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Microbial keratitis: Causative organisms, susceptibilities and trends at a tertiary eye hospital in South Africa

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Background: Microbial keratitis is a sight-threatening disease. Empiric management is based on current regional microbial sensitivity patterns.

Aim: This study aimed to describe the demographics and microbial patterns of keratitis at St John Eye Hospital and compare it with data from the same centre 10 years prior.

Setting: A tertiary eye care centre in Soweto, South Africa.

Methods: A retrospective cross-sectional study of the microbiological reports of patients treated for microbial keratitis between 01 January 2018 and 31 December 2018.

Results: The median age of patients was 42 years (interquartile range [IQR]: 3–77) with a male predominance of 57.0% (n = 65/113). Culture positivity rate was 63.0% (n = 84/133). There was a predominance of Gram-positive organisms of 63.0% (n = 84/133). The most common Gram-positive organism was coagulase-negative *Staphylococcus* (CNS) (32.0%, 42/133), and the most common Gram-negative organism was *Pseudomonas aeruginosa* (6.0%, 8/133). Other common organisms were *Staphylococcus aureus* (14.0%, 18/133), *Streptococcus pneumoniae* (9.0%, 12/133) and *Streptococcus viridans* (5.0%, 6/133). Commonly used fluoroquinolones ciprofloxacin and moxifloxacin had resistance of 4.2% and 10.0%, respectively. Gentamicin had a resistance of 5.8%. Culture positivity rate increased compared to 2008 from 52% to 63%. There was an increase from 2008 to 2018 of *Pseudomonas aeruginosa* from 2% to 6%. There was little change in antibiotic resistance profiles between the two study periods (2008 and 2018).

Conclusion: Culture positivity rate has increased at our institution and suggests improvements in detecting organisms and antibiotic susceptibilities. There does not seem to be any change in the susceptibilities of organisms between the study periods; therefore, it suggests current empiric management remains appropriate.

Keywords: eye; infection; keratitis; microbial; antibiotics.

Introduction

Microbial keratitis is a sight-threatening disease and a major cause of ophthalmic morbidity.[1] Globally, it is estimated that there may be 1.5–2 million cases per year.[1] These patients usually present with pain and decreased vision.[2,3,4] Clinically, they have a corneal infiltrate with an overlying epithelial defect and may have associated anterior segment inflammation.[2,5] There is a large geographic variation of causative organisms of keratitis worldwide, which seems to be climate related.[5,6] Seasonal variation has also been shown to be a factor in the prevalence of certain organisms.[7]

Few studies have assessed the microbiological profile of keratitis in South Africa, with the majority being performed at St John Eye Hospital.[2,8,9] Gram-positive organisms seem to be the most common isolates, with *Staphylococcus aureus* the most common organism in Johannesburg, South Africa, and *Streptococcus pneumoniae* the most common organism in Durban, South Africa.[2,10] Microbial keratitis is initially treated with empiric therapy. This is usually either a fluoroquinolone or a fortified aminoglycoside–cephalosporin combination.[4] There is a growing concern over the increasing rate of antimicrobial resistance worldwide.[11] Importantly for the treatment of microbial keratitis, increased rates of fluoroquinolone-resistant, methicillin-resistant and multidrug-resistant infections are being reported.[6]

Corneal scrapings at St John Eye Hospital are carried out with either surgical blades or 22-gauge needles after instillation of 1% lignocaine for analgesia. Aseptic conditions are observed during

the procedure: a facemask is worn, sterile gloves used and a sterile field for collecting the specimens is laid out. The edges of the corneal ulcer are scraped and plated onto blood agar, chocolate agar, Sabouraud dextrose agar plates, thioglycolate broth and slides. These are sent to the National Health Laboratory Service (NHLS) for microscopy, susceptibility and culture. The laboratory is on site, and specimens are processed on the same day. If specific organisms are suspected, then other culture media may be used (e.g. non-nutrient agar seeded with *Escherichia coli* in suspected *Acanthamoeba* infection). Microbial keratitis at our centre is initially treated with a second-generation quinolone, ciprofloxacin. This is changed if there is poor clinical response, and further antibiotic use is guided by the microbial culture and sensitivity profile.

