In vitro antibiotic resistance in bacterial keratitis in London

Stephen J Tuft, Melville Matheson

Abstract

***Aim*—To document changes in the profile of bacterial isolates from cases of keratitis and changes in their susceptibility to first line antibiotic therapies.**

***Methods*—A retrospective review was performed of all bacterial isolates from cases of keratitis seen between 1984 and 1999. In vitro laboratory susceptibilities to antibiotics were determined by the Kirby–Bauer disc diffusion method. The number of isolates, changes in the proportion of bacterial types, and the number that were fully resistant to monotherapy (ofloxacin), dual therapy (gentamicin and cefuroxime), and prophylactic treatment (chloramphenicol) were calculated.**

***Results*—There were 1312 bacterial isolates over 16 years. Gram positive bacteria accounted for 54.7% of isolates and *Staphylococcus* species (33.4%) were the most frequently isolated organisms. During the study period there has been an increase in the proportion of *Pseudomonas* species isolates but no overall increase in the proportion of Gram negative isolates. There has not been an increase in the proportion of isolates resistant to ofloxacin since 1995 or an increase in resistance to the combination of gentamicin and cefuroxime. However, since 1984 there has been a significant increase in proportion of Gram negative organisms resistant to chloramphenicol (p=0.0019).**

***Conclusions*—An increase in the in vitro resistance of organisms to first line therapies for bacterial keratitis has not been observed. An increased resistance to chloramphenicol indicates that this drug is unlikely to provide prophylactic cover when Gram negative infection is a risk. Continued monitoring for the emergence of antibiotic resistance is recommended.**

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Moorfields Eye Hospital, London EC1V 2PD
S J Tuft

Institute of Ophthalmology, London EC1V 9QS
M Matheson

Correspondence to:
Mr S J Tuft, Moorfields Eye Hospital, City Road, London EC1V 2PD
stuft1@cs.com

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Bacterial keratitis is potentially sight threatening if appropriate antibiotic therapy is not instituted rapidly. Treatment is normally initiated after cultures have been taken from the lesion to enable identification of the organism and its sensitivity to antibiotics. Treatment is then modified according to the laboratory results and the clinical response.[1] The use of a Gram stain to determine initial therapy has been advocated[2] but this technique is not generally available or sufficiently reliable to permit the selection of a specific antibiotic. Empirical treatment with a combination of two fortified antibiotic preparations (dual therapy) selected to cover the entire range of common Gram positive and Gram negative pathogens has been the mainstay of treatment for many years. Although effective there are problems of toxicity of the aminoglycosides and the limited availability and stability at room temperature of fortified preparations.[3–5] Fluoroquinolones were introduced as monotherapy for suspected bacterial keratitis owing to their broad spectrum of activity, low toxicity, good corneal penetration, and their efficacy at a commercially available strength.[6–10] The equivalence of dual therapy using fortified antibiotics and monotherapy with a fluoroquinolone has been demonstrated in controlled clinical trials.[11–13]

The introduction of fluoroquinolones for systemic use was followed by the rapid emergence of significant levels of resistance. Resistance is now common in *Staphylococcus* and *Pseudomonas*, with resistance rates for some strains of *S aureus* as high as 82%.[14–17] In addition, bacteria resistant to fluoroquinolones are often resistant to other antibiotics such as methicillin.[18–20] There followed reports of isolates from bacterial keratitis that were resistant to fluoroquinolones,[21–24] and the documentation of high rates of resistance at some centres[25–27] has led to the continued use of monotherapy with fluoroquinolones being questioned.

To determine any local change in the spectrum of infection and the resistance of isolates to antibiotics we reviewed all cases of bacterial keratitis seen since 1984. We have documented the proportion of Gram positive and Gram negative organisms and looked for changes in the proportions of the five commonest species. During this time our standard initial antibiotic treatment for suspected bacterial keratitis has altered. Before 1993 the preferred initial treatment was hourly treatment with topical fortified cefuroxime (5%) and gentamicin (1.5%), but since 1993 the initial topical treatment for the majority of patients has been hourly ofloxacin 0.3%. The results of in vitro sensitivity testing with these first line antibiotics were therefore examined. We have also recorded resistance to chloramphenicol, as this has been the usual antibiotic for prophylactic treatment of corneal epithelial defects during the study period.

