



Microbial keratitis in Sydney, Australia: risk factors, patient outcomes, and seasonal variation

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Abstract

Purpose To provide recent data on patient demographics, clinical profile and outcomes of patients with microbial keratitis over a 5-year period at the Sydney Eye Hospital, and to identify seasonal variations of the main causative organisms.

Method A retrospective study of patients with a clinical diagnosis of microbial keratitis and corneal scrape performed between 1 January 2012 and 31 December 2016. Clinical information was gathered from medical records and pathology data.

Results One thousand fifty-two eyes from 979 patients with a mean age of 54.7 ± 21.5 years (range 18–100 years) were included. The majority of cases were bacterial (65%) followed by polymicrobial (2.4%), fungi (2.3%), and culture-negative (31%). Common risk factors for microbial keratitis were contact lens wear (63%) and previous topical steroid use (24%). Factors significantly associated with poor patient outcomes in the multivariate model were age, visual acuity, and epithelial defect size ($p < 0.05$). Patients with fungal or polymicrobial keratitis presented with worse clinical features at initial and final presentation ($p < 0.05$). There was a significant variation in the occurrence of *Pseudomonas aeruginosa* ($p = 0.018$) and fungal keratitis (predominately made up of *Candida* and *Fusarium* species) ($p = 0.056$) in the hottest seasons.

Conclusion Poorer outcomes are more likely to be seen in older patients and those presenting with poor visual acuity and large epithelial defects at the initial presentation.

Keywords Keratitis · Bacterial keratitis · Fungal keratitis · Infection · Cornea

Introduction

Microbial keratitis remains a serious cause of corneal opacity and vision loss worldwide [1–3]. The infection rarely occurs in the normal eye due to the human cornea's natural resistance to infection. However, predisposing factors such as preexisting corneal disease, contact lens wear, ocular surface disease, and trauma may change the defence mechanisms of

the ocular surface and permit entry of pathogens. Predisposing risk factors vary from one geographic region to another [3–5]. Recent data on microbial keratitis in Sydney, Australia, is lacking [6].

Epidemiological studies provide vital information to clinicians about patterns of keratitis. Identifying the risk factors and clinical features associated with the causative organism can assist with diagnosis and management. One of the main reasons for delayed initiation of the correct treatment is the difficulty distinguishing between bacterial, fungal, and polymicrobial infections. Studies have identified satellite lesions and a raised surface to be associated with fungal keratitis [4, 7] and larger sized corneal infiltrate to be associated with polymicrobial keratitis [8]. Clinical features may assist in discriminating the causative organism.

Knowledge of the patterns of causative organisms and their antibiotic sensitivities and resistance is vital for clinicians who treat keratitis empirically [9]. To date, there have been no studies showing the seasonal variations of the causative organisms of microbial keratitis within New South Wales (NSW), Australia. Because accurate diagnosis and early

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treatment are important for patient outcomes, determining local epidemiologic patterns is critical to preventing, diagnosing, and treating microbial keratitis. They also add to worldwide knowledge on keratitis epidemiology and treatment.

This retrospective study aimed to provide recent data on patient demographics, risk factors, and clinical outcomes of patients with microbial keratitis over a 5-year period. Furthermore, the study aimed to identify seasonal variations of the main causative organism of the disease at the Sydney Eye Hospital.

Methods

A retrospective case-series study over a 5-year period (2012–2016) was conducted at the Sydney Eye Hospital, Sydney, Australia, a quaternary referral unit for eye diseases. The Sydney Eye Hospital is the major public hospital in Sydney and also serves the rural area of NSW. Patients were identified from the International Classification of Disease (ICD-10) codes: corneal ulcer (H16.0), other superficial keratitis without conjunctivitis (H16.1), keratoconjunctivitis (H16.2), interstitial and deep keratitis (H16.3), other keratitis (H16.8) and keratitis, unspecified (H16.9), and pathology databases. Patients were included if they had a clinical diagnosis of microbial keratitis, corneal scrape procedure performed, were 18 years old or over, and presented to the Sydney Eye Hospital between 1 January 2012 and 31 December 2016. The study adhered to the tenets of Declaration of Helsinki and was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee (HREC ref 14/282). Data were reported in line with the STROBE statement for observational data [10].

Definition of microbial keratitis

The identification of microbial keratitis was based on the patient's medical history and clinical signs at the initial presentation at Sydney Eye Hospital. Furthermore, all suspected infectious corneal ulcers were scraped to obtain samples for microbial culture and antimicrobial sensitivity analysis. Each separate episode of keratitis a patient had during the study period was counted as an individual case.

Data collected

Medical records were reviewed, and the following data were collected: socio-demographic information, clinical presentation, pathology, management, and outcomes. Study data were collected and managed using REDCap (Research Electronic Data capture, Nashville, TN, USA) hosted at The University of Sydney.

Ocular and systemic history such as risk factors for infection, and initial clinical features at presentation such as the size of the epithelial defect and infiltrate, hypopyon, satellite lesions, and/or corneal thinning were also included. Lesion size (i.e., epithelial defect and infiltrate size) were defined as the geometric area (mm^2), i.e., the longest diameter of the epithelial defect and infiltrate, and its perpendicular diameter.