In 2008, Koetsie et al.[2] investigated the microbiological patterns at St John Eye Hospital, a tertiary eye referral centre in Soweto, South Africa. To our knowledge, there has been no recent update on the microbiological profile of keratitis in the Gauteng region. It is recommended that regular analysis of microbial trends is carried out to ensure correct treatment is being prescribed for microbial keratitis.[11] Therefore, the aim of this study was to describe the demographics and microbial patterns of keratitis at St John Eye Hospital and compare it with the analysis performed by Koetsie et al.[2]

Methods and design

Study design

This was a retrospective cross-sectional study of the microbiological reports of patients treated for microbial keratitis at St John Eye Hospital between 01 January 2018 and 31 December 2018.

Setting

This study was conducted at St John Eye Hospital, a tertiary eye care centre in Soweto, South Africa. This is the referral centre for the Southern Gauteng region and the neighbouring province of North West. It is the largest public eye care facility in South Africa.

Study population and data collection

The study population included all patients who had a corneal scrape performed and sent to the lab during their treatment. It excluded any patients with microbial keratitis who were treated without corneal scraping or where culture results could not be traced. The data were obtained from the NHLS after application and approval through the NHLS Academic Affairs and Research Management System (AARMS). The NHLS is the national laboratory service for South Africa and is accredited by the South African National Accreditation System (SANAS). This is a legislated body that ensures compliance with international standards. Academic Affairs and Research Management System is the office of the NHLS that oversees research carried out using NHLS data.

All data provided by the NHLS were anonymous. The data collected included: gender, age, date of collection, Gram stain, cultured organism and the antibiotic sensitivity profile. These data were stored on a password-protected computer.

Data analysis

Data were captured into spreadsheet software. A descriptive analysis was performed using Stata version 15 (StataCorp LLC, College Station, Texas, United States). Categorical data were summarised by their frequencies, and numerical data were summarised by medians, minimums, maximums and range. Selected data were presented. A comparison was made between this data and Koetsie et al.[2]

Ethical considerations

Ethical approval for the study was granted by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg, South Africa (ref. no. M191124).

Results

There were 133 corneal scapings carried out in the study period, compared with 151 performed during the study by Koetsie et al., which was conducted using data from October 2007 to October 2008 (also a 1-year period).[2] There were 20 and 40 entries, respectively, where the gender and age of patients were not specified. Table 1 illustrates the demographics of the study population. The dates on which the scrapings were performed are illustrated in Figure 1. The procedure was performed relatively equally across all months, indicating little seasonal variation.

The median age of the group was 42 years (interquartile range [IQR]: 3–77). Of the cultures where gender was specified, there was a male predominance (57%, 65/113). Most of the samples were from patients over the age of 18 years (> 18 = 77 vs < 18 = 16).

The culture positivity rate was 63% (84/133). Most organisms cultured were gram positive 63% (84/133). Gram-negative and fungal organisms were cultured in 12% (16/133) and 0% (0/133) of scrapes, respectively. Although no fungal organisms were cultured, there were two scrapes that had

TABLE 1: Demographics of study population.

Variable	*n*	%
Gender (*n* = 133)		
Male	65	49
Female	48	36
Not specified	20	15
Age (*n* = 93)		
Age category	-	-
0–18 years old	16	17
> 18 years old	77	82

Note: Age range = 0–83; median age = 42, interquartile range = 3–77.

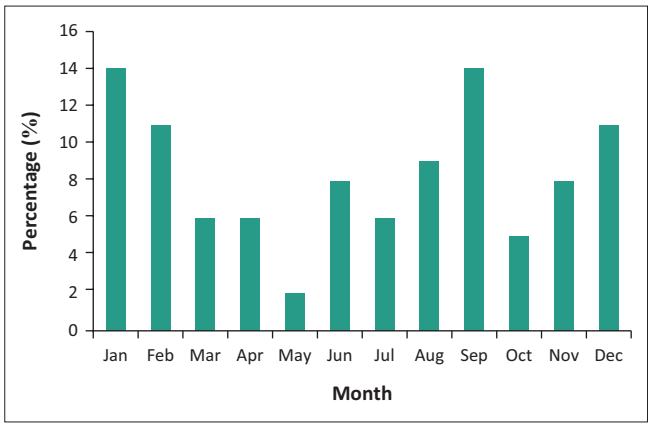

FIGURE 1: The percentage of scapings that were carried out from January 2018 to December 2018 (*n* = 133).

TABLE 2: Comparison of organisms cultured in 2018 versus 2008.

