Microbial keratitis
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Microbial keratitis

B H Jeng, S D McLeod
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Shifting trends in the epidemiology of infectious keratitis demand that we approach all cases thoughtfully

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[1] to 799 per 100 000 person years the developing nation of Nepal.[2] 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,[2–3] at a large county trauma referral centre in the United States, non-surgical eye trauma accounted for only 27% of all cases.[4] 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.[1] 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late 1990s, we found a continuation of this upward trend with 55% of corneal ulcers associated with contact lens wear (unpublished data).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.[5–11] However, later reports showed a declining trend to 9–18% in the late 1990s.[12–13] 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.[13–17]

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 continue to mount both 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.[15–17] 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.[18] 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 *Streptococcus* species by the second generation fluoroquinolones, emerging resistance of *Staphylococcus aureus* to ciprofloxacin and ofloxacin[19–20] 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

exceed minimum inhibitory concentration (MIC) levels as measured in the laboratory based on expected serum levels of antibiotic. Thus, many organisms can be eradicated by an antibiotic to which they are reportedly resistant, and it has been documented that infection by "resistant" organisms treated by a fluoroquinolone alone required a change in therapeutic regimen due to clinical failure only approximately 10% of the time.[19]

Nevertheless, along with assessments of resistance based on MIC tests, reports of an increasing incidence of clinical failure because of emerging resistance to fluoroquinolones continue to mount both within and outside the sphere of ophthalmology. A role for pretreatment scrapings for laboratory testing therefore persists, even in the age of ever more potent empirical treatment afforded by the newest fluoroquinolones. Based on the microbiological data provided by Bourcier et al, it is of interest that the ophthalmic fluoroquinlone preparations now entering practice, gatifloxacin and moxifloxacin, show particular strengths with regard to activity against Gram positive organisms, a significant cause of morbidity even in the setting of contact lens related keratitis. It remains to be seen whether the relative reduction in Gram negative activity will allow monotherapeutic application or, if combination with a second generation fluoroquinolone, will be required to maintain effective empirical coverage of that group of organisms.

Initial treatment of suspected cases of microbial keratitis with topical fortified antibiotics has long been the gold standard for management of the most severe manifestations of this condition, and the role for fluoroquinolone monotherapy for these and less severe cases continues to be debated. However, if one can propose that the "optimal" management of microbial keratitis is that which is the most convenient for both the patient and the physician, the most cost effective, and the most efficacious, then the "optimal" management strategy is as yet undefined. In spite of the advances in antibiotic pharmacology, shifting trends in the epidemiology of infectious keratitis demand that we approach all cases thoughtfully. Studies such as that provided by Bourcier et al provide most valuable information to this end.

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Human papillomavirus
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Does human papillomavirus cause pterygium?

T W Reid, N Dushku

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HPV is not necessary for the formation of a pterygium

Human papillomavirus (HPV) is the only DNA tumour virus where a large body of evidence implicates it in human cancers. The evidence for a causative role of HPV in human cervical cancer, was recently reviewed by zur Hausen,[1] and is the following: (1) expression of specific HPV genes (such as E6 and E7) were shown in cervical cancer cell lines and cancer biopsies[2]; (2) viral DNA was shown to have immortalisation properties[3 4]; (3) viral oncogene expression was shown to be required for the maintenance of the malignant phenotype in specific cervical cancer cell lines[5 6]; (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.[7 8]

Different types of HPV have been identified in a high percentage of nonmelanoma 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 infection.[9] This would 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,[10 11] 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 CD95 signalling in HPV16 immortalised keratinocytes.[12] HPV and p53 overexpression also commonly coexist in oropharngeal carcinomas,[13] penile carcinomas,[14] grade III cervical intraepithelial neoplasia,[15] and invasive squamous cell carcinomas of the cervix.[15] Since increased nuclear p53 expression without apoptosis was found in the limbal epithelium of pterygia, limbal tumours, and most pingueculae,[16] this would be consistent with HPV playing a part in the formation of pterygia.

The paper by Piras et al, in this issue of the BJO (p 864), shows a 100% incidence (17/17) of HPV in pterygia from Italian cases and a 21% (5/24) incidence from Ecuadorean cases. A recent study by Gallagher et al[17] showed a 50% (5/10) incidence of HPV in pterygia in the United Kingdom. Detorakis et al[18] found 15 pterygia contained type 18 HPV, for a total of 30% (15/50) in Greece. In addition they found that 8% of the associated conjunctiva contained HPV (4/50). In other studies Dolmetsch et al[19] found HPV-16 in 100% of their pterygia (16/16) from Canada using immunohistochemical techniques.

