Visual Outcome, Microbiological Profile and Antibiotic Sensitivity of Infectious Keratitis in a Tertiary Referral Center

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Abstract

Purpose:

Treatment of infectious keratitis is chosen by identification of infection source with associated antibiotic susceptibilities. Because culturing corneas may take days to weeks to result, the mainstay of treatment is empirical therapy with broad-spectrum antimicrobials that are started before culture results return. We aim to record the microbiological profiles with associated antibiotic susceptibility patterns isolated from corneal cultures in patients with infectious keratitis, as well as visual outcomes over a 5-year period.

Methods:

A retrospective analysis of medical records of patients who presented to UMMC from 1/1/2014 to 12/31/2018 with keratitis or corneal ulcer were included in this study based off diagnosis codes.

Results:

Of 563 corneal infections analyzed, 202 (35.9%) had positive cultures. The most frequently isolated organism was Coagulative negative Staphylococcus/ *Staphylococcus epidermidis*, followed by *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. *Pseudomonas aeruginosa* was isolated in 37.2% contact lens wearers. We found that 93.3% of gram-positive cultured bacteria were susceptible to vancomycin with no resistance, and 81.8% of gram-negative bacteria were highly susceptible to tobramycin with no resistance. Regardless of treatment, 19.8% of patients needed some type of additional procedure, with the most common procedures being corneal transplant & evisceration.

Conclusion:

CNS, *Pseudomonas aeruginosa,* and *Staphylococcus aureus* were the most common microbes causing infectious keratitis. *Pseudomonas aeruginosa* remains the most commonly identified organism in contact lens wears. The empirical treatment of vancomycin and tobramycin used at our institution remains an excellent treatment for these microbes.

Introduction

Infectious keratitis and corneal ulcers develop after microbiology invades corneal epithelium. Although some bacteria like *Neisseria, Corynebacteria, Listeria*, and *Haemophilus*, can infiltrate an intact corneal epithelium (Raju 2008), most corneal infections propagate when the corneal surface protection is compromised. Epithelial defense can become weakened with various mechanisms including contact lens induced ischemia, ocular surface disease, immunosuppression, diabetes, trauma, and previous surgery (Bourcier et al 2003, Fong et al 2007, Gopinathan et al 2009, Green et al 2007, Liu et al 2020, Mun et al 2019, Raju 2008). In addition to single bacterial infections, multiple bacteria as well as fungi can be present (Bourcier et al 2003, Fong et al 2007, Gopinathan et al 2009).

Of the most common microorganisms, *Pseudomonas aeruginosa, Staphylococcus aureus, and Streptococci* are among the causative culprits in found in recent literature (Fong et al 2007, Fong et al 2004, Liu et al 2020, Mun et al 2019). With this knowledge, hasty treatment with appropriate empirical antimicrobial eye drops can be administered to avoid consequences like corneal damage and vision loss when the infiltrate is small without an overlying epithelial defect and away from the visual axis. However, if this is not the case, corneal scraping and cultures can be obtained to further ascertain exactly what microbe is wreaking havoc.

Through our study, we examined the microbiological profiles of bacteria with antibiotic susceptibilities cultured from corneas of patients diagnosed with infectious keratitis or corneal ulcers. We looked at risk factors and best-corrected visual acuity with treatment as well as associated treatment outcomes over a 5-year period at University of Mississippi Medical Center, a tertiary hospital in Jackson, Mississippi.

Materials And Methodology

This study was approved by the Institutional Review Board at the University of Mississippi Medical Center. A retrospective analysis of medical charts was conducted in patients who were diagnosed with keratitis or corneal ulcer from January 1, 2014 and December 31, 2018 at University of Mississippi Medical Center.

Patient charts were populated based upon diagnosis codes: Corneal ulcer (370.00/H16.00); Marginal corneal ulcer (370.01/H16.04); Central corneal ulcer (370.03/H16.01); Hypopyon ulcer (370.04/H16.03); Mycotic corneal ulcer (370.05/H16.06); Perforated corneal ulcer (370.06/H16.07); Other forms of keratitis (370.8/H16.8).

