Development, implementation and evaluation of evidence-based treatment guidelines for herpes simplex keratitis

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Statement of Originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Maria Paulina Cabrera Aguas

"La vida no es la que uno vivió, sino la que uno recuerda, y cómo la recuerda para contarla"

"What matters in life is not what happens to you but what you remember and how you remember it"

- Gabriel García Márquez

Abstract

Introduction

Herpes simplex keratitis (HSK) is one the major causes of unilateral blindness in the developed world. Evidence-based recommendations for HSK had not been properly translated into practice. The overall aim of this thesis was to develop, implement, and evaluate a local HSK treatment guideline at the Sydney Eye Hospital.

Methods

The Registered Nurses' Association of Ontario (RNAO) Toolkit: 'Implementation of Best Practice Guidelines' was utilised to develop, implement, and evaluate the guideline at the Hospital. A retrospective review was conducted to determine the knowledge gap. All HSK patients prescribed with antivirals, aged 18 years and above, from 2012 to 2013 were included. To assess the response to the guideline, an audit of all HSK patients aged 18 and over presenting during 6-months post-guideline implementation was conducted. A web-based survey assessed clinician awareness, usage and level of knowledge of the guideline. Patients were identified from viral swab results, pharmacy records, and hospital coding data.

Results

296 patients were included in the retrospective review and 85 patients in the audit. The dose of prescribed antiviral medications was in alignment with the local guideline in 80% (51/64) of patients compared to 73% prior to implementation (p = 0.331). Post-implementation alignment was found in 72% (26/36) of patients with epithelial HSK vs 89% prior to implementation (124/139), p = 0.009. With SHSK-U, 33% (1/3) vs 9% (2/22), p = 0.3. With endothelial HSK, 67% (2/3) vs 33% (6/18), p = 0.5. With HSK prophylaxis, 100% (22/22) on prophylaxis vs 70% (31/44), p = 0.003.

The web-based survey was sent to 95 clinicians, 41 (43%) responded. Of these, 35 (85%) were aware of the guidelines, 31 (75%) accessed them through the hardcopy and electronic versions available.

Conclusions

Most clinicians were aware of and adhered to the implemented local HSK treatment guideline. The guideline aided clinicians, mainly trainees, in prescribing antivirals for HSK according to the evidence to improve clinical outcomes.

Acknowledgements

It is with an immense sense of pride and achievement that I am pleased to present this thesis. It is my hope that it makes a meaningful contribution to corneal research, and I have several people I wish to personally thank for their assistance to me in this journey.

Firstly, many thanks to my primary supervisor, Professor Stephanie Watson. She provided an immense amount of support, guidance and patience during my PhD. She provided timely assistance and feedback for the preparation of this thesis and publications. Her friendly attitude; energetic, enthusiastic and driven personality; wonderful mentorship and constant encouragement allowed me to grow and develop as a researcher. I am most grateful and feel privileged to be part of her team.

Equally, I would like to thank my co-supervisors, Dr Yves Kerdraon and Dr Dana Robaei**.** Dr Kerdraon's positive attitude, scientific and clinical knowledge helped me to complete my thesis. He reviewed my work with great attention to detail, always providing thorough feedback and encouraging me to analyse the data from different angles considering several scenarios to draw more conclusions. Dr Robaei provided invaluable guidance and support for the design of this study and assisted with the preparation of publications.

Special thanks to many staff at the Sydney Eye Hospital, without their support this project would not been possible. Firstly, Judith Hampson, pharmacy manager, and Cathy Vlouhos. Judith and Cathy also supported and assisted our group in the development of the herpes simplex keratitis (HSK) local treatment guidelines. Secondly, Lyudmila Nikolenko, medical records manager, and all the medical records staff for promptly retrieving the medical notes for data extraction.

Special thanks to the Sydney Eye Hospital Foundation. I received an annual student stipend from 2014 to 2019. The foundation also provided funding for presenting at local and international conferences and for educational materials in the implementation phase of the HSK guidelines. Many thanks to Kevin Gardner, Chief Executive Officer of the Foundation for his help in administrative matters.

Many thanks to the staff at the Prince of Wales Hospital. Samantha Maroudas, Coding Reporting Officer, promptly provided a list with all HSK patients for the retrospective case series and the post-guideline implementation audit. Keith Westbury and Prof William Rawlinson also provided in a timely manner the list of all HSV PCR tests requested at Sydney Eye Hospital for the retrospective cases series and the post-guideline implementation audit. Further, Prof. Monica Lahra promptly provided culture results from corneal scrapes performed to patients with presumed microbial and HSK.

Most importantly, I would like to thank my husband, Camilo, for his love, patience, encouragement, understanding and endless support throughout our Australian journey. Without him, this would not have been possible.

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Publications and conference presentations arising from thesis

Published articles

1. **Cabrera-Aguas M**, Robaei D, McCluskey P, Watson S. Clinical translation of recommendations from randomized trials for management of herpes simplex virus keratitis. Clin Experiment Ophthalmol. 2018;46(9):1008-16.
   This article was recognised as a top 20 most read paper in Clinical and Experimental Ophthalmology between January 2017 and December 2018.

Conference abstracts arising from presentation.

1. **Cabrera-Aguas M**, Robaei D, Watson S. Evaluation of guidelines for the management of herpes simplex keratitis at the Sydney Eye Hospital. RANZCO Annual Congress. Presentation. Adelaide, Australia 2018

2. **Cabrera-Aguas M**, Robaei D, Khoo P, Watson S. Risk factors, microbiological features and outcomes of patients with microbial and herpes simplex virus keratitis. EU Cornea. Presentation. Vienna, Austria 2018

3. **Cabrera-Aguas M**, Robaei D, Watson S. Outcomes of antiviral therapy in herpes simplex keratitis. The Association for Research in Vision and Ophthalmology Congress. Poster. Honolulu, United States 2018

4. **Cabrera-Aguas M**, Robaei D, Kerdraon Y, Symes R, McCluskey P, Watson S. Development and implementation of herpes simplex keratitis treatment guidelines. RANZCO Annual Congress. Presentation. Perth, Australia 2017

5. **Cabrera-Aguas M**, Robaei D, Watson S. Outcomes of herpes simplex keratitis in patients with a corneal graft. EU Cornea. Presentation. Lisbon, Portugal 2017

6. **Cabrera-Aguas M**, Robaei D, Kerdraon Y, Symes R, McCluskey P, Watson S. Development of Australian Guidelines for the management of Herpes Simplex

Keratitis. Asia- Pacific Academy of Ophthalmology Congress. Presentation. Singapore, 2017

7. **Cabrera-Aguas M**, Robaei D, Watson S. The outcomes of oral and topical antiviral therapy in herpes simplex keratitis and keratouveitis. The Association for Research in Vision and Ophthalmology Asia Congress. Poster. Brisbane, Australia 2017

8. **Cabrera-Aguas M**, Robaei D, Watson S Outcomes of Herpes Simplex Stromal and Endothelial Keratitis and Keratouveitis in a tertiary referral hospital. RANZCO Annual Congress. Presentation. Melbourne, Australia 2016

9. **Cabrera-Aguas M,** Robaei D, Watson S. Clinical translation of recommendations from randomised trials for management of herpes simplex keratitis. RANZCO Annual Congress. Presentation. Wellington, New Zealand 2015

Presentations

1. **Cabrera-Aguas M**, Robaei D, Kerdraon Y, McCluskey P, Watson S. Development and implementation of herpes simplex keratitis treatment guidelines. ANZ Cornea Society & Eye Bank Meeting. 2018

2. **Cabrera-Aguas M**, Robaei D, Kerdraon Y, Symes R, McCluskey P, Watson S. Development and implementation of guidelines for the management of herpes simplex keratitis. Annual HDR Student Symposium: Vision Science and Ophthalmology. Save Sight Institute, University of Sydney, Sydney. March 2017.

3. **Cabrera-Aguas M, Robaei D, Watson S.** Clinical translation of recommendations from randomised trials for management of herpes simplex

keratitis. Annual HDR Student Symposium: Vision Science and Ophthalmology. Save Sight Institute, University of Sydney, Sydney. March 2016

4. **Cabrera-Aguas M.** Clinical translation of recommendations from randomised trials for management of herpes simplex keratitis. Central Clinical School Young's investigators seminar. The University of Sydney, Sydney. October 2015

Articles in submission

1. **Cabrera-Aguas M**, Kerdraon Y, Watson S. Outcomes of herpes simplex keratitis. Eye & Contact lens. October 2019

2. **Cabrera-Aguas M**, Khoo K, Lahra M, Watson S. Predisposing factors, microbiological features and outcomes of patients with concomitant microbial keratitis and herpes simplex keratitis. Eye & Contact lens. October 2019

3. **Cabrera-Aguas M**, Kerdraon Y, Symes R, McCluskey P, Samarawickrama C, Rawlinson W, Watson S. Development, implementation and evaluation of herpes simplex keratitis treatment guidelines. Cornea. October 2019.

Clinical Guidelines

HSK guidelines

https://sites.google.com/view/sydneyeyeschool/clinical-resources/cornea/guidelines

http://www.savesightinstitute.org.au/research-units/corneal-research/clinical-benchmarking/

Statement of Author's Contributions

Chapter 1 provides the introduction to the field of HSK and The RNAO Toolkit: 'Implementation of Best Practice Guidelines'. I conducted a literature review and wrote the chapter. Stephanie Watson and Yves Kerdraon reviewed and provided feedback.

Chapter 2 reports the comparison of the prescribing trends for HSK at the Sydney Eye Hospital with the evidence-based recommendations up to 2013. It also reports the type of clinicians prescribing antiviral therapy. This chapter contains a published publication: Cabrera-Aguas M, Robaei D, McCluskey P, Watson S. Clinical translation of recommendations from randomized trials for management of herpes simplex virus keratitis. Clin Experiment Ophthalmol. 2018;46(9):1008-16. I co-designed the retrospective study with Stephanie Watson and Dana Robaei. I extracted and analysed the data, wrote the manuscript and the chapter. Stephanie Watson, Dana Robaei and Peter McCluskey reviewed and provided feedback for the manuscript. Stephanie Watson and Yves Kerdraon reviewed and provided feeback for the chapter.

Chapter 3 reports the risks factors, diagnostic tests and outcomes of HSK at the Sydney Eye Hospital. This chapter contains a publication in submission: Cabrera-Aguas M, Kerdraon Y, Watson S. Outcomes of herpes simplex keratitis, Eye & Contact lens. I co-designed the retrospective study with Stephanie Watson and Dana Robaei. I extracted and analysed the data, wrote the manuscript and the chapter. Stephanie Watson and Yves Kerdraon reviewed and provided feedback for the chapter and manuscript.

Chapter 4 reports the risk factors, clinical features, microbiology patterns and outcomes of concomitant microbial keratitis and HSK. The findings of this study were compared to other microbial keratitis case series from Australia and of patients aged 60 years and over. This chapter contains a publication in preparation : Cabrera-Aguas M, Khoo K, Lahra M, Watson S. Predisposing factors, microbiological features and outcomes of patients with concomitant microbial keratitis and herpes simplex keratitis. I extracted and analysed the data, wrote the manuscript and the chapter. Stephanie Watson, Yves Kerdraon reviewed and provided feedback for the chapter and manuscript.

Chapter 5 describes the use of The RNAO Toolkit: 'Implementation of Best Practice Guidelines' for the development, implementation and evaluation of local guidelines at the Sydney Eye Hospital. The hospital's pharmacists, Stephanie Watson and I designed the web-survey. This chapter contains a publication in preparation: Cabrera-Aguas M, Kerdraon Y, Symes R, McCluskey P, Watson S. Development, implementation and evaluation of herpes simplex keratitis treatment guidelines. I collected and analysed data for the audit and wrote the chapter. Stephanie Watson and Yves Kerdraon reviewed and provided feeback for the chapter.

Chapter 6 provides the summary and the conclusions of this thesis and further research directions. I wrote the chapter. Stephanie Watson and Yves Kerdraon provided feeback for the chapter.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Prof Stephanie Watson

Date 6/6/19

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Dr Yves Kerdraon

Date 6/6/19

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Chapter 5

List of abbreviations

Abbreviation	Full name
ACV	Aciclovir
AAO	American Academy of Ophthalmology
bd	Bis die sumendum (twice daily)
BCL	Bandage contact lens
CF	Count fingers
CLW	Contact lens wear
CoNS	Coagulase negative *Staphylococci*
DALK	Deep anterior lamellar keratoplasty
DSEK	Descemet's stripping endothelial keratoplasty
DMEK	Descemet membrane endothelial keratoplasty
FML	Fluorometholone 1%
GCV	Ganciclovir
HM	Hand movements
HEDS	Herpetic Eye Disease Study
HSV	Herpes simplex virus
HSK	Herpes simplex keratitis
HZK	Herpes zoster keratitis
KPs	Keratic precipitates
LK	Lamellar keratoplasty

List of abbreviations (continued)

Abbreviation	Full name
logMAR	Logarithm of the minimum angle resolution
LP	Light perception
LSCF	Limbal stem cell failure
NLP	No light perception
Nocte	Omne nocte (every night)
Occ	Ointment
OD	Oculus dexter (right eye)
od	Omne in die (once daily)
OS	Oculus sinister (left eye)
q1h	Quaque hora (every hour)
q2h	Quaque secunda hora (every 2 hours)
PCR	Polymerase chain reaction
PK	Penetrating keratoplasty
PO	Per os (treatment taken orally)
PRN	Pro re nata (When necessary)
RCES	Recurrent corneal erosion
RGP	Rigid gas permeable
RNAO	Registered Nurses' Association of Ontario
QID	Four times daily
SHSK+U	Stromal herpes simplex keratitis with ulceration
SHSK-U	Stromal herpes simplex keratitis without ulceration

List of abbreviations (continued)

Abbreviation	Full name
tds	Ter die sumendum (Three times daily)
TFT	Trifluridine
VA	Visual acuity
VLC	Valaciclovir

Chapter 1 - Introduction

1.1 Aims

The overall aim of this study was to develop, implement and evaluate a local treatment guideline for the initial treatment of herpes simplex keratitis (HSK) at the Sydney Eye Hospital, a quaternary referral eye hospital in Sydney, NSW, Australia. Specific aims were:

- To utilise The RNAO Toolkit 'Implementation of Best Practice Guidelines' for developing, implementing and evaluating a local HSK treatment guideline at the Sydney Eye Hospital.