Variable	2018		2008†	
	n	%	*n*	%
Total corneal scrapes				
Total positive cultures	133	-	151	-
Culture-positive	85	63	78	52
Total organisms cultured				
Gram-positive	84	63	78	52
Gram-negative	16	12	10	7
Fungal	0‡	-	5	3
Mixed growth	14	11	15	10
Gram-positive organisms				
CNS	42	32	23	15
Staphylococcus aureus	18	14	23	15
Streptococcus pneumoniae	12	9	16	11
Streptococcus viridans	6	5	6	4
Enterococcus faecalis	2	2	0	-
Streptococcus pyogenes	1	1	4	3
MRSA	0	-	3	2
Other	3	2	3	2
Gram-negative organisms				
Pseudomonas aeruginosa	8	6	3	2
Pseudomonas fluorescens	3	2	0	-
Escherichia coli	2	2	0	-
Haemophilus influenza	0	-	3	2
Other	3	2	4	3

CNS, coagulase-negative *Staphylococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*. †, Koetsie et al.[2] ‡, No fungi cultured, but two specimens showed fungal hyphae on Gram stain.

fungal hyphae visible on Gram stain. These were not counted as they may have been contaminants. Mixed-growth cultures made up 11% (14/133) of the scrapes. The most common Gram-positive organism was coagulase-negative *Staphylococcus* (CNS), comprising 32% of all scrapes (42/133). The most common Gram-negative organism was *Pseudomonas aeruginosa*, comprising 6% (8/133). No methicillin-resistant *S. aureus* (MRSA) was cultured during this period (Table 2).

The organisms cultured were tested against a wide range of antibiotics. The classes of antibiotics included: penicillins (e.g. co-amoxiclav), cephalosporins (e.g. ceftriaxone), aminoglycosides (e.g. gentamicin), fluoroquinolones (e.g. ciprofloxacin), sulphonamides (e.g. co-trimoxazole) and others. Table 3 illustrates the resistance to commonly

TABLE 3: Organisms resistant to commonly used antibiotics in microbial keratitis cultured in 2018.

Antibiotic tested	Resistant organisms cultured (*n*)			Resistance (%)
	Gram-positive	Gram-negative	Total tested	
Chloramphenicol	12	0	82	14.6
Ciprofloxacin	3	0	72	4.2
Cefazolin	0	0	-	-
Ceftazidime	0	0	-	-
Gentamicin	3	1	69	5.8
Moxifloxacin	1	0	10	10.0
Tobramycin	0	0	-	-
Vancomycin	0	0	-	-

TABLE 4: Comparison of resistance among commonly used antibiotics in microbial keratitis between 2018 and 2008.

Variable	Resistant organisms cultured (*n*)	
	2018	2008†
Gram negatives		
Antibiotic tested		
Gentamicin	1	0
Ciprofloxacin	0	0
Moxifloxacin	0	0
Gram positives		
Antibiotic tested		
Ciprofloxacin	3	5
Moxifloxacin	1	0
Vancomycin	0	0

†, Koetsie et al.[2]

used antibiotics in the treatment of microbial keratitis. Chloramphenicol had the highest resistance percentage of these antibiotics (14.6%). This was only found amongst Gram-positive organisms. The fluoroquinolones commonly used in the treatment of microbial keratitis showed some level of resistance, with ciprofloxacin and moxifloxacin having resistance percentages of 4.2% and 10.0%, respectively. Moxifloxacin was only tested on 10 scrapes. Gentamicin had a resistance percentage of 5.8%. There was only one resistant Gram-negative organism, and this was resistant to gentamicin. None of the organisms tested were resistant to cefazolin, ceftazidime, tobramycin and vancomycin.

Table 4 summarises a comparison in the resistance patterns to commonly used antibiotics in the treatment of microbial keratitis to Koetsie et al.'s study. There was one organism in 2018 with gentamicin resistance, compared with none in Koetsie et al.'s study. There was no Gram-negative organism with resistance to ciprofloxacin or moxifloxacin in both study periods. For Gram-positive organisms, there were three organisms with resistance to ciprofloxacin, compared with five in 2008.[2] There was one organism with resistance to moxifloxacin in 2018, compared with 2008.[2] There was no Gram-positive organism with resistance to vancomycin in either study period.

Discussion

This study reports the microbiological findings of corneal scrapes performed at a tertiary eye care centre over a year and compares its findings with a similar study carried out 10 years ago. Gram-positive organisms were the most

commonly isolated (63% of scrapes), which is comparable to other South African studies.[2,10] Seasonal change has been shown in microbial keratitis. Ting et al. documented the highest rates of infectious keratitis in the summer months, although this difference was not statistically significant.[12] Although there were peaks in the months of January and September in the study, the authors did not think that there was a dramatic seasonal variation across the year. These peaks are likely incidental, although as these months are often the change of season: local environmental factors may have played a role.