The following data were collected from each medical record: medical record number, age, gender, ethnicity, past medical and ocular history, medication use, ophthalmic surgical history, date of initial presentation with disease, visual acuity at first visit, laterality of affected eye, culture results and sensitivities, treatments given for infection, best corrected visual acuity after the treatment typically one month and three months after presentation, and need for additional procedures after treatment. All patient data was entered into Redcap to be further analyzed.

Results

Patient demographics & baseline characteristics

A total of 563 corneal infections were analyzed. There were 263 female patients; of these, 19 females required repeat culturing for a separate corneal infection to total 282 female infections (50.1%). There were 265 male eyes; of these, 16 males required repeat culturing for a separate corneal infection to total 281 male infections (49.9%). The median patient age was 48 years old. Patient population included White/Caucasian (51.3%), Black/African American (44.2%), Hispanic (1.2%), American Indian (0.5%), and

Mississippi Band Choctaw (0.4%). The right eye was affected in 274 (48.7%) and the left eye in 264 (46.9%). Both eyes were affected in 25 (4.4%).

Possible risk factors associated with infectious keratitis were also studied. Of the patients analyzed, 214 were contact lens wearers, and 78 contact lens wearers (36.4%) had positive cultures for bacteria and fungi. Diabetes mellitus was present in 67 eyes (11.9%). Immunologic or autoimmune disease (excluding rheumatoid arthritis, HIV, or diabetes mellitus) was present in 49 (8.7%). Forty-seven (8.3%) of these patients were diagnosed with some form of elevated IOP including glaucoma or ocular hypertension, with 45 of these (95.7%) being treated with drops (44.4% on latanoprost and 37.8% on dorzolamide-timolol). Fifty-six (9.9%) of patients were diagnosed with dry eye syndrome and 41 (73.2%) of these were concurrently taking some form of lubricating drop. Many patients 112 (19.89%) needed additional procedures as part of their keratitis treatment. The most common procedure performed was corneal transplant in 55 eyes (49.1%), followed by evisceration in 13 eyes (11.6%), patch graft in 7 eyes (6.3%), repeat initial procedure in 6 eyes (5.4%), enucleation in 5 eyes (4.5%), and some other procedure not listed elsewhere in 44 eyes (39.3%). See Table 1.

Table 1. Demographics and baseline characteristics of patients with infectious keratitis.

Microorganism characteristics

Of the 563 eyes, 202 eyes (35.9%) had positive cultures, 88 eyes (15.63%) had negative cultures and 273 (48.5%) had no labs run. Of the positive cultures, 166 microorganisms (82.2%) had treatment sensitivities. Many of the cultures were positive for more than one microorganism. In total, there were 134 (63.8%) gram-positive bacteria identified and 76 (36.2%) gram-negative bacteria.

The most frequently identified organism in all cases of keratitis was from the *Staphylococcus* genus (94 eyes, 44.8% of all bacterial infections), with the species *epidermidis* (36 eyes, 38.3% of *Staphylococcus*) being most common followed by coagulase negative (31 eyes, 33.0% of *Staphylococcus*) then *aureus* (27 eyes, 28.7% of *Staphylococcus*). After *Staphylococcus*, the most common genus was *Pseudomonas* (47 eyes, 22.4% of all bacterial infections), followed by *Streptococcus* (23 eyes, 11.0% of all bacterial infections), *Bacillius* (9 eyes, 4.3% of all bacterial infections), *Serratia* (8 eyes, 3.8% of all bacterial infections), *Acinetobacter* (6 eyes, 2.9% of all bacterial infections), and *Moraxella* (5 eyes, 2.4% of all bacterial infections). Thirty-six eyes (21.7% of positive cultures) were identified having fungal infections. These infections included coinfection with multiple organisms at the time cultures were taken. See Table 2 for delineation of bacterial and fungal characteristics.

