

Host, microbial, and pharmacological factors affecting the outcome of suppurative keratitis

DOUGLAS J COSTER AND PAUL R BADENOCH

From the Department of Ophthalmology, Flinders Medical Centre, Bedford Park, South Australia

SUMMARY A review of 87 cases of microbial keratitis in South Australia was made to determine the factors which influence the outcome of the disease. The preceding pathology and the extent of ulceration at presentation were found to be significant, while the presence of hypopyon was less important. Infection with *Pseudomonas aeruginosa* was most likely to result in a poor outcome. Most patients had a history of traumatic injury, herpes simplex keratitis, or a corneal graft. The choice of gentamicin and a cephalosporin as appropriate initial therapy in Australia was supported. The results are discussed with reference to current research objectives.

Microbial keratitis is a common sight threatening disease which occurs in all parts of the world.¹ Rational treatment involves identification of the causative agent and institution of specific antimicrobial chemotherapy. This demands clinical suspicion of a microbial cause for keratitis, knowledge of the likely agents in a particular community, reliable microbiological investigation, and the availability of effective antibiotics. Even under optimal conditions treatment is not invariably successful.

In an attempt to identify factors which may affect outcome we have reviewed the course of the disease in patients presenting to the Department of Ophthalmology at Flinders Medical Centre. Although a number of ophthalmologists have been involved, treatment received has been consistent and according to strict protocol.

Flinders Medical Centre is situated in suburban Adelaide. As the Department of Ophthalmology functions both as a primary care facility and a referral centre for the state of South Australia and beyond, the patients described in this study either presented for primary care or were referred by other ophthalmologists. Although management protocols are firmly established and every attempt has been made to keep consistent records, this study has the disadvantages of being retrospective. Such a limited approach, however, is justified in the case of this disease because of the difficulty of carrying out prospective controlled clinical trials.

Correspondence to Professor D J Coster, Department of Ophthalmology, Flinders Medical Centre, Bedford Park, South Australia 5042

Patients and methods

Between August 1980 and February 1986 material was collected from the corneas of 164 patients for microbiological study. All patients were investigated in whom there was a defect in the corneal epithelium and inflammation in the underlying corneal stroma. Thus both patients in whom microbial infection was strongly suspected as the cause of inflammation and others in whom alternative explanations were possible were similarly tested.

A standardised method of specimen collection was employed. Corneal scrapings were taken in the Eye Clinic or in the ward with an operating microscope or a slit-lamp. Specimens were collected with a platinum spatula. Two horse blood agar plates, a chocolate agar plate, a Sabouraud's agar slope, two glass slides, a cooked meat-glucose broth, and two brain-heart infusion broths supplemented with vitamin K, haemin, and nicotinamide adenine dinucleotide (NAD) were inoculated. The Sabouraud's slope was incubated at 30°C for up to one month for culture of fungi. The other media were incubated at 37°C for two days. One blood plate and the cooked meat broth were incubated anaerobically. The remaining media were incubated in 5% carbon dioxide/air. The slides were used for Gram and Giemsa stains.

Organisms were identified by standard microbiological methods as given in the *Manual of clinical microbiology*.² Susceptibility to antimicrobial agents was determined by a modified Kirby-Bauer technique.³ A growth was considered significant if

organisms were seen on microscopy and grew on at least one medium, or if no organisms were seen on microscopy yet growth occurred on at least two media.

Results

A significant growth of organisms was isolated 87 times from 78 eyes of 76 patients over the 5½-year period. There were 50 males and 26 females, and their ages ranged from 14 months to 96 years with two distinct peaks in age distribution, one in early adult life and one in old age (Fig. 1).

Microbial keratitis occurred predominantly in eyes with existing pathology. Predisposing factors were identified in 84% of the patients (Table 1). Herpes simplex virus (HSV) keratitis was the most common pre-existing disease, these patients having an average age of 59 years. In younger patients (average age 44 years), trauma, including corneal lacerations, abrasions, and foreign bodies, was more common. This difference in corneal status contributed to the two peaks in age distribution. The four cases with exposure ulcers were stroke or comatose patients with inadequate lid closure.

