# Microbial Keratitis in Taiwan: A 20-Year Update

HSIN-YU LIU, HSIAO-SANG CHU, I-JONG WANG, WEI-LI CHEN, AND FUNG-RONG HU

• PURPOSE: To investigate the demographics, risk factors, microbiology, and resistance pattern at a tertiary hospital and to detect the shifting trend over 2 decades.
• DESIGN: A retrospective observational case series.
• METHODS: We reviewed all records of patients with microbial keratitis (MK) that were hospitalized in National Taiwan University Hospital between 2007 and 2016. Demographics, predisposing factors, pathogens, and clinical courses were compared to our previous study conducted from 1992 to 2001. Antibiotic susceptibility was compared with those conducted from 1994 to 2005.
• RESULTS: The percentage of patients 60 years and older in the MK population was increasing ($P = 2.1E-21$). The proportion of trauma-related MK declined while MK related to chronic ocular or systemic disorders rose. The prevalence of nontuberculous mycobacteria (NTM) showed a decreasing trend ($P = .0032$), whereas *Microsporidia* has been increasingly detected. The 2 most common bacterial isolates were *Pseudomonas aeruginosa* (35.2%) and *Staphylococcus* species (13.2%). Management of these infection did not differ in common pathogens between the 2 decades. The susceptibility of *Staphylococcus* species to oxacillin reduced significantly ($P = .002$) and there was an increase in methicillin-resistant *Staphylococcus aureus* keratitis.
• CONCLUSIONS: Contact lens wear remained the most common predisposing factor, with *Pseudomonas* species as the major pathogen. However, chronic disorder–related MK was on the rise along with an increasing trend of oxacillin resistance in *Staphylococcus* species. We found a decreasing trend in NTM keratitis while *Microsporidia* keratitis was considered as an emerging ocular disease. Though gram-negative isolates remained susceptible to all antibiotics tested, antibiotic resistance was more common in gram-positive isolates. (Am J Ophthalmol 2019;205:74–81. © 2019 Published by Elsevier Inc.)

MICROBIAL KERATITIS IS A SIGNIFICANT CAUSE OF ocular morbidity worldwide. Timely selection of an initial antibacterial therapy is important for treatment outcomes. Before there is any laboratory evidence of microbial infection, clinicians can only choose an empiric antibiotic regimen based on clinical findings and the antimicrobial susceptibility data against regional microbiograms. With the ever-changing microbial spectrum and resistance pattern, it is vital for clinicians to be updated with the regional microbiology and antibiotic susceptibility. The purposes of our study were to investigate the demographics and spectrum of pathogens in the recent decade, and to detect the shifting trends in predisposing factors and resistance pattern as a continuation of our previous studies conducted from 1992 to 2001[1] and 1994 to 2005.[2]

## METHODS

THE STUDY CONFORMED TO THE PROVISIONS OF THE DECLARation of Helsinki and was approved by the Institutional Research Ethics Board of National Taiwan University Hospital (IRB number: 201610028RINB). We reviewed the medical records of hospitalized patients with clinically diagnosed microbial keratitis between 2007 and 2016. The following noninfectious corneal diseases were excluded: superficial injury of cornea, open wound of eyeball, corneal opacity, and cases of viral keratitis. Patient demographics, predisposing factors, isolated pathogens, antibiotic resistance, and clinical course were collected.

Corneal scrapings were obtained using a disposable number 15 scalpel blade while culture specimens were collected by a swab with an all-in-one collection and transport system (Culturette; Becton Dickinson and Co, Cockeysville, Maryland, USA). Specimens of scraping smear and culture were collected and sent to the clinical microbiology laboratory at National Taiwan University Hospital. The scrapings for smears were routinely processed for Gram stain, acid-fast stain, and potassium hydroxide test. Selective media were used for cases suggestive of anaerobic bacteria, *Mycobacteria*, *Acanthamoeba*, and other pathogens. A culture was considered positive if any of the following growth characteristics was noted: growth of the same organism on 2 or more media; confluence at the site of inoculation on 1 solid medium; growth on media consistent with scraping smear; or the same microorganism on repeat corneal-scraping cultures. In vitro susceptibility was obtained with Vitek 2 (bioMérieux Inc, Durham, North Carolina, USA) and interpretations were made based on the National Committee for Clinical Laboratory Standards.