Table 2. Microorganism characteristics.

Contact lens wear and keratitis

A number of contact lens wearing patients were identified in this study (214 eyes). Of these, 101 eyes (47.19%) had no labs run at initial appointment, and 3 of these had labs run at a later appointment.

Thirty-five eyes (16.35%) had negative labs and 78 eyes (36.44%) had labs positive for microorganisms. Again, many cultures were positive for more than one microorganism.

In these contact lens patients, the most prevalent organism identified was *Pseudomonas aeruginosa* (29 eyes) followed by *Staphylococcus epidermidis* (11 eyes), *Staphylococcus aureus* (9 eyes), *Staphylococcus* coagulase negative (7 eyes), *Streptococcus viridans* (4 eyes), *Staphylococcus caprae* (2 eyes), *Serratia marcescens* (2 eyes), *Pseudomonas oryzihabitans* (1 eye), *Serratia liquefícians* (1 eye), *Moraxella* (1 eye), *Bacillus* (1 eye), *Diphtheroid* (1 eye), *Neisseria meningitis* (1 eye), *Morganella* (1 eye). Seven eyes were identified with positive fungal cultures. These included *Aspergillus fumigatus* (2 eyes), *Fusarium* (2 eyes), *Curvularia* (1 eye), *Penicillium* species (1 eye), mold (1 eye). See Table 3.

Table 3. Contact lens wear associated keratitis.

Susceptibilities & Resistances

Susceptibility and resistance patterns were provided by the lab in 134 of the gram-positive bacteria and 66 of the gram-negative bacteria. Most gram-positive organisms were susceptible to vancomycin (93.3%), followed by tetracycline (79.1%), and gentamicin (78.4%). Gram-negative bacteria were most susceptible to amikacin (95.5%) followed by levofloxacin (90.9%), and tobramycin (81.8%). See Table 4.

Gram-positive bacteria were mostly resistant to erythromycin (56.0%), followed by oxacillin (25.4%), clindamycin (25.4%), and tetracycline (14.2%). Gram-negative bacteria were mostly resistant to ampicillin (18.2%), followed by trimethoprim/sulfamethoxazole (16.7%), and ceftriaxone (15.2%). See Table 5.

There were only 2 sensitivities reported from fungal cultures; both were *Candida albicans* sensitive to fluconazole.

Table 4. Antibiotic susceptibility of bacteria.

Table 5. Antibiotic resistance of bacteria.

Visual Outcomes

Vision was taken initially at presentation then checked again at 1 and 3 month visits after treatment had been started. Vision improved at 1 month in 18.8% and 24.3% of eyes with gram-positive and gram-negative keratitis respectively; it improved at 3 months in 10.3% and 9.9% of eyes with gram-positive and gram-negative keratitis respectively. Visual acuity neither increased nor decreased in 3.6% and 8.1% of eyes at 1 month in gram-positive and gram-negative infections respectively. At 3 months, visual acuity remained stable in 2.7% eyes with gram-positive infections and 2.7% eyes with gram-negative infections. Vision worsened in 6.7% eyes with gram-positive infections at 1 month and 3.1% eyes at 3 months. Vision worsened in 4.5% eyes with gram-negative infections at 1 month and 2.7% eyes at 3 months. See Table 6.

Table 6. Visual Outcomes.

Discussion

When corneal infections have concerning features like purulent discharge, anterior chamber reaction, significant pain, infection obscuring visual axis, and/or conjunctival infection, culturing should be considered for timely and adequate treatment. The most common way to diagnose infectious keratitis is through culturing corneal samples then subsequently testing for antibiotic susceptibility and resistance. These results help tailor the types of treatment used to eradicate infection while minimizing antibiotic overuse, thus encouraging further microbial antibiotic resistance. It is known that bacteria like *Staphylococcus* are most commonly found in corneal infections from all causes, while *Pseudomonas* is most commonly found in contact lens wearers. While this is true, microorganisms can vary in location and in their antibiotic resistance patterns. This study aimed to outline the microorganism profile causing infectious keratitis in addition to their antibiotic susceptibility and resistance patterns at University of Mississippi Medical Center over a five-year period.