Culture positivity rate is the percentage of specimens that grow an organism on microbiological culture. It is the gold standard for determining the causative organism in microbial keratitis.[1] In a review by Ung et al. that assessed global patterns of microbial keratitis, the median culture positivity rate was found to be 50.3%.[1] The culture-positive rate for the 2018 period at St John Eye Hospital was 63.0%, which was much higher than previously obtained by Koetsie et al. at 52.0%.[2] Reasons for this increase in the rate of culture positivity could be severalfold. Training of staff by corneal subspecialists occurred between 2017 and 2018. This training was specifically on improvement of corneal scrape technique, and this could have improved culture yield. It could also be that over time, there has been greater selectivity in the cases that were chosen for scraping. This could be reflected in that during the study period, a total of 133 scrapes were performed, compared with 151 performed in 2008.[2] The current St John Eye Hospital culture-positive rate is comparable to other studies performed globally.[13,14,15] Khor et al., Khoo et al. and Jin et al. had culture positivity rates of 61.4%, 69.0% and 61.5%, respectively,[13,14,15] These studies were conducted in Malaysia, Australia and the United States, respectively.[13,14,15]

There are concerns globally about increasing MRSA infections.[16] Peng et al. demonstrated a 1.13 increased odds of culturing MRSA per year in their study carried out in San Francisco.[17] In this study, there was no MRSA growth, compared with 2% growth as reported by Koetsie et al.[2] This may represent a decrease in MRSA in the region or reduced contamination by skin commensals during the scraping procedure. This may further reflect the improvement in corneal scraping techniques and training, as mentioned here.

In comparison to Koetsie et al., there was an increase in CNS from 15% to 32%.[2] This was the most isolated organism in this study. Coagulase-negative *Staphylococcus* is commonly the most isolated organism in other microbial keratitis studies carried out worldwide.[11,18,19] The total change in Gram-positive organisms increased from 52% to 63%.[2] This increase was mainly driven by the increase in CNS. This higher rate of Gram-positive organisms could be because of the increased culture-positivity rate that has been observed.

Compared with Koetsie et al., more Gram-negative organisms were cultured in this study period (an increase of 7.0% to 12.0%).[2] More specifically, more *P. aeruginosa* were cultured (an increase of 2.0% to 6.0%).[2] Similarly, Termote et al. found increasing numbers of Gram-negative bacteria in their study in Canada. They showed an increase from 14.2% to 28.0% ($p = 0.008$) over their 5-year study period.[18] Hsu et al. also found a statistically significant increasing trend ($p = 0.023$) of *P. aeruginosa*, which was attributed to the increase in contact-lens-related keratitis.[20] *Pseudomonas aeruginosa* is associated with contact lens wear, and the increase in numbers in this study compared with Koetsie et al. could be related to an increased use of contact lenses in our population. It has been suggested that with the growing middle class of South Africa, there is an increased demand for contact lenses.[21] Wearing contact lenses is a risk factor for microbial keratitis.[22]

There were no fungal organisms isolated in the 2018 study compared with Koetsie et al., where 3.0% of the total organisms were fungi; this seems to be a substantial change.[2] Proxenos et al., who conducted a similar study in Durban, South Africa, had 2.5% fungal growths ($n = 5/199$) in corneal scrapes (although their study period was over four years – 2016 to 2019).[10] It is thus surprising that there were no fungal organisms cultured. The authors do not think that it is because of poor scrape technique, as they believe this has likely improved (as evidenced by the increased culture-positive rate). It is possible that the authors' centre has been seeing fewer patients referred from rural areas as the Gauteng province has become more metropolitan. Agricultural-related injuries are a risk factor for fungal keratitis, which are an uncommon injury seen in the authors' centre.