- To evaluate the treatment trends for HSK at the Sydney Eye Hospital in 2012 and 2013, and to compare these trends to treatment recommendations from published randomised clinical trials up to 2013.

- To report predisposing factors, diagnostic test and outcomes for patients with an active HSK episode (epithelial, stromal, endothelial, keratouveitis) and for those receiving antiviral medications to prevent HSK recurrence in Sydney Eye Hospital in 2012 and 2013.

- To add to the knowledge base of concomitant microbial keratitis and HSK. Specifically, to report the predisposing factors, the clinical and microbiological features and outcomes of patients with concomitant microbial keratitis and HSK through a retrospective cohort study at Sydney Eye Hospital from 2012 to 2016.

1.2 Hypotheses

It was hypothesised that in the Sydney Eye Hospital:

- The RNAO Toolkit: 'Implementation of Best Practice Guidelines' could be utilised in ophthalmic care.
- The management of HSK was not evidence-based up to 2013.
- Prior topical corticosteroid use was the most common predisposing factor for patients with HSK.
- Diverse initial antiviral therapy was more associated with poor clinical outcomes in patients with HSK.
- Patients with concomitant microbial keratitis and HSK would form a unique cohort compared to those with microbial keratitis or HSK alone, with the demographics, clinical and microbiological features, and outcomes identified.

1.3 Significance of research

Herpes simplex keratitis is an important public health issue but there are limited therapeutic interventions available to reduce complications such as corneal scarring and blindness. One fifth of people with ocular herpes simplex virus (HSV) infection develop corneal stromal disease with the attendant risk of blindness, despite the availability of antiviral and topical corticosteroid medications to treat the condition. [1] The Herpetic Eye Disease Study Group (HEDS) clinical trials, published in the 1990s, made a significant contribution to establishing treatment regimens for HSK. [2-6] These trials provided important evidence to improve treatment of this condition via a reduction in cornea opacification and scarring. These studies only investigated the role of aciclovir and trifluridine in the treatment of HSK. Subsequent randomised clinical trials (RCTs) and a Cochrane review have added to the evidence base. [1, 7] The HEDS trials although landmark studies in the 1990's are now outdated and poorly translated into clinical practice. The availability and pricing of antiviral agents varies by geographic location.

The HEDS trials did not evaluate the role of topical aciclovir as it is not Food and Drug Administration (FDA) approved in the United States (USA) for the management of this condition. It is, however, widely used in Australia. Other antiviral agents have been introduced into the market since the HEDS trials for the treatment of HSK. For instance, oral valaciclovir, a pro-drug of aciclovir, is currently widely used across the world but no clinical trials have evaluated its role in the treatment of HSK or in concomitant microbial keratitis cases. The equivalent valaciclovir dose for aciclovir currently used for HSK has been extrapolated from genital HSV and herpes zoster virus (HZV) studies.[8-10]

In Australia, aciclovir is available in tablets of 200 mg and in 3% ointment; Zovirax, GlaxoSmithKline, was available until February 2019, and through the Therapeutics Goods Administration (TGA) Special Access Scheme (SAS); and valaciclovir is available in tablets of 500 mg. The cost of these medications at the Sydney Eye Hospital, in Sydney, Australia is less than in a community pharmacy due to a hospital contract with the pharmaceutical company. At the hospital, the cost of antiviral medications for an average 7-day treatment course is: $23.20 for a tube of aciclovir ointment; $5.40 for aciclovir 400 mg 5 times daily for 7 days ($0.07 per 200 mg tablet), and $4.62 for valaciclovir 500 mg twice daily for 7 days ($0.33 per 500 mg tablet). The cost for prophylaxis per month is $9.36 for aciclovir 400 mg twice daily and $9.90 for valaciclovir 500 mg once daily. The price of valaciclovir has decreased significantly during the last two years, coinciding with the expiry of the patent for the commercial brand, Valtrex. Generic brands of valaciclovir are now available with a lower cost. Valaciclovir is the preferred agent for the management of HSK. Ganciclovir ophthalmic gel 0.15% has been first line therapy for epithelial HSK in the USA since 2009 and commercially available in Europe since 1996; but only available in Australia through the TGA SAS scheme.

Anecdotally, a large variety of antiviral medications and dosages prescribed for HSK were found at the Sydney Eye Hospital in 2013. Valaciclovir 500 mg two to three times daily was the preferred antiviral regimen. In 2013, valaciclovir was an expensive medication as GlaxoSmithKline held the patent. The cost of this regimen was between

$18.62 and $27.93 ($1.33 per 500 mg tablet). Higher dosages of valaciclovir were also found at the Sydney Eye Hospital. Higher dosages may potentially cause side effects and increase risk of recurrence with corneal scarring and poor visual outcomes after failing to comply with the treatment due to the high costs. We identified a gap in implementing the treatment recommendations from RCTs into everyday clinical practice. A systematic approach involving different stakeholders is vital to close the gap between knowledge and action. [11]

Further, for patients with HSK who have concomitant corneal infection with other microbes (microbial keratitis) their outcome may be negatively impacted, with greater morbidity from their treatment. Microbial keratitis is the fourth leading cause of blindness worldwide, and responsible for 10% of avoidable visual impairment in developing countries. [12] While quality of life can be reduced as a result of microbial keratitis; little is known of the patients with concomitant microbial keratitis and HSK.

To address these issues, the following goals were established: one retrospective case series was conducted to confirm the diverse initial antiviral treatments and compare these with the available evidence-based recommendations; and to report the clinical outcomes of patients treated with antiviral medications for therapeutic and prophylactic indications for HSK. A second retrospective case series was conducted to investigate one aspect of the HSK complications by characterising a cohort of patients with concomitant microbial keratitis and HSK. The final goal was to develop, implement and evaluate local HSK treatment guideline at Sydney Eye Hospital. Translation into practice was achieved via the formation of a committee of experts at the hospital to implement and evaluate a local treatment guideline. Standardised initial antiviral therapy based on clinical evidence may improve patient outcomes by reducing side effects, complications, recurrent episodes, and treatment costs. [13]

1.4 Background

1.4.1 Knowledge-to-action translation framework

Currently, translating results from research to routine clinical practice is an important challenge in medicine. Despite the resources invested in research, there is still a gap in implementing these results. Researchers from the USA and the Netherlands have reported that 30% to 45% of patients are not receiving evidence-based care and 20% to 25% receive unnecessary or potentially harmful care. [14] A systematic approach with different stakeholders is needed to close this gap. Since this issue has been recognised, there has been increasing interest in knowledge translation science in recent years. [14]

The general aim of our study was to develop, implement and evaluate local guidelines for the initial treatment of HSK at Sydney Eye Hospital and understand the burden of concomitant microbial keratitis and HSK in order to reduce health costs and improve patient outcomes. For this study, The RNAO Toolkit: 'Implementation of Best Practice Guidelines' [15] was utilised as a guide to the necessary steps to successfully implement the local HSK treatment guideline at the hospital. This Toolkit describes a systematic, well-planned implementation process and was designed to assist health professionals to support evidence-informed clinical and management decision making. The Toolkit was conceptualized using the knowledge-to-action framework. [14]

Knowledge translation is known as the dissemination, diffusion and knowledge transfer in the USA; while it is commonly referred as the implementation science or research uptake in the United Kingdom and Europe. Knowledge translation refers to the bench-to-bedside transfer of knowledge from basic sciences to produce new clinical approaches for prevention, diagnosis and treatment of diseases. [11] Implementation science or research includes the study of influences on health care professionals and organisational behaviours, and of interventions to support them to use research findings more effectively. [14] Dissemination and diffusion are key to the knowledge-to-action plan. They refer to the promulgation of knowledge to increase stakeholders' awareness of them or the specific and discrete strategies used to promulgate knowledge products. [14]

The knowledge-to-action cycle is divided in two parts: knowledge creation, and the action cycle. This model is iterative, dynamic and involves all stakeholders (patients, health care providers, managers and policy makers) (See Figure 1 - 1, page 7). [14]

1.4.1.1 Knowledge creation

The knowledge funnel represents knowledge creation which encompasses three phases: knowledge inquiry, knowledge synthesis, and creation knowledge tools. Knowledge inquiry represents primary studies or information of variable quality. It is considered as first-generation knowledge. Knowledge synthesis represents the aggregation of existing knowledge. This includes systematic reviews which encompass the identification, appraisal and synthesis of knowledge. The aim of the creation of knowledge tools aim is to present knowledge in a clear, concise and user-friendly format for facilitating their use. These tools include practice guidelines, decision aids and rules, and care pathways (See Figure 1 - 1, page 7). [14]

1.4.1.2 Action cycle

The aim of the action cycle is to implement or apply knowledge in clinical care. This cycle encompasses seven phases. [14] The first phase involves identifying the 'problem or issue' and searching for knowledge to address it. This knowledge must be appraised to determine whether there is a knowledge-practice gap that needs to be filled. Next, this knowledge is adapted to the local context. Stakeholders make the decision whether this knowledge is appropriate, useful and valuable to their circumstances. Next, potential barriers that may impede or limit uptake of knowledge use must be assessed. Strategies to overcome the barriers and facilitators must be identified. The next phase consists of planning and executing interventions to facilitate and promote awareness and implementation knowledge. Tailored interventions to the identified barriers and audiences are then selected. [14]

The monitoring phase commences once the implementation is launched. Monitoring is key to determine how, and the extent of the knowledge has spread in the target group. It also determines whether the interventions have been sufficient to bring

up the desire change or same or more interventions are required. If the level of knowledge use is less than expected, it may be necessary to reassess the potential adopters at the phase. [14]

The following phase involves determining the impact of using the knowledge. In this phase, the evaluation of whether the use of the knowledge occurred and made a difference in terms of health, practitioner, and system outcomes is measured. Evaluating the impact is the only way to determine success. The last phase is sustaining the use of knowledge. There must be a long-term plan for managing the change including assessment of potential barriers, tailoring interventions, monitoring ongoing use and evaluating impact of initial and sustained use. The sustainability phase should have feedback loops that cycle through the action phases. [14]

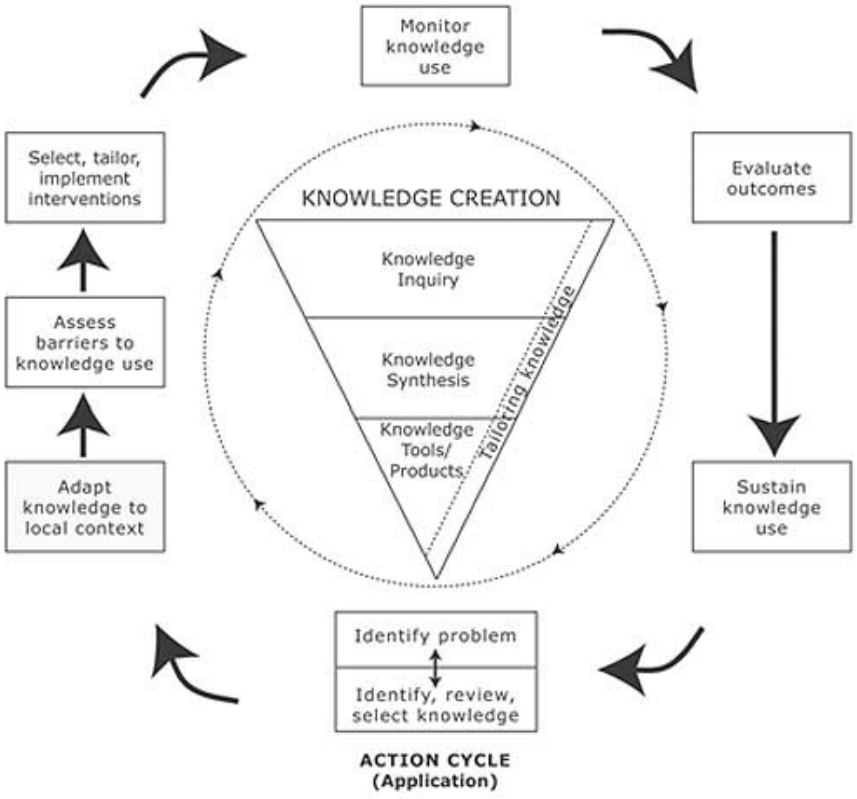


Figure 1 - 1: Knowledge to action process (adapted from Graham [14]).

1.4.1.3 Choice of The RNAO Toolkit: 'Implementation of Best Practice Guidelines'

Several guideline development groups have focus on bringing evidence to practice in different health areas. The Toolkit: Implementation of Best Practice Guidelines developed by the Registered Nurses' Association of Ontario [15] focuses on practice recommendations related to education and policy, maintaining a focus on guidelines implementation and evaluation. The Toolkit was chosen to guide the development, implementation and evaluation of the HSK treatment guidelines as it outlines a systematic, well-planned implementation process designed to assist any health professional. It is user friendly with respect to facilitating systematic identification and implementation of best practice guidelines. Moreover, it brings practical processes, strategies and tools for clinicians and others to initiating and sustaining evidence-based practice. Further, some improvements in the second revision included the use of modified knowledge-to-action-framework, inclusion of sustainability, and the incorporation of tools, related resources and examples in each chapter based on experiences in implementation in acute care, public health, home health and long-term care settings. This Toolkit is based on evidence that successful uptake of the best practices increases when leaders are committed to support guideline implementation, the guideline is tailored to local context, barriers and facilitators are assessed and addressed, guidelines are systematically monitored and sustained, and evaluation is part of the process.