Of the 563 eyes with diagnosed keratitis analyzed, bacteria and/or fungi was identified in 35.9%. The most frequently isolated organism was *Staphylococcus*, with combined *epidermidis* & *coagulase negative* comprising 50% of gram-positive bacterial infections and 27.2% overall infections. The second most common organism isolated was *Pseudomonas aeruginosa*, involving 60.5% of gram-negative bacterial infections and 18.7% overall infections. The third most common organism isolated was *Staphylococcus aureus*, making up 20.1% of gram-positive bacterial infections and 11% overall infections. These results are similar to recent microbiological profiles with coagulase negative *Staphylococcus* being the most common isolate in infectious keratitis (Mun et al 2019).

It has been well documented that *Pseudomonas* is one of the most common causes of infectious keratitis in contact lens wearers (Bourcier et al 2003, Fong et all 2007, Raju 2008), and our study seems to support this data. *Pseudomonas aeruginosa* was the most commonly isolated microorganism in 37.2% of contact lens wearers.

Microorganisms treated with broad spectrum antibiotics naturally have started to develop resistance to treatments[6]. In our hospital, we commonly start using topical broad-spectrum antibiotic drops immediately after culturing. These commonly include a combination of vancomycin to treat gram-positive keratitis and tobramycin for gram-negative infections. We found that 93.3% of gram-positive cultured bacteria was susceptible to vancomycin with no resistance. We found that our cultured gram-negative bacteria were highly susceptible to tobramycin at 81.8% with no resistance. This further proves that our empirical management with vancomycin and tobramycin at our institution remains a robust treatment. With less severe cases of keratitis, moxifloxacin is routinely used. Although not included in our labs, other fluoroquinolones like ciprofloxacin and levofloxacin both had low levels of resistance for both gram positive and gram-negative infections. Also used in more minor cases of keratitis is erythromycin. We found that 38.1% gram-positive infections are susceptible to erythromycin and 56.0% was resistant.

Regardless of treatment, 19.89% of patients needed some type of additional procedure. The most common procedures were corneal transplant in 49.1% and evisceration in 11.6%. We believe this may be due to prior ocular or systemic disease that could include diabetes mellitus, immunocompromised status or autoimmune disease, glaucoma, or dry eye syndrome. Some repeat keratitis cases were in the same individuals that had previously been lost to follow up but then presented with keratitis much later with severe keratitis requiring additional procedures. These patients also had considerably decreased visual acuity upon presentation with not much improved resolution after treatment of any form as compared to other keratitis cases with good follow up. Excluding the percent of patients lost to follow up, most patients improved at least one line of vision at 1 and 3 months after treatment.

Our data was collected from charts that had a diagnosis of 'keratitis'. This did not always necessarily correlate with infectious causes, as peripheral ulcer keratitis and terrien marginal degeneration were sometimes diagnosed at initial presentation and coded as 'keratitis'. This limitation mistakenly includes more cases of keratitis in our study that were not infectious and thus did not necessitate culturing, making the percentage of keratitis cases cultured falsely lowered. On the other hand, this study was completely conducted at a tertiary center, which could make findings less generalizable to other populations. Many infections were referred to our center for treatment, thus possibly falsely elevating the amount of cases recorded. As mentioned earlier, our lab did not test for moxifloxacin, a commonly used fluoroquinolone for empirical treatment, so susceptibility and resistance patterns can only be estimated from similar fluoroquinolones. Another limitation could include the possibility of culture contamination by normal flora thus creating positive cultures like CNS and *Staphylococcus epidermidis.* These bacteria live on ocular surfaces like eyelashes and not commonly known to cause pathogenic keratitis. Along with corneal sampling, there is a possibility that not enough of the microorganism was taken for adequate growth at the time of diagnosis. Another limitation of lab testing with antibiotic susceptibility and resistance in vitro is that there is not always a complete correlation of corneal microorganisms treated with prescribed antibiotics.

