

## APPENDIX 3A Clinical Diagnosis

### Challenges:

#### 1. Misdiagnosis is common and associated with 5x increased risk of vision loss<sup>1</sup>.

*I saw nine ophthalmologists in 4 months before being diagnosed. Awareness of this condition is paramount - imagine, my journey may have had a different outcome. (M. Castle-Genn)*

Because *Acanthamoeba* Keratitis (AK) is rare and accounts for only 5% of the cases of corneal infection, in up to 80% of AK cases, clinicians misdiagnose AK as more common forms of keratitis<sup>2</sup> particularly Herpes Simplex Keratitis. This delays and can initiate incorrect treatment, including the use of steroids.

#### 2. The gold standard diagnosis is traumatic and only 50% sensitive<sup>3</sup>

*I underwent a corneal scraping procedure on the same day I was admitted to hospital. It was particularly painful because the anaesthesia had not taken effect when it began, and I was too frightened to speak up. (M. Leitner)*

Corneal scraping (Figure 3) to obtain a sample for microscopy and culture (growth in the laboratory) is the gold standard for diagnosing and differentiating AK from other infections like bacteria. However, culture has low sensitivity and long turnaround time (up to 10 days) to make a diagnosis.<sup>3</sup> Polymerase chain reaction (PCR, a genetic-based test), has demonstrated better and faster results (a few hours).<sup>4</sup> However, false positive PCR results have been reported. The sample collection varies between clinics and the analysis is lab dependent. An imaging technique called *in vivo* confocal microscopy (IVCM) can visualise *Acanthamoeba* cysts and can be more reliable than other diagnostic techniques but requires trained staff and is not available in all centres.<sup>3</sup>

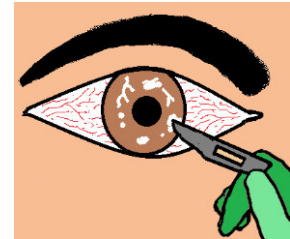


Figure 3. Corneal Scrape

### Recommendations:

#### 1. Clinician network providing peer support and sustained awareness of AK.

A high index of clinical suspicion is crucial and because AK is commonly associated with a recent history of contact lens wear encountering water or ocular trauma, people with any such history should be considered as possible patients with AK. Rarity of the condition could be demystified with a clinician network providing cases and virtual grand rounds.

#### 2. Invest in new technology and improve standardisation.

*My corneal culture and my PCR test both came negative last week. Then we did a confocal microscopy which confirmed I had AK. (AK Warrior)*

IVCM can correctly identify that *Acanthamoeba* is causing the disease about 80% of the time, however IVCM cannot detect the difference between live and dead organisms (i.e. active vs quiet/resolved disease). IVCM also requires highly trained personnel and expensive instrumentation which are not available at all clinical centres. Recent advances are incorporating artificial intelligence (AI) for AK diagnosis.<sup>5</sup> An AK PCR international external quality assurance scheme is now available<sup>4</sup> and Sydney Eye Hospital has developed a culture protocol animation available on [YouTube](#). These initiatives are currently siloed and will benefit from promotion through the Clinical Network.

## APPENDIX 3B AK Treatment

### Challenges:

#### 1. No universally licensed treatments or accepted treatment protocols

*I had 3 options with a 50/50 success rate, so I chose enucleation, as I wanted to be rid of the torturing pain and the constant stress this placed on me and my family. I am now free. (M. Castle-Genn)*

Currently, hourly, mostly unlicensed antiseptics/disinfectant eyedrops are the first-line therapy for *Acanthamoeba* keratitis (AK). These include polyhexanide biguanide (PHMB), chlorhexidine, brolene and hexamidine and it is common for patients to have to use more than one type of drop at the same time. The first and only approved therapy (0.08% PHMB, Akantior, SIFI Pharma) is available only in limited markets.<sup>6</sup> In 50% of patients additional therapy is required, including surgery.<sup>7</sup> When treatments fail, corneal transplantation (keratoplasty), amniotic membrane transplantation, conjunctival flap, glaucoma, cataract surgeries or eye removal (enucleation) might be necessary. In some uncontrolled cases, an oral anti parasitic drug (miltefosine, Impavido) is prescribed off label<sup>8</sup> and requires anti-nausea management and a high fat diet. This drug often results in a severe inflammatory reaction a couple of weeks after initiation which needs to be controlled with steroids. Painkillers and immunosuppressive drugs might also be prescribed. Management varies widely between clinical centres as there is no standardized treatment.

#### 2. Inflammation and its management are a double-edged sword.

*I had four corneal transplants. As I am still very young, my body rejects all the transplants and when 20 years old, I had to start taking Cellcept next to my regular medication. (M. Leitner)*

Steroids are often used to control pain caused by AK inflammation as well as post-transplantation. However, steroids increase the activity of *Acanthamoeba* and if used without anti-*Acanthamoeba* drugs, as in those patients who are misdiagnosed, vision and in some cases eye loss occurs.<sup>1</sup> Steroids also cause side effects like glaucoma which may themselves go on to cause vision loss. Immunosuppressive drugs like Cellcept may be prescribed, which are unsafe during pregnancy.

### Recommendations:

#### 1. Support drug discovery and classification systems for drug sensitivity / resistance in non-responding cases.

Standardised drug efficacy screening and reporting on microbial break points will be essential for developing patient care treatment plans. The use of robotics will eliminate lab-to-lab potential biases and for drug discovery this will allow several thousands of chemical agents to be screened in a robust manner compared to the low-throughput methods currently used. The need to assess and develop new therapies on the encystment or fully mature cysts, and potentially aggregates of *Acanthamoeba* may need to be adopted.

#### 2. Delphi consensus study to determine global standard of practice.

As with diagnosis, peer network support would facilitate better management, but efficiency will be ensured with a Delphi consensus study with experienced clinicians to develop treatment guidelines. This process supports clinician decision making as well as patient care.

1.Carnt N, et al. doi: 10.1097/ICO.0000000000002901; 2.Przybek-Skrzypecka J et al. doi:10.2147/OPHTH.S438990; 3.Azzopardi M et al, doi:10.3390/diagnostics13162655; 4.Sarink M, et al. doi: 10.1097/ICO.0000000000003275. 5.Lincke A, et al. doi: 10.1167/tvst.12.11.29. 6.Dart J et al. doi:10.1016/j.optha.2023.09.0317. Robaei D et al. doi:10.1136/bjophthalmol-2015-307371 8.Thulasi P et al. doi: 10.1016/j.ajo.2020.09.048