Outcome data collected at the final visit (date of healing), visual acuity (VA), surgery performed, and ocular complications were also collected. VA was measured, recorded, and converted from Snellen to logarithm of the minimum angle of resolution (logMAR). The following logMAR values were allocated for non-numeric visual acuities: counting finger 1.7 logMAR, hand movement 2.0 logMAR, light perception 2.3 logMAR, and no light perception 3.0 logMAR [11].

Patient's clinical outcomes were classified as follows: (1) good clinical outcome—final VA of 6/12 or better, and no complications or surgical intervention and no decrease in VA during treatment; (2) moderate outcome—final VA 6/15–6/60, and no complications or surgical intervention, and no decrease in VA during treatment; (3) poor outcome—final VA worse than 6/60, or decrease in VA during treatment (1 line or worse) or complication of infection (perforation or endophthalmitis), or requiring surgical intervention (penetrating keratoplasty, enucleation, or evisceration) [12]. Missing or unavailable data were not included in the data analysis.

Microbiology

Corneal scrapes were taken in accord with local protocols from patients who had a clinical diagnosis of keratitis at presentation to the Sydney Eye Hospital [13]. Briefly, samples were collected using sterile surgical blades or disposables needles. Superficial corneal samples were directly inoculated onto two glass slides for microscopy and culture media (two blood agars, chocolate agar, Sabouraud's agar slope, and cooked meat medium) in the clinic. Corneal swabs are also taken for polymerase chain reaction testing for detection of herpes simplex virus and Acanthamoeba DNA. Samples were then delivered to New South Wales Health Pathology (NSWHP).

Corneal biopsies were also included in our study. The indication and protocol for corneal biopsies were previously described by Robaei et al. [14]. Briefly, a lamellar corneal biopsy was taken using a dermal trephine or by freehand dissection. The specimen was then divided into two halves, for histopathological and microbiological analysis. Patients with a positive corneal scrape and positive corneal biopsy were classified based on results (e.g., if a patient had a positive *Staphylococcus aureus* corneal scrape result and *Candida albicans* corneal biopsy result, they would be classified as polymicrobial infection). Patients with negative corneal scrape but positive corneal biopsy were classified based on corneal biopsy results.

Temperature

The day of the corneal scraping procedure was used to calculate the maximum temperature on the month of scraping. Average monthly maximum temperature data from January 2012 to December 2016 were obtained from historical data supplied by the Australian Bureau of Meteorology. Data were obtained from the weather station closest to the hospital (Sydney – Observatory Hill). The mean maximum temperature was calculated and compared between different groups of organisms.

Statistical analysis

Statistical analysis was performed by using SPSS software (version 24 for Mac, IBM, USA) and R (version 3.5.1 for PC, R Core Team, New Zealand). Socio-demographics and clinical features were compared between organism groups and statistical significance assessed using chi-square test for proportions and Kruskal-Wallis test for non-parametrically distributed variables (age, visual acuity, epithelial and infiltrate size, healing time). Post hoc tests were performed on data where statistical significance was shown. Multivariate logistic regression analyses were performed to assess risk factors associated with age and initial clinical features and risk factors associated with patient outcomes. Variables found to be significant (i.e., $p < 0.1$) in the univariate models were subsequently used as covariates in a multivariate ordinal logistic regression model. A Pearson and Deviance test was used to test the goodness-of-fit of the model. Statistical significance was defined as $p < 0.05$.

Results

Over the 5-year period, a total of 1052 cases from 979 patients were included. Forty-two of these patients had multiple episodes in the same eye during the 5-year study period, 12 had bilateral infections, and 12 had separate episodes in the other eye during the study period. The microbiological results of the cases included have been reported by Cabrera-Aguas et al. [15]. Briefly, the majority of organisms isolated were bacteria (64%). Less frequent infections were polymicrobial (i.e., a combination of bacterial, fungal, and/or acanthamoebae) (2.4%) or fungi (2.3%) (Table 1) [15]. One patient had acanthamoeba only; however, their data were not included in individual group analysis. In 31%, no organisms were detected by the diagnostic procedures (culture-negative cases). The majority of polymicrobial cases were made up of bacterial and fungal organisms ($n = 19$). In total, 63 organisms (33 bacterial, 23 fungal, and 7 acanthamoeba) were isolated. The most common bacterial species isolated were *S. epidermidis* ($n = 14$), followed by *S. capitis* ($n = 5$). The most common fungal species isolated were *Candida* species ($n = 7$), followed by *Fusarium* species ($n = 5$). The main combination of

polymicrobial infection was *S. epidermidis* and *Candida* species ($n = 3$) and *S. epidermidis* and *Fusarium* species ($n = 3$).

The overall mean age and standard deviation of the included patients were 54.7 ± 21.5 years, of whom 52% were male. The majority of patients attending the Sydney Eye Hospital lived within greater Sydney (73%). There were significant differences between the groups (bacterial, fungal, polymicrobial and culture-negative) for age ($p < 0.001$, Kruskal-Wallis test) and admission to hospital ($p < 0.001$, chi-square test). Post hoc test analysis revealed that patients with culture-negative were significantly younger and less likely to be admitted to hospital ($p < 0.05$) than patients with bacterial, fungal and polymicrobial infections.