Material and methods

Details of all isolates from cases of bacterial keratitis seen at Moorfields Eye Hospital between January 1984 and December 1999 were entered onto a database. Corneal scrapings were performed using non-preserved topical anaesthesia and either a Kimura spatula or the tip of a sterile 21 gauge disposable needle. Smears were routinely examined by Gram

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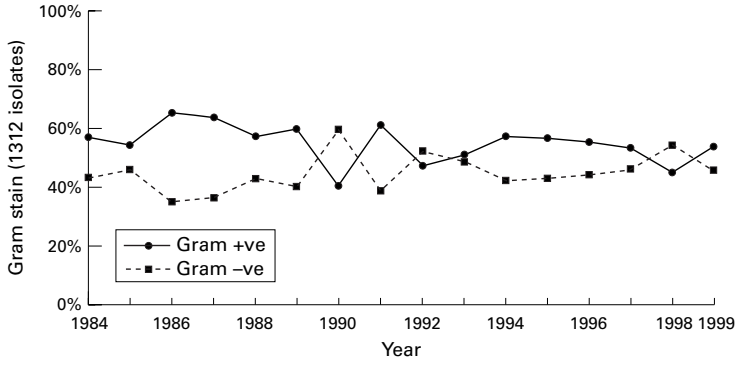

Figure 1 Percentage of total isolates according to Gram stain.

staining and additional samples were inoculated onto solid and liquid phase media (blood agar, Robertson's cooked meat, thioglycolate broth, and brain heart infusion broth). Incubation was performed at 37°C under appropriate atmospheric conditions. Selective media such as Lowenstein-Jensen and Sabouraud's dextrose agar were used if clinically indicated. A positive isolate was defined as a growth along the line of inoculation on solid media, growth in two liquid media, or growth on one medium with consistent microscopy. Only bacteria isolated from the cornea were considered; conjunctival isolates in the presence of a keratitis were not included in this analysis. Isolates were subjected to in vitro antimicrobial sensitivity testing against commonly used antibiotics using the Kirby–Bauer disc diffusion method. The spectrum of antibiotics tested has changed over the years, but since 1994 all isolates have been routinely tested for sensitivity to ofloxacin, gentamicin, and cefuroxime.

Details of the year, associated risk factors, the bacterial types, and the sensitivity spectrum were recorded. Susceptibility was graded as sensitive, intermediate sensitivity, or resistant by comparing the patient isolate with NCTC/ATCC strains known to be sensitive to the antibiotics being tested. Resistance to ofloxacin or chloramphenicol was defined as resistance to that antibiotic alone, while resistance to the combination of cefuroxime and gentamicin was defined as resistance to both antibiotics although each antibiotic was tested separately. The intermediate sensitivity responses were grouped with the sensitive responses. A bacterium isolated from the same patient on more than one occasion was considered to be one isolate if it had the same spectrum of antibiotic resistance.

Data concerning bacterial types were analysed for the full data collection period. Data on resistance to an antibiotic is only presented for years after 95% of isolates were tested. Thus data for resistance to chloramphenicol are presented from 1985, to cefuroxime and gentamicin are presented from 1994, and data for ofloxacin are presented from 1995. Statistical analysis of changing proportions over time was performed using the Spearman rank correlation coefficient.

Table 1 Bacterial isolates 1984–99

Organism	*Number*	*Percentage*
Staphylococcus spp	439	33.4
Pseudomonas spp	326	24.8
Streptococcus spp	250	19.0
Moraxella spp	77	5.9
Serratia spp	40	3.0
Haemophilus spp	29	2.2
Enterobacter spp	27	2.1
Branhamella spp	17	1.3
Diphtheroid spp	17	1.3
Coliforms (non-speciated)	17	1.3
Gram −ve (non-speciated)	15	1.1
Bacillus spp	15	1.1
Corynebacterium spp	9	0.7
Proteus spp	9	0.7
Escherichia coli	8	0.6
Citrobacter spp	5	0.4
Klebsiella spp	5	0.4
Acinetobacter spp	4	0.3
Nocardia spp	2	0.2
Propionibacterium spp	2	0.2
Alcaligenes spp	1	0.1

