Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Improved management of *Acanthamoeba* keratitis

1. Summary of the impact

Our research identified an epidemic of *Acanthamoeba* infection amongst UK contact lens wearers, established the epidemiology of infection, introduced improved approaches to contact lens hygiene, developed the most sensitive test to make a diagnosis and discovered a new treatment for established infection. This has impacted on contact lens wearers around the world, forming the basis for guidelines and patient information leaflets, types of contact lens solutions, and treatments for this rare but devastating condition.

2. Underpinning research

Acanthamoeba keratitis (AK) is a rare corneal infectious disease caused by the pathogenic free-living protozoan Acanthamoeba spp. Incidence of the infection is low (1 in 100,000 in the EU), but has potentially devastating consequences, causing vision to deteriorate and leading to permanent blindness. In countries with a high prevalence of contact lens wearing, this accounts for over 85% of cases of AK infection, but it can also occur after corneal trauma, particularly in rural environments. AK is on the rise in developing economies and there is no approved drug to treat this disease. Through the systematic study of AK at the UCL Institute of Ophthalmology (IoO), including laboratory, epidemiological and clinical research, we have identified avoidable risk factors, developed better techniques for diagnosis, and introduced and developed a novel class of topical disinfectants (the biguanides).

Risk factors:

Through an integrated programme of epidemiological and clinical research we first established that an epidemic of cases of AK had developed in the UK in contact lens users in the 1990s. This was shown to be the result of both reduced lens hygiene compliance, and because of the use of chlorine disinfection solutions, which are ineffective against *Acanthamoeba*. Users of the then newly introduced monthly disposable contact lenses were at particular risk **[1]**. We subsequently showed in two national surveys of AK that the disease was up to 20 times more common in the UK than has been reported elsewhere, and that the incidence was increased in hard water areas; a previous clinical study had shown that limescale build up on domestic taps in hard water areas, harboured *Acanthamoeba*, probably by providing the mixed microbial microenvironment that the organism favours **[2]**. We subsequently demonstrated that genetically identical organisms, present in their contaminated domestic water supply, had infected a high proportion of AK patients **[3]**.

We have shown that good contact lens hygiene practice is critical to the prevention of AK including regular disinfection of lenses and lens case hygiene or the use of daily disposable lenses, which eliminates the need for lens disinfection and contact lens case use. In addition to hygiene we have identified the risks of exposure to contaminated water by showering and swimming whilst wearing contact lenses **[2]**.

Diagnosis

In addition, our research has demonstrated that diagnosis and treatment within 3 weeks of onset improves outcomes **[4]**. We were the first to investigate the value of the identification of *Acanthamoeba* DNA by Polymerase Chain Reaction (PCR) as the most sensitive and specific method for the diagnosis of AK, since confirmed by several other independent studies **[5]**. We have also investigated the use of confocal microscopy, another widely used imaging technique for diagnosis, particularly in the USA. We performed a masked multi-observer study and measured the

sensitivity and predictive value of this technique and the resulting potential for misdiagnosis **[6]**.

Treatment:

Acanthamoeba is notoriously difficult to treat (most patients with cerebral disease die). In the eye, disease persists because the cysts are resistant to most antimicrobials. At the same time that we recognised the epidemic of cases in the UK there was little really effective treatment apart from the use of a diamidine, to which many cases were resistant. The result was that patients needed therapeutic corneal transplant surgery with poor outcomes and high morbidity. In response to this we collaborated with a protozoologist (Dr Simon Kilvington, University of Leicester) who suggested the use of the biguanide Polyhexamethyl biguanide (PHMB) also known as Polyhexanide. This was used as a swimming pool disinfectant, to which the encysted from of *Acanthamoeba* was susceptible. We introduced this in clinical studies with a dramatic and beneficial effect on outcomes **[7]**. The success of polyhexanide as a therapy has been recognised by the awarding of a EU grant of €4,050,255 to the Orphan Drug for Acanthamoeba Keratitis (ODAK) project in 2012. Another biguanide, chlorhexidine, has also been introduced, building on our early work. There are no other anti-amoebics available that are consistently effective against the encysted from of the organism.

