

Microbial Keratitis in Corneal Transplants: A 12-Year Analysis

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Purpose: To investigate the frequencies, trends, and in vitro drug susceptibilities of the causative pathogens in corneal transplant microbial infections in Manchester Royal Eye Hospital.

Methods: Corneal scrape results recorded by the microbiology service between 2004 and 2015 were extracted from an established database. This microbiological data was matched with a separate database of all corneal transplant procedures performed in our centre over this time period. Patient records were examined to collect specific patient data and to confirm the diagnosis of microbial keratitis.

Results: A total of 1508 grafts had been performed at our centre in this period. 72 episodes of graft microbial keratitis were identified from 66 eyes that had undergone keratoplasty procedures. Mean age was 56, and 51% of subjects were male. Ninety-three percent of microbial keratitis episodes occurred in penetrating keratoplasty procedures and 6% in deep anterior lamellar keratoplasty procedures. No endothelial grafts presented with infections throughout this time period. Of the 79 organisms identified, 73% were gram positive, 23% gram negative and 4% fungi. With regard to gram-positive organisms, vancomycin and gentamicin showed 100% and 91% susceptibility, respectively. Ofloxacin had a resistance rate of 13.7%. In terms of gram-negative organisms, gentamicin and chloramphenicol showed 100% sensitivity, with cefuroxime showing 69%. Resistance rates were less than 15% in all tested gram-negative antimicrobials.

Conclusion: This paper describes the largest collection of corneal transplant infections identified within the UK. This finding may aid clinicians in predicting possible causative organisms for microbial keratitis and aid antibiotic choice.

Keywords: cornea, transplant, infection, graft, microbial keratitis

Introduction

Microbial keratitis remains a serious cause of corneal opacification and sight loss worldwide.¹ It can be a particularly devastating complication following corneal transplantation, resulting in reduced best-corrected visual acuity (BCVA), graft rejection or failure. With around 4000 corneal transplant procedures performed each year in the UK,² the incidence of microbial keratitis has been reported to occur in 1.8–7.4% of penetrating keratoplasty (PK) procedures. A higher infection rate has been reported in the developing world.^{3–8} Most infections occur in the first-year post-transplant, with timely diagnosis and appropriate use of topical broad-spectrum antimicrobial therapy being critical for both good visual prognosis and graft survival. Antimicrobial therapy is often tailored according to clinical response, the organisms cultured, and their sensitivities.

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The commonest isolates obtained from corneal transplant infections are reported to be gram-positive species, commonly *Staphylococcus aureus* and *Streptococcus pneumoniae*, with gram-negative infections being less frequent.^{3,6,9,10} Various risk factors have been suggested within the literature to predispose to infection, such as ocular surface disease, persistent epithelial defects and graft hypoaesthesia¹⁰ with prognosis potentially affected by the virulence of the offending pathogen.^{11–13} Geographical variation in microbial isolates has been reported as well as seasonal variation and changing microbiological trends over time,^{14–21} suggesting frequent analysis of microbiological data is beneficial when ascertaining optimal broad-spectrum therapy whilst waiting for microbiological results to allow tailored therapy.

The aim of this retrospective study was to determine and evaluate the frequencies and drug susceptibilities of the causative pathogens resulting in microbial keratitis in transplant patients over a 12-year period at the Manchester Royal Eye Hospital.

Materials and Methods

This study was conducted in strict accordance with the Declaration of Helsinki tenets in terms of data confidentiality, and ethical approval was obtained from the National Integrated Research Application System (IRAS). Patient consent was not sought for this retrospective, non-interventional study as deemed by the IRAS application (no 208721/1020361/37/763) as we utilised anonymised secondary data for analysis. All corneal scrape specimens received and examined by the microbiology service between 1 January 2004 and 31 December 2015 were retrieved from an established electronic database. Data collected include age of patient, date of scrape, microbiology, culture, and sensitivity. Episodes of bacterial and fungal keratitis were included in the study whilst cases of herpetic keratitis were excluded. The technique used for corneal scraping as well as microbiological analysis has been described previously in another publication by the same group of authors.²⁰

The patient identifiers from this microbiological database were then matched with a separate database of all corneal transplant procedures performed in our centre over this time period. This allowed us to identify those transplants that had presented to our department requiring corneal scrapes post-transplant surgery. Medical records were then reviewed in order to confirm that a diagnosis of microbial keratitis was made.