Risk factors

Predisposing factors for microbial keratitis were documented in 908 (86%) cases in 848 patients. Multiple potential predisposing factors were evident in 404 (45%) cases, a single predisposing factor in 504 (48%) cases, and no obvious predisposing factor in 144 (14%) cases. Contact lens wear (393, 63%), previous topical steroid use (253, 24%), and history of ocular surface disease (189, 18%) were commonly observed. A significant difference between the groups was seen with the following risk factors: use of topical steroids prior to presentation ($p = 0.025$), a history of a corneal transplant ($p < 0.001$), or ocular trauma ($p = 0.01$) (Table 2).

Additional analysis showed prior topical steroid use to be associated with fungal and polymicrobial keratitis ($p < 0.05$) compared to bacterial and culture-negative keratitis. Patients with a history of corneal transplantation were more likely to have a bacterial, fungal or polymicrobial infection ($p < 0.05$), and ocular trauma was significantly associated with fungal and polymicrobial ($p < 0.05$).

Multivariate regression analysis showed that increased in age was significantly associated with the following risk factors: history of corneal transplant (OR 2.1, 95% CI 1.1–4.2, $p = 0.025$), previous ocular surgery within in the last 3 months prior to presentation to hospital (OR 2.4, 95% CI 1.1–5.6, $p = 0.032$), diabetes mellitus (OR 6.1, 95% CI 3.0–12.1, $p < 0.001$), and rheumatoid arthritis (OR 4.8, 95% CI 1.4–15.9, $p = 0.011$). The risk of contact lens wear as a predisposing factor decreased with age (OR 0.29, 95% CI 0.20–0.42, $p < 0.001$). A Pearson and Deviance goodness-of-fit test showed that the multivariate model was a good fit to the data ($p = 0.227$, $p = 0.144$, respectively).

Contact lens-related keratitis was mainly associated with regularly replaced lenses (e.g., weekly, fortnightly or monthly lenses) ($n = 220$, 56%), daily-disposable contact lenses ($n = 69$, 18%) and rigid gas permeable lenses ($n = 14$, 4%). Water sport-related activities (e.g. swimming or rowing) ($n = 85$, 22%), showering with lenses ($n = 74$, 19%) and sleeping with lenses ($n = 17%$) were the most common contact lens-related risk factors.

Table 1 Demographics of patients with bacterial, fungal, polymicrobial, and culture-negative keratitis. Patients with fungal and polymicrobial keratitis were older and more likely to be admitted to hospital

	All microbial keratitis <i>n</i> = 1052	Bacterial <i>n</i> = 677	Fungal <i>n</i> = 24	Polymicrobial <i>n</i> = 25	No organism <i>n</i> = 325	<i>p</i>
Socio-demographics						
Age, mean years (SD)	54.7 (22)	56.7 (22)	63.5 (20)	63 (21)	49.5 (21)	< 0.001
Gender, male (%)	544 (52)	344 (51)	16 (67)	11 (44)	173 (53)	0.452
Residence, <i>n</i> (%)						
Within greater Sydney	772 (73)	486 (72)	14 (58)	21 (84)	251 (77)	0.176
Outside greater Sydney (within NSW)	237 (23)	160 (24)	9 (38)	3 (12)	64 (20)	
Interstate	19 (2)	14 (14)	1 (4)	1 (4)	3 (1)	
Overseas	24 (2)	17 (17)	0	0	7 (2)	
Admitted (%)	714 (68)	496 (73)	22 (92)	22 (88)	173 (53)	< 0.001

Socio-demographic and residence data are presented by number of patients (*n* = 979). Admitted data are presented by number of cases (*n* = 1052) *n* number of cases, *SD* standard deviation

Initial clinical features

The median symptom duration before presentation to the hospital was 3 days (IQR 2–7 days). The median overall initial VA in the affected eye was 0.9 (IQR 0.3–2). Post hoc analysis found that patients with fungal and polymicrobial keratitis had worse VA than those with bacterial and culture-negative keratitis ($p < 0.05$), and bacterial keratitis had worse VA than culture-negative keratitis ($p < 0.001$). Significant larger epithelial defects and the presence of a hypopyon were seen in bacterial, fungal, and polymicrobial keratitis compared to culture-negative keratitis ($p < 0.05$). A higher proportion of fungal and polymicrobial infections had corneal thinning compared to bacterial and culture-negative ($p < 0.005$) (Table 3).

Patient outcomes

At the final visit, the overall median VA was 0.3 (IQR 0–1.2) and 62% of epithelial defects had healed in a median healing time of 10 days (IQR 5–22 days). The median days of hospital admission were 8 days (IQR: 5–13 days) (Table 3). On post hoc analysis, bacterial, fungal, and polymicrobial keratitis had significantly worse final VA compared to culture-negative infections ($p < 0.05$). Longer healing time and days of admission were found in fungal and polymicrobial keratitis compared to bacterial and culture-negative keratitis ($p < 0.05$) (Table 3). Of the eyes with known outcomes (*n* = 720) at final follow up, 39% of eyes had a good, 15% had a moderate, and 48% had a poor outcome. A poor outcome was observed more in fungal and polymicrobial keratitis (Table 4).