There were no standards for topical antibiotics in ocular tissues. Serum standards were used to interpret susceptibility,

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based on the assumption that the antibiotic concentrations in ocular tissues, by topical instillation, were at least equal to the levels of antibiotics in the serum. Isolates of intermediate sensitivity were categorized as susceptible organisms, since frequent instillation of fortified antibiotics may yield a higher antibiotic concentration in the corneal stroma than detected in the serum after systemic administration. Besides, our study was a continuation of our previous study from 1994 to 2005; therefore, the same categorization was applied for subsequent trend analysis in the 2 studies. Susceptibility testing of bacterial isolates was performed selectively with cephalosporins (ceftazidime and cefepime), aminoglycosides (gentamicin and amikacin), fluoroquinolones (levofloxacin and ciprofloxacin), oxacillin, piperacillin, vancomycin, teicoplanin, clindamycin, trimethoprim/sulfamethoxazole (TMP/SMX), and fusidic acid. The 2 most frequently isolated bacterial categories, *Pseudomonas* species and *Staphylococcus* species, were further analyzed for antibiotic susceptibility.

We have previously reported the clinical characteristics of microbial keratitis from 1992 to 2001[1] and antibiotic susceptibility of bacterial keratitis from 1994 to 2005,[2] respectively. As a continuation of our previous studies, patient demographics, predisposing factors, isolated pathogens, and clinical courses were compared to our previous study conducted from 1992 to 2001; antibiotic susceptibility was compared with that conducted from 1994 to 2005. Predisposing factors were defined as described in the previous study[1] and were categorized into 4 subgroups: contact lens wear, trauma, chronic ocular and systemic disorders, and recent ocular surgery. Chronic ocular and systemic disorders included glaucoma, trichiasis, dry eyes, lagophthalmos, and systemic disorders with ocular involvement, such as diabetes, rheumatic arthritis, and atopic dermatitis. Recent ocular surgery was defined as surgical-related microbial keratitis that occurred within 3 months of ocular surgery.

For trend analysis, the data were grouped into 4 study periods, either from 1992 to 1996, 1997 to 2001, 2007 to 2011, and 2012 to 2016 or from 1994 to 1999, 2000 to 2005, 2007 to 2011, and 2012 to 2016. $\chi^2$ test or Fisher exact test were used for comparison and the Mantel-Haenszel linear-by-linear association $\chi^2$ test for trend analysis. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, North Carolina, USA). A $P$ value of .05 or less was considered statistically significant.

## RESULTS

• **DEMOGRAPHICS:** The demographic data are summarized in Table 1. From 2007 to 2016, a total of 370 eyes from 363 patients were identified. Seven cases had a simultaneous bilateral infection. Patients included 171 men (47.1%) and 192 women (52.9%), aged from 4 to 93 years (mean age 50.2 ± 23.3 years). The average age of the microbial keratitis population became older (40.7 ± 21.6 years in 1992-2001 vs 50.2 ± 23.3 in 2007-2016; $P$ =3.5E-9). The age distribution in comparison with previous data from 1992 to 1996 and from 1997 to 2001 is depicted in the Figure. There was a growing trend for percentage of patients over 60 years old in the population of microbial keratitis ($P$ = 2.1E-21). No significant differences in sex and eye involvement were demonstrated from between-decades comparisons ($P$ = .22 and $P$ = .06, respectively).