The organism responsible for keratitis comprised about 30 species in 21 genera of bacteria, fungi, and amoebae (Table 2). Bacteria were responsible for 77 cases, fungi for eight, and free-living amoebae for two. All patients were from South Australia except four; three came from Queensland and one from Singapore, all of whom were infected with filamentous fungi. *Staphylococcus aureus* was the most frequently isolated organism, being responsible by itself for 23% of the cases. As *Staphylococcus epidermidis* was isolated alone in 12 cases (13·8%), staphylococcal species were responsible for more than a third of the infections. An obligate anaerobe,

Table 1 Pathology prior to microbial keratitis

	No. (%) of eyes*
Trauma	14 (17·9)
HSV keratitis	12 (15·4)
HSV keratitis and corneal graft	7 (9·0)
Corneal graft	6 (7·7)
Exposure ulcer	4 (5·1)
Bullous keratopathy	3 (3·8)
Herpes zoster ophthalmicus	2 (2·6)
Sjögren's syndrome	2 (2·6)
Bowen's procedure to limbus	1 (1·3)
Vernal catarrh	1 (1·3)
Soft contact lens wear	1 (1·3)
Trauma and corneal graft	1 (1·3)
Stevens-Johnson syndrome	1 (1·3)
H. zoster ophthalmicus and corneal graft	1 (1·3)
Systemic lupus erythematosus	1 (1·3)
Lens extraction and IOL implant	1 (1·3)
Multiple myeloma and malnutrition	1 (1·3)
Epithelial dystrophy	1 (1·3)
Prematurity	1 (1·3)
None apparent	11 (14·1)
Not known	6 (7·7)
Total	78

*In 76 patients. Two patients had infections in both eyes; one had Sjögren's syndrome and the other had previous grafts for keratoconus.

Peptostreptococcus anaerobius, was isolated in only one case. *Pseudomonas aeruginosa* was the most frequently encountered Gram-negative bacillus (GNB), being responsible for 10·3% of the infections. Two or more organisms were cultured from a cornea on 11 occasions (12·6%). In two cases *Acanthamoeba* species were isolated; one of these patients had splashed wood alcohol into his eye and the other had a three-year history of HSV keratitis.

The Gram stain correlated with the culture result in 58% of cases (Table 3). Of the eight instances

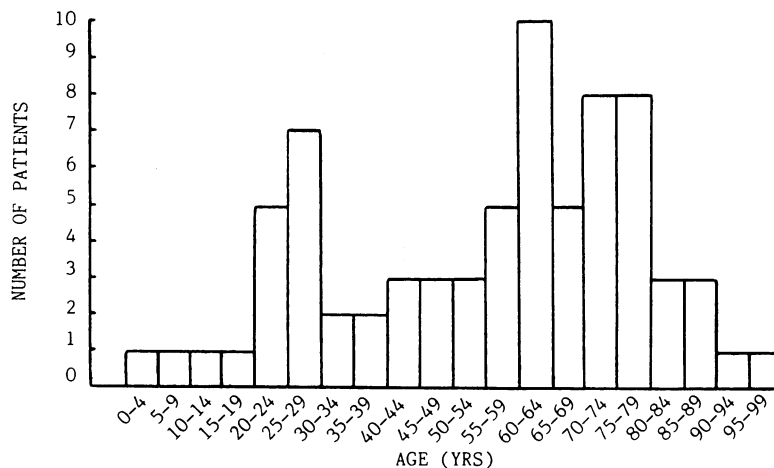


Fig. 1 Age distribution of patients with microbial keratitis.