3. References to the research

[1] Radford CF, Bacon AS, Dart JKG, Minassian DC. Risk factors for acanthamoeba keratitis in contact lens users: a case-control study. Br Med J 1995;310:1567-70. http://dx.doi.org/10.1136/bmj.310.6994.1567

[2] Radford CF, Minassian DC, Dart JK. Acanthamoeba keratitis in England and Wales: incidence, outcome, and risk factors. Br J Ophthalmol. 2002 May;86(5):536-42. http://dx.doi.org/10.1136/bjo.86.5.536

[3] Kilvington S, Gray T, Dart J, Morlet N, Beeching JR, Frazer DG, Matheson M. Acanthamoeba keratitis: the role of domestic tap water contamination in the United Kingdom. Invest Ophthalmol Vis Sci. 2004 Jan;45(1):165-9. http://dx.doi.org/10.1167/iovs.03-0559

[4] Bacon AS, Dart JK, Ficker LA, Matheson MM, Wright P. Acanthamoeba keratitis. The value of early diagnosis. Ophthalmology. 1993 Aug;100(8):1238-43. Copy available.

[5] Lehmann OJ, Green SM, Morlet N, Kilvington S, Keys MF, Matheson MM, Dart JK, McGill JI, Watt PJ. Polymerase chain reaction analysis of corneal epithelial and tear samples in the diagnosis of Acanthamoeba keratitis. Invest Ophthalmol Vis Sci. 1998 Jun;39(7):1261-5. http://www.iovs.org/content/39/7/1261.long

[6] Dart JK, Saw VP, Kilvington S. Acanthamoeba keratitis: diagnosis and treatment update 2009. Am J Ophthalmol. 2009 Oct;148(4):487-499.e2. http://dx.doi.org/10.1016/j.ajo.2009.06.009

[7] Duguid IG, Dart JK, Morlet N, Allan BD, Matheson M, Ficker L, Tuft S. Outcome of Acanthamoeba keratitis treated with polyhexamethyl biguanide and propamidine. Ophthalmology. 1997 Oct;104(10):1587-92. http://dx.doi.org/10.1016/S0161-6420(97)30092-X

4. Details of the impact

Our work has impacted on the prevention, diagnosis and treatment of AK. Guidelines for the prevention of AK now incorporate our findings. For example, the British Contact Lens Association's *Guide for practitioners and support staff on reducing infection risk in contact lens patients* makes several references to our work on risk factors in relation to swimming, extended-wear contact lenses, and hygiene related to contact lens cases **[a]**. Guidance from the College of Optometrists on the treatment of AK cites a study conducted at Moorfields (Lim et al 2008) which built on the underpinning research described above **[b]**. We have also worked to raise practitioner and public awareness of the risks for AK – for example our research was widely reported in 2008 **[c]**, and the topic featured in a 2011 article, *Contact Lens Problems* on patient.co.uk (citing our work), and in a

2013 case study article in The Optician **[d]**.

Our work on risk factors for AK has been incorporated into contact lens packaging. Furthermore, our work led to a new disposable contact lens case being supplied with each bottle of contact lens solution sold. Our research has stimulated further work to develop new and improved cleaning solutions and cases, and has been cited in many patents for such products **[e]**. Our demonstration that chlorine-based solutions are not effective against AK has led to this type of solution being removed from the market – for example Softab in 1995. In 2007, a similar occurrence of an outbreak of AK infection was identified in the USA using our methods, and was associated with the use of Complete Moisture Plus. This solution was withdrawn and accordingly no such solutions were available in the period 2008-13. Our research is used by manufacturers in the development of more appropriate solutions, for example, Menicon cite our research in their evaluation of the efficacy of a new multipurpose solution, MeniCare Soft, against *Acanthamoeba* **[f]**.

PCR for diagnosis of AK is becoming widely used in routine diagnostic laboratories **[g]**. The sensitivity of this technique is between 85-95% (compared to culture, at up to 60%), and with 100% specificity. Our clinical studies have identified the importance of early diagnosis and introduction appropriate therapy (within three weeks of onset) as the major predictor of disease outcomes, since corroborated by independent studies **[h]**.

Biguanides (PHMB and chlorhexidine) with or without a diamidine (propamidine or hexamidine) have become the standard of care for this condition around the world **[i]**. A survey of US ophthalmologists and vision scientists conducted in 2011 revealed that "*most respondents (97.6%) had used combination therapy with multiple agents to treat acanthamoeba keratitis at some point in the past, whereas a smaller proportion (47.6%) had ever used monotherapy. Respondents most commonly chose polyhexamethylene biguanide as the ideal choice for monotherapy (51.4%), and dual therapy with a biguanide and diamidine as the ideal choice for combination therapy (37.5%)*" **[j]**.

