Moraxella Keratitis: Analysis of Risk Factors, Clinical Characteristics, Management, and Treatment Outcomes

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• PURPOSE: **To analyze the risk factors, clinical characteristics, management, and treatment outcomes of culture-proven cases of *Moraxella* keratitis at our center.**
• DESIGN: **Retrospective observational case series.**
• METHODS: **Thirty-nine culture-proven cases of *Moraxella* keratitis (39 eyes) diagnosed and treated between January 2003 and April 2018 at the University of Pittsburgh Medical Center were identified and retrospectively reviewed for ocular and systemic risk factors, treatment modalities, and outcomes, as well as for antimicrobial sensitivity and resistance data.**
• RESULTS: **The mean age of the 39 patients was 63.0 (range 4-95 years) with median follow-up time of 170 days. Thirty-four of 39 patients (87.2%) had an ocular risk factor, the most common of which were blepharitis in 12 (30.8%), dry eyes in 12 (30.8%), and history of ocular surgery in 9 (23.1%). History of diabetes mellitus was found in 8 patients (20.5%). Thirty-six of 39 patients (92.3%) received a fluoroquinolone (92.3%) and 30 of 39 (76.7%) received topical fortified antibiotics. Resistance to fluoroquinolones, gentamicin, and tobramycin was seen in 1 patient each, respectively. Four patients (10.3%) required tarsorrhaphy, 6 patients (15.4%) required penetrating keratoplasty, and 1 patient required enucleation. Of the 35 patients for whom visual acuity information was available, 19 (54.3%) were count fingers or worse at most recent follow-up.**
• CONCLUSIONS: **Ocular risk factors, especially poor ocular surface, were identified in the vast majority of patients with *Moraxella* keratitis. *Moraxella* isolates in our study were susceptible to fluoroquinolones and aminoglycosides. Many patients required surgical intervention and the final visual acuity was often poor. (Am J Ophthalmol 2019;197:17–22. © 2018 Elsevier Inc. All rights reserved.)**

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BACTERIAL KERATITIS IS AN INFECTION OF THE cornea that occurs when local ocular defenses have been diminished, such as in the case of contact lens wear, ocular surface disease, or ocular trauma.[1–3] If left untreated, bacterial keratitis can result in complications such as corneal scarring and perforation, leaving patients with severe loss of vision. The most common organisms identified in scrapings of bacterial keratitis include coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*.[4–6] The clinical presentations, microbiological characteristics, and treatment outcomes of these causative organisms are well characterized in the literature. *Moraxella* species keratitis, while a well-known cause of keratitis, is not as well characterized, especially in the United States. Better characterization of *Moraxella* species keratitis is required to ensure prompt recognition and treatment of this less common cause of bacterial keratitis to ensure patients the best possible visual outcome.

Moraxella species are visualized as diplobacilli on Gram and Giemsa stains, and are characterized as nonmotile, aerobic, glucose-nonfermative, and oxidase-positive. They are commonly isolated as part of normal flora of the upper respiratory tract, skin, and urogenital tract.[7] *Moraxella* species are known to infect various ocular tissues. Cases of angular blepharoconjunctivitis, keratitis, and endophthalmitis have been reported.[8–10] A study of 300 cases of bacterial keratitis in Paris, France, found a single case (0.3%) of *Moraxella* keratitis.[3] An analysis of 427 ulcers in the United States found 5% of all ulcers were *Moraxella* species.[5] A multinational study of 506 ulcers from institutions in India and the United States found *Moraxella* species to comprise 3% of all ulcers.[11] In the past, *Moraxella* keratitis was thought to be a disease of the immunocompromised, specifically associated with chronic alcohol use, malnutrition, and diabetes.[12–14] However, more recent case reviews conducted in Australia, Japan, and the United States have begun to demonstrate associations between *Moraxella* species infection and contact lens wear, trauma, older age, history of herpes keratitis, and corneal transplantation.[9,15–17]

The purpose of this study was to analyze the clinical presentations, microbiological characteristics, antibiotic susceptibility, treatment modalities, and treatment outcomes of *Moraxella* keratitis at our center.