Table 2 Predisposing risk factors of cases (*n* = 908) with bacterial, fungal, polymicrobial and culture negative keratitis. Contact lens wear and previous topical steroid use was the most common risk factors

History	All microbial keratitis	Bacterial	Fungal	Polymicrobial	No organism	<i>p</i>
Contact lens wear (last 1 month) [†]	393 (63)	246 (64)	5 (28)	6 (46)	135 (67)	0.823
Previous topical steroid use	253 (24)	182 (27)	11 (46)	12 (48)	48 (15)	0.025
Ocular surface disease	189 (18)	117 (17)	6 (25)	7 (28)	60 (19)	0.555
Corneal transplant	148 (14)	112 (17)	6 (25)	7 (28)	23 (7)	< 0.001
Ocular trauma	124 (12)	66 (10)	6 (25)	5 (20)	47 (15)	0.01
Previous keratitis	111 (11)	80 (12)	3 (13)	3 (12)	25 (8)	0.068
Diabetes mellitus	109 (10)	79 (12)	2 (8)	5 (20)	23 (7)	0.043
Previous ocular surgery (last 3 months)	89 (9)	64 (10)	5 (21)	4 (16)	16 (5)	0.055
Lid malposition	63 (6)	44 (7)	2 (8)	0	17 (5)	0.345
Rheumatoid arthritis	29 (3)	22 (3)	0	0	7 (2)	0.122

Note: Results are shown as number of cases (percentage). % does not add to 100%, as 404 cases had > 1 risk factor

[†] Percentages only include cases where data were available

Table 3 Clinical features at initial and final visit and patient outcomes in bacterial, fungal, polymicrobial, and culture-negative at presentation. Patients with fungal or polymicrobial keratitis had worse clinical features at initial and final presentation

	All microbial keratitis	Bacterial	Fungal	Polymicrobial	No organism	<i>p</i>
Initial clinical features						
Symptoms duration before presentation to SEH, median (IQR)	3 (2–7)	3 (2–7)	7 (3.5–17)	7 (2–18.5)	3 (1–7)	0.63
VA logMAR, median (IQR)	0.9 (0.3–2)	1 (0.4–2)	2 (1–2.3)	1.3 (0.7–2)	0.5 (0.1–1.7)	<0.001
ED present (%)	859 (82)	555 (82)	20 (83)	22 (88)	262 (81)	0.787
ED size, median mm ² (IQR)	3.8 (1–10.5)	4 (1.2–12)	5.8 (1.8–25.5)	4.3 (2.6–12.2)	1.9 (0.8–7)	0.038
Infiltrate present (%)	787 (75)	497 (73)	19 (79)	17 (68)	250 (77)	0.177
Infiltrate size, median mm ² (IQR)	2 (1.5–5)	2.2 (1–6.4)	3.2 (1.5–8.8)	1.7 (1.4–19.6)	1.5 (0.6–3.4)	0.005
Satellite lesion present (%)	132 (13)	77 (11)	2 (8)	2 (8)	50 (15)	0.2
Hypopyon present (%)	218 (21)	160 (24)	9 (38)	8 (32)	41 (13)	<0.001
Corneal thinning present (%)	148 (14)	108 (16)	8 (33)	5 (20)	27 (8)	0.026
Corneal perforation (%)	38 (4)	26 (4)	2 (8)	2 (8)	8 (3)	0.505
Final clinical features						
VA logMAR, median (IQR)	0.3 (0–1.2)	0.5 (0.1–1.6)	1.5 (0.1–2)	1 (0.5–1.9)	0.2 (0–0.7)	<0.001
ED healed (%) ^{†,‡}	528 (62)	341 (61)	10 (50)	13 (59)	164 (63)	0.669
Scar present (%) [†]	371 (63)	235 (61)	7 (64)	5 (63)	124 (66)	0.733
Days of admission, median (IQR)	8 (5–13)	8 (5–12.2)	13 (8–20)	19 (11–36)	7 (4–10)	<0.001
Healing time, days, median (IQR)	10 (5–22)	11 (5–24)	28 (21–67)	30 (8–48)	7 (4–14)	<0.001

Six cases were excluded from VA data analysis as patients had no light perception at initial and final presentation

SEH Sydney Eye Hospital, VA visual acuity, ED epithelial defect, IQR interquartile range

[†] Percentage only include cases where data were available

[‡] Percentages only include cases where condition was present at baseline

Good outcomes were reported in 279 (39%) cases and poor outcomes in 336 (48%). The following variables were found to be significantly associated with patient outcomes in the univariate analysis: age ($p < 0.001$), duration of symptoms prior to presentation to hospital ($p < 0.001$), risk factors (i.e., all risk factors, except for history of ocular surface disease) ($p < 0.01$) VA at initial presentation ($p < 0.001$), epithelial defect and infiltrate size ($p < 0.001$), hypopyon ($p < 0.001$), and causative organism ($p < 0.001$) (Table 4). Post hoc test analysis revealed patients with recent contact lens wear or ocular trauma presented to the hospital significantly earlier than patients with previous steroid use ($p < 0.001$ and $p = 0.002$, respectively).

