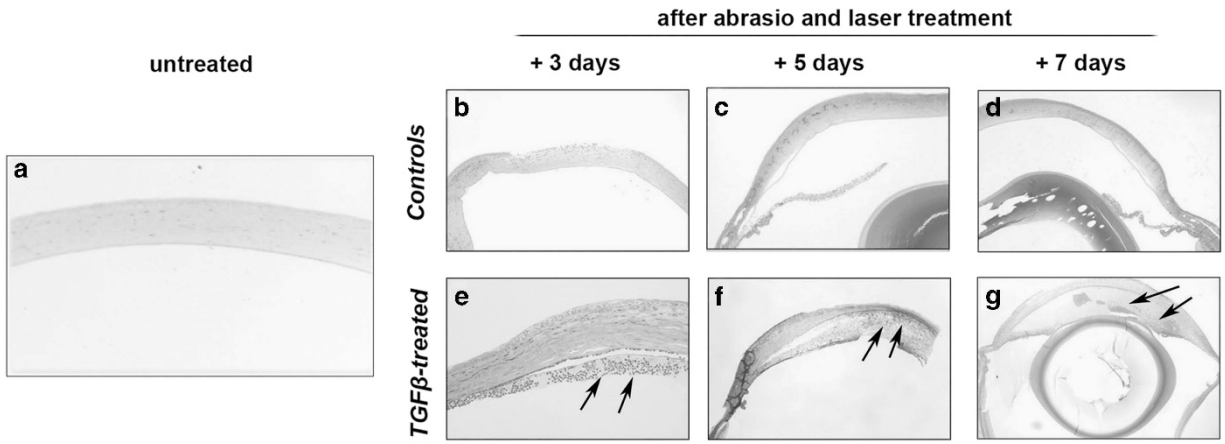

Figure 2 (a) Histological section of an untreated control wild-type mouse. Normal anterior segment. (b–g) Histological section of a wild-type mouse 3, 5, and 7 days after deep stromal ablation (b–d) and deep stromal ablation with TGF-ß treatment (e–g). Note the anterior chamber reaction with massive infiltrates and fibrin production in e–g as indicated by the black arrows.

PRK in the presence and absence of exogenous TGF-ß, indicating that IL-6 has rather a suppressive role in the inflammatory process occurring during excimer laser-mediated corneal wound healing *in vivo*. This presumed inflammatory-constraining role may interfere with the signaling pathway underlying the IL-6 and TGF-ß interaction and requires further investigation. Modulation of IL-6 in the cornea might therefore be a means to influence the corneal wound healing response *in vivo*. Moreover, both TGF-ß and IL-6 appear to exert an angiogenetic effect, which may have significant implications in corneal wound healing after laser refractive procedures.

This study has certain limitations. The relatively low number of animals used in each experiment did not allow a valid statistical analysis between the subgroups. Moreover, the excimer laser ablation alone might have contributed to some extent to the formation of corneal neovascularisation. Further studies are required to validate these results and elucidate the complex interactions between IL-6 and TGF-ß in corneal wound healing after laser ablation procedures.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Study concept and design (FH, LMI); performance of experiments (FH, LMI); data collection, analysis and interpretation (FH, ZG, RA, ME, LMI); drafting of the manuscript (FH, ZG, RA, EM, LMI); critical revision of the manuscript (FH, ZG, RA, ME, LMI).

References

1 O'Connor J, O'Keeffe M, Condon PI. Twelve-year follow-up of photorefractive keratectomy for low to moderate myopia. *J Refract Surg* 2006; **22**(9): 871–877.
2 Amm M, Wetzel W, Winter M, Uthoff D, Duncker GI. Histopathological comparison of photorefractive keratectomy and laser in situ keratomileusis in rabbits. *J Refract Surg* 1996; **12**(7): 758–766.
3 Ebihara N, Matsuda A, Nakamura S, Matsuda H, Murakami A. Role of the IL-6 classic- and trans-signaling pathways in corneal sterile inflammation and wound healing. *Invest Ophthalmol Vis Sci* 2011; **52**(12): 8549–8557.
4 Saika S. TGF-beta signal transduction in corneal wound healing as a therapeutic target. *Cornea* 2004; **23**(8 Suppl): S25–S30.
5 Wilson SE, Liu JJ, Mohan RR. Stromal-epithelial interactions in the cornea. *Prog Retin Eye Res* 1999; **18**(3): 293–309.