This Toolkit has been applied more in issues directly related to nursing and public health. However, we believe that it provides the necessary steps and ground theory to guide us through the local HSK treatment guideline's development, implementation and evaluation pathway. [16] This Toolkit uses the 'Knowledge-to-Action' framework [14] which has previously been used in ophthalmology for investigating whether the evidence-based recommendations by the Paediatric Eye Disease Investigator Group for the initial treatment of amblyopia had been implemented in clinical practice. [11]

1.4.2 The Cornea

This thesis will focus on HSK, an overview of the cornea – the ocular structure affected by HSK is presented below to provide understanding of the condition.

The cornea is a transparent and avascular connective tissue located in front of the eye. It protects the eye against infections and with the tear film provides an anterior refractive surface for the eye. The human cornea's diameter is 11.5 to 12 mm on average, flatter in the periphery and steeper in the centre creating an aspheric optical system. The cornea has five layers; three cellular (epithelium, stroma and endothelium) and two interface layers (Bowman membrane and Descemet membrane) (See Figure 1-2, page 9). [17]

Small vessels at the outermost edge of the cornea from the end branches of the ophthalmic arteries via the aqueous humor and the tear film supply blood components to the cornea. The nasociliary branch of the first (ophthalmic) division of the trigeminal nerve innervates the cornea. The nerves enter the stroma radially in thick trunks perforating Bowman's membrane and providing a rich plexus beneath the basal epithelial layer. The cornea also contains autonomic sympathetic nerve fibres. [17]

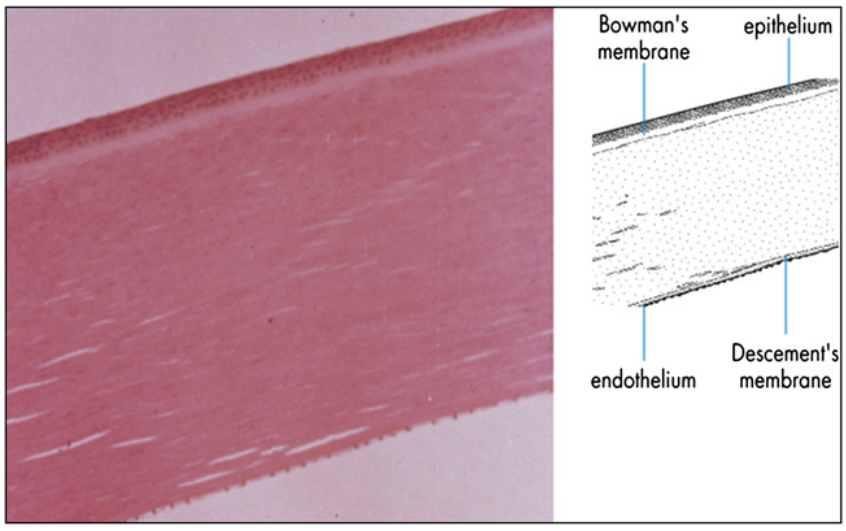


Figure 1- 2: Anatomy of the cornea (adapted from DelMonte [17]).

The epithelium

The epithelium is the first layer from out to inside of the cornea. It is an extremely uniform, stratified, nonkeratinised squamous epithelium, 4 to 6 cell layer thick from limbus to limbus. Corneal epithelial cells have an average lifespan of 7 to 10 days and experience apoptosis and desquamation. A complete turnover of the corneal epithelial layer occurs weekly in a well-organised way as deeper cells replace the superficial cells. The limbal epithelial stem cells provide the progenitor cells that regenerate the corneal epithelium. The most superficial layer of epithelium consists of 2 to 3 layers of flat polygonal cells. These cells have extensive apical microvilli and microplicae which are covered by a glycocalyceal layer. This apical membrane projections increase the surface contact and adherence between tear film's mucinous layer and the cell membrane. This is critical for a smooth and clear optical system. These cells maintain a tight junctional complex to avoid tears from entering the intercellular spaces. This barrier also prevents toxins and microbes from entering deeper corneal layers. [17]

The suprabasal and wing layers are beneath the superficial layer just anterior to the basal layer. This layer consists of 2-3 cells with less deep cells and similar tight lateral intercellular junctions. Stem cells, transient amplifying cells and basal cells are the only corneal cells capable of mitosis. They are the source of superficial and wing cells. They are attached to the basement membrane by a hemidesmosomal system. The deepest layer is a one-cell thick basal layer. This system prevents the epithelium from separating from the underlying corneal layers. Corneal epithelial stem cells are localised in the limbal basal epithelium. As they migrate to the central cornea, they differentiate into transient amplifying cells and basal cells. The epithelial basement membrane comprises type IV collagen and laminin secreted by the basal cells. [17]

The epithelium is covered by a tear film which smooths the irregularities of the anterior epithelial surface. The air-tear film interface with the cornea provides two thirds of the total refractive power of the eye. The tear film also supplies immunological and growth factors which are essential for epithelial health, proliferation and repair. [17]

Bowman membrane

The Bowman membrane is an acellular condensate of the most anterior portion of the stroma. This smooth layer is approximately 15µm thick and maintains the cornea shape. [17]

Stroma layer

The stroma layer comprises 80-85% of the cornea thickness. The organisation of the collagen fibers and the extracellular matrix (ECM) give the characteristic transparency to the cornea. The collagen fibers are organized in parallel bundles called fibrils and these fibrils are packed in parallel arranged layers or lamellae. The human cornea contains 200 to 250 distinct lamellae. The peripheral stroma is thicker than the central. The organisation of the lamellae reduces forward light scatter and contributes to the transparency and mechanical strength of cornea. Further, the ultrastructure within the organisation of the lamella appears to be based on the depth within the stroma. Deeper layers are more organised than the superficial layers and facilitate an easier surgical dissection in a plane as the posterior depth of the stroma is reached. Keratocytes are the major cell type of the stroma and maintain the ECM environment and stromal homeostasis. They are located in the anterior stroma and contain ‘crystallins’ which reduce the backscatter of light from the keratocytes and maintain corneal transparency. [17]

Descemet membrane

Descemet membrane lies between the posterior stroma and anterior surface of the endothelium. During fetal development, the anterior region of Descemet’s is secreted by endothelial cells and is highly organized compared to the posterior amorphous region, secreted after birth. Descemet membrane can measure up to 10 µm in thickness with age. [17]

The endothelium

The endothelium is a monolayer with a honeycomb-like shape from the posterior side. It maintains corneal clarity ensuring its deturgesced state. At birth, the endothelial cells are 10 µm thick flattening to about 4 µm in adulthood. Cells share lateral interdigitations and tight junctions. High density Na+, K+-ATPase pump sites are localized on the lateral membranes and hemidesmosomes on the basal surface. The number of endothelial cells declines throughout life from 3000 to 4000 cells/mm^2 at birth to about 2600 cells/mm^2 in the eighth decade and from 75% of hexagonal cells to 60%. [17]

The endothelial cells maintain the stroma in a relatively deturgesced state to ensure corneal transparency. This is mediated by a pump-leak process as fluid passes from a hypo-osmotic stroma to the hypertonic aqueous humor. The membrane-bound Na+, K+-ATPase pump site and the intracellular carbonic anhydrase pathway produce energy to transport ions generating an osmotic gradient generating a passive fluid movement. Endothelial cells do not have mitotic activity, but humans are born with a significant reserve. The endothelial cell density is about 3500 mm^2 at birth decreasing 0.6% per year due to age, or a faster rate due to trauma, inflammation or other corneal conditions (for example Fuchs endothelial dystrophy). In normal aging, the remaining cells are able to stretch and take over the space left by the others. [17]

1.4.3 The Herpes Simplex virus

Herpes simplex virus is an enveloped double-stranded DNA virus composed of 152 kb and about 80 genes belonging to the Herpesviridae family. Herpes simplex virus has two forms: HSV-1, associated with ocular and perioral pathology and HSV-2 with anogenital infections. [1, 8, 18] The HSV-1 particle is 120-300nm in size with an electroopaque core containing the capsid encapsulating the DNA and the tegument, and a lipid envelope (See Figure 1- 3, page 13). The tegument contains proteins for virion survival in the host cells. Humans are the only natural reservoir of HSV. The envelope contains surface glycoproteins (gB, gC, gD, gH) to enable the virus to host cell

attachment, fusion and permeability. The DNA polymerase transcribes, replicates and assembles viral DNA in the host cell for HSV-1 replication. [8]

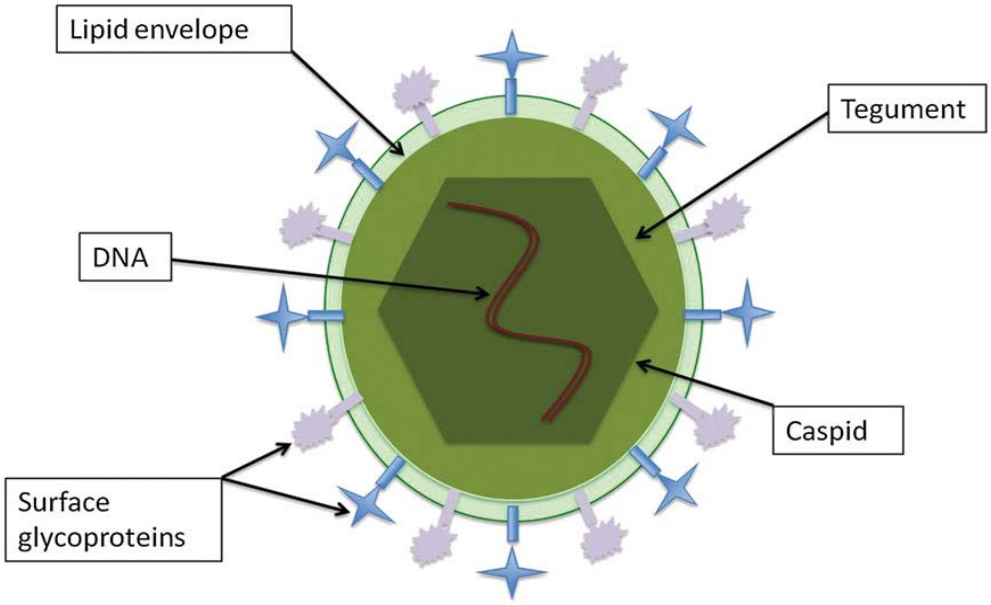


Figure 1- 3: Representation of herpes simplex 1 virion (adapted from Tsatsos [8]).

1.4.4 Herpes Simplex Keratitis

Herpes simplex keratitis is the manifestation of ocular HSV infection in the cornea. HSK can be classified as primary or secondary, and according to the layer of the cornea affected as epithelial, stromal, endothelial. [19]

1.4.4.1 Clinical manifestations

Ocular symptoms include redness, pain, photophobia, blurred vision, tearing, watery discharge, and itching. [19-21] Patients may have corneal hypoesthesia, although this sign is more frequent after recurrent epithelial keratitis episodes. [1]

1.4.4.2 Classification of HSK

Primary infection

Primary ocular HSV infection usually occurs early in life [20] with clinical manifestations occurring in 1% of the infected population. [22] The ocular infection generally manifests, after an incubation period of 1 to 28 days, as a unilateral keratoconjunctivitis with grouped vesicles on the eyelids or surrounding skin. The vesicles are typically accompanied by follicular conjunctival inflammation and preauricular lymphadenopathy. The primary infection may also include dendritic ulcers (epithelial HSK). Stromal HSK or uveitis are rare. In one third of the patients, the primary ocular HSV infection is associated with a HSV upper respiratory infection. [1]

Secondary infection

After the primary infection, HSV spreads via retrograde axon transport to the sensory nerve ganglia including the trigeminal ganglion establishing the latent infection. Recurrent epithelial HSK occurs when the virus is reactivated in the ganglia and transported down the nerve axon to sensory nerve endings infecting the epithelium. (See Figure 1- 4, page 15) Recurrent stromal HSK can present differently and occurs by different mechanisms. Ocular manifestations include recurrent blepharoconjunctivitis, keratitis, uveitis or retinitis. [1] The mean time from onset of symptoms to resolution of active ocular HSV disease is 17.6 days for the first episode and 28.4 for recurrences. [23]

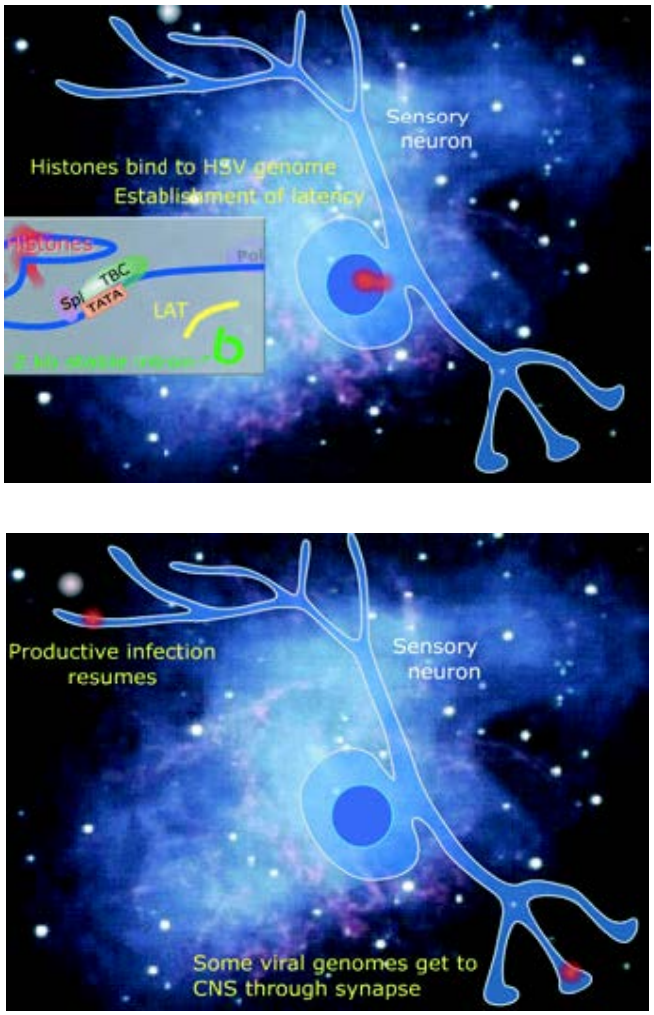


Figure 1- 4: Latent infection and reactivation of HSV occurs in the sensory neurons, mainly in the trigeminal ganglia (adapted from Arduino [24]).