Multivariate ordinal logistic regression analysis showed that an increase in age was associated with a poor outcome, with an odds ratio of 1.5 times that of a younger patient ($p < 0.05$). Clinical features also significantly associated with poor outcome were poor initial VA (i.e., $\geq 6/60$) (OR 3.3, $p < 0.001$), epithelial defect size of $> 9.1 \text{ mm}^2$ (OR 4.2, $p = 0.001$) (Table 5). Gender, symptom duration prior to presentation to hospital, infiltrate size, hypopyon, and causative organism were tested in the multivariate analysis but were insignificant ($p > 0.5$). A Pearson and Deviance goodness-of-fit test showed that the multivariate model was a good fit to the data ($p = 0.827$, $p = 0.999$, respectively).

Complications

A total of 247 cases in 230 eyes (24%) had a complication, of that 58 cases had more than 1 complication. The most common complications across all groups were a non-healing epithelial defect (17%) and corneal thinning/perforations requiring bandage contact lens or glue (6%). A greater proportion of fungal and polymicrobial keratitis cases required corneal transplantation due to progressive infection compared to bacterial and culture-negative cases ($p < 0.001$). Other complications included endophthalmitis, and progressive infection requiring evisceration or enucleation (Table 6).

Frequency of microbial keratitis

The monthly frequency of microbial keratitis over a 5-year period is depicted in Fig. 1. There was a significant difference in the occurrence of culture-negative keratitis ($p = 0.023$) across the seasons, with a significant increase in frequency in autumn and winter compared to spring ($p = 0.004$, $p = 0.013$, respectively, note this data is not shown in Fig. 1). No significant difference was seen with bacterial, fungal or polymicrobial keratitis

Table 4 Demographics, risk factors, and clinical features associated with patient outcomes

	Total	Outcome, n (%)			p
		Good	Moderate	Poor	
Age					
18–49	345	195 (57)	51 (15)	99 (29)	< 0.001
50–69	176	68 (39)	35 (20)	73 (41)	
> 70	193	16 (8)	19 (10)	158 (82)	
Gender					
Female	342	119 (35)	52 (15)	171 (50)	0.074
Male	372	160 (43)	53 (14)	159 (43)	
Symptom duration prior to presentation					
≤ 48 h	255	116 (45)	41 (16)	98 (38)	< 0.001
3–7 days	232	100 (43)	38 (16)	94 (41)	
> 7 days	160	43 (27)	22 (14)	95 (59)	
Risk factors					
Contact lens wear (last 1 month)	280	144 (51)	52 (19)	84 (30)	< 0.001
Previous topical steroid use	167	28 (17)	16 (10)	123 (73)	< 0.001
Ocular surface disease	132	58 (44)	13 (10)	61 (46)	0.167
Corneal transplant	95	2 (2)	6 (6)	87 (92)	< 0.001
Ocular trauma	80	43 (54)	9 (11)	28 (35)	0.017
Previous keratitis	69	18 (26)	9 (13)	42 (61)	0.030
Diabetes mellitus	76	10 (13)	11 (14)	55 (72)	< 0.001
Previous ocular surgery (last 3 months)	57	4 (7)	9 (16)	44 (77)	< 0.001
Lid malposition	41	5 (12)	9 (22)	27 (66)	0.001
Rheumatoid arthritis	20	2 (10)	6 (30)	12 (60)	
Initial VA					
Good (> 6/12)	222	159 (72)	2 (1)	61 (27)	< 0.001
Average (6/15–6/48)	158	85 (54)	38 (24)	35 (22)	
Poor (≥ 6/60)	309	30 (10)	62 (20)	21 (70)	
ED size (mm²)					
≤ 9	304	143 (47)	46 (15)	115 (38)	< 0.001
9.1–16	46	5 (11)	7 (15)	38 (83)	
> 16	115	5 (4)	12 (10)	52 (45)	
Infiltrate size (mm²)					
≤ 9	261	138 (53)	35 (13)	88 (34)	< 0.001
9.1–16	13	4 (31)	3 (23)	6 (46)	
> 16	25	0	5 (20)	20 (80)	
Hypopyon					
Present	143	21 (15)	27 (19)	95 (66)	< 0.001
Absent	571	258 (45)	78 (14)	235 (41)	
Organism					
Bacterial	451	154 (34)	66 (15)	231 (51)	< 0.001
Fungal	19	5 (26)	2 (11)	12 (63)	
Polymicrobial	21	3 (14)	3 (14)	15 (71)	
Culture negative	222	117 (53)	33 (15)	72 (32)	

Three hundred thirty-two cases had unknown outcomes due to missing data; 6 cases were excluded from analysis as they had no light perception at initial and final visit

VA visual acuity, ED epithelial defect

across the four seasons. The months with the highest occurrence of keratitis in each year were March, May, July, and September.

As reported previously [15], the most common causative organisms were Coagulase-negative Staphylococcus (CoNS) and *Pseudomonas aeruginosa*. There was no significant difference in

Table 5 Multivariate logistic regression analyses of factors associated with poor patient outcome. Older patients with poor VA and larger epithelial defect at initial presentation are more likely to have poorer outcomes

	Odds ratio of poor outcome	Ordinal logistic regression 95% confidence interval	<i>p</i>
Age			
> 70	4.035	2.315–7.032	< 0.001
50–69	1.451	0.945–2.228	0.089
18–49	Reference		
Initial VA			
Poor ($\geq 6/60$)	3.303	2.039–5.351	< 0.001
Average (6/15–6/48)	0.583	0.536–1.359	0.504
Good (> 6/12)	Reference		
ED			
> 16	2.499	1.153–5.414	0.02
9.1–16	4.221	1.790–9.955	0.001
≤ 9	Reference		
Risk factor			
Previous steroid use	2.068	1.280–3.341	0.003
Previous corneal transplant	6.659	2.659–15.331	< 0.001

the frequency of CoNS across all four seasons ($p = 0.255$); however, a seasonal variation was observed for *P. aeruginosa*, with an increase in occurrence during summer (December to February) and autumn (March to May) seasons ($p = 0.018$). The frequency of fungal keratitis (specifically *Candida* and *Fusarium* species) during the study period exhibited a peak during spring (September to November) and summer (December to February) ($p = 0.056$) (Fig. 2).

