

External ocular infections due to methicillin-resistant *Staphylococcus aureus* (MRSA)

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Abstract

Purpose To determine the prevalence and clinical characteristics of external ocular infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in an ophthalmic hospital in the UK.

Methods A retrospective analysis of the case notes of patients who had culture proven external ocular *Staphylococcal* infections during a 44-month period was undertaken.

Results There were a total of 548 external eye infections caused by *Staphylococcus aureus*. Of these, 17 (3%) were MRSA positive. The most common presentation was conjunctivitis seen in six patients. All MRSA isolates were sensitive to chloramphenicol. Ofloxacin resistance was observed in all isolates from patients over the age of 50 years. All patients had an underlying history of either an ocular surface disease, malignancy, or a debilitating medical illness.

Conclusions MRSA is as yet an infrequent cause of external ocular infections. Patients typically have underlying ocular risk factors and/or are medically debilitated. Different strains infect young and old age groups with characteristic antimicrobial sensitivity. This study highlights the need for more work to establish the role of MRSA commensals and ocular infections.

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Introduction

The term methicillin-resistant *Staphylococcus aureus* (MRSA) was originally used to describe *Staphylococcus aureus* resistant to methicillin. As

methicillin is rarely used in testing laboratories nowadays, the term is now used to describe strains of *S. aureus* resistant to all β -lactam antimicrobials.

As a result of its multiple drug resistance and its increasing prevalence, MRSA is a serious cause of morbidity and mortality worldwide.¹ Outbreaks of infections have posed difficult challenges for those involved in infection control. Certain hospitals and indeed countries have adopted very robust measures to control the spread of MRSA, the so-called 'search and destroy' policies, whereas others have realised the limitations of the resources available to tackle the problem and have adopted less stringent controls.²

Much has been written on the subject of MRSA and its epidemiology,³ but until recently, there has been a paucity of information relating MRSA to eye disease. We wished to determine the prevalence and clinical characteristics of external eye infections by MRSA in a large British eye unit. In addition, we aimed to establish the underlying antimicrobial sensitivities of the MRSA strains and any associated patient characteristics.

Patients and methods

Using a microbiological database, patients who had MRSA cultured from either a conjunctival swab or a corneal scrape were identified and had their case notes examined retrospectively. We used the same database to determine if screening for MRSA in nonocular sites had been carried out in these patients. We defined the term external ocular infections to include the following structures: the ocular surface, the nasolacrimal system, eyelids, and any conjunctiva in 'empty' sockets. The corneal scrapes that were performed used a 21-gauge needle which was then inoculated onto a

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chocolate and blood agar culture plate, agar blobs for enrichment, and a glass slide for Gram staining in accordance with local protocols.⁴ The conjunctival swabs used were charcoal agar swabs. Sensitivity testing was performed in accordance to the British Society for Antimicrobials Chemotherapy (BSAC) guidelines.⁵

The cultures that were positive for bacteria were graded in terms of the intensity of their growth: heavy (+ + +), moderate (+ +), light (+), and scanty (+ / -). In several cases, there was growth of more than one organism, and we defined MRSA as a commensal when the growth of the significant pathogen was 2 or 3 '+'s greater than MRSA on the scale described above.

Results

There were 548 external ocular infections caused by *S. aureus* over a 44-month period (1997–2001), of which 17 (3%) of the isolates were MRSA. The clinical details of the patients and antimicrobial sensitivities of the isolates are summarised in Table 1. The types of infections were as follows: conjunctivitis (six patients), keratitis (four patients), dacryocystitis (three patients), conjunctival socket infection (three patients), and one patient had a plumb abscess following retinal detachment surgery. In all, 13 patients were over 65 years and the other three under 25 years of age.

All patients had one or a combination of the following: malignancy, an underlying systemic debilitating disease, and a pre-existing history of an ocular surface disorder. Only five of the 17 patients were screened for evidence of MRSA in nonocular sites. This was positive in one patient.

All the MRSA isolates were sensitive to gentamicin and chloramphenicol. Only two of the isolates were sensitive to ofloxacin, both of which were in the younger age group.