For penetrating keratoplasties (PKPs), surgical technique was surgeon dependent, with the majority of grafts sutured

using 10/0 nylon interrupted sutures. Deep anterior lamellar keratoplasties (DALKs) were performed using either Melles'²² or Anwar's technique.²³ Descemet's stripping automated endothelial keratoplasties (DSAEKs) were performed using grafts prepared on the day of surgery using a Moria microkeratome, a Coronet punch and Busin spatula. Selective removal of 10/0 sutures starts at approximately 3–6 months postoperatively guided by refraction and topography data. In PK/DALK sutures were removed after approximately 12 months of uneventful follow-up, unless broken or loose. Postoperatively prophylactic topical antibiotic eye drops are given for 4 weeks. Frequent steroid eye drops were commenced immediately postoperatively and tapered routinely after 1 month. Patients usually remained on a daily steroid eye drop and followed up indefinitely. Regular follow up was undertaken unless the patient presents with an acute issue via our casualty department.

Patient records were examined in order to collect specific patient data, including demographics, indication for transplant, potential risk factors for infection, and further complications within one year of the infectious episode. All data were collated into a spreadsheet, which was then used for data analysis. Descriptive statistics were used to analyse data according to its distribution.

Results

Seventy-two episodes of graft microbial keratitis were identified from 66 eyes that had undergone keratoplasty procedures. A total of 1508 grafts had been performed at our centre in this period (penetrating keratoplasty 66.5%, endothelial keratoplasty 23.7%, anterior lamellar keratoplasty 9.8%), giving an overall infective keratitis risk of 4.77% per graft. Fifty-one percent were male, with a mean age of 56 years. Demographics are provided in [Table 1](#), with the indication for undertaking keratoplasty shown in [Table 2](#). Ninety-three percent of microbial keratitis episodes occurred in penetrating keratoplasty procedures and 6% occurred in DALKs. No endothelial grafts from the 12-year period presented with an infection.

Seventy-three percent of isolated organisms were gram positive, with 23% gram negative and 4% fungi. The commonest isolates were *Staphylococcus aureus* (25%), coagulase-negative *Staphylococcus* (14%) and *Streptococcus pneumoniae* (10%). A full breakdown of isolates is shown in [Table 3](#). Graft infection occurred at a median of 25 months postoperatively, with gram-positive and negative infections occurring at a median of 25 and 22 months, respectively ([Table 4](#)).

Table 1 Patient Demographics

		Total N (%)
Total episodes of keratitis		72
Number of grafts included		66
Age of patients at presentation* (years)		56 (20.7, 1–92)
Age of graft at presentation ^o (months)		25 (8–65)
Sex	Males	37 (51)
	Females	35 (49)
Eye	Right	39 (54)
	Left	33 (46)
Surgery	Penetrating keratoplasty	67 (93)
	Endothelial keratoplasty	0 (0)
	Deep anterior lamellar keratoplasty	4 (6)
	Epikeratophakia	1 (1)

Notes: 6 grafts had more than 1 episode of keratitis; All figures Total (%) unless otherwise stated; *Mean, standard deviation, range; ^oMedian, interquartile range.

Table 2 Indication for Corneal Transplant Being Performed: Indication for Graft

	PK (n=67)	DALK (n=4)	Epikeratophakia (n=1)
Infection	22	–	–
Keratoconus	9	3	1
Keratoconus + hydrops	3	–	–
Fuchs endothelial dystrophy	7	–	–
Graft decompensation	7	–	–
Corneal decompensation	4	–	–
Pseudophakic bullous keratopathy	6	–	–
Other*	11	1	–

Notes: Total count greater than number of cases (n) as some cases recorded as more than one indication for graft; Other*, anterior segment dysgenesis, buphthalmos, corneal dystrophy, corneal melt secondary to rheumatoid arthritis, DALK interface vessels, descmetocele and mucus membrane pemphigoid, lipid keratopathy, peripheral ulcerative keratitis, Steven-Johnson syndrome, thermal injury, traumatic graft dehiscence, WAGR syndrome.

