Microbial profile in infectious keratitis over 8 years in Sao Paulo, Brazil: pathogens and microbial resistance

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Abstract

Objective

Infectious keratitis remains a sight-threatening disease and its prompt diagnosis and treatment are critical. This study investigated the microbiological patterns of isolates in corneal ulcers in a tertiary health center in an 8-year period.

Methods

Retrospective analysis of scrapes of microbial keratitis performed from January 2013 to December 2020. Demographics and microbiological data were collected.

Results

A total of 446 scrapes were performed on eyes of 433 patients, 270 male (62.4%), mean age 51.7 years. 304 organisms were isolated from 248 (55.6%) positive samples. Polymicrobial infections occurred in 47 samples (19.0%). Bacterial isolates represented 86.8%: 53.3% gram-positive (GP), 33.5% gram-negative (GN). *Cutibacterium acnes* (12.2%) and *Pseudomonas aeruginosa* (9.9%) were the most common bacteria. Fungal keratitis comprised 11.8% of the isolates; *Fusarium* sp (6.2%) was the main fungus isolated. GP tested were sensitive to vancomycin, 98.7% of the GN were sensitive to ceftazidime. All *Pseudomonas aeruginosa* were sensitive to gentamicin and ciprofloxacin.

Conclusion

Gram-positive bacteria were predominant in keratitis isolates. In severe bacterial keratitis in our area, vancomycin should be considered as empirical treatment.

Introduction

Infectious keratitis is an ophthalmology emergency that remains sight-threatening and can lead to severe complications, such as corneal perforation, endophthalmitis and *phthisis bulbi*. Corneal scarring and vascularization are common causes of blindness among children and adults^{1,2}. According to a systematic review from 2000 to 2010, corneal opacities were the fourth cause of blindness globally³.

Clinically, it manifests itself as eye pain, redness, decreased vision, ocular discharge and photophobia. The slit-lamp biomicroscopy findings include ciliary injection, epithelial defect, suppurative stromal infiltrates or melting, corneal edema, hypopyon and anterior chamber inflammation². The prompt diagnosis, agent detection and early medical therapy are imperative to avoid vision impairment, blindness and other ocular sequelae^{2,4}.

Before microbiological data is available, there is a strategy of using empirical fortified antibiotics or starting the treatment with a fluoroquinolone. This monotherapy with a fluoroquinolone has been seen as effective as the combined fortified option, with good ocular penetration and a smaller risk of ocular discomfort and chemical conjunctivitis^{2,5}.

The etiology of corneal infection depends on the geography, climate, and socioeconomic status of the countries, as well as ocular diseases endemic in each area. There are different patterns in urban and rural areas as well. Therefore it is important to know the regional microbiological profile to better understand the epidemiology of the disease and decide on the best treatment protocol^{1,2,6-8}.

This study aimed to review the etiology and antimicrobial patterns of isolates in scrapes of corneal ulcers in patients referred to a university hospital in Sao Paulo, Brazil in an 8-year period.

Methods

A retrospective analysis of charts and corneal scrapes results of patients clinically diagnosed with microbial keratitis at the Department of Ophthalmology, Hospital das Clinicas, University of Sao Paulo, School of Medicine, Sao Paulo, Brazil, was performed from January 2013 to December 2020. This study was approved by the Institutional Ethics Committee (CAAE: 67891817.8.0000.0068). All microbiological examinations were conducted at the Department of Microbiology of our Institution, in accordance with relevant guidelines and regulations. Demographics and microbiological data were collected. All patients signed an informed consent approving participation in the study and approving the publication of their images.

Samples for culture were obtained from corneal infiltrate greater than 2 mm in size, centrally located, with deep stromal involvement or melting. Corneal scraping was carefully performed under direct visualization in a slit lamp biomicroscope with topical anesthesia (0.5% proxymetacaine hydrochloride, Anestalcon™ - Alcon Labs, Brazil). Samples were obtained from the margin of the lesions using steel spatulas that were changed for each smear. Specimens were immediately placed on glass plates for Gram stain and also inoculated into the following media: saline solution, thioglycollate broth, brain heart infusion broth with antibiotics, blood agar, chocolate agar and Sabouraud dextrose agar. Since 2018, the non-nutrient agar lawned with *Escherichia coli* has been available for culture if there is suspicion of *Acanthamoeba* keratitis. Inoculated media were promptly taken to the laboratory. After scraping, empirical treatment was initiated with fortified topical antibiotics: a cephalosporin (cefazoline) and an aminoglycoside (gentamicin or amikacin) hourly. If fungi etiology was suspected, topical natamycin was added to the regimen.