Table 2 *Organisms isolated from cases of microbial keratitis*

	No. (%) of isolates
Gram-positive cocci	
<i>Staphylococcus aureus</i>	20 (23.0)
<i>Staphylococcus epidermidis</i>	12 (13.8)
<i>Streptococcus pneumoniae</i>	5 (5.7)
Viridans streptococci	4 (4.6)
<i>Peptostreptococcus anaerobius</i>	1 (1.1)
<i>Staph. aureus</i> and viridans streptococci	2 (2.3)
<i>Staph. epidermidis</i> and viridans streptococci	1 (1.1)
Gram-positive bacilli	
<i>Corynebacterium</i> spp.	5 (5.7)
Gram-negative bacilli	
<i>Pseudomonas aeruginosa</i>	9 (10.3)
<i>Moraxella</i> spp.	4 (4.6)
<i>Haemophilus influenzae</i>	2 (2.3)
<i>Klebsiella oxytoca</i>	2 (2.3)
<i>Proteus mirabilis</i>	1 (1.1)
<i>Serratia marcescens</i>	1 (1.1)
<i>Pseudomonas maltophilia</i> and <i>Achromobacter</i> spp.	1 (1.1)
Mixed	
<i>Staph. epidermidis</i> and <i>Corynebacterium</i> spp.	2 (2.3)
<i>Staph. aureus</i> and <i>Proteus mirabilis</i>	1 (1.1)
Viridans streptococci and <i>Moraxella</i> spp.	1 (1.1)
Viridans streptococci and <i>Corynebacterium</i> spp.	1 (1.1)
<i>Str. pneumoniae</i> , <i>Staph. aureus</i> , and <i>Moraxella nonliquefaciens</i>	1 (1.1)
<i>Escherichia coli</i> , <i>Enterobacter cloacae</i> , <i>Hafnia alvei</i> , <i>Candida krusei</i> , and <i>Pseudomonas acidovorans</i>	1 (1.1)
Fungi	
<i>Candida albicans</i>	2 (2.3)
<i>Fusarium</i> spp.	3 (3.4)
<i>Acremonium</i> sp.	1 (1.1)
<i>Alternaria</i> sp.	1 (1.1)
<i>Aspergillus fumigatus</i>	1 (1.1)
Amoebae	
<i>Acanthamoeba</i> spp.	2 (2.3)
Total	87

where organisms were seen on the smear but did not grow, GNBs were seen six times and Gram-positive cocci (GPC) twice. In three of the six instances the GNBs were large coccobacilli of the *Moraxella* type.

Data for antimicrobial susceptibility of commonly isolated organisms are shown in Table 4. All isolates of each bacterial species were sensitive to at least two antibiotics. Cephadrine was effective in vitro against all isolates except some *P. aeruginosa*. Gentamicin was effective against all isolates except some *Streptococcus pneumoniae*.

Table 4 *Percentage of isolates sensitive to various antibiotics*

	<i>Staph. aureus</i>	<i>Staph. epidermidis</i>	<i>Str. pneumoniae</i>	<i>Coryne. spp.</i>	<i>P. aeruginosa</i>	<i>Moraxella spp.</i>
Penicillin	23	0	75	100	—	100
Cephadrine	100	100	100	100	33	100
Chloramphenicol	100	75	100	80	20	100
Gentamicin	100	100	33	100	100	100
Tobramycin	—	—	—	—	100	—
Carbenicillin	—	—	—	—	100	—

Table 3 *Correlation of Gram stain with culture result*

Organisms cultured seen in Gram stain	45/77 (58.4%)
Some organisms cultured seen in Gram stain	3/77 (3.9%)
Organisms not seen	21/77 (27.3%)
Other organisms seen (with or without cultured organisms)	8/77 (10.4%)

After isolation of the organism responsible the patients received specific antimicrobial chemotherapy and most (70%) also received topical corticosteroids. Corneal transplantation was performed on 18 eyes.

The outcome of treatment of microbial keratitis is given in Table 5. Of the corneal grafts 12 were successful, and one failed owing to allograft rejection. In three cases infection recurred in the grafted eye, but the organisms responsible were other than those which had caused the initial infections. Each of these patients had a history of herpetic ocular infection. All six patients with filamentous fungal infection received a graft; a successful result was achieved in four cases.

Of the 72 eyes for which the outcome was known 13 (18.1%) were lost. As well as the recognised pathogens the organisms that contributed to the loss of eyes included *Corynebacterium* species, *Staphylococcus epidermidis*, and *Streptococcus sanguis* type II. In 14 eyes (19.7%) there was complete resolution of disease and in 25 (35.2%) the infection resolved to useful vision, defined as the hand motion to count fingers range. When the number of cases in which the disease resolved to useful vision or better is added to the number of successful grafts, it can be seen that a good outcome was achieved for 72% of the eyes.

Treatment was successful for all patients with a history of corneal trauma but for only 42% of patients with a history of HSV keratitis (Table 6). On χ^2 analysis the frequency of a poor outcome for patients with a history of HSV infection was shown to be significantly greater than for those with a history of trauma ($p < 0.005$). In comparison with all other previous pathology the probability that the greater frequency of a poor outcome following HSV infection is due to chance is about 6%.