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Sir,

Management of MRSA-positive eye swabs and the potential advantages of chloramphenicol availability in the United Kingdom

Methicillin resistant *Staphylococcus aureus* (MRSA) accounts for 39% of *Staphylococcus aureus* ocular infections.[1] There are limited topical agents available for

Table 1 Table to demonstrate antibiotic susceptibility patterns for MRSA positive eye swabs

	Number of susceptible samples/samples tested	*Percentage of MRSA positive eye swabs susceptible to individual antibiotic*
Vancomycin	91/91	100%
Chloramphenicol	96/97	99%
Gentamicin	89/99	90%
Fusidic acid	69/94	73%
Ciprofloxacin	31/87	36%

ocular MRSA, with little prospect of a new topical antibiotic in the foreseeable future. A previous review from 2004 of the 15 largest pharmaceutical companies found there were 'no antibacterial agents with novel mechanisms of action' currently in development.[2] Thirteen years later, a report from the World Health Organisation in September 2017 identified 51 new antibiotics and biologicals in clinical development to treat priority antibiotic-resistant pathogens, but only 8 were classed as innovative treatments, as the majority in the clinical pipeline were deemed to be modifications of existing classes of antibiotics.[3] Such modifications and developments include the use of small molecules, structurally nanoengineered antimicrobial peptide polymers (SNAPPs), concurrent use of non-antibiotic drugs with failing antibiotics, and utilising the human microbiome, all backed up with financial incentives for the pharmaceutical companies (such as the Generating Antibiotic Incentives Now (GAIN) Act) to develop such products.[3–6] Other groups have also advised the need to revisit, and even revive, the use of older drugs to ensure that they are being utilised effectively and thoroughly, both to optimise clinical practice and reduce inefficiencies leading to drug resistance.[4–7]

Topical chloramphenicol is widely available in Europe (and without prescription in 3 countries including the UK), India, Australia, and New Zealand.[8–10] However, it is not used in the USA due to a controversial association with aplastic anaemia, despite population studies representing 185 million person years of observation not indicating causation.[11–13] We wished to determine our ocular MRSA antibiotic sensitivity patterns and current local management practices to see if they could contribute to the bigger worldwide discussion of 'no new antibiotics'.[2]

Materials and methods

A retrospective review of 100 consecutive MRSA positive ocular swabs processed by the Department of Clinical Microbiology at Glasgow Royal Infirmary, Scotland from 03/02/13 to 28/11/15 was performed. Antibiotic sensitivity patterns using Clinical and Laboratory Standards Institute systemic susceptibility breakpoints were determined in all cases. Indications for ocular microbial investigation and management were identified for the 62 cases originating from hospital care due to availability of hospital casenotes (38 originated from general practice).

Results

There were 53 male and 47 female cases. Mean age was 62 years (median 77, SD = 34). Documented indications for microbial testing included blepharoconjunctivitis (53/62, 86%), MRSA screening (5/62, 8%), and infective keratitis (3/62, 5%). Of those with blepharoconjunctivitis, 92% (49/53) were managed with topical chloramphenicol; variably prescribed as 2–4 times per day (duration range 5 days to 4 weeks). There were no documented complications following chloramphenicol therapy. 27% (17/62) completed 5-day systemic decolonisation with chlorohexidine 4% once daily and mupirocin 2% three times per day.

All ocular MRSA cases were susceptible to vancomycin, and only 1 case was resistant to chloramphenicol. 64% (56/87) were resistant to ciprofloxacin, 24% (25/94) resistant to fusidic acid, and 10% (10/99) resistant to gentamicin (Table 1). Seven percent (3/46) remained MRSA positive on retesting for eradication, though two of these patients did not receive systemic decolonisation. Of patients treated with topical chloramphenicol, there was a confirmed eradication rate of 90% (28/31).

Discussion

We found inconsistent and wide variations in the general management of MRSA positive ocular swabs in this review. This raises issues of cost, antibiotic resistance and the need for a more effective standardised approach. Chloramphenicol is effective for ocular MRSA; we observed a 90% eradication rate on retesting. This compares favourably with a 68.4% eradication rate previously reported following topical vancomycin for treatment of MRSA.[14] Chloramphenicol is also comparatively inexpensive.[8–10] The cost of 1 week treatment with chloramphenicol 0.5% drops is £1.45, chloramphenicol 1% ointment £1.79, compared to £39 for vancomycin 5% drops (personal communication with local hospital pharmacy).

Patients infected with MRSA are believed to be the source population for vancomycin intermediate *Staphylococcus aureus* (VISA).[15] Risk factors for infection with VISA include prior MRSA infection and persistent or recurrent vancomycin use, so the USA-based VISA Study Group recommends reducing vancomycin exposure in MRSA infection wherever possible.[15] Vancomycin resistant *Staphylococcus aureus* (VRSA) was first reported in the USA in 2002 (thirteenth case reported in 2014), and is resistant to both methicillin and vancomycin.[16] Due to previously mentioned concerns, the USA has remained unexposed to chloramphenicol, but this historical conundrum may now represent an opportunity for a novel antibiotic for that population group (and countries with similar practices).[7,13] This is particularly relevant due to the issues of limited effectiveness of current antibiotics and increasing antibiotic resistance.[2–4,7] Indeed, Fraunfelder *et al* in 2013 reviewed this historical

restriction, questioned if it was an over-reaction to a few case reports, and debated if the time would come when topical chloramphenicol could be a viable treatment option in the American market (which would require an appropriate clinical indication).[13]

Conclusion

We believe a rational antibiotic policy will reduce the emergence of resistance, and suggest that 1 week of topical chloramphenicol should be the cheap, effective and safe first-line treatment for MRSA blepharoconjunctivitis, with systemic eradication therapy to reduce reinfection, and vancomycin reserved for only severe or resistant cases. In a world of sparse novel antibiotics, this small study demonstrates that there is still the potential for other countries to identify, revive and utilise already existing antibiotics, which are not currently licensed or available to their populations.[2,4,7,13] This clinical conundrum is currently the case with topical chloramphenicol and the management of MRSA positive ocular swabs.

