

Rising fluoroquinolone resistance rates in corneal isolates: implications for the wider use of antibiotics within the community

Chameen Samarawickrama^{1,2,4} BSc(Med), MBBS, PhD, FRANZCO

Elsie Chan^{1,3} MBBS, FRANZCO

Mark Daniell^{1,3} MBBS, FRANZCO

¹Royal Victorian Eye and Ear Hospital, Melbourne, Vic. 3002, Australia.

²University of Sydney, Sydney, NSW 2000, Australia.

³Centre for Eye Research Australia, The University of Melbourne, Melbourne, Vic. 3002, Australia.

⁴Corresponding author. Email: chameensams@gmail.com

Abstract. *Objective:* To examine microorganisms and their antibiotic susceptibility from corneal specimens for community-acquired microbial keratitis at the Royal Victorian Eye and Ear Hospital.

Methods: A retrospective review of microbiological results from January to April 2014 was undertaken. Patients' medical records were identified from the hospital's dispensing records of ofloxacin eye drops. Corresponding microbiology results from corneal specimens (species of isolated organisms and antibiotic susceptibilities) were recorded.

Results: There were 164 patients included in the study, of which 85 cultured positive, typical for corneal specimens. Of these, 75% were Gram-positive bacteria, 16% Gram-negative and 2% fungi. The commonest organisms were *Staphylococcus* sp. (46%) and *Streptococcus* sp. (10%). Of the 76 cases where fluoroquinolone susceptibility was tested, five (6.6%) demonstrated antibiotic resistance (minimal inhibitory concentration ≥ 4.0 $\mu\text{g/mL}$), significantly higher than the 0% reported in 2000 ($P=0.002$). All *Staphylococcus* isolates resistant to ciprofloxacin were resistant to ceftazolin but susceptible to vancomycin. In ciprofloxacin-resistant isolates of streptococci, susceptibility to ceftazolin and vancomycin was observed.

Conclusions: Most organisms identified on corneal specimens were Gram-positive. Susceptibility to fluoroquinolones was still high, although a trend for increasing ciprofloxacin resistance was noted. Further investigation is necessary to investigate if this reflects a wider antibiotic resistance prevalent within the community.

Additional keywords: antibiotic resistance, keratitis, microbial keratitis.

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Introduction

Microbial keratitis (infection of the cornea) is a serious and potentially sight-threatening ocular disease that is frequently encountered in clinical practice.^{1,2} Vision loss can be from the immediate consequences of the infection itself or from longer-term sequelae such as corneal scarring. As such, it is critical to treat microbial keratitis quickly and effectively to maximise patient outcomes.^{3–6}

Initial treatment by ophthalmologists consists of empirical intensive topical antibiotics,^{7,8} the choice of which is dependent on the local prevalence of common pathogenic microorganisms and their antibiotic susceptibilities.^{9–11} Changes in antibiotic susceptibilities for community-acquired infections are a reflection of the exposure of a microorganism to antibiotic products within the wider community^{12–15} and

rising resistance levels represent concerns for clinicians as well as public policy makers. Thus, it is critical to periodically evaluate the common microorganisms and determine their patterns of resistance to ensure appropriate treatment of this sight-threatening disease.

This study aimed to document the microorganisms identified in patients with microbial keratitis at our institution over a 4-month period in 2014 and determine if their antibiotic susceptibilities had changed over time.

Methods

A retrospective review of all corneal scrapes performed between 1 January and 30 April 2014 was conducted at the Royal Victorian Eye and Ear Hospital, Melbourne, Australia. Hospital ethics committee approval was obtained.

Implications

- An increase in fluoroquinolone resistance among corneal isolates is reported, with a rise from 0% in 2000 to 6.6% in 2014 ($P=0.002$).
- Cases identified were from community-acquired microbial keratitis, implying a rise in the levels of fluoroquinolone resistance in bacteria within the community.

Location

The Royal Victorian Eye and Ear Hospital (RVEEH) is the major ophthalmic centre servicing Victoria and treats a wide range of microbial keratitis cases of varying severity.

