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Disease patterns of microbial keratitis in Singapore: A retrospective case series

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ABSTRACT

Purpose: To investigate the disease patterns of Microbial Keratitis(MK) in patients seen in a tertiary referral hospital, to evaluate the clinical outcomes of MK and the risk factors for poorer visual outcomes.

Methods: This is a retrospective case series of all culture-positive corneal scrapings between April 2012 and October 2016. A total of 230 patients(n = 230) were included into this study. Patient demographics, clinical information and microbiological characteristics of organisms are collected.

Results: 64.3% of patients with MK are contact lens(CL) users. Among CL users, there is a preponderance of females(68.9%) and they tend to be younger (27.1 ± 10.6 years).

The most frequently isolated organism in this study is Pseudomonas aeruginosa(51.7%) with 69.6% of cases belonging to CL users. MK in non-CL users tend to involve other organisms, such as coagulase-negative Staphylococci, Staphylococcus aureus and Streptococcus pneumoniae.

Pseudomonas aeruginosa exhibits good sensitivity rates to ciprofloxacin, levofloxacin and gentamicin. Non-Pseudomonas organisms display similar sensitivities to ciprofloxacin, levofloxacin and gentamicin.

MK in non-CL users is related to predisposing factors of prior ocular trauma and concomitant ocular pathology. They tend to have worse visual acuity(VA) on presentation and after treatment compared to CL users. Poorer VA outcome is associated with larger ulcers, increasing age, trauma and non-CL wearers.

Successful clinical outcome is achieved in 97.8% of patients, with only 2.2% requiring further surgical intervention.

Conclusion: CL use alters the disease patterns of MK as well as the underlying microbiological etiology. Fluoroquinolones and aminoglycosides are good empirical antibiotics for MK treatment. Early referral to a tertiary centre will likely allow for earlier treatment, which can result in better VA outcome, especially so in patients who are older, non-CL wearers and have larger ulcers with associated trauma.

1. Introduction

Microbial keratitis(MK) is a sight threatening condition. It is a relatively common disease encountered by doctors in various settings, such as in primary care, private practice and in tertiary hospitals. Incidence of MK is estimated to be 0.63/10000 population annually [1]. Incidence of contact lens(CL)-related MK is much higher, estimated to be about 2.2–4.1/10000 population annually [2–4].

Being one of the most feared complications of CL wear, MK can lead to corneal scarring or even worse complications such as endophthalmitis, causing devastating visual impairment [5]. Other risk factors that increase the risk of infection include extended hours of wear, overnight usage, poor compliance with hygiene and lack of lens case replacement [6]. Protective factors do exist, such as rigid contact lens wear and good daily CL case maintenance habits [6].

A vast range of causative organisms lead to MK, including bacteria, fungi and protozoa. Antibiotic eye drops remain the mainstay of treatment of MK. In general, the majority of community-acquired cases of bacterial keratitis resolve with empirical therapy and are managed without smears or cultures [7]. In Singapore's context, the majority of patients present to general practitioners in government polyclinics and private clinics first. They are then usually referred to tertiary hospitals for their first assessment by an ophthalmologist if MK is suspected. Prompt recognition of MK will allow patients to be referred early on in the disease, for assessment by a specialist. Corneal cultures are then usually taken, followed by treatment using antibiotic eyedrops.

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Initiation of empirical treatment often requires a good understanding of disease patterns and antibiotic susceptibilities of organisms encountered in the region. Only then, will we be able to treat patients early with the correct medications prior to obtaining culture results, leading to better outcomes.

Various studies from many countries in the world have previously described MK organisms and antibiotic susceptibility patterns in their regions. However, it is important to note that patterns of MK and shifting trends of microbial resistance do vary along with geographical locations. For example, a study in Jerusalem found that MK caused by Methicillin-Resistant Staphylococcus Aureus(MRSA) appeared to decrease while another study in San Francisco found that MRSA-related MK cases were rising [8,9].