Antibiotic susceptibilities of the isolates are shown in Table 5. With regards to gram-positive organisms, vancomycin and gentamicin showed 100% and 91% susceptibility, respectively. Ofloxacin had a resistance rate of 31%. In terms of gram-negative organisms, gentamicin and chloramphenicol showed 100% sensitivity, with cefuroxime showing 69%. Resistance rates were less than 14% in all tested gram-negative antimicrobials.

Table 3 Organism Identified from Corneal Scrape Sample

Organisms		Total (n=79) N (%)
Gram positive	<i>Staphylococcus aureus</i>	58 (73)
	Coag. Negative <i>Staphylococcus</i>	20 (25)
	Other <i>Staphylococcus</i>	13 (16.5)
	MRSA	2 (3)
	<i>Streptococcus pneumoniae</i>	8 (10)
	Other <i>Streptococcus</i>	8 (10)
	AHS	4 (5)
	<i>S. viridans</i>	2 (3)
	GBS	1 (1)
	<i>S. sanguinis</i>	1 (1)
	Others	7 (9)
Gram negative	<i>Pseudomonas</i>	18 (23)
	<i>Moraxella</i>	4 (5)
	<i>Sphingomonas</i>	4 (5)
	<i>Serratia</i>	3 (4)
	<i>Haemophilus influenzae</i>	2 (3)
	Others	2 (3)
	Others	3 (4)
Fungi	<i>Candida parapsilosis</i>	3 (4)
	<i>Candida albicans</i>	2 (3)
	Others	1 (1)

Notes: Organisms identified from corneal scrapes of corneal graft; 5 episodes of keratitis were coinfections; Other gram positive, *Diphtheroids*, *Abiotrophia*, *Corynebacterium*, *Enterococcus*, *Fingoldia*, *Mycobacterium*; Other gram negative, *Citrobacter*, *E. coli*, *Stenotrophomonas*.

Abbreviations: MRSA, methicillin resistant *Staphylococcus aureus*; AHS, alpha haemolytic *Streptococcus*; GBS, haemolytic *Streptococcus* group B.

Table 4 Age of Graft at Presentation Stratified According to Infective Organism

Infective Organism	Age of Graft at Presentation Months Median (IQR)
Gram +ve (n=50)	25 (8–55)
Gram -ve (n=14)	22 (4–121)
Coinfection (n=5)	58 (23–58)
Fungal (n=3)	13 (1–26)

Eighty-nine percent of patients were using topical steroid medication, with 32% using anti-glaucoma drops. Twenty-six percent of patients had suture problems noted around the time diagnosis. Potentially predisposing factors are shown in Table 6. Outcomes following infective episodes are shown in Table 7. Thirteen percent resulted in corneal perforation, and 11% in graft rejection. Twenty-four percent of microbial keratitis episodes in these patients required a further corneal graft. Four percent of eyes required evisceration as a direct result of infection.

Table 5 Antibiotic Susceptibility and Resistance in Both Gram-Positive and Gram-Negative Organisms

		Total Susceptible	Total Resistant	Susceptibility (%)
Gram positive (n=58)	Chloramphenicol	45	3	94
	Vancomycin	41	0	100
	Gentamicin	32	3	91
	Ofloxacin	28	13	68
	Fusidic acid	25	4	86
	Ciprofloxacin	23	3	88
	Cefuroxime	17	3	85
Gram negative (n=18)	Gentamicin	15	0	100
	Ciprofloxacin	13	1	93
	Chloramphenicol	12	0	100
	Amikacin	9	0	100
	Cefuroxime	9	4	69
	Ceftazidime	8	3	73
	Ofloxacin	8	3	73