Management of microbial keratitis

All cases of microbial keratitis treated at our institution are managed according to a standard protocol. On presentation, corneal specimens are obtained from scrapings of the infiltrate and are sent to the microbiology laboratory at St Vincent's Pathology, St Vincent's Hospital, Melbourne, for microscopy with Gram and Blankophor staining and culture on blood, chocolate and Sabouraud agar and thioglycollate broth. Once a presumed causative organism is identified, antibiotic susceptibilities are performed for penicillin, fluoroquinolones (ciprofloxacin), cefazolin and vancomycin (the common antibiotics used in the treatment of microbial keratitis). Chloramphenicol, being bacteriostatic rather than bacteriocidal, is not used for the treatment of acute microbial keratitis and so its susceptibility is not routinely tested.

The initial empirical antibiotic used in all cases of microbial keratitis is ofloxacin eye drops (Ocuflox, Allergan) prescribed at hourly intervals throughout the day and night for 48 h and then a weaning course thereafter, depending on the clinical response and microbiological results. Ofloxacin is a restricted antibiotic that requires authority approval before dispensing under the Pharmaceutical Benefits Scheme.

Data collection

All patients with a presumed microbial keratitis at our institution have a corneal scrape performed (where possible) and were prescribed ofloxacin eye drops. Inclusion criteria were patients who were dispensed ofloxacin drops within the hospital who also had microbiological samples taken. Patients who didn't have a corneal scrape performed (e.g. children with small infiltrates where a scrape would require general anaesthesia) were excluded from the study. Organism genus, species and antibiotic susceptibilities were recorded. Where no microbiology results were obtained, a 'no result' was recorded. In reporting ciprofloxacin susceptibilities, an organism was deemed resistant to ciprofloxacin if the minimal inhibitory concentrations (MIC) was greater than or equal to 4 µg/mL and intermediate resistance was documented if the MIC was between 2–4 µg/mL.^{16,17}

Susceptibility to cefazolin and vancomycin were also tested as these antimicrobials are the main second-line treatments for microbial keratitis.

Statistical analysis

Comparisons were made with previously published data from our centre in the years 2000 (a retrospective review of 140 microbial keratitis patients with similar methods and patient demographics as our study),¹⁸ 2006⁴ and 2007.¹ Comparison of fluoroquinolone resistance between 2000 and 2014 was performed using the Chi-squared test.

Results

A total of 164 patient records met the inclusion criteria for our study. None had recent (within 30 days) hospital admissions. No organism was seen on microscopy nor identified on culture in 39 cases. Of the remaining 125 cases, 167 organisms were identified of which 82 (49%) were isolated from the thioglycollate broth only, which may have questionable significance due to the risk of growth from contamination. The remaining 85 organisms were directly identified from culture on agar plates and the results are shown in Table 1. Seventy-five percent of all bacteria isolated from agar plates were Gram-positive, 16% Gram-negative, 6% were mixed organisms and 2% fungi. *Staphylococcus* species were the commonest isolate (47%) followed by *Streptococcus* species (18%).

Organisms resistant to ciprofloxacin are shown in Table 2. Resistance to ciprofloxacin (defined as MIC ≥ 4 µm/mL) was noted in five (6.6%) isolates; three isolates of methicillin-resistant *Staphylococcus aureus* (MRSA), one isolate of *Staphylococcus haemolyticus* and one isolate of *Burkholderia cepacia*. This is markedly higher than the 0% resistance rate reported by our centre in 2000 ($P=0.002$; Fig. 1).¹⁸ When intermediate resistance was included (MIC ≥ 2), all the additional resistant organisms were *Streptococcus* species.

Table 3 shows the antibiotics susceptibilities of the isolated organisms to penicillin, cefazolin and vancomycin. Of note, cefazolin resistance was found in 16% of isolates, with most being *Staphylococcus* species (19% of all *Staphylococcus* were resistant). All bacteria tested were susceptible to vancomycin. All *Staphylococcus* species resistant to ciprofloxacin were also resistant to cefazolin but susceptible to vancomycin. All *Streptococcal* species resistant to ciprofloxacin were susceptible to both cefazolin and vancomycin.

Discussion

We present data on the microorganisms cultured from microbial keratitis patients presenting to our institution from January to April 2014. Gram-positive cocci represented close to 60% of isolates, with the commonest genera being *Staphylococcus* species. Empirical monotherapy with a second-generation fluoroquinolone remains a valid choice in our region, though a rising trend for fluoroquinolone resistance was noted between

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