Discussion

The majority of previous studies on MRSA ocular infections are from the USA and Japan and have been in the form of individual case reports, case series with small numbers, or descriptions of ocular infections within a part of an outbreak of MRSA (see Table 2). Recently, two centres from Japan have published more comprehensive work in this field looking at several aspects of MRSA ocular infections.^{6,7} Interesting comparisons of the cases in our study and that of previous work can be made.

Our study showed that MRSA external ocular infections were uncommon, representing only 3% of all the *S. aureus* external ocular infections. In Japan, Fukuda et al⁷ demonstrated that of 115 *S. aureus* isolates from patients with bacterial conjunctivitis, 74 (64%) were

MRSA. An earlier study, also from Japan, put this figure at 25% but included all ocular infections and not just conjunctivitis.⁸ This illustrates the marked variation in the prevalence of MRSA ocular infections geographically and at different time points.

The type of infections described in previous studies are broadly the same, with conjunctivitis and keratitis the most common manifestations. The cases of keratitis we observed consisted of a minimal superficial defect with an associated subepithelial infiltrate and was nondestructive. Only in one case (patient no. 4) was there a frank ulcer and this was associated with marked superficial punctate erosions. Adenovirus was also co-cultured and the infection healed without any serious sequelae with chloramphenicol treatment. These findings are similar to the majority of cases observed in a large series of MRSA and methicillin-resistant *Staphylococcal epidermidis* ocular surface infections.⁶ The authors proposed a four level grading system for the methicillin-resistant keratitis, one being the mildest referring only to carriers and four for destructive keratitis leading to perforation. Three of the cases of isolated conjunctivitis in our series were noted to have a purulent discharge. There were no real or pseudomembranes reported on examination. In one case (patient no. 10), there were prominent papillae but this was likely to be secondary to atopic eye disease. The dacryocystitis in this series presented with an inflamed nasolacrimal swelling and discharge in two cases although this was only described as purulent in one case (patient no. 14). The same patient also had a delayed response to treatment presumably due to repeated infections. Thus, from our review, we could not establish any clear and specific signs on examination that indicated that the ocular infections were caused by MRSA.

Several patients in the above study who suffered from Stevens-Johnson syndrome and ocular cicatricial pemphigoid were considered to be 'ocular immunocompromised hosts.' Pre-existing ocular surface disease was seen in 10 of our patients, and dry eyes was the most common finding. This is not surprising as ocular surface disease is a significant risk factor for microbial keratitis.⁹

In our study, the spectrum of antibiotic sensitivity broadly fell into two groups: that seen in young and old patients. The strains affecting older patients were resistant to ofloxacin unlike two out of the three younger patients (patient nos. 9 and 10 in Table 1). The reasons behind this are not clear. All our cases were treated successfully and this was in part due to the universal efficacy of chloramphenicol, which was the most commonly used first-line topical antibiotic for external eye infections. The success of chloramphenicol as an effective agent against MRSA in the UK may be due to its

Table 1 Summary of the clinical features of patients with MRSA external ocular infections

No/age/sex	Previous ocular history	Type of ocular surface infection	Sensitivities to antimicrobials	Other medical details
1/70/F	Dry eyes	Purulent conjunctivitis	S—CPL/GENT/FUS R—CIP/OXF/CEF	Rheumatoid arthritis/Sjogrens syndrome Nursing home resident
2/80/F	Dry eyes/entropion	Purulent conjunctivitis	S—CPL/GENT/FUS R—CIP/OXF/CEF	COPD/Recurrent chest infections Nursing home resident
3/69/M	Dry eye/trichiasis	Purulent conjunctivitis	S—CPL/GENT/FUS R—CIP/OXF/CEF	COPD/Pneumonia Positive for MRSA in nonocular sites
4/54/M	Meibomianitis with associated tear film dysfunction	Keratitis—corneal ulcer. Adenovirus also isolated	S—CPL/GENT/FUS R—CIP/OXF/CEF	Congestive cardiac failure/ascities/alcoholism
5/67/F	Herpes simplex keratitis	Conjunctivitis. <i>H. influenzae</i> also isolated	S—CPL/GENT/FUS R—OXF/CEF	Asthma/hypertension
6/74/M	<i>Streptococcus pneumoniae</i> keratitis/HZO	Conjunctivitis. <i>H. influenzae</i> also isolated	S—CPL/GENT/FUS R—CIP/OXF	COPD/systemic immunosuppression
7/85/M	Retinal detachment repair with a plomb	Plomb abscess and preseptal cellulitis	S—CPL/GENT/FUS R—OXF/CEF	Prostatic carcinoma, diverticulitis. Negative for MRSA in other nonocular sites
8/67/M	Dry eyes	Keratitis	S—CPL/GENT/FUS R—OXF	Myotonic dystrophy Negative for MRSA in other nonocular sites Nursing home patient
9/23/M	Contact lens wearer	Keratitis. Coliforms also isolated	S—CPL/GENT/FUS/ OXF R—CEF	
10/16/M	Atopic conjunctivitis	Muco-purulent conjunctivitis	S—CPL/GENT/OXF	Atopic patient on systemic immunosuppression
11/82/F	Previous microbial keratitis/Band keratopathy/HZO	Keratitis	S CPL/GENT/FUS R OXF/CEF	NIDDM/CVA Negative for MRSA in other nonocular sites
12/74/M	Enucleation following pthisis from neovascular glaucoma	Socket/Conjunctival infection	S CPL/GENT/FUS R OXF/CEF	COPD/NIDDM
13/71/F	Nil of note	Dacrocystitis	S—CPL/GENT/FUS R—OXF/CEF/	Lymphoma Negative for MRSA in other nonocular sites