Table 6 Potential Exacerbating Factors Present at the Time of Keratitis

Risk Factor	Total N (%)
Topical steroids	64 (89)
Topical glaucoma drops	23 (32)
Suture problem: loose or removed	19 (26)
HSV	18 (25)
Atopy/eczema	16 (22)
Decompensated graft	13 (18)

Table 7 Complications Occurring Within 1 Year of Keratitis Episode

		Total N (%)
Graft decompensation		8 (11)
Graft rejection episode		2 (3)
Perforation		9 (13)
Crystalline keratopathy		4 (6)
Orbital cellulitis		1 (1)
Endophthalmitis		1 (1)
Further surgery	Penetrating keratoplasty	14 (24)
	Evisceration	3 (4)

Discussion

Microbial keratitis in corneal transplant patients is a feared complication with potentially devastating outcomes. Our analysis shows a graft infection risk of 4.77%, which is in concordance with other reports from the literature. Most

reports within the literature suggest an infection rate between 1.76% and 7.4%,^{6,10,24–26} but centres from the developing world report rates as high as 25%.²⁷

The literature points towards gram-positives as the most likely infective organisms to be cultured,^{6,7} and our findings support this. Commensals appear to show a predilection for corneal transplants, most likely due to co-existing ocular surface disease. This is reinforced by our findings that only PKs and anterior lamellar grafts had infective episodes, with no endothelial graft infections reported from over 300 endothelial transplants. This is in stark contrast to the organisms cultured from contact lens wearers and non-transplanted eyes, where gram-negative infections are most prevalent in the developed world.^{19,20,28}

Graft infections have been reported to occur most commonly in the first year post-surgery by some authors.^{5,6} This was not shown by our data, with a median graft age of 25 months at presentation, which varied little depending on whether gram-positive or negative organisms were identified. This is supported by other large studies.⁷

Interestingly, fungal infections seem to occur earlier, although the numbers of such infections were small, and conclusions should be drawn carefully. Similarly, infections with more than one organism identified appear to occur later than single isolates, nearly five years post-operatively. The causative organisms have been shown to exhibit seasonal variation,^{14,17,18,29} with data from our own unit suggesting that gram-positive bacteria are

associated with increasing temperatures whilst fungi and *Moraxella* sp. are associated with decreasing temperatures. Culture positivity was significantly less likely in the Summer months.¹⁴ To the best of our knowledge, seasonal variation amongst transplant patients has not yet been investigated. It is worth alerting readers to the limitations of such retrospective studies, which have been discussed in previous publications.²⁰

In terms of antibiotic sensitivities, excellent susceptibilities were shown by our study for both gram-positive and negative species, suggesting adequate antibiotic treatment is available for this group of patients. In our unit, monotherapy is often used as first-line treatment, but as would be expected, antibiotic dual-therapy offers greater coverage, and this should be considered in severe infective episodes. Given that cultured organisms are most likely to show gram positivity, it may well be worth initiating treatment with a higher-order fluoroquinolone with better coverage for such organisms.³⁰ Similarly, there may well be an argument for the addition of chloramphenicol as a broad-spectrum antibiotic with good sensitivity. Chloramphenicol is often described as a bacteriostatic agent, deemed to be less efficacious than bacteriocidal agents. However, a recent large meta-analysis suggests that these definitions are not so clear cut, with no statistical significance shown between cure rates of the two antibacterial classes.³¹ This is an interesting concept that requires further research, and may not be applicable to ophthalmic practice as ocular infections were not included as part of this analysis.

It is worth noting that the main indication for the initial transplant in our series was in fact microbial keratitis. It is important to bear in mind the dynamic nature and trends of transplantation over the last decade, with endothelial grafts being used more commonly than PKs in the UK³² for conditions such as pseudophakic bullous keratopathy and Fuchs Endothelial dystrophy, whilst the use of DALKs for keratoconic patients has also increased during this period.³³ Given that our analysis found no infective episodes in endothelial grafts, this trend is likely to have impacted on overall rates of microbial keratitis in corneal transplants. With advancements in lamellar surgery, it may well be that if PKs are more likely to be performed for severely infected eyes, they are potentially self-selecting for a patient population that is more at risk of future infections due to other confounding factors that are innate to the patient. Other authors have shown these patients to have worse graft survival outcomes, and interestingly, keratoconic patients

have better graft survival outcomes post-infection.⁷ Presentation with hypopyon is said to indicate worse outcomes, as well as co-existent glaucoma. Rather counter-intuitively, graft survival has not been shown to be affected by different infective organisms.^{6,10} We did not examine this in our current study, but certain organisms, such as *Moraxella* have been reported to cause more severe infections with worse patient outcomes.^{12,34,35}