The pathogens of positive samples were identified and analyzed by the Matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry (Vitek MS™ system, bioMérieux, Marcy l'Etoile, France); the antimicrobial susceptibility testing (AST) was performed using Vitek 2™ and tests disk diffusion method (Kirby-Bauer, 1966). Evaluation of the zone diameters followed the Clinical and Laboratory Standards Institute (CLSI) current guidelines of each period^{9–11}.

Results

Over these 8 years, a total of 446 consecutive corneal scrapes were performed on eyes of 433 patients, 163 female (37.6%) and 270 male (62.4%), mean age 51.7 +/- 21.0 years (1 to 90). The mean number of corneal scrapings per year was 55.7 (21 to 100). A total of 304 organisms were isolated from 248 (55.6%) positive samples. The percentage of positive cultures per year ranged from 41.7–66.7% in these 8 years. Infections due to a single organism occurred in 201 (81.0%) of the samples, and multiple agent were found in 47 (19.0%). (Table 1 and Graphic 1)

Table 1
Corneal scrapes analysis over the 8 years

Year	2013	2014	2015	2016	2017	2018	2019	2020	2013 to 2020
Gram-positive	37 (52.1%)	9 (30%)	25 (51.0%)	8 (47.0%)	24 (70.6%)	14 (45.2%)	34 (60.7%)	11 (68.7%)	162 (53.3%)
Gram-negative	23 (32.4%)	17 (56.7%)	16 (32.7%)	8 (47.0%)	6 (17.6%)	11 (35.5%)	17 (30.4%)	4 (25%)	102 (33.6%)
Fungi	11 (15.5%)	4 (13.3%)	8 (16.3%)	1 (5.9%)	4 (11.8%)	4 (12.9%)	3 (5.4%)	1 (6.3%)	36 (11.8%)
Ameba	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (6.5%)	2 (3.6%)	0 (0%)	4 (1.3%)
Total of agents	71	30	49	17	34	31	56	16	304
Multiple isolates	8 (13.1%)	5 (20.0%)	8 (20.5%)	2 (13.3%)	5 (17.9%)	5 (19.2%)	12 (30.0%)	2 (12.5%)	45 (18.1%)
Total of scrapes	100	58	70	36	54	46	61	21	446

Bacterial isolates accounted for 86.8% of positive cases: 53.3% were gram-positive and 33.5% gram-negative. *Cutibacterium acnes* (12.2%), formerly *Propionibacterium acnes*, *Staphylococcus epidermidis* (6.6%) and *Streptococcus pneumoniae* (6.6%) were the most common gram-positive bacteria; *Pseudomonas aeruginosa* (9.9%) and *Serratia marcescens* (8.9%) were the most frequently gram-negative bacteria detected. Fungal keratitis comprised 11.8% of the total positive cultures; *Fusarium* sp (6.2%) and *Candida* spp (2.3%) were the main fungi isolated. *Acanthamoeba* was isolated in 1.3%. (Table 2)

Table 2
Organisms Isolated from Scrapes (n = 304)

Bacteria	264	86.8%
Gram-positive	162	53.3%
<i>Cutibacterium acnes</i>	37	12.2%
<i>Staphylococcus epidermidis</i>	20	6.6%
<i>Streptococcus pneumoniae</i>	20	6.6%
<i>Corynebacterium sp</i>	19	6.2%
Coagulase negative <i>Staphylococcus</i>	15	4.9%
<i>Staphylococcus aureus</i>	13	4.3%
Other <i>Staphylococcus</i>	13	4.3%
Other <i>Streptococcus</i>	4	1.3%
Other gram-positive	21	6.9%
Gram-negative	102	33.5%
<i>Pseudomonas aeruginosa</i>	30	9.9%
<i>Serratia marcescens</i>	27	8.9%
<i>Moraxella sp</i>	10	3.3%
<i>Klebsiella spp</i>	6	2.0%
Other <i>Enterobacterales</i>	15	4.9%
Other gram-negative	14	4.6%
Fungi	36	11.8%
<i>Fusarium sp</i>	19	6.2%
<i>Candida spp</i>	7	2.3%
<i>Aspergillus sp</i>	3	0.9%
<i>Rhodotorula sp</i>	3	0.9%
Other fungi	4	1.3%
Ameba	4	1.3%
<i>Acanthamoeba</i>	4	1.3%
Total of microorganisms	302	100%