Discussion

This study reports the predisposing factors, clinical features, and temperature trends of a large series of microbial keratitis over a 5-year period from a quaternary eye care centre in Australia. Our

study showed that poor outcomes were significantly associated with older patients, poor VA and large epithelial defects at the initial presentation, and previous topical steroid use and/or history of a corneal transplant. There was a peak in the occurrence of *P. aeruginosa* and fungal keratitis in the hottest seasons.

Over the 5 years, contact lens wear and prior use of topical steroids were the most common predisposing factors. Our study identified bacterial and culture-negative keratitis to be the most common infection type associated with contact lens-related keratitis. Existing studies have shown similar results [2, 5, 16]. The multivariate analysis showed that the risk of contact lens-related keratitis decreased with age. It was more common in the 18–49 year age group. Similar results have been seen in Queensland [5] and Melbourne [2]. The rate of contact lens-related keratitis in our study was 63%, which was

Table 6 Number of complications ($n = 247$) and their management in eyes ($n = 230$) with bacterial, fungal, polymicrobial, and culture-negative keratitis. Patients with fungal or polymicrobial infection more likely required a corneal transplant due to progressive infection

Complications	All microbial keratitis	Bacterial	Fungal	Polymicrobial	No organism	<i>p</i>
Corneal thinning/perforations:						
Requiring BCL or glue	63 (6)	48 (7)	2 (8)	4 (16)	9 (3)	0.999
Requiring transplant or graft	29 (4)	28 (4)	2 (8)	3 (12)	6 (2)	0.356
Non-healing/slow-healing ED ^{†,‡}	142 (17)	104 (19)	7 (35)	4 (18)	27 (10)	0.615
Progressive infection:						
Requiring transplant or graft	30 (3)	15 (2)	5 (21) *	7 (28) *	3 (1)	0.037
Requiring evisceration or enucleation	34 (3)	25 (4)	2 (8)	1 (4)	6 (2)	0.186
Endophthalmitis	20 (2)	18 (3)	0	0	2 (1)	0.971

BCL bandage contact lens, ED epithelial defect. Note: Results are shown as number of cases (percentage).

* Statistical significance ($p < 0.05$) from post hoc test comparing bacterial fungal, polymicrobial, and culture-negative keratitis