Classification by corneal layer affected

The appropriate therapy for each type of HSK depends on the correct diagnosis made by clinical observation on slit-lamp examination. Many terms have been used to describe the types of HSK such as “immune stromal”, “necrotizing”, “disciform”, “endotheliitis”. These terms are not well understood and can be confusing. A simple classification system was introduced in the “Herpes Simplex Virus Keratitis: a treatment guideline” by the American Academy of Ophthalmology (AAO) in 2014, and is shown in Table 1 - 1, page 16. [23]

Table 1 - 1: The American Academy of Ophthalmology classification of herpes simplex keratitis (adapted from White and Chodosh [23]).

Key: SHSK-U = stromal HSK without ulceration, SHSK+U = stromal HSK with ulceration.

Corneal layer	Nomenclature	Alternate terms
Epithelium	Epithelial keratitis	Dendritic epithelial ulcer Geographic epithelial ulcer
Stroma	SHSK-U	Non-necrotizing keratitis Interstitial keratitis
	SHSK+U	Immune stromal keratitis Necrotizing keratitis
Endothelium	Endothelial keratitis	Disciform Endotheliitis

1.4.4.3 Pathogenesis of HSK

The primary infection occurs through direct contact with oro-labial lesions or infected secretions such as saliva and tears. Individuals can also acquire the virus through direct contact with the saliva of asymptomatic people. Seroprevalence is affected by degree of exposure to the virus, socioeconomic class, poor hygiene and age. A study reported that around 80% of children in lower socioeconomic populations are seropositive by adolescence, whereas 40-60% of middle-class children will be seropositive by the third decade of life. However, this trend may be changing with recent data reporting that the prevalence among adolescents in the USA declined from 42.6% between 1976 and 1980 to 30.1% between 2005 and 2010. In Africa, the seroconversion was greater than 80% of the population in every age group except in young children. [23] The virus can also be transported in a retrograde form through sensory neurons producing secondary infections. The virus becomes latent in ganglia, brainstem or in sensory neurons re-emerging to active forms later in life leading to recurrent infections. [8] Studies have suggested that most of the population will show serological evidence of

HSV infection by middle age and 100% of people over 60 years will harbor the virus in the trigeminal ganglia. [1]

Herpes simplex virus infects diverse cells including epithelial cells, fibroblasts, neurons and lymphocytes. First, the viral glycoproteins bind to the host cells receptors; then the viral envelope either fuses with the plasma membrane or undergoes endocytosis (See Figure 1 - 5, page 17). Next, the viral nucleocapsid and tegument proteins are released to the host cytoplasm where the dynein-dynactin protein complex transports the tegument proteins to the host nucleus. The capsids are pushed through the negative end of microtubules and released to the nucleus through nuclear pore complexes. [8]

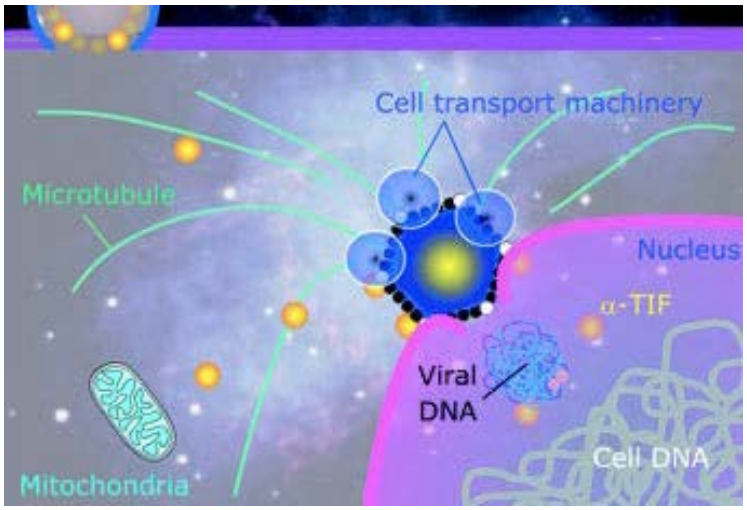


Figure 1 - 5: Receptor binding for HSV to enter cell and initiate the infection (adapted from Arduino [24]).

Once the capsids are in the nucleus, the host RNA polymerase II starts viral gene expression. Herpes simplex virus genes are expressed in three different forms. A procapsid is built in the nucleus and packaged with viral DNA which will become a mature capsid. The mature capsid will initially fuse with inner nuclear membrane (primary envelopment) to form an enveloped particle which subsequently fuses with an outer nuclear membrane (de-envelopment) to release the capsids to the cytoplasm. Finally, capsids re-envelope (secondary envelopment) with the Golgi compartment and are secreted from the infected cells. [8]

The mechanism of recurrent infection is poorly understood; however, cornea cells infected with HSV produce an immune response rather than only a cytolysis of corneal cells by HSV. This response consists of polymorphonuclear leucocytes, macrophages, natural killer cells and Langerhans cells, travelling in a chemokine-dependent manner to the corneal stroma. Further, corneal fibrosis is produced after inflammatory cells release pro-inflammatory cytokines, chemokines and growth factors that remove the virus but later cause tissue destruction and scarring. The connective tissue in scars is constantly remodeled but the re-organisation is different than in a normal corneal tissue, leading to a loss of corneal transparency. [8]

1.4.4.3.1 Disease modifiers

The severity and frequency of recurrent HSK episodes is determined by the susceptibility of the host to the virus and the local susceptibility of the host target tissue. Studies in animal models have shown that the virulence of the virus strain also has a role in the capacity of the virus to induce disease; however, this has not been translated into human studies. [23]

Susceptibility of the host to the herpes simplex virus

The general susceptibility of the host to the HSV depends on their immune status. Any inherited or acquired condition that suppresses the immune system and age increase the risk of frequent ocular HSV recurrences or severe disease, mostly HSK. [23] The immune system of organ transplant recipients is compromised due to corticosteroids and immune suppressive medications. [23] Individuals after organ transplants shed virus more frequently experiencing ocular HSV that is more severe, recurs frequently and responds slower to treatment than immunocompetent patients.[25] HSV disease occurs in these individuals due to reactivation of the disease particularly early after the transplantation and during antirejection therapy. [25]

Patients with long-standing diabetes mellitus apparently have impaired cell mediated immunity and often present with microvascular complications. [23, 26] Therefore, diabetic patients have a higher risk of presenting with more severe infections. [26]

Evidence on the association between diabetes mellitus and ocular HSV disease is sparse and conflicting. One study from Israel reported that 123 diabetic patients presented with ocular HSV disease more frequently compared with 586 nondiabetics (5.49% vs 4.27%, $p < 0.0001$). [26] In the same study, there was a significantly higher prevalence of ocular HSV disease in patients aged 60 to 79 years and more recurrent episodes in diabetic patients than in nondiabetics (25.2% vs 16.6%, $p = 0.05$). [26] On the other hand, a study from Philadelphia reported that the prevalence of type 1 diabetes mellitus in patients with ocular HSV disease was not significantly higher than in matched control patients ($p = 0.375$); and the prevalence of type 2 diabetes mellitus was similar in patients with and without ocular HSV disease ($p = 0.981$). Further, there was no association between diabetes mellitus and severity of ocular HSV disease ($p = 0.120$). [27]

Ocular HSV disease can be considered as an AIDS-defining opportunistic infection; however, there is conflicting evidence in whether the incidence of HSK is higher in human immunodeficiency virus (HIV)-positive patients than in HIV-negative patients. [23] One series of 6 patients reported that HIV-positive patients presented with more peripheral epithelial HSK which needed longer topical antiviral therapy compared to HIV-negative patients. [23] A Romanian retrospective study found a higher rate of incidence of HSK in HIV-positive patients compared with HIV-negative patients (24% vs 3.57%) and a longer median healing time (3 weeks vs 2 weeks). [28] On the other hand, another study conducted in San Francisco, of patient visits from 1984 to 1994, reported that HIV-positive patients had a higher recurrence of the disease, but similar lesions and similar treatment time than HIV-negative patients. [23]

Diagnosing and treating children with ocular HSV disease is challenging. They are typically more difficult to examine leading to misdiagnosis; and have compliance issues with the antiviral therapy. For instance, they may miss dosages as they are dependent on their parents for eye drops application and the medication may dilute in their tears as they may cry during the eye drops application. [29] Children tend to present with severe ocular HSV inflammatory disease, more recurrences, and complications compared to adults. [23, 29] The inflammatory response of the stromal HSK is more aggressive leading to stromal scarring, corneal opacification, and irregular astigmatism.

If the vision is reduced by these changes children, typically before the age of 8 years, are likely to develop amblyopia. [23] Bilateral ocular HSV disease occurs more frequently in children with rates of 3.4-26% and a recurrence rate within the first year of 45-50%, when compared to adults (1.3-12% and 18%, respectively). Bilateral presentation usually occurs as a manifestation of primary infection and causes more complications. [23]

Epidemiological studies have reported that the incidence of ocular HSV disease in children and adolescents in 1967 has decreased from 29% and 64% to 7% and 41% in 1985, respectively. [23] One retrospective study of 23 children reported that 60% had epithelial and stromal HSK. Another retrospective study of 57 children under 16 years with ocular HSV disease reported misdiagnosis in 30% of patients before presentation. Thirty-nine patients were diagnosed with HSK. Of these, 74% (n = 29) had stromal HSK. Most patients presented with recurrent infection (73%) and residual corneal scarring (79%); and a third had best corrected visual acuity of 20/40 or worse at last follow-up visit. [30]

Bilateral ocular HSV disease tends to occur more frequently in patients with atopy. [31] Atopy refers to patients with personal or family history of one or more of these diseases: hay fever, asthma and atopic eczema. [23] Atopic patients have a persistent and abnormal activation of helper T cell, subtype 2 (T_H2), lymphocytes generating cytokines which stimulate B-lymphocyte synthesis of IgE antibody and eosinophils. [23] Atopic disease intensifies the T_H2 response and weakens T_H1 response. Cell-mediated immunity, including T_H1, plays an important role in the response against HSV and herpes zoster ophthalmicus. [31] Therefore, patients with atopic disease are more prone to suffer from ocular HSV disease. A retrospective population-based case-control study in California reported that patients with ocular HSV had greater prevalence of atopy than the controls (34% vs 25%). [32] Moreover, the association of ocular HSV with severe atopy was greater compared with the controls (13% vs 6%). [32] Another retrospective population-based case-control study in California reported that patients with atopic disease had 2.6-fold higher odds of having ocular HSV disease compared with patients without the disease. Further, patients with two or more atopic conditions had 8.9-fold higher odds of having ocular HSV disease. [31]

Atopic patients also tend to present with unusually severe HSK and respond better to oral antiviral agents (within 48 to 72 hours) than to topical agents. If patients are treated with topical agents, they may need a longer treatment. [23] The prevalence of atopic disease has increased in the developed world. Some factors are increased pollution and indoor allergens, increased awareness among the population and a reduction of breast-feeding. Therefore, it is valuable to identify a history of atopic disease in patients with severe HSK, bilateral disease and disease recalcitrant to topical antiviral therapy. [23]

Local susceptibility of cornea

Cornea susceptibility may increase under certain conditions, including administration of medications, trauma, and local inflammation. [23] Medications such as prostaglandin agonists and corticosteroids may increase the risk of recurrent ocular HSV disease. Prostaglandin analogs (such as latanoprost) are topical hypotensive agents used to manage elevated intraocular pressure. [23] Epithelial HSK episodes in patients on latanoprost treatment have been reported. In two separate case reports, three patients from the USA [33] and two from Greece, [34] presented with bilateral disease within three months of latanoprost treatment. When the medication was ceased, the epithelial HSK resolved and if the medication was restarted, the epithelial HSK reappeared. It may be advisable to avoid this type of medication in patients with a history of ocular HSV disease. However, further well-designed prospective studies are needed to firmly establish a link between topical prostaglandin agonists and HSK occurrence. Corticosteroids are potent anti-inflammatory mediators with significant effects on the immune response. Topical, intravitreal and/or systemic use of corticosteroids can predispose to severe ocular HSV disease when the infection is treated only with topical corticosteroids. [23]