• **PREDISPOSING FACTORS:** In comparison with our previous study,[1] there was a decreasing trend in trauma-related microbial keratitis ($P$ = .0182) and an increasing trend in chronic ocular and systemic disorder–related keratitis ($P$ = .0248), as shown in Table 2. In 2007-2016, predisposing factors were identified in 277 eyes (277 of 370 eyes, 74.9%). Contact lens wear remained the most common predisposing factor (35.7%). Chronic disorder–related microbial keratitis accounted for 6.7% of patients aged less than 60 years while it was 23.7% among those aged 60 years or older. Pathogens were identified in 56 cases associated with contact lens wearing, with *Pseudomonas* species making up 46.4% (n = 26), followed by *Staphylococcus* species (12.5%, n = 7) and *Acanthamoeba* species (10.7%, n = 6). Among all trauma-related cases, pathogens were identified in 28 cases, including 10 cases of *Pseudomonas* species (35.7%), followed by fungi (25.1%, n = 7). In addition, *Staphylococcus* species were the major pathogens (31.8%, n = 7) among the 22 cases that had chronic ocular or systemic disorders with identified pathogens. Among the 11 cases with *Serratia marcescens* keratitis, 6 were contact lens wearers, 4 had chronic ocular surface disorders, and 1 was associated with the use of topical medications.

• **PATHOGENS:** During 2007 and 2016, 187 positive results (51.0%) were reported from 367 cultures. Both scraping smear and culture were performed in 334 eyes, with consistent smear and culture results in 230 (68.9%) eyes, a percentage similar to that of the earlier study period (65.6%, $P$ = .409). From 2007 to 2016, gram-negative bacteria were the most commonly isolated pathogens, accounting for 103 isolates (47%), followed by 66 gram-positive bacteria (30.1%), 27 fungal isolates (12.3%), 9 nontuberculous *Mycobacteria* (NTM) (4.1%), 9 *Acanthamoeba* (4.1%), and 4 *Microsporidia* species (1.8%), as shown in Table 3. *Pseudomonas* species was the most commonly isolated gram-negative organism (35.2% of total), while *Staphylococcus* species (11% of total) were the most common gram-positive isolates. *Serratia* species was the second most common isolate of all gram-negative pathogens, with an increasing incidence. Comparing our previous study period of 1992-2001 with the current study period, we found a reduced proportion of NTM and an increased proportion of *Microsporidia* species in 2007-2016 ($P$ = .0032 and $P$ = .0008, respectively). There were no reported hospitalized cases of *Microsporidia* species during 1992-1996, 1997-2001, and 2007-2011, but there

**TABLE 1.** Demographics of Patients With Microbial Keratitis Between 2007 and 2016

| Characteristics | Result |
|---|---|
| Number of patients | 363 |
| Number of eyes | 370 |
| Laterality, n (%) | |
| Unilateral | 356 (98.1) |
| Bilateral | 7 (1.9) |
| Age (y) | |
| Mean ± SD (range) | 50.2 ± 23.3 (4-93) |
| <16 | 26 (7.2) |
| 16-30 | 68 (18.7) |
| 31-45 | 59 (16.3) |
| 46-60 | 71 (19.6) |
| >60 | 139 (38.3) |
| Sex | |
| Male | 171 (47.1) |
| Female | 192 (52.9) |

Results are n (%), unless indicated.

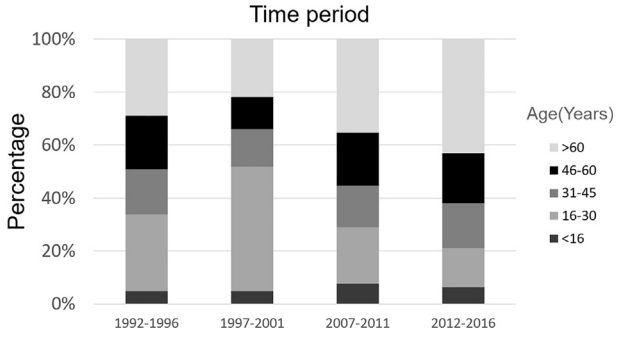


**FIGURE. Age distribution for patients with microbial keratitis from 1992-1996, 1997-2001, 2007-2011, and 2012-2016.**

were 4 cases during 2012-2016. As for fungal keratitis, the proportion of *Fusarium* keratitis among all microbial keratitis increased from 4.0% during 1992-2001 to 6.4% during 2007-2016, while the proportion of *Aspergillus* keratitis decreased from 2.0% during 1992-2001 to 0.5% during 2007-2016. The percentage of *Fusarium* keratitis showed a trend of increase during the 4 study periods ($P = .056$).