[†] Percentage only include cases where data were available

[‡] Percentages only include cases where condition was present at baseline

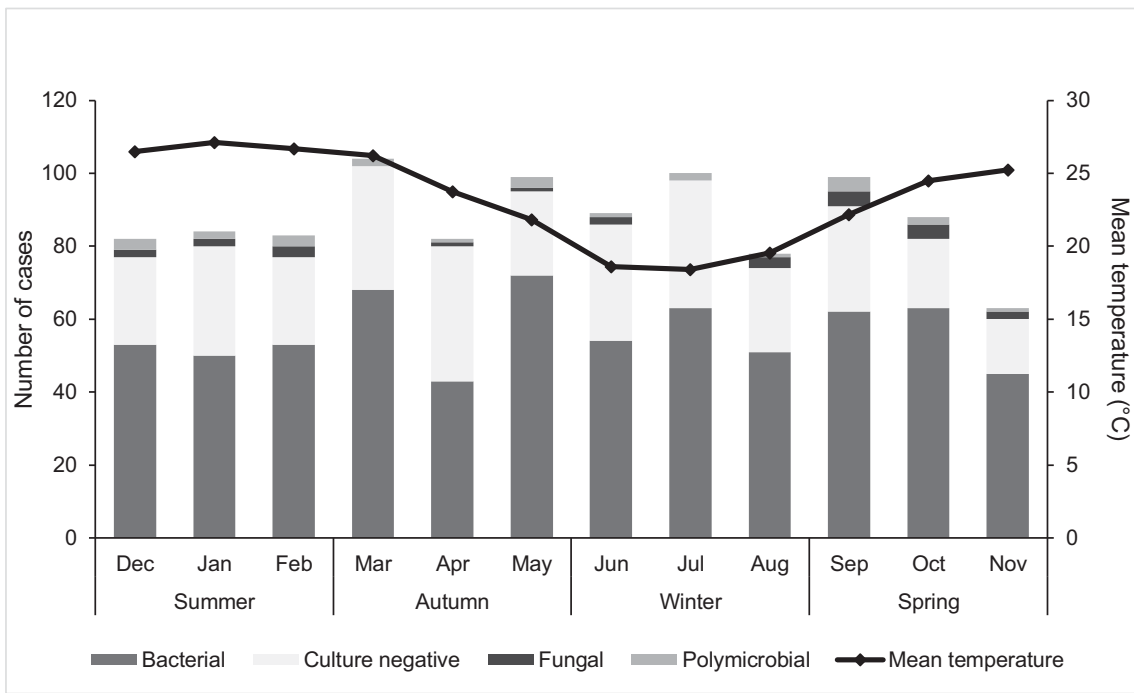


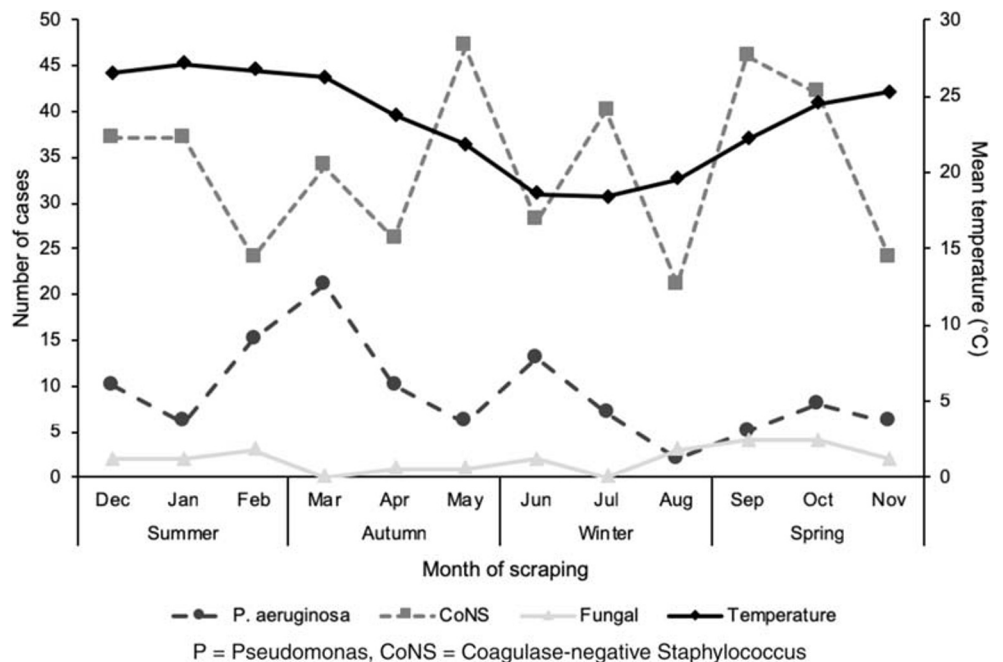
Fig. 1 Monthly frequency of bacterial, fungal, polymicrobial, and culture-negative keratitis and mean temperature over 5 years

higher than other studies (22–35%) [2, 6, 17]. The disparity is most likely due to differences in the documentation of contact lens use. Contact lens wear was documented as “yes” or “no” in 622 cases and ‘not recorded’ in 430 cases (41%). If all ‘not recorded’ cases were considered not to have worn contact lenses, then overall 37% of our cases would have been contact lens-related keratitis, which is similar to other studies. In our study, only cases which specifically documented the use of contact lenses were included in the data analyses comparing

pathology and clinical outcomes of contact lens wear (i.e., Tables 2 and 4). Nevertheless, contact lens-related keratitis should be considered in younger cohorts.

Prior use of topical steroids is a known risk factor for developing infectious ulcers, specifically *Pseudomonas* species and fungus [18, 19]. Our study found previous topical steroid use was the most common risk factor for fungal and polymicrobial cases and associated with poor patient outcome. Topical steroids are widely used in every subspecialty

Fig. 2 Monthly frequency of *Pseudomonas aeruginosa*, Coagulase-negative Staphylococcus, and fungal species and mean temperature over 5 years



field of ophthalmology to suppress inflammation and reduce scarring [20] including external eye disease (i.e., blepharoconjunctivitis and allergic eye disease), postoperative intraocular surgery (e.g., cataract surgery), herpetic eye diseases, and anterior uveitis [21, 22]. The prolonged use of steroid decreases the efficacy of the local immune response, increasing patient's susceptibility to infection [23]. This is a possible explanation for prior use of topical steroid as a risk factor for microbial keratitis. Steroids suppress immunologic defence mechanisms and inflammatory reactions as well as increase the risk of glaucoma and cataract formation, they can also mask the severity of the infection [24]. Additionally, studies have suggested eyedropper tip contamination as a possible source of pathogenic bacteria [25]. Schein et al. have suggested that topical medication may provide a reservoir for contamination and a potential source of infection [26].

In our study, the patient outcomes are similar to that of other studies, with poor outcomes significantly associated with older age [17, 19], poor VA at presentation [4, 17], and large epithelial defects [4]. Our study further showed contact lens wearers and patients with ocular trauma were more likely to have a good outcome compared to patients with previous steroid use. This is possibly due to age and presentation to hospital, as in our study, patients with a history of contact lens wear or ocular trauma were younger (age ranging from 18 to 59 years) than patients with previous steroid use (age ranging from 20 to 97) and presented to the hospital earlier. Although existing studies reporting keratitis outcomes have had different definitions of poor outcome, similar results were seen. A plausible explanation for poorer outcomes in older patients is the human body's immune system declines with age, making it more susceptible to infectious agents [27].