For 22 patients the outcome of treatment of

Table 5 Outcome of microbial keratitis

	No. (%) of eyes
Eye removed	13 (16.7)
Corneal graft—successful	12 (15.4)
—rejected	1 (1.3)
—recurrence of infection	3 (3.8)
Failure of previous graft	4 (5.1)
Recurrence of infection	2 (2.6)
Resolution to useful vision	23 (29.5)
Complete resolution	14 (17.9)
Not known	6 (7.7)
Total	78

microbial keratitis was not successful. This group had a total of 26 culture-proved infectious episodes in 23 eyes. Additional data are given in Table 7. Of these patients 70% had had either HSV keratitis or a previous graft, or both, compared with 38% overall. The extent of ulceration at presentation was classified as slight if less than 10% of corneal area was suppurating, moderate if 10–30% was suppurating, and severe if more than 30% was involved. The association between a patient presenting with moderate or severe ulceration and a poor outcome was significant ($p < 0.05$). The presence of hypopyon did not significantly affect outcome. *P. aeruginosa* and mixed infections predominated among the patients having a poor outcome, though the total number of cases is not sufficient to show any significant associations. A poor outcome could not be correlated with the use of inappropriate antibiotics before the antimicrobial sensitivity data became available.

A successful outcome was achieved in 69% of cases where topical corticosteroid was included in the therapy compared with 78% where no steroid was given. However, these figures are biased by the consideration that the more severe cases generally received steroid. Infection recurred in 13% (7/54) of

Table 6 Relationship of previous pathology to outcome of microbial keratitis

	No. (%) of patients	
	Trauma	HSV
Eye removed	0	4 (21.1)
Corneal graft—successful	2 (13.3)	4 (21.1)
—rejected	0	1 (5.3)
—recurrence of infection	0	2 (10.5)
Failure of previous graft	0	2 (10.5)
Recurrence of infection	0	2 (5.9)
Resolution to useful vision	7 (46.7)	4 (21.1)
Complete resolution	6 (40.0)	0

patients given steroid compared with 0% (0/23) of patients who did not receive steroid.

Discussion

The pattern of disease in this series of cases was similar to that seen in other studies from urban communities in temperate climatic zones.⁴⁻⁶ Thus the range of organisms, antimicrobial sensitivity, and predisposing disease were perhaps to be expected. Although there have been no published reports of the outcome of microbial keratitis, less than optimal results are commonly experienced by all ophthalmologists dealing with this condition.

Infection is often responsible for ultimate loss of sight in an eye ravaged over a period of time by chronic relapsing disease consequent upon epithelial disruption and stromal derangement. The frequency of poor outcome of bacterial infection in patients who have chronic herpetic keratitis, and who often have had previous corneal surgery as well, attests to this. It also emphasises the role of the intact epithelium as a primary defence mechanism; corneal infection seldom occurs in otherwise healthy eyes.

Only one case of infection attributable to contact

Table 7 Data on patients with poor outcome*

Average age (yrs)	Preceding pathology†	Extent of ulceration†	Hypopyon present†	Organisms†	Antibiotics used†
60.3 (53-4)	HSV and graft	26	Slight 9 (43)	<i>P. aeruginosa</i>	Correct 92 (80)
	HSV	17	Moderate 57 (47)	<i>Staph. aureus</i>	Incorrect 0 (0)
	Graft	17	Severe 17 (10)	<i>Coryne. spp.</i>	None used 0 (16)
	Graft and SCL	4	Unknown 17 (0)	<i>Str. pneumoniae</i>	Unknown 8 (4)
	H. zoster and graft	4		<i>Moraxella lacunata</i>	
	Bullous keratitis	4		<i>H. influenzae</i>	
	SLE	4		<i>Serratia marcescens</i>	
	Cat. extract and IOL	4		<i>Str. sanguis</i> II	
	None apparent	17		<i>Staph. epidermidis</i>	
				<i>Alternaria sp.</i>	
				Mixed	19 (4)

*Eye removed, graft rejected, recurrence of infection, or failure of a previous graft.

†Expressed as % of cases. Figures in brackets are for patients with successful outcome. SCL=soft contact lens. SLE=systemic lupus erythematosus. IOL=intraocular lens.

lens wear was encountered, though perhaps more might have been expected in view of the findings of others.⁷ The patient concerned had been wearing an extended-wear soft lens over an aphakic corneal graft, and had received no routine care for the lens or the eye. Lax aftercare by the ophthalmologist or optometrist and non-compliance on the part of the patient are the major sources of risk to an eye wearing a contact lens. During the period of this study the Contact Lens Clinic at Flinders Medical Centre had as many as 200 patients with extended-wear lenses in its care at any one time.