Table 1 Continued

No/age/sex	Previous ocular history	Type of ocular surface infection	Sensitivities to antimicrobials	Other medical details
14/6/F	Recurrent episodes of dacryocystitis	Dacryocystitis with purulent discharge. <i>H. influenzae</i> and <i>Moraxella</i> also isolated	S—CPL/GENT/FUS R—OXF/CEF	Dysmorphic/choanal atresia
15/71/F	Nil of note	Dacryocystitis	S—CPL/GENT/FUS R—OXF/CEF	Bronchiectasis
16/74/M	Eye enucleated following neovascular glaucoma	Socket/purulent conjunctival infection	S—CPL/GENT/FUS R—CIP/OXF/CEF	COPD/Asthma/IHD/NIDDM/Epilepsy
17/82/F	Left exenteration for maxillary tumour	Socket infection	S—CPL/GENT/FUS R—CIP/OXF/CEF	Nursing home patient. Previous history of coliform ocular commensals

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; NIDDM, noninsulin dependent diabetes mellitus; IHD, ischaemic heart disease; *H. influenzae*, *Haemophilus influenzae*; HZO, herpes zoster ophthalmicus; CPL, chloramphenicol; GENT, gentamicin; Fus, fusidic acid; CIP, ciprofloxacin; OXF, ofloxacin; CEF, cefuroxime.

limited use systemically for nonocular MRSA infections. As a result, there has not been an overexposure of MRSA to chloramphenicol and thus resistance has not yet developed. However, MRSA ocular infections resistant to chloramphenicol treatment have been described¹⁰ and we observed one such case in the year prior to this study of an 82-year-old lady who presented late with a destructive keratitis that later perforated. MRSA infections in nonocular sites can behave very aggressively and it was surprising that we did not encounter more severe or resistant cases of ocular infections. However, the above example suggests that aggressive strains of MRSA that affect the eye exist in the UK but at the time of writing are very rare.

Chloramphenicol may appear to be the drug of choice but its use is not widespread because of the perceived risks of aplastic anaemia¹¹ especially in the USA where it has been withdrawn. However, as Fukuda *et al*'s⁷ study demonstrated, chloramphenicol was clinically effective in 81% of cases with MRSA conjunctivitis and this may gain favour as a first-line choice of antibiotics outside the USA. The choice of antibiotics used in other studies varied but resistance to aminoglycosides and other antimicrobials, particularly ofloxacin, has been well documented. Tazawa and Ooishi's⁸ work on MRSA ocular infections demonstrated increasing resistance to ofloxacin, over time during the 1980's. While vancomycin-resistant MRSA has been described,¹² this fortunately has not yet been reported in MRSA ocular infections. Vancomycin has been used frequently with success, although in rare instances in-house preparations of higher strength 5% vancomycin were required.⁶

Underlying medical problems are a common finding in several studies including ours where respiratory, malignant, and cerebrovascular disease was prominent. Fukuda *et al*⁷ reported MRSA conjunctival commensals to be three times higher in chronically bedridden patients and 1.5 times greater in patients with anaemia, malignancy, and liver dysfunction when compared with normals.⁷ The high incidence of chronic systemic illness may simply be a reflection that these patients require care in a nursing home or repeated admissions to hospital wards where MRSA colonisation is endemic. This is illustrated by Brennen and Muder¹³ who described episodes of conjunctivitis in a long-term care facility where the majority of patients had severe neurological impairment and where seven of the 19 patients were colonised with MRSA in nonocular sites. Four of our patients were nursing home residents of whom only one was screened for MRSA and was negative.