Results

A total of 1312 bacterial isolates from 1239 episodes of bacterial keratitis were included. Gram positive organisms accounted for 54.7% of isolates. While there generally seems to have been an increase in Gram negative isolates over the study period, there has been a great deal of variability between annual intervals and the Spearman test was not significant ($\rho = 0.407$, $p = 0.117$) (Fig 1). The most commonly isolated organisms are presented in Table 1. When the five most commonly isolated groups of bacteria were considered individually, there was evidence that there has been an increase in the proportion of *Pseudomonas* species and *Serratia* species between 1984 and 1999 ($\rho = 0.4971$, $p = 0.0501$ and $\rho = 0.5133$, $p = 0.0420$) and a reduction in the percentage of *Moraxella* species ($\rho = -0.5235$, $p = 0.0374$). There was no significant alteration in the proportion of *Staphylococcus* species or *Streptococcus* species isolates.

The in vitro resistance of isolates to gentamicin and cefuroxime was determined separately and the resistance of an organism to both antibiotics was then used as an index of resistance to dual therapy. Since 1994 a total of 634 (96.6%) of 656 isolates were tested against both antibiotics. Five isolates (0.8%) were fully resistant to both cefuroxime and gentamicin and four (0.6%) had intermediate sensitivity to only one or both antibiotics. There has been no trend for increasing numbers of isolates resistant to the combination of antibiotics over the study period (Fig 2), and no increase in either Gram positive isolates resistance to cefuroxime since 1994 or Gram negative isolates resistant to gentamicin since 1984. Since 1995 a total of 524 (99.0%) of 529 isolates were tested against ofloxacin. Twelve isolates (2.3%) were fully resistant to ofloxacin and five (0.9%) were of intermediate sensitivity. There has been no trend for an increase in the proportion of all isolates fully resistant to ofloxacin, or an increase in resistance when the Gram positive or Gram negative isolates were analysed separately (Fig 3). All seven isolates resistant to ofloxacin that were also tested against ciprofloxacin were resistant.

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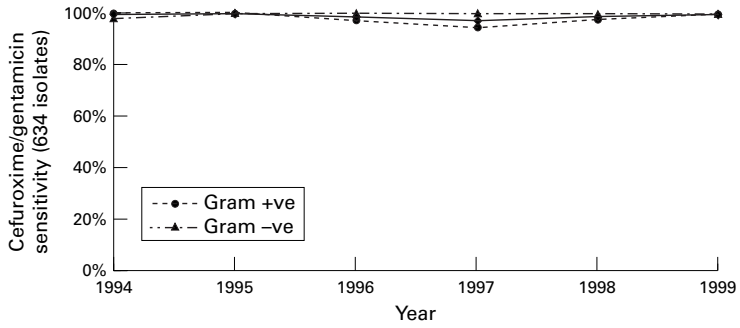

Figure 2 Percentage of all isolates sensitive and partially sensitive to cefuroxime and gentamicin (solid line). Gram positive (broken line, circles) and Gram negative isolates (broken line, triangles) are shown separately.

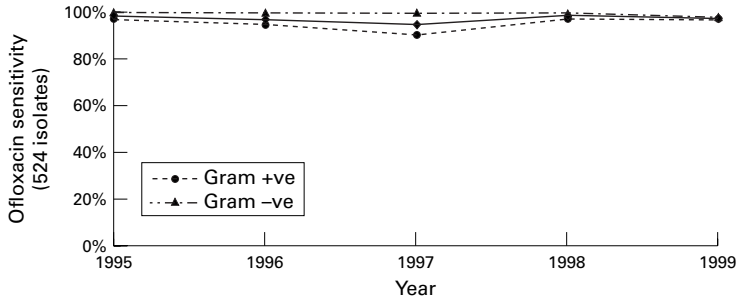

Figure 3 Percentage of all isolates sensitive and partially sensitive to ofloxacin (solid line). Gram positive (broken line, circles) and Gram negative isolates (broken line, triangles) are shown separately.