The management of microbial keratitis was consistent over the five-year period of the study. Initial treatment was based on the Gram stain. If the Gram stain revealed GPCs, a first generation cephalosporin was given topically every hour, either 50 mg/ml cephadrine or, more recently, cephazolin. If GNBs were seen, the patient was treated with 10 mg/ml gentamicin eye drops every hour. If no organisms were seen, no antimicrobial was given unless the clinical course of events strongly suggested bacterial infection, in which case both gentamicin and cephadrine eye drops were administered. In the event of a negative culture, the clinical picture and laboratory results were considered after 24 hours, and the indications for therapy were reviewed after another Gram stain and culture. In all cases the appropriateness of the antimicrobial chemotherapy was reviewed as the results of culture and antimicrobial sensitivity tests came to hand, but with the clinical course always the dominant consideration. Topical corticosteroids were not begun until appropriate antibiotics had been given for 24 hours.

Although most failures to respond to treatment occurred in patients whose eyes were moderately or severely diseased at the time of presentation, either due to the existing predisposing condition or because of late presentation, poor results did occasionally occur unexpectedly. The prognosis may be unfavourable even when a patient presents early, the causative organism is identified, treatment is initiated, and susceptibility of the organism to the antimicrobial agent prescribed is confirmed. A number of factors may account for this. They relate to the interaction of organism, host mediated mechanisms, and pharmacological considerations.

Motivated by the results of this clinical study and the need to identify effective therapeutic regimens, we used a quantitative model in rats to investigate factors influencing the outcome of corneal infection.⁸ Both bacterial and host cells were counted to compare the effectiveness of various treatments. This is necessary because both bacterial and host factors contribute to corneal destruction.⁹⁻¹²

The role of topical corticosteroids in microbial

keratitis remains controversial. They do not compromise the effectiveness of appropriate antibiotics.^{8,13-15} However, when used for the treatment of pseudomonas keratitis without effective antimicrobial chemotherapy, the growth of organisms is significantly enhanced.^{8,16} In addition to replicating organisms both the breakdown products of dead bacteria, for example endotoxin,¹⁷ and the products of tissue damage¹⁸ are chemotactic for leucocytes. It would seem that corticosteroids may have an important role in limiting leucocyte recruitment occurring after microbial replication has been halted. In experimental *Staph aureus* keratitis prednisolone acetate was shown to add significantly to the anti-inflammatory effect of cephadrine only late in the course of the infection.⁸ Presumably at this time bacterial turnover is less and antimicrobial sensitivity is reduced, or, alternatively, non-replicative elements are responsible for leucocyte recruitment. In either case the suggestion is that in clinical practice little is to be gained by beginning topical corticosteroid therapy before the causative agent has been identified and specific antimicrobial chemotherapy instituted.

The essential element of treatment is delivery of adequate levels of antimicrobial agents to the focus of infection. Animal models are vital for determining the important aspects of drug kinetics in microbial keratitis.

Clinical studies suggest that currently employed doses of most antibiotics, applied topically or subconjunctivally, produce concentrations in the infected cornea that should be effective on the basis of minimum bactericidal concentration (MBC) tests. Carbenicillin,¹⁹ cephalothin,²⁰ gentamicin,²¹ and tobramycin,^{22,23} reach useful concentrations in the aqueous humour of patients with uninflamed eyes. Since the corneal concentration of an antibiotic is usually at least as high as the aqueous humour concentration,²⁴ and the presence of inflammation is known to increase antibiotic penetration into the anterior segment,^{21,25,26} it is likely that the peak corneal concentration obtained in patients with suppurative keratitis is well above the MBCs of common pathogens. However, using rats we have found with cephadrine that a 'passing through' effect can occur after topical administration on to an inflamed eye in which the tissue concentration fell to sub-MBC levels more rapidly than it would do in a normal eye.²⁶ This suggests that applications may need to be made more frequently than is usual.

An MBC must be considered only as a guide to the likely susceptibility of an organism to an antibiotic in vivo. It is determined with the use of organisms in logarithmic growth. However, in established infections the rate of cell turnover is less, so that the

in-vivo MBC is in effect increased. We have found that the ratio of the antibiotic concentration required for 99% killing in the cornea to that in vitro is as high as 70:1 (presented at the Ocular Microbiology and Immunology Group Meeting, Atlanta, 1984).

Helpful as these animal studies are in increasing our understanding of microbial keratitis and its treatment, and difficult as it is to conduct clinical trials with a condition so diverse in its features, it is nevertheless necessary to pursue these trials if we are to improve our treatment of this important condition.

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