While the majority of the cases described in this study are predominantly primary MRSA infections, some had occurred postoperatively (patient nos. 7, 16 and 17). It is reassuring that during the period of this study no cases

Table 2 Summary of studies looking at MRSA ocular infections

Author Year Country of study	Type of study (no. of patients)	Type of MRSA infections	Treatment (topical unless stated otherwise)	Other details of note
Ribner ²¹ 1987 USA	Case series (1)	Conjunctivitis	Not specified	Retrospective study over 7 years characterising MRSA infections in a paediatric unit
Ross and Abate ²² 1990 USA	Case report (1)	Conjunctivitis	Vancomycin	Methicillin-resistant <i>Staphylococcal epidermidis</i> also isolated
Brennen and Muder ¹³ 1990 USA	Case series (19)	Conjunctivitis	Systemic ciprofloxacin, vancomycin	Outcome of 20 episodes of conjunctivitis in a long-term care unit. A total of 17 patients had severe neurological impairment. Nine were colonised with MRSA before the onset of conjunctivitis
Inslar <i>et al</i> ²³ 1991 USA	Case reports (3)	Postoperative keratitis	Ciprofloxacin	
Eiferman <i>et al</i> ²⁴ 1991 USA	Case reports (3)	Keratitis	Vancomycin used only. Resistant to aminoglycosides	One patient was from a nursing home
Tazawa and Ooishi (In Japanese) ⁸ 1992 Japan	Case series (46)	Conjunctivitis, keratitis, endophthalmitis	Ofloxacin, minocycline, netilmicin, amikacin used.	10-year analysis with increasing ofloxacin resistance over time
Muder <i>et al</i> ²⁵ 1993 USA	Case series (1)	Conjunctivitis	Vancomycin	Describes MRSA infections of healthcare workers
Mitsuda <i>et al</i> ²⁶ 1995 Japan	Case series (4)	Conjunctivitis	Ofloxacin	Describes all types of MRSA infections in three outbreaks in a neonatal nursery
Spindel <i>et al</i> ²⁷ 1995 USA	Case series (28)	Conjunctivitis	Not specified	All types of MRSA and methicillin-susceptible infections over 5 years in a 120-bed nursing home. Patients were typically debilitated. 62% of patients had an CVA
Jernigan <i>et al</i> ²⁸ 1996 USA	Case series (1)	Conjunctivitis	Vancomycin not stated if systemic or topical	Describes a 7-month outbreak of MRSA colonisation and infections in neonatal ITU