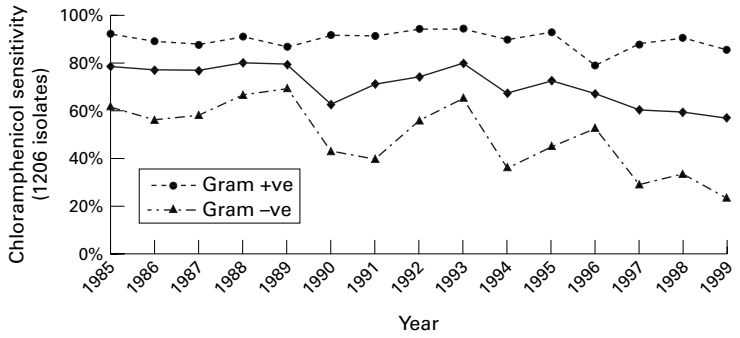

Figure 4 Percentage of all isolates sensitive and partially sensitive to chloramphenicol (solid line). Gram positive (broken line, circles) and Gram negative isolates (broken line, triangles) are shown separately.

The characteristics of the isolates resistant to the combination of cefuroxime and gentamicin or ofloxacin, including their sensitivity to other commonly used ocular antibiotics, are presented in Table 2. It should be noted that bacteria resistant to both cefuroxime and gentamicin were isolated from two patients on two separate occasions and bacteria resistant to ofloxacin were isolated from three patients on two separate occasions. Multiple drug resistant coagulase negative staphylococci were isolated from one eye of a patient (No 6) on four separate occasions over 18 months, suggesting that resistance is not lost when treatment is stopped. Two isolates of multidrug resistant coagulase negative staphylococci were resistant to cefuroxime, gentamicin, and ofloxacin.

Since 1985 a total of 1206 (98.0%) of 1231 isolates were tested for resistance to chloramphenicol. A total of 367 (30.4%) isolates were resistant and an additional 20 (1.7%) were partially resistant. A total of 67 (10.2%) Gram positive organisms and 300 (54.4%) Gram negative organisms were fully resistant to chloramphenicol. There has been a significant increase in the proportion of isolates resistant to chloramphenicol ($\rho = 0.7$, $p = 0.0037$). However, this change was almost entirely the result of a marked increase in the proportion of Gram negative organisms resistant to chloramphenicol ($\rho = 0.73$, $p = 0.0019$), as there was no increase in resistance among the Gram positive group ($\rho = 0.03$, $p = 0.9144$) (Fig 4).

Discussion

Treatment of bacterial keratitis requires the use of an effective antibiotic delivered at a dose sufficient to achieve therapeutic concentrations in the cornea. Fortified preparations of some antibiotics—for example, cefuroxime 5% and gentamicin 1.5%, are required to achieve therapeutic concentrations,[28] and results suggest that this regimen is effective in vitro against at least 98% of our isolates. Fluoroquinolones were introduced as a commercially available alternative to topical fortified

Table 2 Details of all bacterial isolates (1984–99) resistant to ofloxacin, and both cefuroxime and gentamicin