Among the 248 positive samples, 143 (57.7%) antibiograms were performed. We analyzed the susceptibility of Gram-positive species to gentamicin, ciprofloxacin, moxifloxacin, vancomycin, chloramphenicol and tetracycline, which are the topic drugs available in our region. From all gram-positive isolates, the susceptibility to gentamicin was 83.3%, 75.9% to ciprofloxacin, 70.8% to moxifloxacin, 100% to vancomycin and chloramphenicol, 60.0% to tetracycline. The susceptibility of *Staphylococcus epidermidis* was 72.2% to gentamicin, 70.6% to ciprofloxacin, 58.3% to moxifloxacin and 100% to vancomycin. The susceptibility of *Staphylococcus aureus* was 100% to gentamicin and vancomycin, 83.3% to ciprofloxacin and moxifloxacin. The susceptibility of *Streptococcus pneumoniae* was 100% to vancomycin and chloramphenicol, 60.0% to tetracycline. Gram-negative species tests to amikacin, gentamicin, ciprofloxacin and ceftazidime were studied. From all gram-negative isolates, the susceptibility to amikacin, ciprofloxacin and ceftazidime was 98.7% and 97.5% to gentamicin. The susceptibility of *Pseudomonas aeruginosa* was 96.8% to amikacin and ceftazidime, 100% to gentamicin and ciprofloxacin. The susceptibility of *Serratia marcescens* was 100% to these four antibiotics. The susceptibility of the other *Enterobacterales* (formerly *Enterobacteriaceae*) tested was 100% to amikacin and ceftazidime, 90.9% to gentamicin and 98.7% to ciprofloxacin. (Table 3)

Table 3. Antibiotic susceptibility of gram-positive and gram-negative bacteria

Gram (+)	Isolates Tested	Amikacin	Gentamicin	Ciprofloxacin	Moxifloxacin	Vancomycin	Ceftazidime	Chloramphenicol	Tetrac
<i>Staphylococcus epidermidis</i>	19	—	13/18 (72.2%)	12/17 (70.6%)	7/12 (58.3%)	18/18 (100%)	—	—	—
<i>Staphylococcus aureus</i>	12	—	12/12 (100%)	10/12 (83.3%)	10/12 (83.3%)	12/12 (100%)	—	—	—
<i>Streptococcus pneumoniae</i>	20	—	—	—	—	20/20 (100%)	—	20/20 (100%)	12/20 (60%)
All Gram (+) Tested	83	—	25/30 (83.3%)	22/29 (75.9%)	17/24 (70.8%)	50/50 (100%)	—	20/20 (100%)	12/20 (60%)
Gram (-)	Isolates Tested	Amikacin	Gentamicin	Ciprofloxacin	Moxifloxacin	Vancomycin	Ceftazidime	Chloramphenicol	Tetrac
<i>Pseudomonas aeruginosa</i>	31	30/31 (96.8%)	31/31 (100%)	31/31 (100%)	—	—	30/31 (96.8%)	—	—
<i>Serratia marcescens</i>	27	27/27 (100%)	27/27 (100%)	27/27 (100%)	—	—	27/27 (100%)	—	—
Other <i>Enterobacterales</i>	22	22/22 (100%)	20/22 (90.9%)	21/22 (95.5%)	—	—	22/22 (100%)	—	—
All Gram (-) Tested	80	79/80 (98.7%)	78/80 (97.5%)	79/80 (98.7%)	—	—	79/80 (98.7%)	—	—
All isolates tested	131	79/80 (98.7%)	103/110 (93.6%)	101/109 (92.7%)	10/12 (83.3%)	50/50 (100%)	79/80 (98.7%)	20/20 (100%)	12/20 (60%)

Other *Enterobacterales*: *Citrobacter koseri* (diversus), *Enterobacter cloacae*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Morganella morganii*, *Pantoea agglomerans*, *Proteus mirabilis*, *Providencia rettgeri*, *Raoutella ornithinolytica*.