In this region, current literature is lacking. The last major study was done back in 1995, on a review of 103 cases of bacterial keratitis in 2 institutions of Singapore [10]. Since then, there are no large studies with updates on the disease patterns and antibiotic susceptibility trends on MK. Smaller studies were conducted in 1997 and 2013 [11,12]. The study in 1997 compared 29 cases of fungal keratitis against 51 cases of culture-positive MK, showing an association between fungal keratitis and ocular trauma, while MK was associated with CL use and pre-existing ocular disease [11]. The study in 2013 once again confirmed CL use as the most common risk factor in patients with MK. Disease patterns and trends may have since changed and it is essential to have updated information in order to guide current treatment of MK.

Our aim in this study is to investigate the disease patterns of MK in a tertiary referral hospital in Singapore. We also aim to evaluate the clinical outcomes of MK and the risk factors for poorer visual outcomes. With this larger study, we seek to better illustrate and update current understanding about the latest disease trends of MK.

2. Methods

This is a retrospective case series of all culture-positive corneal scrapings between April 2012 and October 2016 in National University Hospital Singapore. Corneal scrapings from patients with MK are routinely sent for microbiological analysis via gram stain, fungus smear, chocolate agar medium, Sabouraud agar medium and blood agar medium. A total sample size of 377 culture-positive corneal scrapings were collected(n = 377).

Clinical information was collected from medical records via a standardised form (Fig. 1) by a single person. Patient demographics, predisposing factors (e.g. contact lens use, details of contact lens use, trauma, concomitant ocular pathology), clinical and microbiological characteristics were reviewed from medical records. Clinical characteristics reviewed included the size and location of corneal ulcer, presence of hypopyon, pre and post-treatment best-corrected visual acuity(VA), antibiotics used and treatment outcomes. VA was recorded using Snellen's VA chart and eventually converted into LogMAR (Logarithm of Minimum Angle of Resolution) acuity for the purpose of statistical analysis. The diameter of the ulcer was measured in millimetres and the location was classified as central, paracentral and peripheral. The central zone was defined as the central 3 mm of the cornea. All patients were initially treated with broad-spectrum topical antibiotics which were subsequently changed according to culture and sensitivity results as required. Topical antifungals were administered if fungal keratitis was suspected clinically or when fungal organisms were detected microbiologically. Clinical outcome was considered "successful" when the patient developed a corneal scar and did not require further treatment, or "failure" if further surgical intervention such as therapeutic keratoplasty or evisceration was required.

Statistical software used was R Statistical Software(version 3.3.3, R Foundation for Statistical Computing, Vienna, Austria). Both univariate and multivariate analysis were carried out. Categorical variables were analyzed by Pearson's Chi-Square test or Fisher's exact test. Non-categorical variables were analyzed by Welch's unequal variances t-test. For risk factor analysis, logistic regression was used. Statistical significance was set at $p < 0.05$.

This study was approved by the Institutional Review Board of Singapore.

3. Results

A total of 230 patients were included in this study. These patients had corneal ulcers with positive growth on corneal scraping cultures. A number of cases were excluded from the study after data collection, with reasons for exclusion as shown in Table 1.

Of these patients, 148(64.3%) were CL wearers. Demographic details are summarised in Table 2. Patients with CL-related MK tended to be younger, and were more likely to be female.

Table 3 summarizes the clinical characteristics of MK cases in our series. In terms of risk factors for MK, non-CL wearers were significantly more likely to have had prior ocular trauma and concomitant ocular pathology. On both presentation and 1 month after presentation, non-CL wearers had worse VA. Non-CL wearers also tend to have larger ulcers as compared to CL wearers.

A number of organisms were isolated from the cultures, with Pseudomonas aeruginosa being the most common in 119 cultures (51.7%). Pseudomonas aeruginosa predominantly affected CL wearers more than non-CL wearers. Other organisms isolated include coagulase-negative Staphylococcus, Staphylococcus aureus, Serratia marcescens, Streptococcus pneumoniae and others (Figs. 2 & 3). Some cultures isolated fungi, such as Aspergillus and Candida, but the number of cases were low.