Patient	*Organism*	*Chl*	*Gen*	*Cef*	*Ctn*	*Ofl*	*Cip*	*Van*	*Ami*	*Pen*	*Fuc*	*Tob*	*Tic*	*Risk*
Ofloxacin:														
1	Viridans-type *Streptococcus*	s	r	s	s	r	r	s	r	s	r			Vernal keratoconjunctivitis
2	Viridans-type *Streptococcus*	s	r	s		r				s	r			Herpetic keratitis
3	Coagulase negative *Staphylococcus**		r	r		r					s			Bullous corneal oedema
4	*S aureus*	s	s	s		r					s			Corneal exposure
5	*Rhodococcus*		r		r	r								
6	Coagulase negative *Staphylococcus*	r	s	r		r	r				r			Corneal graft, dry eye
6	Coagulase negative *Staphylococcus*†	r	r	r	r	r	r	s	s					Corneal graft, dry eye
7	*S aureus*	s	s	r	r	r		s	r					Bullous corneal oedema
7	Viridans-type *Streptococcus*	s	r	s		r		s		s				Foreign body
8	*S aureus*	s	s	s	s	r	r				s			Dry eye
9	β *Streptococcus*			p		r	r	s		p				Corneal graft
9	*S aureus*	r	r	s	s	r					r			Corneal graft
10	*E cloacae*	r	s	r	s	r	r	r	s		r	r	r	Graft *v* host disease
11	Coagulase negative *Staphylococcus*	r	s	s	r	r	r	r	s		s			Corneal graft
Cefuroxime and gentamicin:														
12	Coagulase negative *Staphylococcus*	s	r	r							s			Corneal graft
3	Coagulase negative *Staphylococcus**		r	r		r					s			Bullous corneal oedema
13	*Streptococcus* spp	r	r	r		s				s	r			Foreign body
6	Coagulase negative *Staphylococcus*	s	r	r		s					s			Corneal graft, dry eye
6	Coagulase negative *Staphylococcus*†	r	r	r	r	r	r	s	s					Corneal graft, dry eye
14	*P maltophilia*	s	r	r	s		r		r			r	s	Herpetic keratitis
14	*P aeruginosa*	r	r	r	s	s	r		r			s	s	Herpetic keratitis

Chl = chloramphenicol, Gen = gentamicin, Cef = cefuroxime, Ctn = ceftazidine, Ofl = ofloxacin, Cip = ciprofloxacin, Van = vancomicin, Ami = amikacin, Pen = penicillin, Fuc = fucidic acid, Tob = tobramicin, Tic = ticarcillin, r = resistant, s = sensitive, p = partially resistant.
Two isolates (* and †) resistant to cefuroxime, gentamicin, and ofloxacin appear twice.

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antibiotics because they were effective against most common pathogens. Although the MIC of some Gram positive organisms is relatively high[7] fluoroquinolone penetration exceeds the MIC90 of most bacteria after therapeutic treatment.[8 9] They were shown to be as effective but less toxic than dual therapy[11–13] and they were therefore widely adopted as the first line treatment for suspected bacterial keratitis.[29] Although significant resistance to fluoroquinolones has been reported from India and the United States,[25–27] our results indicate that in London ofloxacin is still effective, in vitro, against 97% of isolates from keratitis with no evidence of increasing resistance since 1995. As there is almost complete cross resistance among the DNA gyrase inhibitors this result is probably representative of the other topically used fluoroquinolones such as ciprofloxacin.

The emergence of pathogens resistant to fluoroquinolones was expected to be slow because a chromosomal mutation is required[30] and resistance cannot be transferred by plasmid mediated mechanisms.[31 32] Resistance is, however, more common in some bacterial genera than others, notably the staphylococci and the pseudomonads,[33] both of which are common causes of bacterial keratitis. In addition, the relatively low bacterial load in keratitis and the high drug concentrations achieved does not favour the local selection of resistant organisms.[7] Despite this, fluoroquinolone resistance has become a significant clinical problem in some countries. Kunimoto *et al* reported that in Hyderabad resistant cases had increased significantly since 1993 and that by 1997 32.5% of Gram positive cocci (principally *S aureus*) and 13.3% of Gram negative organisms were resistant to ciprofloxacin.[25] There was no change in resistance among *Streptococcus* species or coagulase negative staphylococci. Also from Hyderabad, Garg *et al* reported that *Pseudomonas aeruginosa* resistance to ciprofloxacin had increased to over 20% by 1998.[27] In the USA Goldstein *et al* reported a significant increase in resistance of *S aureus* to a level of 35% by 1997.[26] They also noted a stable but high level of resistance among coagulase negative staphylococci and streptococci (18.7% and 49.6% resistant to ciprofloxacin respectively), although there was no increase in resistance of Gram negative isolates (2.7%). Multiple drug resistance can be a problem in fluoroquinolone resistant isolates. Although Kunikoto *et al* reported that 79.1% of their isolates that were resistant or partially resistant to ciprofloxacin were sensitive to cefazolin, a first generation cephalosporin,[25] Garg *et al* found that 63.6% of their *Pseudomonas* isolates that were resistant to ciprofloxacin were resistant to gentamicin.[27]