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METHODS

THE INSTITUTIONAL REVIEW BOARD OF THE UNIVERSITY OF Pittsburgh approved this single-center retrospective observational case series prior to initiation of data collection. This study is in compliance with the Health Insurance Portability and Accountability Act (HIPAA). Following Institutional Review Board approval, corneal culture records from the Charles T. Campbell Microbiology Laboratory were queried for culture-proven *Moraxella* keratitis cases. All cases of culture-proven *Moraxella* keratitis seen and treated at the University of Pittsburgh Department of Ophthalmology between January 2003 and April 2018 were included in this study.

Both the clinical and microbiological records of these patients were retrospectively reviewed. At our center, infectious bacterial keratitis cultures include samples of the cornea, conjunctiva, and eyelid on 5% sheep blood–supplemented agar, chocolate agar, and mannitol agar. In addition, corneal scrapings are stained with Gram and Giemsa for the direct visualization of bacteria. Fungus cultures, viral testing for herpes simplex virus (HSV), and testing for Acanthamoeba and other etiologic agents were performed if clinical suspicion dictated. *Moraxella* susceptibility to the following antibiotics was tested: bacitracin, cefazolin, ciprofloxacin, gatifloxacin, gentamicin, moxifloxacin, ofloxacin, polymyxin B, sulfacetamide, tobramycin, vancomycin, and cefoxitin. For each patient, the following microbiological data were collected: type of cultures performed, speciation information, antibiotic sensitivity and resistance information, and the speciation of additional microbes if present.

The following clinical data were collected from each patient's medical record: age, sex, ocular risk factors, systemic risk factors, length of follow-up, initial and final visual acuity, initial and final intraocular pressure, symptom duration prior to presentation, infiltrate size and shape (when available), presence of hypopyon, presence of hyphema, hospitalization, recurrence of *Moraxella* keratitis, medical management, necessity and type of adjunctive treatment, duration of treatment, time to epithelial defect closure, presence of polymicrobial infection, and presence of concurrent HSV infection. Statistical analysis was performed using R 3.4.4 (R Foundation, Vienna, Austria). Interval data were presented with mean, standard deviation, and the 5-number summary (minimum, first quartile, median, third quartile, and maximum), and categorical data were presented with frequency count and percentage, where appropriate.

RESULTS

A TOTAL OF 1040 SUBJECTS WITH MICROBIAL KERATITIS were seen during the study period. Of these, 46 subjects (4.42%) had culture-proven *Moraxella* keratitis. Thirty-nine subjects (17 male, 22 female) with complete clinical data were included. The average age at time of presentation was 63.0 ± 21.7 years, with age ranging from 4 to 95 years in our series of patients. The vast majority, 31 of 39 patients (79.5%), were aged 50 or older. The median follow-up time was 170 days in this study.

Thirty-four of 39 patients (87.2%) had an associated ocular risk factor (Table 1); the most common were blepharitis in 12 patients (30.8%), dry eyes in 12 patients (30.8%), and history of ocular surgery in 9 patients (23.1%). Six patients (15.4%) had a history of recent corticosteroid use. Only 2 patients (5.1%) had a history of contact lens use. Three patients (7.7%) had a recent

TABLE 1. Ocular Risk Factors Associated With *Moraxella* Keratitis

Risk Factor	Frequency (N = 39 Patients)	Percentage
Dry eyes	12	30.8%
Contact lens use	2	5.1%
History of ulcer	6	15.4%
History of *Moraxella* ulcer	1	2.6%
History of diabetic retinopathy	3	7.7%
History of retinal detachment	1	2.6%
Trauma	3	7.7%
Uveitis	1	2.6%
Thryoid eye disease	1	2.6%
Glaucoma	12	30.8%
Chronic low IOP	2	5.1%
Blepharitis	12	30.8%
Exposure keratopathy	3	7.7%
History tarsorrhaphy	2	5.1%
Neurotrophic	7	17.9%
Lagophthalmos	3	7.7%
Abrasion within last month	1	2.6%
History of allergic conjunctivitis	1	2.6%
History of amblyopia	2	5.1%
Corticosteroid use	6	15.4%
Previous surgery	9	23.1%
PKP	2	5.1%
Poor ocular surface	27	69.2%
ABMD	2	5.1%
Fuchs dystrophy	2	5.1%
Rosacea	1	2.6%
Band keratopathy	1	2.6%
Ocular HSV	6	15.4%
History of nasolacrimal duct obstruction	1	2.6%
CRVO	1	2.6%
History endophthalmitis	1	2.6%
Blindness	1	2.6%

ABMD = anterior basement membrane dystrophy; CRVO = central retinal vein occlusion; HSV = herpes simplex virus; IOP = intraocular pressure; PKP = penetrating keratoplasty.