Table 4 outlines the antibiotic sensitivities of the organisms isolated. Pseudomonas aeruginosa was largely sensitive to ciprofloxacin, levofloxacin and gentamicin. It exhibited complete resistance to amoxicillin-clavulanate. The trend of antibiotic resistance of Pseudomonas aeruginosa over the years is shown in Fig. 4. Susceptibility testing to cephalosporins was mostly not done in the laboratory as they were of minimal clinical relevance, given that most of them are not available commercially in eye drop formulation. Non-Pseudomonas organisms displayed similar sensitivities with slightly better sensitivity to amoxicillin-clavulanate. They were also largely sensitive to ciprofloxacin, levofloxacin and gentamicin.

Logistic regression was carried out to look for risk factors for poorer VA outcomes. Patients with poorer VA outcomes tended to be older, non-CL wearers, have larger ulcers and have associated trauma (Table 5**).**

Clinical outcomes of the patients were mostly successful, with the majority(97.8%) avoiding any need for surgical intervention.

4. Discussion

Soft CL use has been well established as a risk factor for MK. [14] Based on our findings, CL use remains to be a very important risk factor for MK. Back in a 1995 study, CL wear represented the largest single predisposing factor to MK [10]. 34% of the patients that suffered from MK were CL wearers [10]. This was followed by trauma and pre-existing ocular disease [10]. This similar finding was also obtained in a study in 2013 [12]. As shown in the results section, CL usage is still the single most important risk factor predisposing to MK in 64.3% of the patients.

In our series, patients with CL-related MK were usually young females. However, MK also affected non-CL users, especially in patients with prior ocular trauma and concomitant ocular pathology. This group of patients tended to have worse VA outcomes than CL users even after treatment. In terms of offending organisms in MK, Pseudomonas aeruginosa was still the most prevalent organism in our case series, with good sensitivity to fluoroquinolones and aminoglycosides. The racial profiles of patients in this study do not correlate with the demographics of Singapore's population. This is likely related to the variety of patients

Subject Code			
Date of birth		Gender	

Past Medical History		
DM	Yes / No	
SLE	Yes / No	Others: _____
Past Ocular History		
Contact Lens Wear	Yes / No	
Type of lens	Daily / Weekly / Monthly / RGP / OKN / Others: _____	
Colored lens	Yes / No	
Previous Infectious Keratitis	Yes / No	Specify: _____
Ocular Surface Disease	Yes / No	Specify: _____
Previous Ocular Surgery	Yes / No	Specify: _____
Previous Ocular Trauma	Yes / No	Specify: _____
Past Medication History		
Topical steroid use	Yes / No	Specify: _____
Topical antibiotic use	Yes / No	Specify: _____
Systemic steroid use	Yes / No	Specify: _____
Systemic antibiotic use	Yes / No	Specify: _____

Visual Information			
UCVA	**BCVA**	**IOP**	**Method of IOP**
Presenting: _____	Presenting: _____	Presenting: _____	GAT / TP / AP
1 week: _____	1 week: _____	1 week: _____	GAT / TP / AP
1 month: _____	1 month: _____	1 month: _____	GAT / TP / AP
Resolution: _____	Resolution: _____	Resolution: _____	GAT / TP / AP
Last visit: _____	Last visit: _____	Last visit: _____	GAT / TP / AP

Ulcer information			
Location		Central / Paracentral / Peripheral	
Size of ulcer		_____	
Size of epithelial defect		_____	
Anterior chamber activity		Trace / 1+ / 2+ / 3+ / 4+ / Hypopyon	
Hypopyon		Yes / No	
Microbiological information			
Organism 1:	_____	Susceptibility:	_____
Organism 2:	_____	Susceptibility:	_____
Organism 3:	_____	Susceptibility:	_____
Treatment information			
Initial antibiotics			
Date antibiotics started			
Date antibiotics stopped			
Total number of antibiotics used			
Topical steroid usage		Yes / No	Specify: _____

Fig. 1. Standardised Data Collection Form.

Table 1
Cases excluded from the study.

Reason for exclusion	No. of cases
Duplicated culture results of patients	121
Unavailable medical notes	10
Cultures mislabelled as corneal samples	16

referred to the tertiary centre, including foreign workers, of whom a great proportion are of Malays and other races from various countries.