Table 2 Continued

Author Year Country of study	Type of study (no. of patients)	Type of MRSA infections	Treatment (topical unless stated otherwise)	Other details of note
Saitoh A <i>et al</i> ²⁹ 1997 Japan	Case reports (2)	Endophthalmitis acute dacryocystitis	Vancomycin systemically	Describes methodology of dose adjustment in patients on systemic vancomycin treatment
Oshima <i>et al</i> ³⁰ 1999 Japan	Case series (7)	Scleral buckle infections Endophthalmitis	Vancomycin. Used via systemic, intravitreal and subconjunctival routes in cases of endophthalmitis	MRSA infections associated with patients with atopic dermatitis
Rubinfeld and Negvesky ¹⁴ 2001 USA	Case report (1)	Bilateral keratitis postlaser <i>in situ</i> keratomileusis	Tobramycin, vancomycin	Patient had positive culture of MRSA from nares and also had a previous MRSA infection following abdominal surgery
Horil <i>et al</i> ¹⁰ 2001 Japan	Case series (6)	Conjunctivitis	Benzethonium chloride 0.02% solutions used	Patients were bed-ridden and came from a single stroke unit
Rudd and Moshirfar ¹⁵ 2001 USA	Case report (1)	Keratitis postlaser <i>in situ</i> keratomileusis	Vancomycin, gentamicin and ofloxacin	
Cosar <i>et al</i> ³¹ 2001 USA	Case series (2)	Corneal wound infections postphacoemulsification	Vancomycin and tobramycin. Systemic levofloxacin	Describes case series of seven corneal wound infections postphacoemulsification
Forster <i>et al</i> ¹⁶ 2002 Germany	Case report (1)	Keratitis postphotorefractive keratectomy	Systemic gentamicin and clindamycin. Topical erythromycin	Patient had postoperative bandage contact lens and given ofloxacin drops
Kubo <i>et al</i> ³² 2002 Japan	Case reports (4)	Acute and chronic dacryocystitis	Povidone-iodine or vancomycin. One patient also had dibekacin sulphate	Patients were treated successfully with a dacryocystorhinostomy. Postoperative cultures taken from the nose and conjunctiva were negative for MRSA
Sotozono <i>et al</i> ⁶ 2002 Japan	Case series (30)	Conjunctivitis, keratitis	Vancomycin, arbecakacin	Study also included methicillin-resistant <i>Staphylococcus epidermidis</i>
Fukuda <i>et al</i> ⁷ 2002 Japan	Case series (74)	Conjunctivitis	Vancomycin, chloramphenicol	Investigated prevalence of MRSA and methicillin-resistant coagulase-negative <i>Staphylococcus</i> infections on the ocular surface
Donnenfeld <i>et al</i> ¹⁷ 2003 USA	Case series (1)	Keratitis postphotorefractive keratectomy	Tobramycin until culture results were available; then vancomycin and ofloxacin	Case was bilateral

of MRSA endophthalmitis had been recorded. However, serious infections of postoperative keratitis have been reported particularly after refractive surgical procedures.^{14–17} One of these cases was MRSA positive in the nares and had a past history of MRSA postoperative wound infection of the abdomen.¹⁴ In our own series, only five patients were screened for nonocular MRSA colonisation of which one was positive. This low rate of swabbing nonocular sites was due to the fact that many of the infections resolved quickly and patients were discharged following treatment in the eye casualty or outpatients before any microbiological results were made available.

MRSA is a significant cause of postoperative morbidity, particularly in patients who have undergone vascular procedures.¹⁸ There has been much debate on how to tackle the problem. In addition to infection control of outbreaks, screening to rule out MRSA colonisation also needs to be considered. However, issues such as cost effectiveness and staff screening make providing straightforward guidelines difficult, especially in hospital wards where MRSA is now endemic. The British working party on the control of MRSA has provided guidelines but these offer flexibility by allowing individual hospitals to interpret these guidelines in the context of the local situation.³ Our own unit screens preoperative patients who are resident in long-term care facilities or who have been in hospital as an in-patient up to 6 months prior to surgery. However, policies vary widely in specialist ophthalmic units in the UK (personal communication). From a review of our database it was clear that there were several cases where MRSA must have been an ocular commensal. There have been several previous studies investigating bacterial flora on clinically healthy conjunctivas preoperatively.^{7,19,20} These studies have found high rates of positive bacterial growth particularly Gram-positive cocci. More specifically, the rates for MRSA vary. Kato and Hayasaka²⁰ report 13/978 (1.33%) eyes swabbed preoperatively grew MRSA compared with 6.58% of eyes in Fukuda's study of 1000 asymptomatic eyes.

However, several important unanswered questions remain. Firstly, what is the risk of MRSA colonisation leading to ocular infection, be it primary or postoperative? Does MRSA colonisation in nonocular sites increase the risk of colonisation within the conjunctiva? What are the implications for preoperative screening in an ophthalmic setting?

In summary, to the best of our knowledge, this is the first case series describing MRSA external ocular infections in the UK. We conclude that MRSA is an infrequent cause of external ocular infections in the UK and currently infections are readily treated in most instances with topical chloramphenicol. However,

resistance to ofloxacin is widespread. Comparisons with other work show similarities in terms of the type of patients prone to MRSA infections, but there are clear geographic differences in the spectrum of sensitivity and severity of ocular surface MRSA infections that have been reported. This study also highlights the need for further work to determine the relationship between MRSA colonisation and ocular infections. This will assist in formulating guidelines for the screening of patients before ocular surgery.

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