TABLE 2. Systemic Risk Factors Associated With *Moraxella* Keratitis

Risk Factor	Frequency (N = 39 Patients)	Percentage
Diabetes mellitus type 2	8	20.5%
Hypertension	17	43.6%
Autoimmune disease	4	10.3%
Polymyalgia rheumatica	1	2.6%
Graves	1	2.6%
Rheumatic heart disease	1	2.6%
Scleroderma	1	2.6%
Systemic steroids	1	2.6%
Cancer patient on chemotherapy	1	2.6%
Herpes zoster	2	5.1%
Cognitive impairment	4	10.3%
Coma intubated	1	2.6%
Multisystem organ failure	1	2.6%
Candedemia	1	2.6%
Substance abuse	2	5.1%
Chronic kidney disease	2	5.1%
Cirrhosis	1	2.6%
Allergies	1	2.6%
HIV	1	2.6%
Hepatitis C	1	2.6%

history of trauma to the eye. A composite variable for poor ocular surface was constructed that took into account presence of 1 or more of the following: history of dry eyes, blepharitis, exposure keratopathy, neurotrophic cornea, lagophthalmos, recent abrasion, anterior basement membrane dystrophy, and/or rosacea. Twenty-seven patients (69.2%) were found to have a history of poor ocular surface by these criteria.

Systemic risk factors were also identified in our patient population (Table 2). Of 39 patients, 8 (20.5%) had a history of diabetes mellitus and 4 (10.3%) had a diagnosis of an autoimmune disorder in their medical record. These autoimmune diagnoses were polymyalgia rheumatica, Graves disease, rheumatic heart disease, and scleroderma. No patients were found to have a history of alcohol use disorder documented in their problem list.

Initial visual acuity information was present for 36 patients. Of these 36 patients, 23 (63.9%) were count fingers or worse on presentation, 10 (27.8%) were from count fingers up to 20/60 vision, and 3 (8.3%) presented with visual acuity better than 20/60.

Symptom duration prior to presentation was available for 34 patients. The median symptom duration prior to presentation was 5 days. Presence of absence of hypopyon and hyphema was able to be determined in 32 patients. Twenty of these 32 patients (62.5%) presented with hypopyon and 3 patients (9.4%) presented with hyphema. Fourteen of 39 patients (35.9%) were admitted for further management of their ulcer as inpatients.

TABLE 3. Medical Management of Patients With *Moraxella* Keratitis

Antibiotic	Frequency (N = 39 Patients)	Percentage
Valacyclovir	5	12.8%
Acyclovir	5	12.8%
Antiviral	9	23.1%
Fluoroquinolone drop	36	92.3%
Gatifloxacin	8	20.5%
Moxifloxacin	27	69.2%
Ciprofloxacin	12	30.8%
Ofloxacin	6	15.4%
Levofloxacin	2	5.1%
Fortified antibiotics	30	76.9%
Fortified tobramycin	12	30.8%
Fortified cefazolin	25	64.1%
Fortified vancomycin	8	20.5%

Medical management of the ulcers was highly variable, with most patients receiving multiple classes of antibiotics during their management (Table 3). Of the 39 patients, 36 (92.3%) received a topical fluoroquinolone, 30 (76.9%) received a fortified topical antibiotic, 12 (30.8%) received fortified topical tobramycin, 25 (64.1%) received fortified cefazolin, and 8 (20.5%) received fortified vancomycin. Nine patients (23.1%) received antiviral therapy owing to suspicion for herpesvirus family keratitis. Seventeen patients (43.6%) received either topical or oral steroids.