In our study, there was a high prevalence of CL use in 64.3% of patients [10]. Among CL users, there was also a preponderance of females(68.9%) and they tended to be younger(27.1 ± 10.6 years). Reasons for high rates of CL usage are likely multi-factorial. CL are readily available in the modern world, especially with easy access to the internet and online shopping, letting people avoid the hassle of using spectacles in daily life. Many of these consumers purchase over-the-counter CL without being counselled on the importance of good CL hygiene [15]. In a survey in Hong Kong, over 90% of CL users were using soft CL, with silicone hydrogel and daily disposable CL becoming increasingly popular [16]. Prevalence of myopia is very high in young

Table 2
Patient Demographics.

Characteristic	Overall (n = 230)	CL wearers (64.3%) (n = 148)	Non-CL wearers (35.7%) (n = 82)	p-value
Mean age, years (SD)	33.6 (17.2)	27.1 (10.6)	45.5 (20.2)	< 0.01
Female gender, n (%)	123 (53.5)	102 (68.9)	21 (25.6)	< 0.01
Right eye, n (%)	116 (50.4)	78 (52.7)	38 (46.3)	0.36
Race, n (%)				
Chinese[a]	124 (53.9)	82 (55.4)	42 (51.2)	0.54
Malay[b]	59 (25.7)	41 (27.7)	18 (22.0)	
Indian[c]	13 (5.7)	10 (6.8)	3 (3.7)	
Others[d]	34 (14.8)	15 (10.1)	19 (23.1)	

Abbreviations: CL, contact lens; SD, standard deviation.
[a] 74.3% of population in Singapore [13].
[b] 13.4% of population in Singapore [13].
[c] 9.1% of population in Singapore [13].
[d] 3.2% of population in Singapore [13].

Table 3
Clinical characteristics of Microbial Keratitis cases.

Characteristic		Overall (n = 230)	CL-wearers (64.3%) (n = 148)	Non-CL wearers (35.7%) (n = 82)	p-value
Initial visual acuity, median LogMAR (IQR)		0.48 (0.18, 2.60)	0.30 (0.18, 0.70)	0.88 (0.30, 2.90)	< 0.01
VA at 1mth, median LogMAR (IQR)		0.18 (0.00, 2.60)	0.97 (0.00, 0.18)	2.60 (0.30, 2.90)	< 0.01
Initial intraocular pressure, median mmHg (IQR)		14.0 (12.0, 18.0)	14.0 (12.0, 16.0)	16.0 (13.5, 20.0)	< 0.01
Prior ocular trauma, n (%)		9 (3.9)	1 (0.7)	8 (9.8)	< 0.01
Concomitant ocular pathology, n (%)		23 (10.0)	2 (1.4)	21 (25.6)	< 0.01
Prior ocular surgery, n (%)		5 (2.2)	1 (0.7)	4 (4.9)	0.06
Prior treatment with ocular steroids, n (%)		2 (0.9)	0 (0.0)	2 (2.4)	0.13
Prior treatment with ocular antibiotics, n (%)		0 (0.0)	0 (0.0)	0 (0.0)	–
Ulcer Location[a]	Central(%)	53(25.5)	32(22.7)	21(31.3)	0.25
	Paracentral(%)	71(34.1)	47(33.3)	24(35.8)	
	Peripheral(%)	84(40.4)	62(44.0)	22(32.8)	
Ulcer Diameter in millimetres(SD)[b]		1.9(1.8)	1.5(1.3)	2.8(2.3)	< 0.01
Organism, n (%)					
Pseudomonas aeruginosa		119 (51.7)	103 (69.6)	16 (19.5)	< 0.01

Abbreviations: CL, contact lens; LogMAR, Logarithm of the Minimum Angle of Resolution; IQR, inter-quartile range; SD, standard deviation.
[a] 22 cases with missing data.
[b] 23 cases with missing data.

adults in East Asia, going up to as high as 80–90% [17]. With the primary reason for CL use being optical in nature, it comes as no surprise that CL use is common, with more and more people hearing about them from various media platforms. Apart from optical usage, other reasons for CL use also exist, such as cosmetic CL and Orthokeratology CL for slowing myopia progression [18]. Such CL are also known for causing MK [7,19–21].