• **TREATMENT:** All patients in the present study were initially treated with antimicrobial therapy, while surgical interventions were only reserved for those who responded poorly to medication. Medical treatment was successful for 275 eyes (74.3%), while 95 eyes (25.7%) required additional surgical intervention. To understand if there was any difference in treatment response among different pathogens, we compared the proportion of medical and surgical management in microbial keratitis where only a single pathogen was identified between 1992 and 2001 and between 2007 and 2016. There was no difference detected in treatment options in the main causative agents of microbial keratitis between the 2 study decades, as demonstrated in Table 4. Response to medical treatment was sufficient in most common bacterial infections, for example, *Staphylococcus* species, *Streptococcus* species, and *Pseudomonas* species. In contrast, NTM and fungal keratitis had a relatively poorer response to medical treatment in the 2 study decades, so that over 60% of the cases required surgical intervention. Among those receiving surgical intervention, the proportion of cases requiring destructive surgery, which included evisceration and enucleation, was highest in fungal keratitis (Supplemental Table 1). Comparing the surgical treatment options for microbial keratitis during the 2 10-year study periods (1992-2001 and 2007-2016), the proportion of cases requiring destructive surgeries, which included evisceration and enucleation, was less in the latter period. Among those who receiving corneal surgery, which included lamellar keratectomy/corneal biopsy and therapeutic/tectonic keratoplasty, the proportion of therapeutic/tectonic keratoplasty decreased in the latter period (62.9% vs 52%) (Supplemental Table 2). No definite pathogen was identified in 13 (24.5%) patients receiving therapeutic/tectonic keratoplasty. For those requiring therapeutic/tectonic keratoplasty, *Pseudomonas* species was the most common isolated organism in bacterial keratitis, whereas *Candida* species was the leading pathogen for fungal keratitis.

• **ANTIBIOTIC SUSCEPTIBILITY PATTERN:** For gram-negative bacteria, more than 95% of the isolates during 2007 and 2016 were susceptible to ciprofloxacin, levofloxacin, and cefepime (97%, 97.8%, and 95.9%, respectively). Gentamicin and amikacin susceptibility of gram-negative bacteria were 92.7% and 92.8%, respectively. Both *Pseudomonas* species and *Serratia* species showed more than 95% susceptibility to aminoglycosides and fluoroquinolones in our study. For gram-positive bacteria, 97% of the isolates during 2007 and 2016 were susceptible to vancomycin, while oxacillin covered only 35.7% of the isolates in the same period. Compared with the previous study period of 1994 and 2005, there were no statistical differences detected in the susceptibility of the antibiotics against gram-negative and gram-positive bacteria between the 2 decades. The 2 most commonly identified categories of the bacterial isolates, *Pseudomonas* species and *Staphylococcus* species, were subjected to trend analysis for their antibiotic susceptibility by the study periods of 1994-1999, 2000-2005, 2007-2011, and 2007-2016 (Table 5). The antibiotics analyzed had no statistically significant trend throughout the 4 study periods for *Pseudomonas* species. However, *Staphylococcus* species showed a significantly increasing trend in the proportion resistant to oxacillin.

From 2007 to 2016, all isolated *Staphylococcus* species were 100% susceptible to vancomycin and teicoplanin (24 of 24). There was an increase in methicillin-resistant

**TABLE 2.** Predisposing Factors of Microbial Keratitis

| Predisposing Factors[a] | 1992-1996 N (%) | 1997-2001 N (%) | 2007-2011 N (%) | 2012-2016 N (%) | *P* Value[b] |
|---|---|---|---|---|---|
| Contact lens wear | 58 (32.6) | 134 (52.5) | 70 (35.5) | 50 (36.0) | .5449 |
| Trauma | 52 (29.2) | 51 (20.0) | 36 (18.3) | 26 (18.7) | .0182 |
| Chronic ocular and systemic disorder | 39 (21.9) | 41 (16.1) | 69 (35.0) | 34 (24.5) | .0248 |
| Recent ocular surgery | 29 (16.3) | 29 (11.4) | 22 (11.2) | 29 (20.9) | .3720 |

[a]One patient may carry more than 1 predisposing factor.
[b]*P* value calculated by the Mantel-Haenszel linear-by-linear association $\chi^2$ test.