Any type of ocular surgery on an eye with previous ocular HSV disease increases the risk of recurrence of the disease. [23] The trauma of the surgery with the local immunosuppression of the perioperative corticosteroids may be contributors. [23] Antiviral prophylaxis is therefore recommended in the immediate perioperative period especially

while the patient is on corticosteroids. [23] Cases of HSK have been reported after laser procedures such as laser assisted *in situ* keratomileusis (LASIK), laser iridotomy, laser trabeculoplasty, and therapeutic laser keratectomy. The pathogenesis of ocular HSV disease in the setting of laser procedures is still unknown; however, possible contributing factors include the focal laser trauma to the cornea nerves and the tissue itself, direct activation of the virus by laser light, and postoperative corticosteroid use. [23] Seven case reports/series, describing 9 patients in total, have reported epithelial HSK on the first postoperative day and stromal HSK several weeks after. [35-41] Three interventional case series with a total of 36 patients with history of epithelial HSK suggested that prophylactic therapy is effective in preventing recurrence. [42-44] In patients diagnosed with epithelial HSK immediately post-LASIK, topical corticosteroids should be tapered, and the infection treated with antiviral agents. Therefore, LASIK may be not recommended for patients with previous stromal HSK as there are no prophylactic studies investigating stromal HSK after LASIK. [23]

Excimer laser phototherapeutic keratectomy (PTK) is an alternative to lamellar or full thickness corneal transplantation for treatment of scarring and surface irregularities caused by HSK. [23] In a case series of 20 patients with history of HSK, 25% of patients presented with a recurrence of keratitis after excimer laser surface ablation during the 17-month follow-up period. [45] A retrospective case review of 13,200 patients with no history of HSV disease reported 19 cases of HSK after photorefractive keratectomy. [46]

Graft failure after penetrating keratoplasty (PK) in patients with previous ocular HSV disease occurs due to viral reactivation leading to recurrence, and simple allograft rejection. Possible reasons for recurrence include the activation of latent virus in the host trigeminal ganglion or transmission from subclinical infection of the donor cornea. Patients with previous ocular HSV, particularly recurrent HSK, have a higher incidence of allograft rejection with subsequent graft failure. [23] Indeed, grafts with active HSV at the time of the graft showed poorer graft survival than in those eyes with inactive disease. The probability of graft survival was 0.53 at 6 years with active HSV and 0.75 in eyes with no active HSV. [47]

Randomized clinical trials and retrospective cohort studies have reported the recurrence rate of HSK in patients without prophylaxis post-PK to be 32% at four months, [48] 44% at 21 months, [49, 50] 39% to 46% at one year,[51, 52] and 27% to 50% at two years. [53, 54] Further, the recurrence rate in patients on a prophylactic dose of aciclovir treated for 3 weeks was 30%, [55] for 3 months 18%; [52] for six months, 5.7%; [53] and for one year 0 to 5%. [49, 50, 55] These studies concluded that patients on a prophylactic dose of oral aciclovir had fewer recurrences compared to those not treated and that the recurrence rate of HSK seemed to be inversely related to the length of prophylactic therapy. As a result, it was recommended to continue antiviral prophylaxis as long as the patient is treated with topical corticosteroids. [23]

1.4.4.4 Epidemiology of herpes simplex keratitis

Studies from Denmark, Croatia, the USA and France have estimated the incidence of ocular HSV disease. Norn estimated the incidence of dendritic keratitis in 5.8 (CI, 4-7.6) [56] in 1970, and Mortensen and Sjolie in 12 per 100,000 person-years in 1979. [56, 57] Ribaric estimated the incidence of HSK at 4.1 per 100,000 people in Croatia in 1976 (See Table 1 - 2, page 27). [56, 57]

The most notable epidemiological study was conducted in Rochester, Minnesota including 122 patients diagnosed with their first episode of ocular HSV from 1950 to 1982. [58] The incidence of ocular HSV was 8.4 new cases per 100,000 person-years (95% CI, 6.9 to 9.9) in the white population of 1980 in the USA. The overall incidence for all episodes of ocular HSV was 20.7 per 100,000 person-years (95% CI, 18.3 to 23.1). The incidence for all episodes was similar for men and women. Two hundred and twelve of 294 (72%) episodes of epithelial HSK and 36 (12%) of stromal HSK were reported during the study. The incidence of new epithelial HSK cases was 5.6 per 100,000 person-years and of all epithelial cases was 15.6 per 100,000 person-years. For stromal HSK, the incidence of new cases was 0.6 per 100,000 person-years and of all cases (new and recurrent) was 2.6 per 100,000 person-years. Overall, the incidence of all cases of HSK was 18.2 per 100,000 person-years. These values were sex-adjusted to the

population of 1980 US whites. A medical records linkage system was used to minimize referral bias (See Table 1 - 2, page 27).

A second retrospective study from Minnesota provided a more recent estimate of the incidence of ocular HSV disease and investigated the effect of prophylactic oral antiviral therapy. The study included 394 ocular HSV cases from 1976 to 2007. The incidence of ocular HSV disease was 11.8 new cases per 100,000 person-years (95% CI, 10.6 to 13) and of HSK 9.2 new cases per 100,000 person-years (95% CI, 8.1 to 10.3) (See Table 1 - 2, page 27). [57]

A national multi-centre, prospective study also estimated the incidence and clinical characteristics of HSK in France from September to December 2002. [56] Four-hundred and twelve ophthalmologists, representative of the 5471 French ophthalmologists, participated in the study. The overall incidence of HSK was 31.5 per 100,000 person-years (95% CI, 25.5-37.5). The incidence for new and recurrent cases was 13.2 (95% CI, 10.4-15.9) and 18.3 (95% CI, 14.6-22.1) per 100,000, respectively. Epithelial HSK accounted for 56.3% of patients, stromal keratitis for 29.5% and geographic HSK for 9.9%. As a result, the estimate incidence of epithelial HSK was 22 (95% CI, 18.7-25.4) per 100,000 person-years and for stromal HSK 9.2 (95% CI, 7-11.3) per 100,000 persons-years. The estimated incidence rate of highly probable HSK cases (epithelial or geographic ulcer or stromal HSK with identical previous events) was 25.8 per 100,000 person-years (95% CI, 21.2-30.4) (See Table 1 - 2, page 27). [18, 56]

The HEDS V trial reported a cumulative probability of ocular HSV recurrence of 32% during the one-year period. [6] The rates of epithelial HSK are similar in patients with a history of non-epithelial ocular HSV, other than epithelial HSK, compared to those with a history of epithelial HSK, 12% and 15%, respectively. On the other hand, the recurrence rates for stromal HSK with a history of non-stromal ocular HSV, but not stromal HSK is 3% compared to 28% of patients with a prior stromal HSK. The number of recurrences is strongly associated with the number of any type of past episodes. [23, 59]

Farooq and Shukla estimated the worldwide incidence of HSK extrapolating data from epidemiological studies from France and the USA. [18] These studies seemed to be

the most generalizable and detailed in the literature. There are some African studies with limited external validity, conducted in single centres with incomplete data or poor methodology; they cannot be used to estimate incidence rate in developing countries. However, the data reviewed suggested that developing countries have a significant burden of risk factors associated with HSK such as stress, ultraviolet radiation, corneal trauma and immunosuppression. These factors with a limited access to health services suggest that the rates might be high. As a result, the incidence of HSK was estimated at 23.3 per 100,000 person-years for developed countries and unknown for developing countries.

The burden of HSK

Ocular HSV infections represent a significant burden of disease worldwide. [23] An estimated 500,000 people have ocular HSV in the USA alone, and treatment of new and recurrent cases costs the country US$ 17.7 million annually. [18] Extrapolation of the incidence of new and recurrent cases to 2011 estimated the USA population yields an estimate of 64,499 new and recurrent cases per year in the USA. [23]

Herpes simplex keratitis is an important cause of unilateral infectious blindness in developed countries due to stromal opacification. One fifth of people with ocular HSV infection develop stromal HSK with the attendant risk of blindness. [1] Despite the increase of HSK incidence, the overall visual burden apparently remains stable due to an acceptable access to health care and antiviral medications. This is less likely to occur in developing countries, where surveillance focuses on causes of blindness that affect a large part of the population such as age-related impairment or onchocerciasis. Therefore, the impact of HSK in developing countries is as yet unknown. [18] Farooq and Shukla also estimated that at least 1.5% of clinical HSK leads to vision worse than 20/200 (WHO definition of severe visual impairment) based on data from Moorfields Eye Hospital NHS Foundation Trust, the United Kingdom, with the assumption that a reduction in recurrence rate leads to a proportional decrease in visual impairment.

Worldwide the incidence of HSK in 2012 was estimated conservatively at about 1.5 million, with 40,000 new cases of severe monocular visual impairment or blindness

each year. [18] Patients with stromal HSK, which is a potentially blinding condition, require frequent visits to an ophthalmologist resulting significant loss of time at work and reduced productivity. Patients see an ophthalmologist on average four times during the first episode and six times during a recurrence of ocular HSV. A doctor's visit for ocular HSV leads to an estimated loss of one full day of work or leisure per visit. An estimated 58 million days of work (444,000 in the USA) are lost treating ocular HSV worldwide. [23]

Surgical intervention for HSK also causes loss of work and productivity. Corneal transplantation may be required when multiple recurrences of HSK cause corneal damage. Over 1,000 procedures performed annually in the USA in patients with HSK. In the United Kingdom, about 10% of all corneal transplants were performed on HSK scarred eyes between 1987 and 1991. [23] In Australia, the Australian Corneal Graft Registry (ACGR) has been operating since 1985 and has collected information on more than 33,000 corneal grafts. Herpetic disease was the indication for 4% (1109 of 24827) of registered grafts (PK) by 31 July 2017. [47]

Table 1 - 2: Epidemiological studies of HSK.

Key: CI = confidence interval.

First author (year)	Location	Dates	Method of inclusion	Incidence/100,000 person-years
Norn (1970)	Copenhagen, Denmark	1958-1964	Epithelial HSK	5.8 (CI, 4-7.6)
Whitcher (1976)	Tunisia	Oct 1972- Jun 1973	Epithelial HSK	1.4
Mortensen and Sjolie (1979)	Funen, Denmark	1976-1978	Epithelial HSK	12 (CI, 7.5-16.5)
Ribaric (1976)	Rijeka, Croatia	Not reported	Keratitis	4.1 (CI, 2.7-5.5)
Liesegang et al (1989)	Rochester, Minnesota (The USA)	1950-1982	All ocular HSV events (lid and conjunctival, epithelial and stromal HSK)	Combined HSK: 18.2* *New and recurrent epithelial HSK*: 15.6 *New and recurrent stromal HSK*: 2.6
Labetoulle et al (2005)	France	Sept to Dec 2002	Epithelial and stromal HSK	All HSK cases: 31.2 (CI, 24.8-37.6) *Epithelial HSK*: 22 (CI, 18.7-25.4) *Stromal HSK:* 9.2 (CI, 7-11.3)

First author (year)	Location	Dates	Method of inclusion	Incidence/100,000 person-years
Young et al (2010)	Rochester, MN (The USA)	1976-2007	All ocular HSV events (lid and conjunctival, epithelial and stromal HSK)	New HSK cases: 9.2 (CI, 8.1-10.3)

***Incidence directly age-and sex adjusted to the population structure of 1980 US whites**

1.4.4.5 Clinical features of HSK

1.4.4.5.1 Epithelial HSK

Epithelial HSK is characterised by the presence of a punctate, linear, dendritic or geographic lesion. [1, 21] This lesion is caused by direct invasion and active replication of the virus. [19, 21] It starts as fine granular spots developing into a punctate epithelial keratopathy. Then, the epithelial cells nuclei became overloaded with replicating virus which is released into adjacent cells within a day. This process destroys the basement of the membrane within 24 hours forming a dendritic shaped ulcer which stains with fluorescein. The ulcer has a branching linear shape with large terminal bulbs, swollen epithelial borders and intraepithelial cell infiltration. The borders stain negatively with fluorescein but are demarcated with lissamine green or rose bengal dye. [19, 21, 22] The ulcer may enlarge forming a geographic or amoeboid ulcer containing desquamated virus-infected epithelial cells. [20-22]

1.4.4.5.2 Stromal HSK

Stromal keratitis present as a recurrent infection accounting for 20-48% of cases; or as the primary manifestation of HSV ocular infection in 2% of cases. This type of HSK is caused by HSV invasion of the stroma either from the reactivation of latent virus in the trigeminal ganglion or within the stroma, or direct invasion from the epithelium together with a marked immune response. [22]

Clinical findings include stromal opacity, corneal oedema, and neovascularization and result from recurrent bouts of HSV reactivation and shedding into the cornea. The direct effect of the virus and the immune response to the viral proteins trigger ingrowth of blood vessels, infiltration of leucocytes and damage of the corneal stroma and endothelium that combine to promote corneal opacity and oedema. Inflammation of the cornea may clear with topical corticosteroids, but corneal scarring may remain. Repeated bouts of HSK can lead to progressive irreversible corneal scarring and blindness. [20]

‘The AAO HSK treatment guideline’ described a simple classification system based on anatomical localization. [23] In alignment with this guideline, the terms ‘stromal HSK with ulceration’ (SHSK+U) instead of ‘necrotizing stromal HSK’, and ‘stromal HSK without ulceration’ (SHSK–U) instead of ‘non-necrotizing HSK’ will be used in this study.