The most commonly isolated causative organism of MK in our study was Pseudomonas aeruginosa. This is a similar finding with various previous studies [10,22–24]. Of those cultures that isolated Pseudomonas aeruginosa as the cause, 69.6% of them belonged to CL wearers ($p < 0.01$). The above suggests that CL wear greatly alters the disease pattern of MK as well as the underlying microbial etiology, predisposing them to infection by Pseudomonas aeruginosa. Pseudomonas aeruginosa has exoproducts that contributes directly to MK via toxic effects on corneal cells and degradation of corneal proteins [25–27].

There were not many cases that isolated fungi on cultures in our study. Fungal keratitis is often related to ocular trauma [11]. Most cases are reported from developing countries such as India, where people are more involved in agriculture, increasing their risk of vegetative corneal injury [28]. This is not the case in Singapore where the environment is mostly urbanised, which is the likely reason why we do not have as many cases of fungal keratitis.

MK in non-CL wearers tend to involve other organisms, including coagulase-negative Staphylococcus, Staphylococcus aureus and Streptococcus pneumoniae. At this point, it is important to note that MK

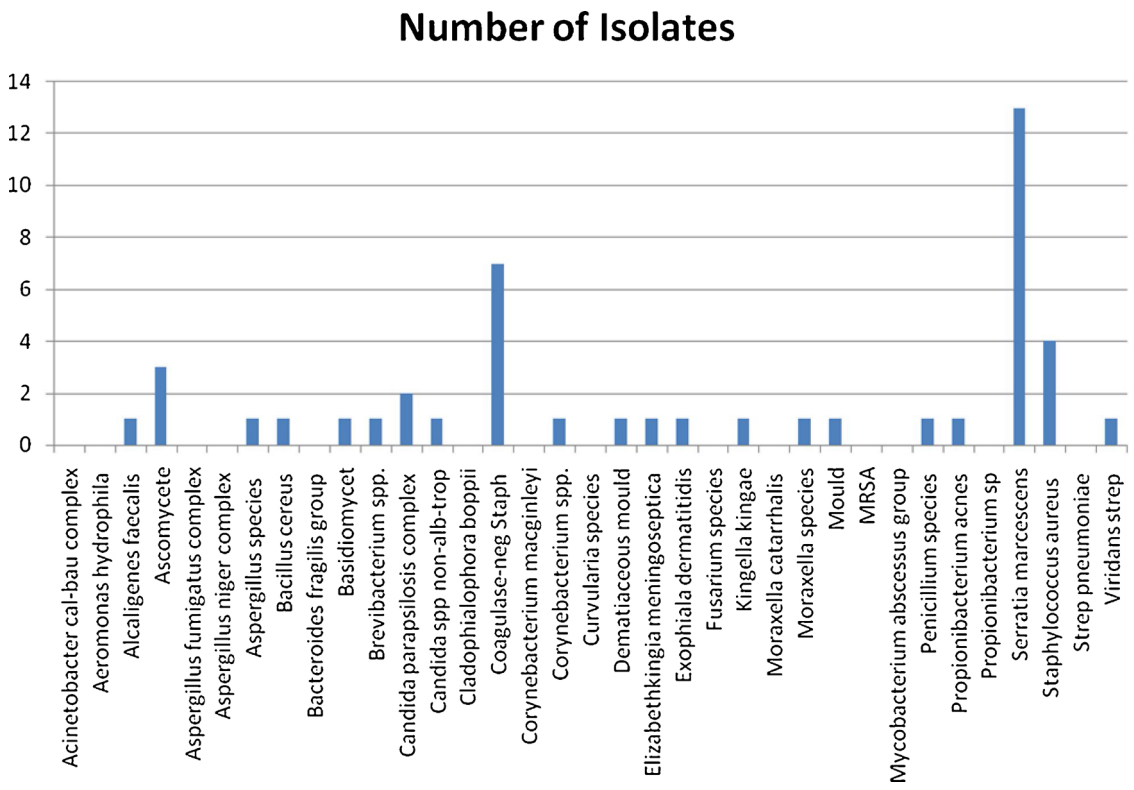


Fig. 2. Other organisms isolated from Contact Lens Users.