Conflict of interest

The authors declare no conflict of interest.

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References

1 Haas W, Pillar CM, Torres M, Morris TW, Sahm DF. Monitoring antibiotic resistance in ocular microorganisms: results from the Antibiotic Resistance Monitoring in Ocular micRorganisms (ARMOR) 2009 surveillance study. *Am J Ophthalmology* 2011; **152**(4): 567–574.e563.
2 Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr. Trends in antimicrobial drug development: implications for the future. *Clinical Infect Dis* 2004; **38**(9): 1279–1286.
3 World Health Organisation. Antibacterial agents in clinical development. 2017. WHO/EMP/IAU/2017.11. 7. Available at: http://www.who.int/medicines/areas/rational_use/antibacterial_agents_clinical_development/en/ (accessed on 9 October 2017).
4 Buckland D. Antimicrobial resistance and the race to find new antibiotics. *Prescriber* 2017; **28**: 12–15.
5 Bush K, Page MG. What we may expect from novel antibacterial agents in the pipeline with respect to resistance and pharmacodynamic principles. *J Pharmacokinet Pharmacodyn* 2017; **44**(2): 113–132.
6 Falagas ME, Mavroudis AD, Vardakas KZ. The antibiotic pipeline for multi-drug resistant gram negative bacteria: what can we expect? *Expert Rev Anti Infect Ther* 2016; **14**(8): 747–763.
7 Theuretzbacher U, Van Bambeke F, Cantón R, Giske CG, Mouton JW, Nation RL *et al.* Reviving old antibiotics. *J Antimicrob Chemother* 2015; **70**(8): 2177–2181.
8 Both L, Botgros R, Cavaleri M. Analysis of licensed over-the-counter (OTC) antibiotics in the European Union and Norway, 2012. *Euro Surveill* 2015; **20**(34): pii = 30002.
9 Lam RF, Lai JS, Ng JS, Rao SK, Law RW, Lam DS. Topical chloramphenicol for eye infections. *Hong Kong Med J* 2002; **8**(1): 44–47, Review.
10 Robaei D, Naunton M, Watson S. Seeing red: over-the-counter chloramphenicol. *Clin Exp Ophthalmol.* 2015; **43**(2): 99–100.
11 Thomseth V, Cejvanovic V, Jimenez-Solem E, Petersen KM, Poulsen HE, Andersen JT. Exposure to topical chloramphenicol during pregnancy and the risk of congenital malformations: a Danish nationwide cohort study. *Acta Ophthalmol.* 2015; **93**(7): 651–653.
12 Wiholm B-E, Kelly JP, Kaufman D, Issaragrisil S, Levy M, Anderson T *et al.* Relation of aplastic anaemia to use of chloramphenicol eye drops in two international case-control studies. *BMJ* 1998; **316**(7132): 666–666.
13 Fraunfelder FW, Fraunfelder FT. Restricting topical ocular chloramphenicol eye drop use in the United States. Did we overreact?. *Am J Ophthalmol* 2013; **156**(3): 420–422.
14 Sotozono C, Fukuda M, Ohishi M, Yano K, Origasa H, Saiki Y *et al.* Vancomycin Ophthalmic Ointment 1% for methicillin-resistant *Staphylococcus aureus* or methicillin-resistant *Staphylococcus epidermidis* infections: a case series. *BMJ open* 2013; **3**(1): e001206.
15 Fridkin SK, Hageman J, McDougal LK, Mohammed J, Jarvis WR, Perl TM *et al.* Epidemiological and microbiological characterization of infections caused by Staphylococcus aureus with reduced susceptibility to vancomycin, United States, 1997-2001. *Clinical Infect Dis* 2003; **36**(4): 429–439.
16 Limbago BM, Kallen AJ, Zhu W, Eggers P, McDougal LK, Albrecht VS. Report of the 13th Vancomycin-Resistant Staphylococcus aureus Isolate from the United States. *J Clin Microbiol* 2014; **52**(3): 998–1002.

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Sir,

The importance of immunosuppression as risk and prognostic factor for periorbital non-melanoma skin cancers

We read with great interest the article by RC Gerring *et al*[1] regarding prognostic factors and survival rates in a retrospective case series of patients who underwent orbital exenteration for non-melanoma skin cancers (NMSC). The authors have thoroughly described the correlation between survival rates and some factors which are thought to influence the prognosis after orbital exenteration.

Their article does not make any reference to the important relation between immunosuppression and the