Adjunctive treatments were required in 27 of 39 patients (69.2%) (Table 4). Of the 39 patients, 20 (51.3%) had a bandage contact lens placed, 4 (10.3%) required tarsorrhaphy, and 6 (15.4%) required penetrating keratoplasty (PKP) owing to the severity of damage to the cornea. One patient required enucleation.

Treatment duration and time to defect closure information was available for 27 patients. For these patients the average duration of medical treatment was 65.6 ± 56.1 days with a median duration of 54 days. The range of duration was 1-256 days. The median time to epithelial defect closure was 19 days, ranging from 8 to 170 days.

In our study, 39 out of 39 patients presented with *Moraxella* growth on corneal culture. Of these 39 patients, 13 (35.1%) were found to have polymicrobial infection of the cornea. The most common additional bacteria isolated included *Staphylococcus* species (9) and diphtheroids (3). Three patients (7.9%) were found to have concurrent HSV infections.

Antimicrobial susceptibility testing was performed for isolated colonies of *Moraxella* (Table 5). All isolates were found to be susceptible to bacitracin (39/39), gatifloxacin (38/38), moxifloxacin (39/39), and ofloxacin (39/39). Of the 39 patients tested, 4 were found to have resistance to vancomycin. Resistance to ciprofloxacin was found in 1 patient, though this was only intermediate resistance. Resistance to tobramycin was also found in 1 patient.

TABLE 4. Adjunctive Therapy Used in Patients With *Moraxella* keratitis

Adjunctive Therapy	Frequency (N = 39 Patients)	Percentage
Adjunctive treatment	27	69.2%
Bandage contact lens	20	51.3%
Glue	6	15.4%
Punctal plug	1	2.6%
Amniotic membrane	1	2.6%
Tarsorrhaphy	4	10.3%
Vigamox collagen shield	1	2.6%
Pro-Kera Plus	1	2.6%
Debridement	1	2.6%
Corneal surface curretage	1	2.6%
Pentrating keratoplasty	6	15.4%
Synechiolysis	1	2.6%
Enucleation	1	2.6%

TABLE 5. Antimicrobial Susceptibility of *Moraxella* Isolates

Antibiotic	Susceptible Patients	Resistant Patients	Not Performed	Total Patients
Bacitracin	39	0	0	39
Cefazolin	38	1	0	39
Ciprofloxacin	38	1	0	39
Gatifloxacin	38	0	1	39
Gentamicin	38	1	0	39
Moxifloxacin	39	0	0	39
Ofloxacin	39	0	0	39
Polymyxin B	38	1	0	39
Sulfa	37	1	1	39
Tobramycin	38	1	0	39
Vancomycin	35	4	0	39

Final visual acuity was recorded for 35 patients. This was defined as best-corrected visual acuity at their most recent follow-up appointment. Only 5 of these 35 (14.3%) were found to have visual acuity greater than 20/60 at their most recent follow-up appointment. Eleven patients (31.4%) had visual acuity between count fingers and 20/60 vision; 18 patients (51.4%) were count fingers or worse. Only 1 patient was found to have recurrent *Moraxella* keratitis in our study.

DISCUSSION

IN THIS STUDY, 39 CASES OF CULTURE-PROVEN *MORAXELLA* species keratitis were diagnosed and treated at our center. Similar case series have been performed in Australia,[9] India,[14] the United States,[15] and Japan.[16,17] Our study represents the largest to date in the United States.

The majority (79.5%) of patients at our center were older than 50 years of age at the time of diagnosis, which is in concordance with previous reports from other countries.[9,14–17] Given the consistency of this finding, increasing age may represent an independent risk factor for *Moraxella* keratitis.