**TABLE 3.** Prevalence of Pathogens Causing Microbial Keratitis During 1992-2001 and 2007-2016

| Organisms | 1992-2001 N (%) | 2007-2016 N (%) |
|---|---|---|
| Gram positive | 67 (26.6) | 66 (30.1) |
| *Staphylococcus aureus* | 10 (4.0) | 8 (3.7)[a] |
| *Staphylococcus epidermidis* | 5 (2.0) | 3 (1.4) |
| Other coagulase-negative *Staphylococci* | 6 (2.4) | 13 (5.9) |
| *Streptococcus pneumoniae* | 10 (1.0) | 5 (2.3) |
| Other *Streptococcus* spp. | 9 (3.6) | 7 (3.2) |
| *Propionibacterium spp.* | 16 (6.3) | 10 (4.6) |
| *Corynebacterium spp.* | 5 (2.0) | 12 (5.5) |
| Others | 6 (2.4) | 8 (3.7) |
| Gram negative | 120 (47.6) | 103 (47) |
| *Pseudomonas spp.* | 95 (37.7) | 77 (35.2) |
| *Serratia spp.* | 6 (2.4) | 10 (4.6) |
| *Burkholderia cepacia* | 6 (2.4) | 0 |
| *Acinetobacter spp.* | 3 (1.2) | 3 (1.4) |
| Others | 10 (4.0) | 13 (6.0) |
| Nontuberculous *Mycobacteria*[b] | 20 (7.9) | 9 (4.1) |
| Fungus | 34 (13.5) | 27 (12.3) |
| *Fusarium spp.* | 10 (4.0) | 14 (6.4) |
| *Aspergillus spp.* | 5 (2.0) | 1 (0.5) |
| *Candida spp.* | 10 (4.0) | 8 (3.7) |
| Others | 9 (3.6) | 4 (1.8) |
| *Microsporidia* spp.[b] | 0 (0) | 4 (1.8) |
| *Acanthamoeba* spp. | 11 (4.4) | 9 (4.1) |
| Unknown bacteria | 0 (0) | 1 (0.5) |
| Total | 252 (100) | 219 (100) |

N = number of eyes.
[a]Among the 8 cases of *Staphylococcus aureus*, 6 were methicillin-resistant strains.
[b]Represents a significant difference between the 2 decades ($P < .05$).

*Staphylococcus aureus* (MRSA) among *Staphylococcus aureus* keratitis from 1 in 2 cases during the 5-year period of 2007-2011 to 5 in 6 cases during 2012-2016 ($P = .02$). Compared with oxacillin-susceptible (OS) *Staphylococcus* species, oxacillin-resistant (OR) *Staphylococcus* species in the present study were generally less susceptible to other tested antibiotics, such as gentamicin (OR *Staphylococcus* species 50% vs OS *Staphylococcus* species 87.5%), ciprofloxacin (OR *Staphylococcus* species 75% vs OS *Staphylococcus* species 100%), levofloxacin (OR *Staphylococcus* species 75% vs OS *Staphylococcus* species 100%), and TMP/SMX (OR *Staphylococcus* species 85.7% vs OS *Staphylococcus* species 100%) (Supplemental Table 3). *Staphylococcus* species were further categorized into *Staphylococcus aureus* (SA) and coagulase-negative *Staphylococcus* (CNS). SA had a higher proportion of OR strains (7 of 8, 87.5%) compared to CNS (9 of 16, 56.3%). Six out of 7 of the OR SA and 5 of 7 OR CNS were community acquired.

It is to be noted that, since isolates of intermediate sensitivity were categorized as susceptible organisms in our study, the possibility of underestimating the resistance of the organisms should be considered. However, the number of isolates with intermediate sensitivity was negligible among all isolates.