Although this study was not designed to assess the effect of certain risk factors for graft infections, a significant proportion of patients were using glaucoma medications, which have been shown by other authors to increase the risk of graft failure post-infection.²⁶ Ocular surface disease has been shown to occur as a result of preserved anti-glaucoma medications, with a reduction in superficial epithelial cells suggested as one mechanism for resultant epithelial toxicity.³⁶ Benzalkonium chloride of 0.001% or lower appears to be the least toxic to the ocular surface.³⁷

Over a quarter of eyes in our cohort developed infections as a result of suture-related problems, such as loose or broken stitches. Other reports from the literature suggest that this may be the major cause for such infections,^{38,39} with loose or exposed sutures allowing for direct invasion of microorganisms. They tend to accumulate mucus and can act as a nidus for colonization of pathogens which can attack an already compromised epithelium.²⁴ Other surface-related issues such as herpetic infections and atopy were present in our cohort, and these have been shown to increase the risk of infection by other studies.³⁹

Knowledge of the bacteria that contribute to the normal ocular surface microbiome is increasing with the advent of sequencing techniques capable of detecting⁴⁰ paucibacterial species. *Staphylococcus*, *Streptococcus*, *Pseudomonas* and *Sphingomonas* species have all been reported as commensal bacteria on the ocular surface even in the absence of disease.⁴⁰ Interestingly, such bacteria make up 73% of our culture results, demonstrating the importance of an intact epithelium as a mechanical barrier to infection.

The immunosuppressive role of topical steroids has been suggested as an increased risk factor for infective keratitis, but the evidence for this is inconclusive,^{6,39} as many patients, unfortunately, exhibit multiple predisposing factors for infection. A large proportion (89%) of our cohort were using topical steroids; however, this means a small number (11%) of infections occurred without using these medications. As previously discussed our median age of graft at the time of infection was 25 months, and by this point, the topical steroids have usually been tapered

to a low dose, such as prednisolone sodium phosphate 0.5% once a day. It would be reasonable to expect that if steroids played a significant role in precipitating infections that the majority of cases would occur within the first few months after surgery where higher frequencies and strengths of topical steroids were used.

The outcomes of such infections are varied but can be devastating. One infection progressed to endophthalmitis in a patient. This is said to be a rare complication,^{10,24,41} although higher rates of endophthalmitis have been reported from India,³⁸ with suture infections said to play a role in endophthalmitis rates. It has been suggested that if a full-thickness suture tract exists, this can act as a conduit for organisms into the anterior chamber. A small percentage of eyes (4%) required evisceration either for endophthalmitis that threatened to progress to orbital infections or for painful non-seeing eyes. Nearly a quarter of patients requiring secondary grafts as a result of corneal opacification suggesting that a large proportion of these patients suffer severe visual loss as a result of these episodes.

The authors feel it is imperative to examine local microbial trends to enable effective, evidence-based treatment strategies to be used during the initial stages of clinical management for such patients, as prompt diagnosis and initiation of optimal antimicrobials are required to give the best chance of graft survival. Geographical variation in the microbial spectrum and therapeutic ranges have been well documented, and it is encouraging to see colleagues from other areas of the UK^{10,12,14,20,35,42,43} and worldwide examine local microbiological trends.^{18,44–47} Here we report the UK's largest data set of graft associated microbial keratitis, and we hope that these findings will aid clinicians in understanding and treating this potentially devastating complication.

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Disclosure

The authors have no conflicts of interest to disclose.

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