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Discussion

Infectious keratitis is a potentially blinding condition, therefore proper and rapid identification of the causative organism are imperative to guide the management to pursue better visual outcomes. Although early treated patients may successfully recover (Fig. 1), some infections are real challenges and may result in severe complications. (Fig. 2) The main pathogens found in these infections are gram-positive and gram-negative bacteria, fungi and *Acanthamoeba*. (Fig. 3)

The present study investigated the microbiological patterns of the infectious keratitis of patients admitted to our hospital. The positive rate found in these 8 years was 55.6%, which is in agreement with the rates reported by other authors in Brazil^{12,13}, Paraguay¹⁴, Mexico¹⁵, United States^{16,17}, Canada¹⁸, United Kingdom¹⁹, Spain⁴, Portugal²⁰, Sweden²¹, Israel²², India²³, Nepal²⁴, Korea²⁵, China²⁶, Taiwan⁹ and Australia²⁷ (32.6–89.6%).

The profile of etiologic pathogens worldwide depends on different risk factors related to specific characteristics of population and environment. Usual predisposing factors related to the individual are occupation, contact lens use, eyelid/ocular or systemic illness, previous ocular traumas or surgeries and use of topical steroids. Environmental-associated risk factors comprises climate, socioeconomic and virulence of the microbial^{1,7,28}. Reports from North America, Europe, Australia and Singapore reveal the highest rates of bacterial etiology, regions in which the prevalence of contact lens wear is remarkable²⁸. Mycotic keratitis is more frequently reported in developing and tropical countries, particularly in poor rural populations, in which agriculture-related trauma with soil or vegetable matter consists in predisposing factor of fungal ulcer³⁰. Reviews from Paraguay¹⁴, India²³, China¹⁸ and Nepal²⁴ found 44.5–64.5% of keratitis with fungal etiology. Other studies from Canada¹⁸, USA^{16,17}, Mexico¹⁵, Brazil^{12,13}, United Kingdom¹⁹, Spain⁴, Sweden²¹, Portugal²⁰, Israel²², Korea²⁵ and Taiwan⁸ reported rates from 0.2–23.3% of mycotic keratitis.

Bacterial isolates were most of the cases in this review, 86.8% of the positive isolates, which was similar to studies from Brazil^{12,13}, Korea²⁵, Taiwan⁸, Israel²², Australia²⁶ and countries from North America and Europe^{15–21} (76.7–100.0%). Polymicrobial infection represented 19.0% of the isolates, comparable to other series (0.7–26.8%)^{4,8,12,17–19,21,22,23–26}.

The study revealed a predominance of Gram-positive in bacterial keratitis isolates. *Cutibacterium acnes* (12.2%) *Staphylococcus epidermidis* (6.6%), *Streptococcus pneumoniae* (6.6%) and *Corynebacterium* (6.2%) were the most common gram-positive bacteria. This high rate of Gram-positive pathogens was similar to other series^{4,8,12–14,17–21,24–27}, however coagulase negative *Staphylococcus*^{4,9,13,17–20,22,23,28,29}, *Staphylococcus epidermidis*^{5,13} and *Streptococcus* spp.^{24,25} were the most common gram-positive isolated in the literature.

Sagerfors reported anaerobic diphtheroid rods (predominantly *C.acnes*) as the second main agents in a study performed in Sweden²¹. Tena found *C. acnes* and *Corynebacterium* as the second and third agent, respectively, in a study from Guadalajara⁴. A New Zealander study also reported *C.acnes* as the second most common gram-positive bacteria in infectious keratitis, after coagulase negative *Staphylococcus*²⁹. In a Portuguese tertiary centre, the most common

bacteria was *Corynebacterium macginleyi*²⁰. Although *C. acnes*³⁰ and *Corynebacterium* may be considered as contaminants, since they are part of eyelid and ocular surface microbiota, its role as pathogenic agents in corneal affections has been described³¹.

In our patients, *Pseudomonas aeruginosa* was the predominant gram-negative specie isolated, accounting for 9.9% of the positive samples, which was a similar result to rates in other centers (ranging 2.2–24.4%)^{4, 8, 12–20, 22, 23–28}.