All together, our data concludes that CNS, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* were the most common microbes causing infectious keratitis. *Pseudomonas aeruginosa* is the most commonly identified organism in contact lens wears. The empirical treatment of vancomycin and tobramycin used at our institution remains an excellent treatment for these microbes based off susceptibility and resistance patterns. After accounting for patients lost to follow up, most patients' visual outcomes improved the most at 1 month then at 3 months after treatment.

Declarations

Ethics approval and consent to participate

This retrospective study involving human participants was approved by the IRB and all patient protected health information was collected into REDCap collection system.

Consent for publication

Not applicable

Availability of data & materials

All data analyzed from this study are not publicly available due to protected patient health laws covering protected medical charts of patients treated at University of Mississippi Medical Center's Ophthalmology Department, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Kristina M. Stanfield, MD collected and analyzed data as well as wrote majority of manuscript. Bo Huang, MD, PhD read and approved final manuscript. Blake J. Matherne, MD collected data from patient charts and was a contributor in writing the manuscript. Osasu N. Adah collected data from patient charts. Daniel McClung collected data from patient charts. Thuy Phuong T. Le ran statistical analyses and collected data from patient charts. Morgan Ladner collected data from patient charts and facilitated IRB approval process.

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References

Bourcier, T., Thomas, F., Borderie, V., Chaumeil, C., & Laroche, L. (2003). Bacterial keratitis:

predisposing factors, clinical and microbiological review of 300 cases. *The British journal of ophthalmology*, *87*(7), 834–838. https://doi.org/10.1136/bjo.87.7.834

Fong, C. F., Hu, F. R., Tseng, C. H., Wang, I. J., Chen, W. L., & Hou, Y. C. (2007). Antibiotic

susceptibility of bacterial isolates from bacterial keratitis cases in a university hospital in Taiwan. *American journal of ophthalmology*, *144*(5), 682–689. https://doi.org/10.1016/j.ajo.2007.06.038

Fong, C. F., Tseng, C. H., Hu, F. R., Wang, I. J., Chen, W. L., & Hou, Y. C. (2004). Clinical

characteristics of microbial keratitis in a university hospital in Taiwan. *American journal of ophthalmology*, *137*(2), 329–336. https://doi.org/10.1016/j.ajo.2003.09.001

Gopinathan, U., Sharma, S., Garg, P., & Rao, G. N. (2009). Review of epidemiological features,

microbiological diagnosis and treatment outcome of microbial keratitis: experience of over a decade. *Indian journal of ophthalmology*, *57*(4), 273–279. https://doi.org/10.4103/0301-4738.53051

Green, M. D., Apel, A. J., Naduvilath, T., & Stapleton, F. J. (2007). Clinical outcomes of

keratitis. *Clinical & experimental ophthalmology*, *35*(5), 421–426. https://doi.org/10.1111/j.1442-9071.2007.01511.x

Liu, H., Chu, H., Wang, I., Chen, W., & Hu, F. (2020). Microbial Keratitis in Taiwan: A 20-Year

Update.. *American journal of ophthalmology*, 205, 74-81.

Mun, Y., Kim, M. K., & Oh, J. Y. (2019). Ten-year analysis of microbiological profile and

antibiotic sensitivity for bacterial keratitis in Korea. *PloS one*, *14*(3), e0213103. https://doi.org/10.1371/journal.pone.0213103

Raju, K V. (2008). Bacterial Keratitis. *Kerala Journal of Ophthalmology*, XX(1), 77-83.

ksos.in/ksosjournal/journalsub/Journal_Article_11_150.pdf.

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