Shifting trends in the epidemiology of infectious keratitis demand that we approach all cases thoughtfully

Microbial keratitis
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Microbial keratitis is a potentially vision threatening condition that requires prompt diagnosis and treatment to prevent untoward outcomes. The incidence of this condition varies from 11.0 per 100,000 person years in the United States to 799 per 100,000 person years in the developing nation of Nepal. Microbial keratitis is thus a significant public health problem, and numerous studies have been performed describing the microbiology of corneal infection. As would be expected, there are regional differences in the organisms that are cultured from infected corneas, but for the most part, in the United States, Staphylococcus species seem to predominate.

On a global level, predisposing risk factors for microbial keratitis vary tremendously with geographical location. Although non-surgical trauma to the eye accounted for 48.6–65.4% of all corneal ulcers in the developing countries of Nepal and India at a large county trauma referral centre in the United States, non-surgical eye trauma accounted for only 27% of all cases. In the United States, it is contact lens wear that has emerged as a major risk factor for microbial keratitis. The reported percentage of corneal ulcers associated with contact lens wear has increased in the general population from 0% in the 1950s and 1960s, to 31% in the 1970s, and to 52% in the 1980s. In our own community based population study during the late 1990s, we found a continuation of this upward trend with 55% of corneal ulcers associated with contact lens wear (unpublished data).

Similarly, in academic referral institutions in the United States, there was a well documented upward trend in the incidence of contact lens related corneal ulcers from 9% in the late 1970s to 44% in the late 1980s. However, later reports showed a declining trend to 9–18% in the late 1990s. This reduction in corneal ulcers seen at academic referral centres coincident with an increase in the community might be attributed to more successful community treatment of ulcers since the introduction of the topical fluoroquinolones ciprofloxacin and ofloxacin in the 1990s.

In this issue of the BJO (p 834), Bourcier et al have reported that contact lens wear accounted for over half of all cases of bacterial keratitis in their study. Although the study originates from a large ophthalmic centre that provides tertiary care, most (76%) of the cases presented for the first time in their emergency room, and only 24% were referred by either general practitioners or ophthalmologists. In this mostly non-referral based population, the finding of over 50% of cases of bacterial keratitis being contact lens related is consistent with the previously mentioned community based studies from the United States. As the authors discuss, however, some of the suspected cases of contact lens related bacterial keratitis may actually include contact lens related sterile inflammatory infiltrates that resolve spontaneously upon discontinuation of contact lens wear, rather than true cases of bacterial keratitis. Thus, the authors may have undercalculated the culture positivity rate and overcalculated the percentage of cases of bacterial keratitis with contact lens wear as a risk factor.

Emerging resistance to fluoroquinolones continues to mount within and outside the sphere of ophthalmology

It is interesting that in this study, while there were more culture positive contact lenses and/or storage cases than culture positive corneal scrapings, similar bacteria were isolated from the two sources in only 25% of all cases. This demonstrates that while organism recovery from a lens or case may be easier than from the cornea, the identity of organisms recovered from the contact lens and case cannot be considered a reliable guide for directing antimicrobial therapy. As was shown in this study and has been demonstrated by previous studies, contact lens storage containers are frequently contaminated, commonly with Gram negative organisms. While it has been recognised that Gram negative organisms such as Pseudomonas aeruginosa are associated with contact lens related corneal ulcers, Gram positive organisms such as Staphylococcus species and Streptococcus species have also often been shown to be responsible for a significant portion of these ulcers even when Gram negative organisms are recovered from the lens and case. Indeed, the current study reports a higher incidence of Gram positive organisms than Gram negative organisms recovered from infections associated with contact lens wear. Thus, exclusive reliance on culture data from contact lenses and/or cases may result in suboptimal treatment of corneal ulcers.

Bourcier et al, as well as most authors of studies from academic referral centres, followed the textbook practice of scraping of all suspected cases of microbial keratitis for smear and culture. Since the Gram stain might fail to reveal culpable organisms and it is inadvisable to delay treatment while awaiting the results of cultures, it is common practice to begin empirical treatment with broad spectrum antibiotic drops. Treatment can then be modified later based on clinical response and, if necessary and available, on culture results. Traditionally, specially prepared fortified combined antibiotics were used to provide broad spectrum coverage, but the limited availability, cost, and inconvenience of these fortified preparations have led many academic and community based ophthalmologists to embrace the use of the commercially available topical fluoroquinolones (ciprofloxacin, ofloxacin and, more recently, levofloxacin) since their introduction in the 1990s. These antibiotics have good ocular penetration and provide broad spectrum coverage against most aerobic Gram negative and Gram positive bacteria. They also are safe, do not require refrigeration, and are easily available. In addition, many clinical studies have demonstrated excellent efficacy of these drugs in treating bacterial keratitis. In a questionnaire based study, 82% of a random sampling of non-cornea fellowship trained ophthalmologists reported that they would treat less severe cases of suspected bacterial keratitis with a single fluoroquinolone, and 62% reported that they would treat more severe cases in this manner. Our own study of corneal ulcers in a non-referral based population found that 75% of corneal ulcers were in fact treated with a single fluoroquinolone agent (unpublished data).

Although there has always been a known gap in coverage for Staphylococcus species by the second generation fluoroquinolones, emerging resistance of Staphylococcus aureus to ciprofloxacin and ofloxacin has raised concern over the use of monotherapy with these agents for suspected cases of bacterial keratitis. This is especially true given the high rates of microbial keratitis caused by Gram positive organisms. It is well recognised that the levels of drugs in the cornea obtained with topical therapy far
Human papillomavirus expression was shown to be required for the maintenance of the malignant phenotype in specific cervical cancer cell lines; (4) a substantial number of epidemiological studies have been performed which point to high-risk HPV as a primary risk factor for cervical cancer. In addition, large case-control and prospective epidemiological studies supported this idea, and indicated that persisting HPV infections were the most significant risk factor in cervical cancer.1,7

Different types of HPV have been identified in a high percentage of non-melanoma skin cancers (basal and squamous cell carcinomas). However, these basal and squamous cell carcinomas occur preferentially in light exposed sites. This could suggest an interaction
between ultraviolet light and a low risk (non-mutagenic) papillomavirus in sunlight could make it a possible candidate in pterygia, which are thought to have aetiology involving ultraviolet irradiation.

The binding to the p53 protein of the E6 oncoprotein, encoded by HPV types 16 and 18, results in the rapid degradation of p53 protein through the ubiquitin-mediated pathway. This HPV infection mechanism leads to a damaged p53-dependent programmed cell death pathway, which is similar to that caused by mutations in the p53 gene. Low levels of normal nuclear p53 protein permit mutations in other genes to accumulate and allow the multistep development of tumours. Also, reduced bioavailability of p53 protein has been shown to be a key regulatory event in perturbation of tumours. Also, reduced bioavailability of p53 protein sensitizes human papillomavirus type 16 immortalized human keratinocytes to CD95-mediated apoptosis. Oncogene 2002;21:165–75.


Responding to readers’ and authors’ needs

Andrew D Dick, Creig Hoyt

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Br J Ophthalmol 2003;87:808

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