The profile of the causative organisms isolated from series of bacterial keratitis must be considered when reviewing changing patterns of drug resistance. Differences in temperature, humidity, and the aetiology of the ulceration may alter the pattern between geographic regions—for example, contact lenses are a major source of corneal ulcers in the United Kingdom while agricultural injuries are more common in India. Although there has not been an overall change in the proportion of Gram positive to Gram negative isolates in our series there were changes in subgroups of bacteria, with an increase in the proportion of *Pseudomonas* and *Serratia*, and a decrease in the proportion of *Moraxella* isolates. The reasons for these changes are unclear although the increased use of contact lenses during the study period may have increased the number of Gram negative infections. A decrease in the number of Gram positive isolates but stable numbers of Gram negative isolates was reported by Goldstein *et al* who considered that this was the result of an alteration in their patient referrals pattern.[26] Unfortunately, a reliance on broad spectrum therapy has led to a tendency for routine investigation of suspected microbial keratitis to be omitted.[26 29] Because of the need to monitor for emerging resistance it is essential in at least some representative centres to culture all new cases of keratitis. From these types of data we have established that at present London differs from some other locations in the prevalence of fluoroquinolone and aminoglycoside resistance in isolates from keratitis. Clearly, a conclusion that monotherapy with a fluoroquinolone is no longer appropriate[27] only applies to areas where fluoroquinolone resistance is demonstrably increasing or to patients who have recently arrived from such an area. Importantly, patients who contract their infection in certain environments, such as intensive care units, are also at risk as patients in these locations tend to be colonised with multidrug resistant organisms.

The efficacy of antibiotics used for topical prophylaxis for corneal disease is controversial. Chloramphenicol is commonly used in the United Kingdom, although a purported risk of aplastic anaemia has led to its general abandonment in the United States, where fluoroquinolones are commonly used for prophylaxis.[34] The results of our in vitro tests indicate that there has been a significant reduction in the proportion of Gram negative isolates that are sensitive to chloramphenicol. This is a potential area of concern, especially as there has been a concurrent increase in the proportion of *Pseudomonas* isolates over the same period. This suggests that chloramphenicol is no longer an appropriate antibiotic for the prophylactic treatment of corneal disease secondary to contact lens wear.

The Kirby-Bauer disc diffusion assay estimates sensitivity to drug levels that are attainable in the serum, while the clinical response depends on the corneal penetration of the antibiotic and the host response to the infection. The degree of concordance between the in vitro result of antibiotic sensitivity and the clinical response is not known and an assessment of the clinical response should ideally be included in a survey of clinical resistance. The high levels of antibiotics attainable in the cornea may mean that in vitro antimicrobial susceptibility testing overestimates clinical resistance.[7] For this reason bacteria

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with a partial sensitivity response were included with the sensitive organisms when considering changes in the pattern of resistance. However, including them with the resistant organisms does not materially affect our conclusions. Although the vitro response does not always reflect the clinical response,[11 12 35] Garg *et al* reported that their *Pseudomonas* isolates classed as resistant to ciprofloxacin by in vitro testing also tended to fail to respond to topical treatment.[27]

The phenomenon of increasing resistance to antibiotic therapy is a matter of urgent concern in the UK and worldwide.[36] Multidrug resistant bacteria are particularly difficult to treat and although new antibiotics have been developed that are active against multidrug resistant Gram positive organisms there is no new class of drug in near prospect with activity against Gram negative organism. The excessive and inappropriate systemic use of antibiotics is thought to be one of the most important factors influencing the increased prevalence of antibiotic resistance. The impact of ophthalmic prescribing practices on antibiotic resistance is unknown. Fortunately, multidrug resistant keratitis is rare in the UK, possibly because such organisms are typically acquired in hospital while most keratitis is acquired in the community. However, we can no longer assume that our first line antibiotics will continue to cover all commonly encountered corneal pathogens. The indiscriminate use of antibiotics for prophylaxis and trivial infection may still jeopardise the availability of effective treatments for severe disease. Data from one country can not be extrapolated to another and there is a need for continued monitoring of the type and sensitivity of corneal isolates in representative centres in each country. This evidence should then form the basis for antibiotic prescribing guidelines.

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