by resistant pathogens to our clinic.

Conclusion

In our clinic, the most common etiology of microbial keratitis was bacteria (83.3%). *Pseudomonas aeruginosa* and *Staphylococcus aureus* were the most prevalent pathogens. *Candida* species were responsible for most fungal keratitis. Based on our antibiogram results, a combination of vancomycin with cephalosporin or aminoglycoside can be selected as the initial therapy in the empirical treatment of bacterial keratitis. Patients should be closely followed, and early treatment modification may be considered if there is no clinical response. We presented the data of our clinic, which is a tertiary center in Istanbul, the most populated city in Türkiye. We believe that our study may contribute to the literature on microbiological profiles and antibiotic susceptibility of keratitis.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee (approval number: HNEAH-KAEK 2022/218), and the results were consistent with the tenets of the Declaration of Helsinki.

Informed Consent: Informed consent was not required as the design of the study was retrospective.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B.Y., E.Y., E.T.U., R.B., N.K., Concept: M.B.Y., E.Y., E.T.U., R.B., N.K., S.A., Design: M.B.Y., E.Y., E.T.U., R.B., N.K., S.A., Data Collection or Processing: M.B.Y., E.Y., E.T.U., R.B., N.K., S.A., Analysis or Interpretation: M.B.Y., E.Y., E.T.U., R.B., N.K., S.A., Literature Search: M.B.Y., E.Y., E.T.U., Writing: M.B.Y., E.Y., E.T.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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