Initial work on *Moraxella* keratitis suggested that chronic alcohol use, malnutrition, and diabetes were the risk factors most commonly associated with *Moraxella* keratitis.[12–14] In our study, none of the patients had a documented history of alcohol use disorder in their problem list. Recent work with *Moraxella* keratitis in conjunction with results from our study suggests that chronic alcohol use is not as prevalent a risk factor as once thought. Malnutrition at the time of diagnosis was difficult to assess in our study. The most prevalent associated systemic factor in our patients was diabetes mellitus (20.5%), which compares favorably with other studies of *Moraxella* keratitis where the prevalence of diabetes ranged from 5.9% to 23.8%.[9,14–17] These patients with diabetes ranged in age from 38 to 85 years old, with half being under the age of 65. It is worth noting that the prevalence of diabetes is on the rise in the United States; a recent cross-sectional survey in 2012 estimated a prevalence of 14.3%.[18] In their study of 300 cases of bacterial keratitis, Bourcier and colleagues[3] reported 7 cases (2.3%) in which the patient had a history of diabetes.[3] While the prevalence of diabetes in our patient population is in line with that of national prevalence, it appears that the rate of diabetes is enhanced in patients with *Moraxella* keratitis compared to other types of bacterial keratitis. Future studies can corroborate the results of our study. The hyperglycemia associated with diabetes mellitus is known to cause an immunocompromised state and may lead to impaired host defenses against opportunistic *Moraxella* species.

The second most prevalent associated systemic factor in our study was a history of autoimmune disease, which was present in 10.3% of our patients. Previous reports have linked *Moraxella* keratitis to autoimmune diseases. Das and colleagues[9] reported 5.2% of patients had rheumatoid arthritis.[9] Inoue and colleagues[17] reported 4 cases out of 30 (13.3%) with autoimmune disease (Sjögren syndrome, Graves disease, allergic purpura, and systemic lupus erythematosis). Tobimatsu and colleagues[16] reported 2 out of 17 patients (11.8%) with a history of atopic dermatitis and suggested that allergic inflammation may weaken ocular surface defense mechanisms. It is possible that increased baseline inflammation throughout the body secondary to autoimmune disease may weaken ocular defense mechanisms, as suggested by Tobimatsu, or weaken the ocular surface itself. Further work into the association between autoimmune disease and keratitis is warranted.

The association between bacterial keratitis and impaired local host defenses is well known and *Moraxella* keratitis is no exception. In our study, 87.2% of patients were found to have an associated ocular factor, with blepharitis (30.8%),

dry eyes (30.8%), and history of ocular surgery (23.1%) being the most frequent. To date, only 1 study has looked at the prevalence of blepharitis in the United States. A survey of 120 ophthalmologists and 84 optometrists about the frequency of blepharitis in their practices found that 37% and 47% of their patients, respectively, had blepharitis.[19] This is in line with our results of 30.8% of our patients having a history of blepharitis. Blepharitis may not be a true risk factor for *Moraxella* keratitis, given its high prevalence throughout ophthalmology practices across the United States. A few studies have looked at the estimated prevalence of dry eyes in men and women in the United States. An analysis of men in the Physicians' Health Study estimated the prevalence of dry eyes in United States men 50 years and older to be 4.3%.[20] An analysis of the Women's Health Study cohort found the prevalence in United States women to be 7.8%.[21] The rate of dry eyes was significantly elevated in our patient population (30.8%) with *Moraxella* keratitis when compared to the prevalence of dry eyes across the United States and further suggests that dry eye disease may be a risk factor for *Moraxella* keratitis. The third most commonly associated ocular risk factor in our study was a history of ocular surgery (23.1%). In patients with a history of poor ocular surface and/or previous ocular surgery, *Moraxella* keratitis should be a part of the initial differential diagnosis and considered when making decisions regarding empiric treatment prior to culture results.

A comparison of the associated risk factors found in our study and previous work on *Moraxella* reveals other key similarities and differences. In a series of Australian patients, the most commonly associated ocular risk factors were PKP (15.7%), herpes simplex keratitis (15.7%), blepharitis (12.6%), and glaucoma (12.6%).[9] Mian and Malta[15] found blepharitis, history of corneal transplantation, and diagnosis of glaucoma as the most common ocular risk factors in their patients. Inoue and colleagues,[17] in their series of Japanese patients, found contact lens use (16.7%) and trauma (10%) to be the most prevalent ocular risk factors. A more recent study of 17 Japanese patients found similar results as Inoue and colleagues; 21.4% of patients had a history of contact lens wear and 21.4% of patients had a history of trauma.[16] In our study, contact lens use (5.1%) and trauma (7.7%) were less prevalent than in Japanese patients. The rate of ocular HSV infection (15.4%) in our study was similar to that of Australian patients. We did find that a significant number of our patients (30.8%) also had glaucoma, similar to the Australian study and previous study in the United States. The results from our study suggest that poor ocular surface, whether owing to intrinsic disease or disruptions caused by previous ocular surgery, may predispose patients to *Moraxella* keratitis.