1.4.4.5.2.1 Stromal HSK with ulceration

Active viral replication and the immune response cause this type of HSK. [20, 21] Clinical findings include necrosis, dense infiltration of the stroma with or without an overlying epithelial defect. Greyish white homogeneous abscesses with oedema, keratic precipitates, severe iridocyclitis, and raised intraocular pressure may develop. The epithelium may break down over an abscess. The cornea maybe left with oedema, ulceration, and neovascularization. This type of stromal HSK may merge with the non-necrotizing type and manifest as immune Wessely rings. Cases with severe inflammatory response are often refractory to high dose anti-inflammatories and antiviral medications. This may lead to corneal thinning and perforation especially when bacterial infection is also present. [21, 22] It is an eye threatening emergency requiring aggressive management to prevent corneal melting and perforation. [20]

1.4.4.5.2.2 Stromal HSK without ulceration

Stromal HSK without ulceration accounts for 20% of patients with chronic or recurrent disease and is caused by immune-mediated destruction of the corneal stroma without virus replication. [20] It may present some days or years after an epithelial HSK episode. Generally, the clinical findings include an intact epithelium with different degrees of stromal inflammation (focal, multifocal or diffuse). Anterior uveitis may be associated. Corneal stromal inflammation may be chronic, recurrent, or recrudescent, leading to scarring, thinning, neovascularization and lipid deposit. Occasionally an immune ring representing an antigen-antibody complement precipitate, similar to a Wessely ring, is seen in the central or paracentral midstroma. Stromal neovascularisation may be sectorial or diffuse and occurs in several layers of the cornea. [21, 22]

1.4.4.5.3 Endothelial HSK

Endothelial HSK, also known as disciform keratitis, has been thought by many clinicians as a category of stromal keratitis. It may better be considered as an inflammatory reaction of the endothelium with secondary stromal and/or epithelial oedema. [21] Clinical findings include corneal stromal and epithelial oedema, in a round or oval distribution, with keratic precipitates underlying the area of oedema and iritis. [1, 19, 21] This type of HSK may represent viral infection and/or an immune reaction to the endothelium. [21]

Three forms of endothelial HSK have been identified and are described below: [22]

1.4.4.5.3.1 Disciform

Disciform is the most common form of endothelial HSK. Clinical findings include a disc-shaped area of stromal oedema overlying keratic precipitates (KPs) in the central or paracentral cornea with a mild-to-moderate iritis. [19, 21, 22] No stromal infiltrates or neovascularization are present. Endotheliitis usually rapidly resolves with topical corticosteroids with the KPs resolving slower than the oedema. Severe cases may progress to non-necrotizing HSK with permanent stromal oedema, scarring and neovascularization. [21]

1.4.4.5.3.2 Diffuse

Diffuse endotheliitis presents with diffuse stromal oedema with KPs over the entire posterior cornea and a mild-to-moderate iritis. [21, 22] Diffuse epithelial oedema is present due to endothelial dysfunction. A dense retrocorneal plaque of inflammatory cells with hypopyon may manifest in severe cases. Trabeculitis often causes elevated intraocular pressure which responds to the topical corticosteroid therapy.

1.4.4.5.3.3 Linear

A serpiginous line of KPs progressing centrally from the limbus, accompanied by peripheral stromal, and epithelial oedema between the KP and the limbus

characterises linear endotheliitis. [21, 22] Generally, there is a well-demarcated line between oedematous and non-oedematous cornea. [21]

1.4.4.5.4 Keratouveitis

Keratouveitis is a rare manifestation of primary HSV ocular infection; it most commonly occurs in recurrent disease. Herpes simplex virus reaches primarily the anterior segment of the eye through sensory innervation affecting the endothelium secondarily. [21] Clinical findings include corneal epithelial and/or stromal edema, stromal keratitis, fine KPs, endotheliitis, and anterior chamber cells (mild to severe) and flare. [21, 60] Focal iritis, posterior synechiae, iris masses, haemorrhages, and hyphema may occur. The uveitis commonly presents with non-necrotizing or endothelial HSK; diffuse endothelial HSK usually presents with uveitis. [21]

1.4.4.6 Diagnostic tests

A diagnosis of HSK is mainly made clinically after assessing the patient's history, symptoms and signs. A dendritic ulcer is usually sufficient to diagnose epithelial HSK. Investigations are performed for atypical or complicated cases or when the diagnosis is uncertain and in all cases of suspected neonatal HSV infection. Viral culture and antigen or DNA detection can be useful in primary epithelial infection but not in stromal HSK as most adults are latently infected with HSV (antibody-positive). [1, 23] Serology may be useful in children and in primary infections but it is not a diagnostic tool in suspected recurrent infections unless negative. [1] The laboratory tests used in HSK diagnosis are described in this section.

1.4.4.6.1 Culture

Viral culture is considered "the Gold Standard" for isolating HSV-1. It can detect virus from a primary infection but only detects latent virus when reactivated. [61] There are several techniques used to culture HSV including conventional tube cultures, centrifugation enhancement (spin amplification) of HSV replication (shell vial assay), a high-speed rolling technique, and suspension-infection culture. In some cases, tube cultures are used in conjunction with shell vial assay to detect low viral loads. [62]

Corneal scrapings are the most commonly used specimen for laboratory diagnosis of HSK. Specimens obtained with corneal scraping should be transferred to a vial and transported to the laboratory immediately. [62] A culture swab can also be used to obtain a specimen from the cornea; it is placed in viral or Chlamydia transport media and maintained at 4ºC until plated on cell culture. Staining with Rose Bengal must be avoided prior to obtaining corneal specimens since it is viricidal when exposed to light such that if used, the test may yield false negative results. The yield may be lower if antiviral therapy has been used. [23]

Despite being the gold standard for diagnosing HSK, viral culture has some disadvantages including low sensitivity, delay (up to ten days after incubation) to yield a result and need of a skilled virology laboratory. [19, 23]

1.4.4.6.2 Direct Fluorescent Antibody

The direct fluorescent antibody (DFA) test consists of HSV antigen detection. A corneal swab is smeared on a slide and observed under an ultraviolet microscope. Positive staining was determined by cells with a specific bright apple green fluorescence. A minimum of 20 basal epithelial cells were examined before the test was considered negative. [63] The results can be obtained within minutes. The application of fluorescein prior to taking the sample for DFA interferes with the test. Subhan et al. reported a relative high sensitivity (85.7%) and specificity (85.3%) of DFA. Moreover, the specificity of DFA (85.3%) was higher than polymerase chain reaction (PCR) test (67.9%) for HSV. [63]

DFA may be useful in settings where a fast result is needed, and a PCR test is not available. Some disadvantages include the need of expensive equipment (ultraviolet microscope) and the lower sensitivity (85.7) compared to the sensitivity of the PCR test (100%). [63]

1.4.4.6.3 Polymerase chain reaction

Polymerase chain reaction test can detect viral DNA and quantify the number of viral copies differentiating viral shedding from replication. As preparations of rose

Bengal, lissamine, and calcium alginate inhibit viral detection, PCR may produce false negative results if these agents have been given prior to corneal sampling for PCR. Notably, solutions of oxybuprocaine and fluorescein, even if diluted 32-fold, inhibit the capacity of the PCR to detect HSV. To minimize the risk of misdiagnosis, the clinician must rinse the eye well before taking the sample to avoid introduction of residual fluorescein or topical anaesthetics agents into the tube containing the specimen to be tested with PCR. [64]

Variable reports of the sensitivity of PCR testing exist in different studies (70%, [65] 98% [66] and 100%). [63] PCR is more likely to diagnose patients with typical lesions or patients who have not used antiviral medications than the DFA test. [19] For example, one study reported an 80% decrease in detectable virus in patients who used aciclovir 400mg twice daily. [19] The negative PCR results for stromal HSK might be explained by the immune response to the virus in this type of HSK rather than the infection itself

Advantages of this test include its high sensitivity and fast results. Disadvantages include the need for a skilled technician, special equipment and appropriate parameters for ocular specimens in a clinical setting. In addition, the interpretation of this test is limited by the inability to differentiate HSV disease level from asymptomatic HSV shedding in the tear film. [23]

1.4.4.6.4 Serology

Serology, a widely available and an easy to perform test, can be used to detect antibodies to HSV glycoproteins G-1 (type-1) and G-2 (type-2). [67] Immunoglobulin G (IgG) and M (IgM) for HSV-1 and HSV-2 are routinely requested at the same time and serial titers tested one month apart can be informative. IgM antibodies are found in primary infection and seroconversion with IgG occurs within 2-4 weeks after infection. IgM may be useful in children and young adults in cases of primary infections. [23] IgG levels to HSV fluctuate over time limiting its use in the diagnosis of HSK unless it is negative and even then, it cannot absolutely rule out the infection.

1.4.4.6.5 Enzyme linked immunosorbent Assay

Enzyme linked immunosorbent assay (ELISA) detects HSV specific antigens using monoclonal antibodies. The advantages include high specificity (100%), [68] prompt result, widely available, low cost, and easy to perform. Despite its low sensitivity (65%),[68] a clinician may use it when there is a diagnostic dilemma and need a prompt result or when other tests are not available. [23]

1.4.4.7 Treatment

Topical and oral antiviral medications and topical corticosteroids are used for the management of HSK. There are three topical antiviral agents (aciclovir, ganciclovir, and trifluridine) and three systemic agents (aciclovir, valaciclovir, and famciclovir) available for the treatment of this condition. Trifluridine and ganciclovir are the only two agents approved by the FDA in the USA for the treatment of HSK. Topical aciclovir is commonly used in Australia and in general outside the USA. [23] In Australia, the first line antiviral medications are aciclovir and valaciclovir. Second line medications include trifluridine and ganciclovir via the Special Access Scheme.

1.4.4.7.1 Antiviral medications

1.4.4.7.1.1 Aciclovir

Aciclovir is a synthetic purine nucleoside analogue (See Figure 1- 6, page 36) that is converted to aciclovir monophosphate by the virus-encoded enzyme thymidine kinase (TK) and then to the aciclovir triphosphate by human enzymes. [1] Aciclovir triphosphate inhibits viral DNA polymerase resulting in chain termination and preventing further elongation of the DNA chain. [8] Aciclovir is highly specific for HSV and HZV but is also active for Epstein-Barr virus and cytomegalovirus (CMV). It is partially absorbed by the gastrointestinal tract. Peak plasma concentrations are achieved about 1.5 h after ingestion with a half-life of 2 to 3 hours. The bioavailability of therapeutic doses is limited to 20%; as a result, the medication must be given in high doses frequently. [8]

Topical and oral aciclovir have adequate aqueous humor concentrations (greater than the median effective dose [ED50]. [23] Topical aciclovir achieves ED50 with an intact corneal epithelium and oral aciclovir in a dosage of 400 mg five times daily. [23] In Australia, aciclovir is available in tablets of 200 mg and in 3% ointment. Topical aciclovir is branded as Zovirax (GlaxoSmithKline, Australia).

In clinical use, oral aciclovir has become popular due to its advantages including lack of ocular surface toxicity and systemic antiviral activity. [1] Most common side-effects of aciclovir include gastrointestinal discomfort (vomiting, nausea, diarrhea, constipation, abdominal pain, indigestion) and headache. [69]

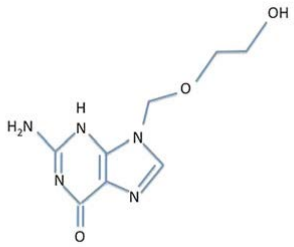


Figure 1- 6: Molecular structure of aciclovir (adapted from Tsatsos [8]).

1.4.4.7.1.2 Valaciclovir

An amino acid, L-valine, is added to the aciclovir molecule to obtain a synthetic valaciclovir. (See Figure 1- 7, page 37). Valaciclovir is a pro-drug of aciclovir as it rapidly converts into aciclovir and L-valine. This leads to a greater bioavailability of aciclovir (3 to 5 times) which is more than 50% after the valaciclovir ingestion. Studies have compared aciclovir and valaciclovir dosing finding that an equivalent dose of 800 mg of aciclovir five times daily for HZV, would be valaciclovir 500 mg twice a day, or 250 mg four times daily. [9] Good drug delivery is achieved with valaciclovir as it is almost fully converted to aciclovir during first pass metabolism. After the absorption of valaciclovir, L-valine moiety is hydrolysed to yield aciclovir (See Figure 1- 8, page 37). The increase uptake and rapid hydrolysis results in a greater systemic aciclovir concentration which is comparable with intravenous aciclovir concentrations. [8]

Most common side-effects of valaciclovir include gastrointestinal discomfort (vomiting, nausea, diarrhea, constipation, abdominal pain, indigestion) and headache. Rare side effects include sensitivity to UV light presenting as rash or sunburn after short exposure, dizziness, confusion, drowsiness, damage to kidney and liver. [70]

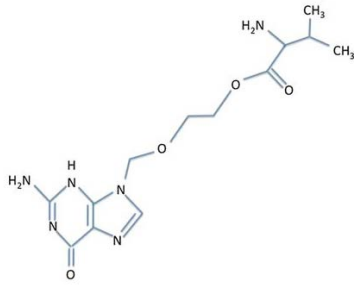


Figure 1- 7: Molecular structure of valaciclovir (adapted from Tsatsos [8]).

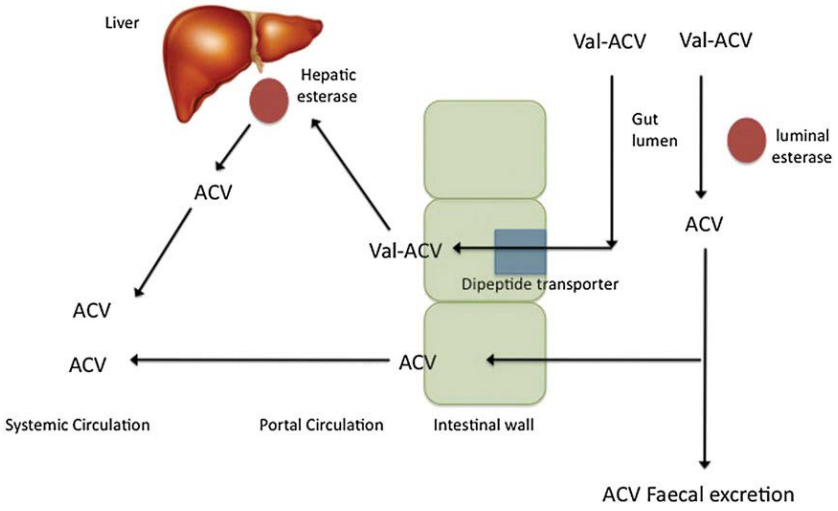


Figure 1- 8: Absorption of valaciclovir (adapted from Tsatsos [8]).