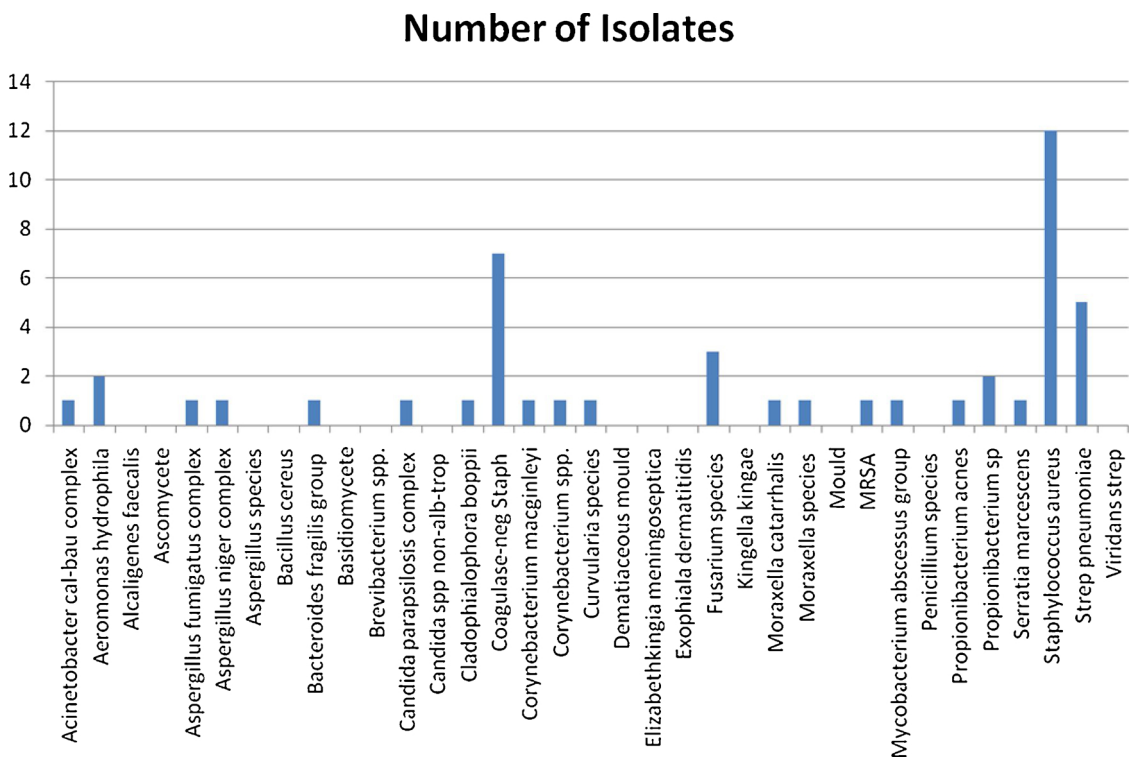


Fig. 3. Other organisms isolated from Non-Contact-Lens Users.

Table 4
Sensitivities of Pseudomonas Aeruginosa and non-Pseudomonas organisms to antibiotics.

Sensitivity of Pseudomonas Aeruginosa(n = 119)			
	Sensitive(%)	Resistant(%)	No. of cases untested for this antibiotic
Amoxicillin-clavulanate	0	113 (100)	6 of 119
Ciprofloxacin	113 (96.6)	4 (3.4)	2 of 119
Levofloxacin	112 (95.7)	5 (4.3)	2 of 119
Gentamicin	116 (99.1)	1 (0.01)	2 of 119
Cefuroxime	0	1 (100)	118 of 119
Ceftriaxone	0	1 (100)	118 of 119
Ceftazidime	1 (100)	0	118 of 119
Cefepime	1 (100)	0	118 of 119
Sensitivity results of non-Pseudomonas organisms(n = 111)			
Amoxicillin-clavulanate	3 (13.0)	20 (87.0)	88 of 111
Ciprofloxacin	45 (95.7)	2 (4.3)	64 of 111
Levofloxacin	27 (100)	0	84 of 111
Gentamicin	43 (95.6)	2 (0.04)	66 of 111