Several studies have shown fungal and polymicrobial keratitis cases to have poor patient outcomes despite the availability of effective treatment [4, 8]. Additionally, studies have shown antifungals are not as effective as antibacterial due to poor tissue penetration [28, 29]. Our study showed patients with fungal and polymicrobial keratitis had symptoms for longer prior to their presentation to our institution compared to bacterial and culture negative keratitis. Clinical diagnosis of fungal and polymicrobial keratitis can be problematic especially when there is a delay in presentation or multiple medications administered prior to presentation to the hospital. This can lead to a delay in laboratory confirmation and initiation of antifungal treatment. Statistical analysis did not identify fungal or polymicrobial infections to be associated with poor outcomes or symptom duration before presentation to the Sydney Eye Hospital to be significant. This is most likely due to the small sample size of these groups. However, an

index of suspicion of fungal and/or polymicrobial keratitis should be taken in patients with a hypopyon and corneal thinning at initial presentation.

Our study also found an increase in age to be significantly associated with a history of a corneal transplant and previous ocular surgery. Several retrospective studies have shown similar results [5, 30]. The incidence of microbial keratitis after a corneal transplantation range from 1.8 to 4.9% [31, 32]. Microbial keratitis caused by a history of corneal transplantation or ocular surgery is possibly due to suture-related issues, topical steroid use, graft failure and graft denervation. Prevention of the infection may be improved by regular clinical check-ups, removal of sutures prior to degradation or loosening, controlled topical steroid use and patient education regarding the risks and signs of keratitis [33]. This should be especially observed in older patients.

In our study, culture-negative keratitis had less severe infection than bacterial, fungal and polymicrobial keratitis. These patients had significantly smaller ulcers, better VA at initial and final presentation, and shorter healing time. Our results differ to existing studies [4, 34], which found culture-negative keratitis to have worse VA at the initial presentation and larger ulcer size. However, the patients included in those studies do not represent the spectrum of disease in Sydney, as they were based in India. Our study showed culture-negative keratitis in Sydney to have better outcomes; however, caution should be taken when treating these patients.

Infectious keratitis exists in all geographic regions of the world [35] and knowledge of the pathogenic patterns of the infections is important for clinicians who treat keratitis empirically. The study identified several seasonal trends in microbial keratitis in the NSW, Australian population. Increase in the occurrence for fungal keratitis was observed from September to February corresponding with the warmer seasons (spring and summer) in NSW, Australia. It is likely the increase in the occurrence of fungal keratitis specifically *Candida* and *Fusarium* species during spring and summer seasons could accompany seasonal fluctuations in agriculture.

In contrast, bacterial keratitis did not follow a statistically significant seasonal pattern except for *P. aeruginosa* keratitis. A higher rate of isolation of *Pseudomonas aeruginosa* was seen from December to March, which is Australia's dry season. Similar results have been seen in other studies conducted in Australia [12, 36, 37]. Existing literature has suggested higher temperatures are associated with bacterial and fungal keratitis [2, 12]. A study in the Netherlands investigated whether an outbreak of acute otitis externa (inflammation of the ear canal) was correlated with exposure to *P. aeruginosa* in a freshwater lake [38]. They confirmed that the predominance of *P. aeruginosa*

during the summer months was associated with increased exposure to the pathogen in contaminated water. During the warmer season, clinicians should consider fungi and/or *Pseudomonas* species (especially in contact lens wearers) as the possible causative organisms in microbial keratitis.

The pattern of keratitis in our study is a representation of patients that present to a large quaternary hospital; therefore, differences may exist between this case series and keratitis in the general population. Our data may show an overrepresentation of severe cases due to the referral services and surgical facilities at the hospital. Referrals to corneal specialists would increase the presentation of severe keratitis and active surgical facilities can increase admission of keratitis related to ocular surgery. However, as the main eye hospital in NSW, cases would include a greater rural population than other institutions. Our data is also slightly skewed to older patients, as the hospital does not have a paediatric facility. The retrospective nature of this study may also show an overestimation of risk factors as 45% of cases had more than one risk factor. Nevertheless, our findings highlight the main risk factors associated with poor patient outcomes and the seasonal variations of organisms within NSW, Australia.

The responsibility for communication of medical information of patients' must be shared amongst clinicians providing care. There is a risk that as this information is passed between clinicians, it can be altered or misinterpreted [39]. Our study identified substantial gaps in clinical documentation, such as a history of contact lens wear, systemic diseases and medications and ocular conditions. Our recommendation for clinicians is to provide comprehensive clinical documentation of the patient's medical history as this can improve patient outcomes by allowing a full understanding of potential risk factors and clinical findings.

In summary, our study demonstrates that older patients and those presenting with poor VA and large epithelial defect at initial presentation are more likely to have poor outcomes. Seasonal variations occurred with fungus (specifically *Candida* and *Fusarium* species) and *Pseudomonas* species, with an increase in frequency in the hottest seasons. Overall, the spectrum of microbial keratitis varied with geographical location and was influenced by local climate and risk factors. Knowledge of the factors associated with microbial keratitis can aid the successful prevention, diagnosis, and management of the disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Participant consent was not required due to the retrospective nature of the study. This was approved via our ethics committee (i.e., South Eastern Sydney Local Health District, Australia).

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