The authors' institution uses a second-generation fluoroquinolone (ciprofloxacin) as empiric therapy for microbial keratitis. Only 4.2% ($n = 3$) of organisms tested showed resistance to ciprofloxacin. Koetsie et al. had five resistant organisms to ciprofloxacin in 2008 ($n = 5/54$ tested, 9.2%).[2] This is reassuring as there does not seem to be any increase in resistance to this antibiotic. It is thus safe to continue to use it. Moxifloxacin, a fourth-generation cephalosporin also used in the empiric management of microbial keratitis, was found to have resistance in only one organism (10.0%). This percentage may be misleading, because resistance to this antibiotic was only tested in 10 organisms – possibly creating a false-high result. In 2008 in Koetsie et al.'s study, there was no resistance was found to moxifloxacin.[2] There was thus just a one-organism increase from 2008 to 2018 in moxifloxacin resistance. Whether this suggests an actual increase in resistance is difficult to elicit from such small numbers. Moxifloxacin resistance in microbial keratitis has been found to be increasing in several studies worldwide.[16,17,23] Chang et al. showed statistically significant increasing trends of moxifloxacin resistance in both methicillin-susceptible ($p = 0.001$) and MRSA ($p = 0.022$) over a 20-year period.[16] Das et al. demonstrated a decrease in moxifloxacin susceptibility among *Pseudomonas* species from 95.3% to

76.6% between their study periods ($p = 0.016$).[23] Peng et al. found a 1.26-fold increase in risk of culturing a moxifloxacin-resistant organism each year over their study period (1996–2015).[17] Thus, further surveillance studies may be warranted to monitor these patterns in the population.

Aminoglycosides and vancomycin are also used as part of management of microbial keratitis. There was no vancomycin or tobramycin resistance among the organisms in this study. It is reassuring to have 100.0% susceptibility to vancomycin, as most of the organisms cultured were Gram-positive, and vancomycin can be used in cases of empiric treatment resistance. There was, however, 5.8% resistance ($n = 4/69$) to gentamicin found. Increasing gentamicin resistance has been reported by Hsu et al., who found Gram-positive organisms susceptibility to gentamicin to decrease significantly ($p = 0.005$) over their study period (1999–2013).[20] These results suggest low-level resistance in this population, and thus gentamicin will still likely be used as an alternative empiric therapy to the fluoroquinolones.

Chloramphenicol is an antibiotic that is often prescribed at the clinic level for ocular infections. It is also used at the authors' centre as an adjunct to second-generation fluoroquinolones in the treatment of microbial keratitis for its lubricating properties (dispensed as an ointment), ability to disrupt biofilm and its antibiotic properties. It is not routinely prescribed elsewhere, but Termote et al. found that there seemed to be a decreasing trend of susceptibility in their study among Gram-negative organisms (50.0% – 33.0%), although this was not statistically significant ($p = 0.53$).[18] It was found that 14.6% ($n = 12/82$) of tested organisms were resistant. Koetsie et al. also showed the sensitivity profiles among *S. aureus* (89.5%), CNS (75.0%), *Haemophilus influenzae* (66.7%) and Gram-positive organisms (50.0%).[2] Thus, there has always been resistance to this antibiotic, but it is used as an adjunct and so its use is likely to continue.

The strengths of this study is that it is a comparative study that is conducted after a 10-year time period. The study design, the study setting and the demographics of the study populations between this study and Koetsie et al. were largely unchanged, which allowed a direct comparison between the two groups.[2] This enabled the authors to make several deductions about the microbes and antibiotic sensitivities.

The limitations of this study are that the data were collected retrospectively and missing data like age and sex could not be verified. Clinical data were not available, which may have ameliorated and contextualised the findings differently. A shorter period between studies may have illustrated unchanged trends better.

Conclusion

The comparison between this study and Koetsie et al. showed an increase in culture positivity rate, which suggests improvements in detecting organisms and antibiotic sensitivity patterns.[2] There was little change in the organisms cultured and their antibiotic resistance profiles, and the current empiric treatment therefore remains appropriate for this setting. There is a continued struggle with emerging antimicrobial resistance locally and globally, and this necessitates continued vigilance in monitoring the causative organisms and antibiotic susceptibility profiles for keratitis at St John Eye Hospital. Further research with larger sample sizes and over longer study periods and with shorter intervals between studies may show more precise trends in the organisms and antibiotic profiles at the institution, which may further improve clinical management and quality of care.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

C.D.A. and K.K. were involved in study design. C.D.A., A.M. and K.K. were responsible for data collection. C.D.A., A.M., A.R. and K.K. performed data analysis. C.D.A., A.M., K.K., A.R. and N.R. were involved in article drafting and review.

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Data availability

Raw data were provided by the NHLS through their Academic Affairs and Research Management System (AARMS) application process – these data can only be obtained from the NHLS through application. Summary data from the author are available on reasonable request and in consultation with the NHLS.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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