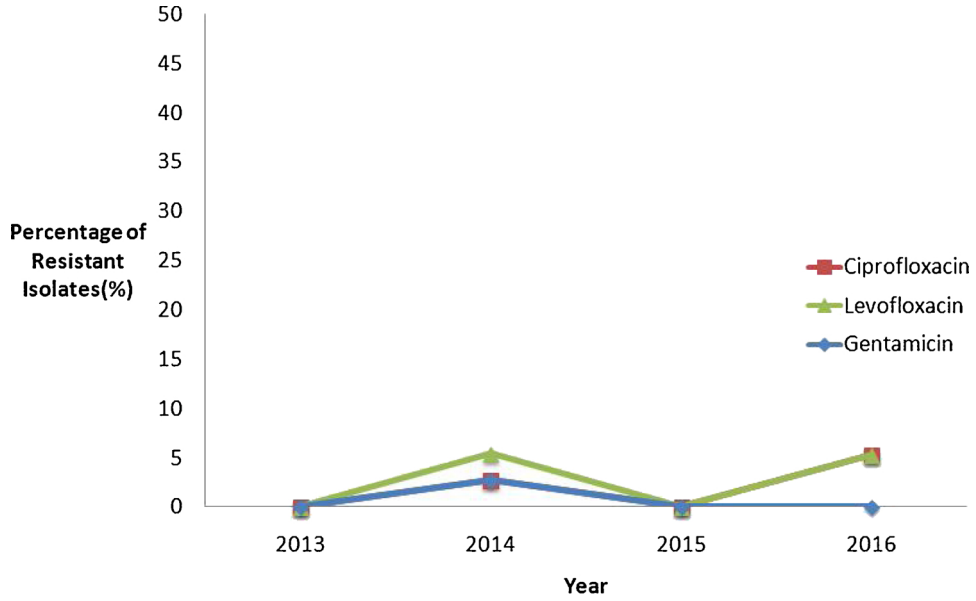
in non-CL users is related to other predisposing factors such as prior ocular trauma. Staphylcocci is one of the many organisms that form a large proportion of the normal skin flora and can also be found in the environment [29]. Ocular trauma can directly introduce these organisms into the eye from the surrounding skin and the environment.

Baseline intraocular pressure (IOP) was significantly higher for non-CL wearers at presentation. This may be attributed to the higher mean age in the non-CL wearer group. However, as the IOP readings were within the normal range in both groups, this may not be clinically relevant.

Another predisposing factor for MK in non-CL users was concomitant ocular pathology. The patients with concomitant ocular pathologies had a range of ocular diseases such as pseudophakic bullous keratopathy, glaucoma, proliferative diabetic retinopathy, neurotrophic keratopathy, filamentary keratitis and ischemic central retinal vein occlusion. For some of these conditions, it is not entirely clear how it predisposes non-CL users to MK, such as in glaucoma. It is possible that in patients with glaucoma, this predisposition is due to medication-related factors [7]. Prolonged use of glaucoma medication eyedrops containing preservatives may have contributed to ocular surface disease, predisposing them to MK. For some of those conditions listed above, the link to MK is clear. For example, pseudophakic bullous keratopathy and neurotrophic keratopathy are known to put patients at risk of secondary MK [7].

A number of antibiotics have been in use for treatment of MK for the past few decades, especially fluoroquinolones and aminoglycosides [10]. Examples include ciprofloxacin, levofloxacin and gentamicin. These antibiotics exhibit good cover against gram-negative organisms and have been recommended for treatment of MK in various previous studies [23,30–32]. Our results show that the above three antibiotics are good medications against Pseudomonas aeruginosa, with high rates of susceptibility. As to other antibiotics, such as amoxicillin-clavulanate, Pseudomonas aeruginosa remains resistant. This is likely attributed to its high intrinsic resistance to antibiotics [33]. Such resistance mechanisms include low permeability of its cell wall, genetic capacity to express resistance mechanisms, mutation in chromosomal genes which regulate resistance genes and ability to acquire additional resistance genes from other organisms [34]. Multidrug efflux pumps have also been known to contribute as an important mechanism for antibiotic resistance for Pseudomonas aeruginosa [33,35]. For the other non-Pseudomonas organisms, the above three antibiotics prove to be effective in most cases. The above antibiotic susceptibility patterns will require continued monitoring in future to pick up new emerging trends of antibiotic resistance to guide treatment of MK.