## DISCUSSION

THIS STUDY UPDATED THE MICROBIOLOGY DATA AND PAtient demographics of microbial keratitis in Taiwan to establish reference information for clinicians. There was a slight female preponderance in our cases and the commonest risk factor documented was contact lens use, consistent with other domestic data.[3,4] This may be owing to a greater proportion of contact lens–associated keratitis composed of female patients, as previous studies suggested.[5,6] However, the absolute number of contact lens–related infectious keratitis was reduced during 2007-2016 compared with the prior study during 1992-2001. We postulate that the reduction of the absolute number of contact lens–related infectious keratitis may be due to an increasing popularity in using daily-disposable soft contact lens or the greater success in treating contact lens–related microbial keratitis with topical fluoroquinolone eye drops in local eye clinics, which made less necessity of referral. However, further studies are necessary to conclude such a causal association. It is to be noted that

**TABLE 4.** Treatment for Microbial Keratitis With Single Pathogen Identified[a]

| Organisms | Treatment | 1992-2001 N (%) | 2007-2016 N (%) | *P* Value |
|---|---|---|---|---|
| *Staphylococcus* spp. | Medical | 12 (80.0) | 12 (60.0) | .2814 |
| | Surgical[b] | 3 (20.0) | 8 (40.0) | |
| *Streptococcus* spp. | Medical | 14 (87.5) | 9 (75.0) | .6239 |
| | Surgical | 2 (12.5) | 3 (25.0) | |
| *Pseudomonas* spp. | Medical | 76 (84.4) | 58 (85.3) | .8829 |
| | Surgical | 14 (15.6) | 10 (14.7) | |
| Nontuberculous *Mycobacteria* | Medical | 3 (15.0) | 2 (33.3) | .5581 |
| | Surgical | 17 (85.0) | 4 (66.7) | |
| Fungi | Medical | 9 (29.0) | 10 (38.5) | .4519 |
| | Surgical | 22 (71.0) | 16 (61.5) | |
| *Acanthamoeba* | Medical | 5 (45.5) | 4 (57.1) | 1.0000 |
| | Surgical | 6 (54.5) | 3 (42.9) | |

N = number of eyes.

[a]All the cases with mixed infection were excluded.

[b]Surgical treatment includes lamellar keratectomy, penetrating keratoplasty, enucleation, and evisceration.

the frequency distribution of predisposing factors was different from Taiwan subgroup data reported in the Asia Cornea Society Infectious Keratitis Study (ACSIKS).[4] The data from our study and ACSIKS both demonstrated that contact lens wear was the most common risk factor. However, chronic ocular or systemic disorders was the second most common risk factor in our study, while chronic ocular or systemic disorders was the least common risk factor in Taiwan data in ACSIKS. Since our results were based on hospitalized patients in a single tertiary center, whereas those reported from Taiwan in the ACSIKS combined both hospitalized and nonhospitalized patients in 3 tertiary centers, the difference may be partially explained by the real-world outpatient clinic experience and between-hospital variability.

Age distribution showed a single peak, with more patients aged 60 and beyond during 2007 to 2016. Our previous studies during 1992-2001 demonstrated bimodal age distribution,[7] with the peaks in young and old age related to contact lens wear and ocular surface disorders, respectively.[7,8] During 2007-2016, we found not only an increased proportion of chronic ocular or systemic disorder–related infectious keratitis but also a decreasing trend in infectious keratitis due to trauma.

Positive culture rate of the present study was consistent with previous reports, ranging from 40% to 68%.[9–11] The positive culture rate decreased mildly, from 56% during 1997-2001 to 51% during 2007-2016. The slight decline may indicate a higher rate of patients receiving antibiotics before referral, as suggested in the literature.[12] *Pseudomonas aeruginosa* remained the most commonly isolated pathogen over our 2-decade study period, consistent with other published reports from Taiwan.[3,4,13] Interestingly, there was a shifting trend toward decreasing cases with NTM infections and increasing cases with *Microsporidia* species in our study. The declining trend in NTM keratitis in our study was the opposite of that reported by certain domestic and international studies or predicted trend in the literature.[14,15] However, it must be noted that these studies reported increasing NTM infection in multiple organs or in ocular tissue, without particular emphasis on keratitis. It is widely known that the major risk factors for NTM keratitis were preceding surgery (most commonly LASIK) and trauma.[16] There was a reduced incidence of post-LASIK NTM infection, which has been attributed to the common use of fourth-generation fluoroquinolones, changing from microkeratome to femtosecond LASIK, and more awareness in water sterilization perioperatively.[17,18] We considered the decline in NTM keratitis in our study the result of reduced incidents of trauma-related and post-LASIK NTM keratitis.