1.4.4.7.1.3 Ganciclovir

Ganciclovir is a synthetic nucleoside analogue of 2'-deoxyguanosine. The structure is 9-(1,3-dibydroxy-2-propoxymethyl) guanine. (See Figure 1- 9, page 38). It inhibits the replication of all human herpes viruses, including HSV-1 and HSV-2, herpes zoster virus, Epstein-Barr virus, CMV and human herpes virus-6. Ganciclovir triphosphate is produced by a series of enzyme-catalyzed conversions. Ganciclovir is

converted to ganciclovir monophosphate by viral thymidine kinase, only present in HSV infected cells. Human thymidine kinase does not recognize ganciclovir as a substrate; therefore, the effects of ganciclovir are basically limited to HSV infected cells making it less toxic than other medications. Subsequently, ganciclovir monophosphate is converted to ganciclovir diphosphate and finally to ganciclovir triphosphate. Ganciclovir triphosphate inhibits DNA synthesis in two forms: competitive inhibition of viral DNA-polymerase and direct incorporation into the viral primer strand DNA, resulting in DNA chain termination and disruption of replication. Ganciclovir can penetrate the corneal stroma and reach the aqueous humor in therapeutic levels. Topical ganciclovir is available from Laboratoires Théa (Louis-Bleriot, Clermont-Ferrand, France) and is marketed under the names Virgan® and Zirgan® as 1.5 mg/g eye gel 0.15% in tubes of 5 g each. Ganciclovir dosage is one drop into affected eye (s) five times daily while awake until healing of corneal ulcer, followed by one drop, three times daily for 7 days. [23] Ganciclovir is well tolerated and has fewer adverse events including less blurred vision, eye irritation, punctate keratitis, conjunctival hyperemia and eyelid erythema than topical aciclovir. [71, 72]

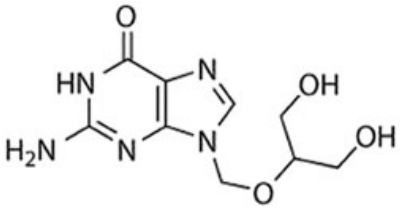


Figure 1- 9: Molecular structure of ganciclovir (adapted from Tsatsos [8]).

The AAO recommends prescribing ganciclovir for HSK, under the following circumstances: [23]

- An ulcer refractory to trifluridine;
- An ulcer requiring a prolonged treatment (trifluridine is limited to 21 days);
- Patients unable to apply eye drops every 2 hours while awake; or
- Children between the ages of 2 to 6 years.

1.4.4.7.1.4 Trifluridine

Trifluridine (trifluorothymidine) is a fluorinated pyrimidine nucleoside that acts as a thymidine analogue. Trifluridine penetration doubles in patients after corneal debridement or in patients with corneal epithelial defect. [23] It is FDA approved for the treatment of epithelial keratitis. [1]

The AAO recommends prescribing trifluridine for HSK, under the following conditions: [23]

- Contact lens wear (ganciclovir has a warning against contact lens use);
- Ulcer refractory to ganciclovir therapy;
- If a lower medication cost is needed; or
- In children aged 6 years and older

Notably, the cost and availability of trifluridine will vary across the globe preventing universal uptake of this guidance.

1.4.4.7.2 Ocular corticosteroids

Several ocular topical corticosteroids are available on the market. Corticosteroids inhibit the inflammatory response (oedema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen and scar formation) of different agents. The mechanism of action of ocular corticosteroids is not clear; however, it is believed that they act by the induction of phospholipase A2 inhibitory proteins (lipocortins). Lipocortins are thought to control the biosynthesis of prostaglandins and leukotrienes by inhibiting the release of arachidonic acid from membrane phospholipids by phospholipase A2. [73]

Indications to prescribe topical corticosteroids include treatment of corticosteroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye. [73] Contraindications include acute, untreated bacterial infections; fungal infections, epithelial HSK; vaccinia, varicella and other viral diseases

of the cornea and conjunctiva, fungal disease or in patients with hypersensitivity to corticosteroids. [73-76]

Adverse reactions of the use of topical corticosteroids include glaucoma with optic nerve damage, [75, 76] visual acuity and field defects; posterior subcapsular cataract formation; perforation of the globe; development of secondary ocular infections (fungal and viral) in long-term users. [73-76] Other minor adverse events include ocular irritation, allergic reactions, foreign body sensation, erythema of the eyelid, eyelid oedema, eye discharge, eye pain, eye pruritus, lacrimation increased, rash, headache, dysgeusia and blurry vision. [73, 74]

The following ocular corticosteroids are in clinical use in Australia and were prescribed at Sydney Eye Hospital to the patients included in this study: preserved fluorometholone ophthalmic suspension 0.1% (FML, Allergan, The USA), [73] preserved fluorometholone acetate 0.1% suspension drops (Flarex, Alcon, The USA), [75] preserved dexamethasone 0.1% ophthalmic suspension (Maxidex, Alcon, The USA), [76] preserved prednisolone acetate 1% with phenylephrine hydrochloride 0.12% ophthalmic suspension (Prednefrin Forte, Allergan, Australia), [74] unpreserved dexamethasone sodium phosphate 0.1% ophthalmic solution (Minims dexamethasone sodium phosphate), unpreserved prednisolone sodium phosphate 0.5% eye drops (Minims prednisolone sodium phosphate), and hydrocortisone acetate 1% eye ointment (Siguent Hycor, Aspen Pharma, Australia). [77]

1.4.4.8 Clinical evidence for treatment recommendations

1.4.4.8.1 Herpetic Eye Disease Study Group

The Herpetic Eye Disease Study (HEDS) clinical trials published in the 1990's made a significant contribution to the development of treatment recommendations for HSK. [1] Their initial aim was to evaluate the efficacy of topical corticosteroids and oral aciclovir in stromal HSK and iridocyclitis. [3] Eight centers across the USA were involved in the studies. Five randomised double-masked placebo-controlled multicenter clinical trials studied treatment protocols for the management of ocular HSV disease. These

trials included well-defined inclusion criteria, standardised treatment protocols, careful monitoring of patient compliance during the study and precise outcome measures. [78]

1.4.4.8.1.1 HEDS I: A controlled trial of oral aciclovir for herpes simplex stromal keratitis

This study aimed to evaluate the efficacy of oral aciclovir in treating stromal HSK patients receiving topical corticosteroids and trifluridine. Stromal keratitis included non-necrotizing keratitis and necrotizing stromal keratitis. [3, 78]

One hundred and four patients were randomised to receive a 10-week course of either oral aciclovir 400 mg 5 times daily or placebo. Fifty-three patients were allocated in the placebo group. Of these, 48 (91%) had SHSK-U, 2 (4%) SHSK+U, and 3 (6%) mixed HSK. Fifty-one patients were allocated in the oral aciclovir group. Of these, 44 (86%) had SHSK-U, 5 (10%) SHSK+U and 2 (4%) mixed HSK. All patients also received standard prednisolone phosphate eye drops and trifluridine.

The median time to treatment failure (defined as worsening or no improvement or the occurrence of an adverse event) was 84 days for the aciclovir group and 62 days for the placebo group. At week 16, 75% patients in the aciclovir group and 74% in the placebo group failed treatment.

By week 16, the infection was resolved with trial antiviral medications and topical corticosteroids. There was no subsequent worsening in 18% of patients in the aciclovir group and 19% in the placebo group. None of these results were statistically significant. Visual acuity improved in significantly more patients in the aciclovir group than in the placebo group.

The study concluded that there is no clinically significant beneficial effect of oral aciclovir in treating patients receiving topical corticosteroids and trifluridine in regard to time of treatment failure, proportion of patients that failed treatment, proportion of patients whose keratitis resolved, resolution time, or the 6-month best corrected visual acuity. (See Table 1 - 5, page 60)

1.4.4.8.1.2 HEDS II: A controlled trial of topical corticosteroids for herpes simplex stromal keratitis

The efficacy of topical corticosteroids in treating stromal HSK was evaluated in HEDS II. [2, 78] One hundred and six patients with stromal HSK who had not received topical corticosteroids in the last 10 days were enrolled. Forty-nine patients were allocated in the placebo group. Of these, 45 (92%) had SHSK-U, 3 (6%) SHSK+U, and 1 (2%) mixed HSK. Fifty-seven patients were allocated in the corticosteroid group (prednisolone phosphate eye drops). Of these, 51 (89%) had SHSK-U, 3 (5%) SHSK+U, and 3 mixed HSK (5%). Topical corticosteroid and placebo therapies were tapered over 10 weeks and both groups received trifluridine.

The risk of persistent or progressive stromal keratouveitis was reduced by 68% in the topical corticosteroid group compared to the placebo group, and there was a shorter time to resolution of stromal keratitis. Postponing corticosteroid therapy delayed resolution of stromal keratitis but there was no adverse effect on visual acuity at 6 months. The incidence of recurrent infection was not altered by the topical corticosteroid therapy.

The study concluded that topical corticosteroid treatment was significantly better than placebo in reducing stromal inflammation and in shortening the duration of stromal HSK. (See Table 1 - 5, page 60)

1.4.4.8.1.3 HEDS III: A controlled trial of oral aciclovir for iridocyclitis caused by herpes simplex virus

This study aimed to evaluate the benefit of adding oral aciclovir to topical prednisolone phosphate and trifluridine for treatment of iridocyclitis. [4, 78] Patients were randomised into a 10-week course of either aciclovir 400mg 5 times daily or oral placebo along with prednisolone phosphate and trifluridine. The patients were then followed for 26 weeks. The trial was stopped due to slow recruitment, [4] only 50 patients were enrolled of the planned 104 after 4 years. Treatment failure was determined as persistence or worsening of ocular inflammation, withdrawal of medication (e.g. toxicity) or request by the patient to withdraw from the trial.

Treatment failed in half of patients in the aciclovir group (n = 22) and in two-thirds of patients (n = 68) in the placebo group. The possible benefit of aciclovir was evident after 3 weeks of follow up. These results were not statistically significant due to the small number of patients enrolled in the study. However, the study suggested a benefit of oral aciclovir in the treatment of iridocyclitis (See Table 1 - 7, page 65).

1.4.4.8.1.4 HEDS IV: A controlled trial of oral acyclovir for the prevention of stromal keratitis or iritis in patients with herpes simplex virus epithelial keratitis

This study aimed to evaluate the efficacy of oral aciclovir in preventing stromal HSK or iritis in 287 patients with epithelial HSK of one week or less of duration. [5, 78] Patients with signs of stromal with or without ulceration HSK were excluded. One hundred and fifty-three patients randomly received a 3-week course of oral aciclovir 400 mg 5 times daily; and 134 received oral placebo. Both groups also received trifluridine. The development of stromal HSK or iritis was assessed during 12 months of follow-up.

Stromal HSK or iritis occurred in 11% (17 of 153) of patients in the aciclovir group and in 10% (14 of 134) in the placebo group. Stromal HSK was more frequent in patients with a history of stromal HSK or iritis than in those without a history (23% vs 9%, $p = 0.01$).

In conclusion, there was no apparent benefit of treating patients with epithelial HSK with a 3-week course of oral aciclovir for preventing stromal keratitis during 12 months of follow-up. (See Table 1 - 8, page 66)

1.4.4.8.1.5 HEDS V: Oral aciclovir in the prevention of recurrent herpes simplex virus eye disease

The efficacy of oral aciclovir as a prophylaxis for the prevention of recurrent ocular HSV disease was evaluated in HEDS V. [6, 78] Seven hundred and three patients with a history of ocular HSV disease within the previous year were randomly assigned to receive 400 mg of aciclovir (n = 357) or placebo (n = 346) twice daily. The study outcomes were the rates of development of ocular or non-ocular HSV disease during a 12-month treatment period and a 6-month post-treatment observation period.

The cumulative probability of recurrence of any type of ocular HSV during the 12-month period was 19% in the aciclovir group and 32% in the placebo group. In patients with a history of stromal HSK, the cumulative probability of recurrent stromal HSK was 14% in the aciclovir group and 28% in the placebo group.

In conclusion, long-term oral prophylaxis is effective in reducing the rate of recurrent ocular HSV disease mainly in patients with history of prior stromal disease (See Table 1 - 8, page 66). This prophylactic benefit only lasted while the patient was receiving the treatment. Clinical benefits were apparent and cost effectiveness seemed justified. The study also raised the possibility of using oral aciclovir as prophylaxis in another group of patients prone to recurrent herpetic disease that is patients undergoing penetrating keratoplasty for corneal scarring or other ocular surgery.

In summary, the HEDS trials provided evidence that: [78]

- Topical corticosteroids along with antiviral medications contribute to a faster resolution of stromal HSK without serious adverse events and without recurrent episodes.
- Oral aciclovir may be effective for herpetic iritis and should probably be used with topical corticosteroids.
- There is no benefit of adding oral aciclovir to topical trifluridine in patients with epithelial HSK to prevent stromal HSK.
- Patients with a history of recurrent HSK received a benefit from having oral aciclovir in a prophylactic dose (400mg twice a day) for a year.