The above results are in contrast with the results of McDonnell et al,[20] who found HPV-16 in 88.1% (37/42) of their patients with conjunctival epithelial neoplasia but none in six pterygia from America. Dushku et al[21] also found no evidence of HPV in 13 pterygia and 10 limbal tumours from American cases. McDonnell et al[20] also found HPV in tissue swabs from eyes with no visible lesions in 66.7% (4/6) of patients with unilateral conjunctival epithelial neoplasia and in one patient who showed a persistence of infection many years after successful eradication of the lesion. This is consistent with the finding of Karcioglu and Issa[22] who found HPV in 57% of in situ squamous cell carcinomas, 55% of invasive squamous cell carcinomas; however, they also found HPV in nonneoplastic lesions (20% of climatic droplet keratopathy and 35% of scarred

corneas) as well as 32% of normal conjunctival tissue obtained during routine cataract extractions. Thus, it would appear that HPV is not required for a pterygium and that even in its presence it cannot act alone in the development of conjunctival epithelial neoplasia.

At the moment several companies and research laboratories are carrying out preclinical and clinical trials of vaccines against high risk HPV.[23–25] Since experiments with purified papillomavirus structural proteins as vaccines showed protection against the primary infection of dogs and rabbits,[26 27] an effective prevention can also be expected for the human vaccine. If this is true it may allow us to know whether prevention of HPV decreases or blocks the incidence of different cancers. It would also be of interest to see whether vaccinated individuals show a lower incidence of pterygia.

Since Koch's postulates cannot be fulfilled and unless more definitive results are obtained such as those from future HPV vaccine trials, we can only make the following statements for the role of HPV in the occurrence of pterygia: (1) HPV is not necessary for the formation of a pterygium; (2) it is unlikely that HPV can act as the sole cause of a pterygium; (3) HPV may have a role in the formation of some pterygia; (4) pterygia and limbal dysplasias in the interpalpebral area, which regress after topical antiviral treatment with interferon α2b, may be due to HPV.[28 29]

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BJO
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Responding to readers' and authors' needs

Andrew D Dick, Creig Hoyt

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Future changes to the *BJO*

As editors, keeping a pace with changes in publishing, pleasing both readers and authors without creating chaos or anarchy is challenging. We continue to respond to the voices of both readers and authors alike and will continue as such to change the journal format to maintain and fulfil its mission of supplying high quality information in its most relevant and readable form. We acknowledge that the readers and authors may have different expectations of the journal. Firstly, readers wish to be assisted in their continual professional development and revalidation and require easy access to information that is readable and succinct. Secondly, there is a need to assist researchers with information pertinent to their individual needs and, thirdly, of course, we need to give the authors the medium to present their findings and views in the most expeditious manner and which will sell to the widest audience.

As such, the *BJO* is committed, along with the rest of the BMJ Publishing Group, to provide a medium to satisfy all. Although the *BJO* has seen a dramatic increase in submissions, now over 1300 articles a year, with an acceptance rate of 34%, going online has enabled our mean time to decisions on papers to be cut drastically to three weeks. We aim to please authors further within the next 12 months as we launch the capability to publish manuscripts as soon as they are accepted—on the website—followed in print by the technically edited version a few months later. This will provide immediate dissemination of up to date work to all. In addition, this will hopefully create fruitful correspondence, which will be all web based; you will be asked to submit your correspondence (Mailbox) directly to *eBJO*. We will also increase page provision in the print journal to ensure that print publication time is around four months from acceptance.

What about the readers? The *BMJ* has reiterated from its studies that readers do not read traditional long full original articles, and the need for such articles to be so long has been questioned. We wish to encourage articles that are written succinctly and, in time, we will be providing a modified "Instructions to authors" that will have link sites to assist prospective authors less experienced in writing. The articles will be divided into *Clinical science* and *Laboratory science* as is the case at present and, within each section, there will be the opportunity to submit either *extended* or *scientific* reports. There will be strict word counts of 3000 and 1500 words, respectively, and we will be encouraging authors where appropriate to submit their work in the shorter version. Letters to the editor will remain but we will be focusing our attention, because of priority and space, on case series, genetic reports, and clinicopathological reports. Perspectives will also remain but again will be limited strictly to 4000 words. We still encourage and solicit editorials, commentaries, and world views and maintain our commitment towards globalisation, publishing work from, and provision of information to all.

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