Despite no significant increase in overall fungal keratitis, there was a higher percentage of *Fusarium* keratitis and a lower percentage of *Aspergillus* keratitis in our cases. As we previously reported,[19] most of those with *Fusarium* or *Aspergillus* keratitis were associated with contact lens use or trauma, respectively. Therefore, the decreasing proportion of trauma as a risk factor could explain the reduction in *Aspergillus* keratitis, whereas the rise in *Fusarium* keratitis correlated with the substantial proportion of contact lens wearer among our patient population.

The percentages of medical vs surgical treatments for microbial keratitis with a single identified pathogen did not change over the 2-decade study period. Medical treatment alone was sufficient to clear the infection in a majority of common bacterial keratitis. However, the success rate of medical treatment alone was lower in our study compared

**TABLE 5.** Trend Analysis of Antibiotic Susceptibility Patterns of *Pseudomonas* Species and *Staphylococcus* Species From Bacterial Keratitis Cases by Year Period 1994-1999, 2000-2005, 2007-2011, and 2007-2016

| Organisms | Antibiotics | 1994-1999 N (%) | 2000-2005 N (%) | 2007-2011 N (%) | 2012-2016 N (%) | *P* Value |
|---|---|---|---|---|---|---|
| *Pseudomonas* species | Amikacin | 56 (93.3) | 65 (98.5) | 50 (98.0) | 21 (100) | .1382 |
| | Gentamicin | 52 (86.7) | 62 (95.4) | 18 (94.7) | 16 (88.9) | .4809 |
| | Ceftazidime | 60 (100) | 65 (98.5) | 53 (100) | 20 (95.2) | .2943 |
| | Ciprofloxacin | 60 (98.4) | 66 (100) | 53 (100) | 20 (95.2) | .7324 |
| | Levofloxacin | NA | NA | 51 (98.1) | 20 (95.2) | .4954 |
| | Piperacillin | 57 (96.6) | 65 (98.5) | 42 (100) | 15 (93.7) | 1.0000 |
| | Cefepime | NA | NA | 52 (100) | 16 (100) | NA |
| *Staphylococcus* species | Cefazolin | 9 (100) | 5 (71.4) | NA | NA | .1750 |
| | Clindamycin | NA | NA | 9 (56.3) | 2 (25.0) | .4285 |
| | Vancomycin | 11 (100) | 16 (100) | 11 (100) | 8 (100) | 1.0000 |
| | Oxacillin | 8 (88.9) | 7 (50) | 7 (43.8) | 1 (12.5) | .0021 |
| | Sulfamethoxazole-trimethoprim | NA | NA | 11 (91.7) | 6 (75.0) | .3428 |

N = number of eyes; NA = not applicable.

to the ACSIKS data from Taiwan (74.3% vs 96.6%). The difference in response rate to medical treatment may be partially explained by a higher disease severity in general, since our study included only hospitalized patients. Similar to previous reports,[20–22] NTM keratitis and fungal keratitis, unlike other microbial keratitis, often had a less satisfactory result with medical treatment, owing to delayed diagnosis, slow response to treatment, and poor drug penetration to deep infiltration. It should be noted that despite that microsporidial keratitis has rarely been reported previously, it was increasingly identified in our investigation and other recent studies.[23] Microsporidial infection can manifest as 2 distinct clinical entities: stromal keratitis or superficial punctate keratoconjunctivitis.[24] Keratoconjunctivitis is more prevalent than stromal keratitis and has been reported in several published case series.[25,26] Immunosuppression, contact lens wear, refractive surgery, soil or mud exposure, and trauma have all be proposed as predisposing factors of microsporidial keratitis.[27] As for treatment, microsporidial keratoconjunctivitis may be self-limiting or medically treated. However, there is no definite medical treatment for microsporidial stromal keratitis. Surgical intervention after the failure of medical treatment was not uncommon in previous case series.[28,29] Since we only enrolled hospitalized patients in our study, all 4 cases were of the stromal type. Two of the 4 cases had a history of trauma, while no specific predisposing factors could be identified in the other 2. The 4 cases in our study all received penetrating keratoplasty owing to poor responses to medical treatment. The high rate of patients requiring surgery was consistent with previous reports.[28,29]