In our study, median symptom duration prior to presentation was 5 days, and 62.5% of patients presented with a hypopyon. The median time to epithelial defect closure was 19 days and median duration of medical therapy was 54 days. A total of 35.9% of patients were admitted for inpatient management of their ulcer owing to concerns for perforation or ability to properly administer antimicrobial therapy at home. The prolonged time to defect closure and high rate of admission highlights the seriousness of *Moraxella* keratitis and the high risk of perforation if inadequately treated.

The vast majority of our patients (92.3%) received a topical fluoroquinolone as well as a fortified antibiotic (76.9%) during their treatment, the most common fortified being cefazolin (64.1%). In our study, 4 patients were resistant to vancomycin and a single case of resistance to cefazolin, ciprofloxacin, gentamicin, and tobramycin was observed. Previous studies of *Moraxella* keratitis[9,14,16,17] have demonstrated resistance to cefazolin, with Garg and colleagues[14] showing 44.4% of their cases having resistance to cefazolin.

Despite aggressive medical management, a significant number of our patients required surgical intervention: 6 patients (15.4%) required PKP and 1 patient required enucleation. Of these 6 patients requiring PKP, 1 of these patients had a concurrent methicillin-resistant *S aureus* infection of the cornea, which was resistant to fluoroquinolones, resulting in perforation; 2 had a history of corneal transplantation with infected grafts; 1 had a perforation at the time of presentation and refused admission against medical advice; and 1 patient healed but developed bullous keratopathy. Regarding the patient who required enucleation, they were already no light perception secondary to a retinal detachment and were enucleated once the eye became painful. In all these cases, extenuating circumstances such as prior ophthalmic conditions, poor compliance, or superinfection played a role in these poor outcomes. In total 7 patients (17.9%) required surgical intervention. Other case series on *Moraxella* have reported varying degrees of surgical intervention. None of the patients in a series by Inoue and colleagues[17] required surgical intervention, whereas Das and colleagues[9] reported 11.6% of their patients required PKP or enucleation. Mian and Malta[15] reported 28.6% of their patients required KPro, PKP, or enucleation. Likewise, the final visual acuity was count fingers or worse in 18 patients. Further review of these patients' charts demonstrated that 4 patients had 20/400 or worse vision prior to presenting with *Moraxella* keratitis; 4 patients were lost to follow-up prior to completing treatment; 4 required PKPs, which eventually failed; 3 healed with central scarring; 1 presented with a necrotic ulcer after a week of purulent drainage; 1 patient's poor visual acuity was attributable to glaucoma progression; and 1 patient was enucleated, as discussed above.

Kowalski and colleagues[22] demonstrated that moxifloxacin monotherapy provided statistically equal empiric coverage to cefuroxime/gentamicin and cefazolin/tobramycin for cases of bacterial keratitis, including cases of *Moraxella* keratitis. Suzuki and Ohashi[23] showed in their study that a combination consisting of a

fluoroquinolone with tobramycin had a synergistic effect in vitro against gram-negative rods. Given the poor visual outcomes and frequent need for surgical intervention found in our study, it is reasonable in cases of suspected *Moraxella* keratitis to prescribe a topical fluoroquinolone in combination with fortified tobramycin as empiric therapy to assure proper coverage of this serious cause of keratitis. Indeed, Inoue and colleagues[17] most commonly prescribed this regimen in their case series and found that no cases required surgical intervention. Fortified vancomycin and fortified cefazolin, though found to be commonly prescribed as empiric therapy in our study, are not ideal for cases of *Moraxella* keratitis, given the resistance to vancomycin seen in our patient population and frequent reports of cefazolin-resistant *Moraxella* at other centers.

In conclusion, *Moraxella* keratitis, though uncommon, can cause devastating visual consequences if not adequately treated. The clinical presentation of *Moraxella* keratitis can vary in terms of presenting visual acuity and physical characteristics of the ulcer. Our study suggests that the most commonly associated factors for *Moraxella* infection include a history of diabetes, poor ocular surface, and a history of previous ocular surgery.

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