In terms of visual outcome, patients with poorer VA outcomes tended to be older, non-CL wearers, have larger ulcers and trauma. Non-CL wearers had worse VA on both presentation and at one month after presentation. It is possible that these patients were diagnosed with MK later compared to CL wearers. Diagnosis may have been made later compared to non-CL wearers due to the absence of CL wear as a risk factor, and perhaps the initial attribution of symptoms to their



Year	2013	2014	2015	2016
Total Number of Isolates	30	37	16	19
Ciprofloxacin	0	1	0	1
Levofloxacin	0	2	0	1
Gentamicin	0	1	0	0

Fig. 4. Trend of Antibiotic Resistance of Pseudomonas aeruginosa*.
*Pseudomonas aeruginosa has 100% resistance to amoxicillin-clavulanate

Table 5
Risk factors for poorer VA Outcomes.

Risk Factor	OR(95% CI)	p-value
Age	1.08 (1.02, 1.14)	0.01
Non-CL wearers	13.1 (1.1, 155.2)	0.04
Ulcer Diameter	2.05 (1.1, 3.9)	0.03
Trauma	10.8(1.2, 95.5)	0.03

Abbreviations: OR, odds ratio; CI, confidence interval.

previously known ocular issues by their general practitioners. Referral to our tertiary centre may have occurred only after VA had deteriorated or non-response to initial therapy. This may have contributed to a delay in treatment, resulting in larger ulcers, poorer VA on presentation and poorer VA at one month in non-CL wearers. Underlying reasons for these findings are currently uncertain and hopefully future studies will be able to provide more information.

Of all the patients with MK, the majority treated(97.8%) had a successful clinical outcome, avoiding surgical intervention. The most common initial antibiotic regimen used locally usually involves starting frequent cefazolin and gentamicin eyedrops, to be used once every hour. This is maintained for a further 48–72 h while awaiting culture results. If there is clinical suspicion for other organisms or when culture results are out, antibiotics used for treatment are changed accordingly. The high success rates achieved suggest that this current approach is adequate for treatment of MK.

This is a retrospective study hence limitations exist. This study was conducted in a single institution in a single country of Asia. Hence the results above may only be applicable to this region and cannot be generalised to the rest of the world due to geographic variations in disease trends. In this study, only cases with positive cornea cultures were included, information from culture-negative cases were not included. This may lead to a bias of including mainly larger ulcers which provide a better chance of getting a positive culture. This can contribute to inaccuracies of analysis results, such as the ulcer characteristics differences. There is also loss of data from patients with MK diagnosed clinically, that is caused by organisms that are hard to isolate, such as amoeba. In addition, the lack of data in some aspects should also be taken into account for this retrospective study. Examples of these include relevant systemic conditions not documented in the traced medical notes and the numbers of untested cases for antibiotic sensitivities in non-pseudomonas organisms. This can contribute to an incomplete assessment of disease trends. The above limitations will require further studies in future in order to be addressed adequately.

5. Conclusion

This is the largest local case series reviewing cases of MK. It is important to have a high suspicion for Pseudomonas aeruginosa causing MK in patients with history of CL use. This higher index of suspicion also holds true for non-CL wearers, especially so if they are older, have large ulcers and have the risk factors of prior trauma and concomitant ocular pathology. Early referral to a tertiary centre for eye care may allow for an early diagnosis and earlier commencement of treatment which may lead to better VA outcomes. In view of their high rates of susceptibility, fluoroquinolones and aminoglycosides are good empirical antibiotics for treatment of MK, even when corneal culture results are not yet available. In future, disease trends and susceptibility patterns need to be continually monitored, to pick up new emerging trends.

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Declarations of interests

None.

Submission declaration

This work has not been published previously elsewhere and is not currently under consideration for publication elsewhere.

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