Fusarium was the most common fungal isolate (6.2% of all isolates), also similar to other studies (ranging 2.6–39.5%)^{12–15, 18, 19, 23, 24, 26}. Farrell reported *Aspergillus* and *Candida* as the fungi most found in a series of cases in Ireland³² and Oliveira-Ferreira²⁰, Sagerfors²¹ and Tena⁴ found *Candida* as the first fungal etiology in Portugal, Sweden and Spain, respectively.

All gram-positive tested were sensitive to vancomycin; studies from Korea, Taiwan, United Kingdom, Spain, USA and Canada also described high rates of susceptibility to this antibiotic (99.4%–100%)^{4, 8, 17, 18, 19, 24}. There was a high rate of gram-positive resistance to moxifloxacin (29.2%), higher than the range in other series (0–6.2%)^{24, 25}.

The resistance to ciprofloxacin was found in 24.1% and 1.3% of the gram-positive and gram-negative tested, respectively. Other reports also showed higher ciprofloxacin resistance rates in gram-positive bacteria (10.3–45.0%)^{4, 17, 25} than in gram-negative (1.0–8.8%)^{4, 8, 18, 19, 26}. The resistance to gentamicin was 16.7% and 2.5% in gram-positive and gram-negative, respectively, which was in accordance with other series findings, that revealed rates ranging from 12.1–19.0% for gram-positive^{4, 17, 19, 25} and rates ranging from 0–15.3% for gram-negative bacteria^{4, 8, 17, 18, 19, 25, 26}.

The analysis of gram-negative resistance to amikacin and ceftazidime revealed rates of 1.3% for both antibiotics; other authors reported amikacin resistance rates ranging from 0–11.7%^{8, 17, 19, 25} and ceftazidime resistance rates ranging from 0–16.7%^{4, 8, 17, 18, 19, 25}.

The method of obtaining the corneal scrapes has been described with many instruments, such as sterile cotton swab, sterile calcium alginate swab, heat-sterilized platinum (Kimura) spatula, 26 or 23-gauge needle, blade, cotton-tipped applicator^{2, 33, 34}. In our study, we used sterile steel spatulas that were changed for each smear.

In 2020, due to the COVID-19 pandemic, the visits of patients at the Ophthalmology Emergency Room decreased compared to prior years. The number of corneal scrapes was significantly lower than in the other years studied; it happened because the total number of patients presenting infectious keratitis dropped and many patients that were referred to our hospital came with more severe cases of infections, in which the corneal scrape was not safe because of perforation or risk of perforation. Agarwal also reported a reduction in the eye-specific emergency department visits in India³⁵.

Our study had some limitations: it was a retrospective review of microbiological data; we did not correlate the laboratory results with the clinical outcomes. Moreover, we could not exclude the possibility that some of our positive isolates could be a result of a contaminant germ or non-pathogenic agent, a part of the ocular surface microbiome of the patients.

Conclusion

Gram-positive bacteria were predominant in keratitis isolates. *Cutibacterium acnes* and *Pseudomonas aeruginosa* were the most common bacteria isolated. Our results suggest that in case of severe bacterial keratitis in our area, vancomycin should be considered as empirical therapy

Declarations

Author contributions: Conception and design: LMSO, TT and JMK; Data collection: LMSO, RSYS, JMK and KLGC; Drafting manuscript: LMSO and JMK; Data analysis: LMSO, TT, JMK, RSYS, TSG, FR; Critical revision: TT and RMS; Supervision: TT and RMS; All authors reviewed the manuscript and approved the final manuscript.

The authors declare no competing interest.

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Figures

Figure 1

Staphylococcus epidermidis keratitis: diagnosis at an early stage and proper treatment. Pictures: João Felipe Bertocco MD

Figure 2

Severe microbial infection resulted in phthisis bulbi. Corneal scrape was not performed because of risk of perforation. A: Initial presentation. The patient underwent corneal suture and anterior chamber washout; B: 40 days after the first exam; C: 4 months after first exam: phthisis bulbi. Pictures: A, C: Juliana Mika Kato MD; B: Luiza Manhezi Shin de Oliveira MD

Figure 3

A. Streptococcus pneumoniae infection in a blind eye (previous rhegmatogenous retinal detachment); B. Acanthamoeba necrotizing keratitis in a contact lens wearer; C. Mycotic keratitis caused by Fusarium solani. Pictures: A, B: Daniel de Souza Costa MD; C: Fernanda Cristina Bakkar MD

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