Several recent studies[30–32] reported no significant trends in antibiotic resistance patterns of gram-positive and gram-negative organisms in the past 20 years. Consistently, the susceptibility patterns to commonly used antimicrobials did not change significantly for gram-negative isolates during our 20-year study period. For gram-negative bacteria, we found good susceptibility in that less than 10% of the isolates were resistant to the antibiotics tested, including fluoroquinolones, aminoglycosides, and fourth-generation cephalosporin. Prior study has reported that abnormal ocular surface, use of topical medications, and contact lens wear were associated with *Serratia marcescens* keratitis.[33] Since our data showed an increasing trend in chronic ocular or systemic disorders and aging population, *Serratia marcescens* keratitis warranted more attention, particularly in those without contact lens use or in elderly patients using multiple eye drops.

In recent years, methicillin/oxacillin-resistant *Staphylococcus* species have become an important issue worldwide.[34–36] We found an increasing trend in oxacillin resistance in *Staphylococcus* species along with an increasing trend of MRSA in the recent decade. In addition, a higher proportion of oxacillin-resistant *Staphylococcus* species also had resistance to gentamicin, ciprofloxacin, levofloxacin, and TMP/SMX than the oxacillin-susceptible *Staphylococcus* species in the present study. Our findings were consistent with other reports that MRSA or ORSA can carry multidrug resistance.[37] Among the oxacillin-resistant SA and CNS in the current study, although more than 70% were not associated with exposure to the healthcare environment, most of them carried multidrug resistance. Furthermore, *Staphylococcus* species were the leading pathogens in those with chronic ocular or systemic disorder–related microbial keratitis. Therefore, the absence of healthcare exposure may have less predictive value in ruling out patients with multidrug-resistant SA, and one shall not underestimate the burden of community-acquired multidrug-resistant SA infection, especially those with chronic ocular or systemic disorders. Considering our data and the relatively high

prevalence of methicillin-resistant *Staphylococcus* species in Taiwan,[36] empirical monotherapy with fluoroquinolone should be used judiciously, with close follow-up of clinical response. It has been reported that CNS was the most common microbial isolate among those with presence of keratopathy or ocular surface disease and systemic disorders.[31] Therefore, the clinical significance of CNS microbial keratitis may warrant attention. However, it should be noted that although we tried to minimize the misclassification of microbial keratitis owing to CNS contamination by defining the diagnosis of CNS keratitis only when the same isolate was consistently identified in at least 2 corneal scraping cultures and smear, it remains a challenge to judge whether a CNS isolate from a clinical specimen reflects a true infection or not.

The potential limitations of our study included its retrospective nature, the catchment area of our hospital and its population from the hospitalized patients of a tertiary hospital, and the discrepancy between clinical response and in vitro antibiotic sensitivity. Therefore, attention should be paid when applying our findings to different geographic areas or specific populations.

In summary, we documented a decreasing trend in the percentage of NTM keratitis, whereas *Microsporidia* keratitis and *Serratia* keratitis are considered as emerging ocular diseases that warrant more attention. Since there was not an overall significant trend in antibiotic resistance, the regimen of cephalosporin plus aminoglycoside or fluoroquinolone was considered as a reasonable empirical combination, as advised in our prior study.[2] However, fluoroquinolones as the monotherapeutic agent in gram-positive keratitis should be applied with caution owing to the increasing antibiotic resistance in gram-positive isolates and a higher rate of cross-resistance to other common antibiotics in oxacillin-resistant *Staphylococcus* species.

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