We have also formulated the only available guidelines both for the management of persistently culture positive cases (about 5% of our series), and for the management of the severe scleral inflammation that is associated with the disease but which is unrelated to direct invasion of organisms, and which has been the major reason for enucleation at our centre; this treatment involves the use of systemic immunosuppressive therapy and effective topical anti-amoebic therapy **[k]**.

5. Sources to corroborate the impact

[a] Bowers S. BCLA guide for practitioners and support staff on reducing infection risk in contact lens patients. December 2011. Copy available on request.

[b] College of Optometrists. Clinical Management Guidelines: Microbial keratitis (Acanthamoeba sp.) http://www.college-optometrists.org/en/utilities/document-summary.cfm/docid/2DD414AE-DCD7-45E8-AB9A1EC9FC3C4E5C The guidelines cite the following Moorfields study: Lim N, Goh D, Bunce C, Xing W, Fraenkel G, Poole TR, Ficker L. Comparison of polyhexamethylene biguanide and chlorhexidine as monotherapy agents in the treatment of Acanthamoeba keratitis. Am J Ophthalmol. 2008 Jan;145(1):130-5. http://dx.doi.org/10.1016/j.ajo.2007.08.040

[c] CBS News: http://www.cbsnews.com/2100-500368_162-4499756.html; WebMD: http://www.webmd.com/eye-health/news/20081003/newer-contact-lenses-dont-cut-infections

[d] *Contact Lens Problems*, professional reference article on patient.co.uk website, 2011 http://www.patient.co.uk/doctor/Contact-Lens-Problems.htm
Carnt, N *Minimising contact lens adverse events - in practice with Josie*, The Optician 2013 Apr; 245 (6396):14-23.

[e] See, for example:

A process for reducing microbial growth in contact lens storage cases, WO2012145790 A1, priority filing date April 2011
https://www.google.com/patents/WO2012145790A1
An apparatus, system and method for preventing biological contamination to materials during storage using pulsed electrical energy, WO2010113150 A2, priority filing date March 2009
https://www.google.com/patents/WO2010113150A2

[f] Menicon's evaluation of of their Menicare Soft multipurpose solution; see references 3 and 4. http://www.menicon.com/pro/soft/soft-lens-care/menicare-soft/acanthamoeba-and-viruses

[g] Clarke B, Sinha A, Parmar DN, Sykakis E. Advances in the diagnosis and treatment of acanthamoeba keratitis. J Ophthalmol. 2012;2012:484892. http://dx.doi.org/10.1155/2012/484892.

[h] For example: Claerhout I, Goegebuer A, Van Den Broecke C, Kestelyn P. Delay in diagnosis and outcome of Acanthamoeba keratitis. Graefes Arch Clin Exp Ophthalmol. 2004 Aug;242(8):648-53. http://dx.doi.org/10.1007/s00417-003-0805-7; Patel DV, Rayner S, McGhee CN. Resurgence of Acanthamoeba keratitis in Auckland, New Zealand: a 7-year review of presentation and outcomes. Clin Experiment Ophthalmol. 2010 Jan;38(1):15-20; quiz 87. http://dx.doi.org/10.1111/j.1442-9071.2009.02182.x.

[i] See for example, recommendations on Medscape: http://emedicine.medscape.com/article/211214-treatment. Reference is made to Clarke et al. 2012, which in turn refers to our 2009 review.
Ophthalmologists at Moorfields Eye Hospital and the Royal Liverpool University Hospital can also corroborate this standard practice. Contact details provided.

[j] Oldenburg CE, Acharya NR, Tu EY, Zegans ME, Mannis MJ, Gaynor BD, Whitcher JP, Lietman TM, Keenan JD. Practice patterns and opinions in the treatment of acanthamoeba keratitis. Cornea. 2011 Dec;30(12):1363-8. http://dx.doi.org/10.1097/ICO.0b013e31820f7763.

[k] Pérez-Santonja JJ, Kilvington S, Hughes R, Tufail A, Matheson M, Dart JK. Persistently culture positive acanthamoeba keratitis: in vivo resistance and in vitro sensitivity. Ophthalmology. 2003 Aug;110(8):1593-600. http://dx.doi.org/10.1016/S0161-6420(03)00481-0