1.4.4.8.2 American Academy of Ophthalmology recommendations for HSK treatment

The AAO released a treatment guideline for HSK in June 2014. This guide was developed for use by American ophthalmologists. However, it could not be used directly as a guideline for HSK management in Australia as it did not include topical aciclovir for epithelial HSK. Topical aciclovir is widely used in Australia. We therefore used this guideline to complement the available evidence from clinical trials and a consensus

meeting of local specialists in order to develop the local guidelines for Sydney Eye Hospital. See Appendix A, page 313.

1.4.4.8.3 Treatment recommendations for HSK

Treatment recommendations for the different types of HSK have been based on clinical trials which had studied topical antiviral medications vs topical antiviral medications; or topical antiviral medications (aciclovir) vs oral aciclovir. However, available randomised clinical trials have not evaluated valaciclovir or famciclovir in HSK. [1] Therefore, equivalent valaciclovir dose for aciclovir, obtained through pharmacokinetic data, has been used in clinical practice. [8, 9]

1.4.4.8.3.1 Treatment for epithelial HSK

Clinical trial evidence

Trifluridine and ganciclovir gel are safe, effective, and FDA approved for the treatment of epithelial HSK. These agents have not been compared directly in any clinical trials; however, there are clinical trials which had compared one or the other with topical aciclovir. [23]

Three double blind randomised clinical trials compared topical aciclovir 3% with trifluridine eye drops 2% concluding that there was no significant difference in the healing time between the two groups. [23] La Lau et al. reported that 87% of patients treated with aciclovir and 82% with trifluridine healed after two weeks of treatment. [79] Hovding reported a healing time of 7 days for aciclovir and 6 days for trifluridine [80] and Panda et al. reported cure rates of 90% for patients in both groups and a healing time of 9 days (See Table 1 - 3, page 54). [81]

Furthermore, ganciclovir ophthalmic gel 0.15% has been first line therapy for epithelial HSK in the USA since 2009 and commercially available in Europe since 1996, but only available in Australia through the Therapeutics Goods Administration (TGA) Special Access Scheme. Studies have compared ganciclovir 0.15% ophthalmic gel and topical aciclovir, concluding that ganciclovir is as effective as topical aciclovir for the

treatment of epithelial HSK, with better tolerance and a lower rate of blurred vision, eye irritation, and punctate keratitis (See Table 1 - 3, page 54). [82, 83] There are no studies comparing directly ganciclovir and trifluridine. Because there are studies comparing topical aciclovir and trifluridine, ganciclovir and trifluridine can be considered to have similar efficacy for the treatment of epithelial HSK.

Oral antiviral medications such as aciclovir, valaciclovir, and famciclovir are safe and effective for the treatment of epithelial HSK but are not FDA approved for this condition. [23] Two double-blind placebo controlled randomised clinical trials compared oral aciclovir 400 mg five times daily with topical aciclovir five times daily. Collum et al. concluded that oral aciclovir is as effective as topical aciclovir for the treatment of epithelial HSK; they found no significant difference in the proportion of healed patients in both groups with a median healing time of 5 days (See Table 1 - 3, page 54). [84, 85]

Systematic review evidence

A Cochrane systematic review compared the effectiveness of antiviral agents, interferon and corneal debridement for the treatment of epithelial HSK. The authors included in the review randomised clinical trials of patients with epithelial HSK (dendritic and geographic) which reported healing times at one week, two weeks or both after enrolment. One hundred and thirty-seven studies including 8,333 eyes met the inclusion criteria. The review concluded that vidarabine, trifluridine, aciclovir, and brivudine were more effective than idoxuridine; and trifluridine and aciclovir more effective than vidarabine. There were no significant differences in healing among trifluridine, aciclovir, brivudine, and foscarnet. Oral aciclovir or the combination of oral aciclovir with a topical antiviral was effective as a topical antiviral agent alone (See Table 1 - 4, page 58). [7]

Guess et al. carried out a systematic review of evidence-based treatment for epithelial and stromal HSK. [1] Thirty publications of randomised clinical trials on epithelial HSK were included in the systematic review. Seven studies compared trifluridine with other treatments, including mechanical debridement, other chemical antiviral compounds, and human interferon. Trifluridine demonstrated greater (or no

less) efficacy than other topical agents. [1] Sixteen studies compared aciclovir ophthalmic ointment to placebo and/or another treatment, or as a baseline treatment along with a medication under study. There were 12 studies where aciclovir ointment was compared directly with other antiviral agents. Twenty studies showed no statistically significant differences between treatment groups. Aciclovir ointment was the most studied agent, less toxic, and as efficient as other topical therapies tested.

In conclusion, the randomised clinical trials included in the systematic review by Guess supported the use of aciclovir ophthalmic ointment 3% (depending on availability) five times daily, topical trifluridine 1% solution 8 times daily, or oral aciclovir 3 to 5 times daily (See Table 1 - 4, page 58). [1]

1.4.4.8.3.2 Treatment of stromal HSK

Evidence from the HEDS trials

Oral antiviral medications are the preferred agents for the management of stromal HSK. They are safer for long-term use compared to topical antiviral agents. Long term use of trifluridine may cause toxic keratoconjunctivitis, allergic conjunctivitis, and punctal stenosis; and long-term ganciclovir use has not been studied. Further, trifluridine and ganciclovir do not have adequate penetration into the corneal stroma. [23] Oral aciclovir had been widely used due to its advantages including lack of ocular surface toxicity, better corneal stroma and anterior chamber bioavailability, and systemic antiviral activity. [1] Currently, valaciclovir has replaced oral aciclovir in prescription preference due to its greater bioavailability compared to aciclovir. Thus, patients only take the medication once to three times daily instead of two to five times daily. [8]

The results of the clinical trials conducted by the HEDS group supported the use of antiviral medications and topical corticosteroids for the management of stromal keratitis. In HEDS I, patients received a 10-week course of either oral aciclovir or placebo, a standard regimen of topical prednisolone phosphate and trifluridine. The median time to treatment failure was 84 days (95% CI, 64-93 days) for the aciclovir

group vs 62 days for the placebo group (95% CI, 57-90 days). Nineteen of 51 patients in the aciclovir group (38%) and 26 of 53 in the placebo group (49%) were treatment failures before the 10-week course of trial medications. By 16 weeks, 75% (n = 38) failed treatment in the aciclovir group compared with 74% (n = 39) in the placebo group. The authors concluded that a tapered corticosteroid course longer than 10 weeks is needed and there is no benefit of adding an oral antiviral to a topical antiviral regimen (See Table 1 - 5, page 60). [3, 23]

In HEDS II, patients were treated with a 10-week taper of topical prednisolone phosphate plus trifluridine or topical placebo with trifluridine. During the 10-week trial, 26% (15/57) of patients failed treatment in the corticosteroid group compared with 73% (36/49) in the placebo group. In conclusion, patients treated with corticosteroids plus trifluridine were found to have a more rapid resolution than when treated only with trifluridine. However, 10-week tapered corticosteroids may be too short as 50% of patients with the combination of antiviral agent and topical corticosteroid; and 76% of the patients in the placebo group failed within six weeks after the treatment was ceased (16 weeks after treatment started). Therefore, a tapered course of topical corticosteroids for greater than 10 weeks is recommended (See Table 1 - 5, page 60). [2, 23]

It should however be noted that the HEDS I and II trials mostly enrolled patients with SHSK-U. Only 7% [3] and 6% [2] of patients in these trials presented with SHSK+U, respectively. Evidence to guide the appropriate treatment of patients with stromal keratitis with epithelial ulceration is lacking.

Systematic review evidence

Seven randomised clinical trials for stromal keratitis were included in a systematic review conducted by Guess et al. These articles supported the use of topical corticosteroids given to shorten the duration of active HSK and the use of long term suppressive oral aciclovir to reduce the recurrence of the infection (See Table 1 - 4, page 58). [1]

White and Chodosh in their review recommended for SHSK-U, a prophylactic dose of an oral antiviral medication, for example aciclovir 400 mg twice daily or valaciclovir 500 mg once daily, and topical corticosteroid (prednisolone 1% drops) tapered over greater than 10 weeks; [1, 23] and for SHSK+U, a therapeutic dose of an oral antiviral medication, for example valaciclovir 1 g, three times daily or aciclovir 800 mg three to five times daily, and a topical corticosteroid also tapered over greater than 10 weeks . [23]

1.4.4.8.3.3 Treatment of endothelial HSK

Clinical trial evidence

There are few randomised clinical trials conducted for endothelial HSK. The HEDS trials did not study this type of keratitis. Collum and Grant compared the efficacy of topical aciclovir and adenine arabinoside in combination with betamethasone. They concluded that there was no statistical difference between the two treatment groups for efficacy parameters. [86] In another study, Collum et al. compared the efficacy of topical aciclovir plus betamethasone vs topical aciclovir plus placebo. All patients who received the combination healed in a median time of 12 days, while 57% (11 of 19) of patients who received the topical antiviral medication plus placebo were withdrawn as their condition remained static or worsened. Collum et al. concluded that the combination of aciclovir and betamethasone was effective in the management of disciform HSK with a faster rate of healing (p = 0.004). [87] In another study, Porter et al. compared topical aciclovir to oral aciclovir in patients also receiving topical prednisolone. The patients in the oral group showed greater improvement in visual acuity and in resolution of lacrimation; however, healing times were similar in both groups. The findings from these trials supported the use of oral aciclovir as an effective alternative to topical aciclovir (See Table 1 - 6, page 62). [88]

In summary, the available evidence supports the management of endothelial HSK with a topical corticosteroid and an oral antiviral agent. [23] Further, evidence is needed to determine the correct dosage regimen.

1.4.4.8.3.4 Treatment of herpes simplex virus keratouveitis

The HEDS III trial assessed the benefit of oral aciclovir added to a regimen of topical prednisolone phosphate and trifluridine for the treatment of HSV iridocyclitis. Fifty patients were enrolled and randomly received a 10-week course of either oral aciclovir 400 mg 5 times daily or oral placebo along with trifluridine and topical prednisolone phosphate. There were weekly follow-up examinations for 10 weeks, every 2 weeks for an additional 6 weeks, and at week 26. Fifty percent (11/22) of patients failed treatment in the aciclovir group and 68% (19/28) in the placebo group.

The treatment effect was only slightly greater when patients with persistence or worsening of the infection were considered as treatment failures (excluding terminations due to toxic effects of medications and patient's withdrawals). In conclusion, the number of patients recruited was too small to achieve statistically conclusive results but a benefit of oral aciclovir in the treatment with topical corticosteroids and trifluridine prophylaxis was suggested. [4, 89] A limitation of the study was the difficulty of differentiating cases caused by HSV as compared to HZV. For HZV cases, the aciclovir dose used in the study to treat presumed HSV infection would been insufficient leading to treatment failure and limiting the interpretation of the results (See Table 1 - 7, page 65). [89]

Oral antiviral medications are preferred to treat HSV keratouveitis over topical agents. Oral aciclovir is the most studied and able to achieve adequate therapeutic levels in tears and aqueous humor. Controlled comparisons have not been done for valaciclovir and famciclovir. However, valaciclovir 1 g three times daily and famciclovir 500 mg three times daily are thought to be equivalent to oral aciclovir for the treatment of non-ocular herpes infections. [89] Most patients also require a cycloplegic and a topical corticosteroid to prevent posterior synechiae formation and improve comfort. Cunningham stated that a typical treatment for keratouveitis might be an oral antiviral plus a topical corticosteroid (prednisolone acetate 1%) and a cycloplegic (tropicamide, 1% four times daily). Corticosteroids are then tapered over time, this may take months and in some patients long term control of the inflammation with very low dose of topical corticosteroids maybe needed. [89]

1.4.4.8.3.5 Prevention of HSK recurrence

Recurrent stromal HSK can cause further corneal scarring, vascularisation, astigmatism and corneal perforation leading to vision loss. Therefore, it is important to prevent further episodes of the infection in patients who have experienced multiple episodes of HSK.

HEDS study evidence

The HEDS V group trial enrolled 703 patients with prior HSK within the preceding year. Oral aciclovir was given to 357 patients and placebo to 346. The patients were followed up for 12 months [59] and observed for an extra 6 months. [6] During the 12-month period, patients treated with oral aciclovir experienced about half as many recurrences of ocular HSV as the placebo group. There was no statistical difference in recurrences between the two groups in the six months after cessation of treatment suggesting the absence of a prolonged effect of the aciclovir once the medication is ceased. The benefit whilst on treatment was only seen in patients with prior stromal HSK or with multiple recurrences of any type of ocular HSV (See Table 1 - 8, page 66). [59]

The HEDS IV trial evaluated the efficacy of oral aciclovir in preventing stromal HSK or iritis in patients with epithelial HSK. The study enrolled 287 patients who presented with epithelial HSK and were treated with trifluridine and received either a 3-week course of oral aciclovir 400 mg five times daily or a placebo. The authors concluded that there was not evident benefit of adding oral aciclovir to topical trifluridine to prevent stromal HSK or iritis (See Table 1 - 8, page 66). [5, 23]

Clinical trial evidence

A randomised, unmasked clinical trial compared the efficacy of one-year treatment of valaciclovir vs aciclovir in preventing recurrence of HSK. Patients either received aciclovir 400 mg twice daily or valaciclovir 500 mg once daily. The recurrence rate was 23.1% in both groups. The study concluded that aciclovir was as effective as valaciclovir in preventing recurrent infections. Both medications were well-tolerated

during the study period. There was no clinical difference of the adverse events and no serious adverse reactions reported for both groups. (See Table 1 - 8, page 66). [10, 23]

A retrospective observational study compared oral and topical aciclovir for the prevention of the recurrence of HSK after a penetrating keratoplasty (PK). Twenty-six patients received aciclovir 400 mg twice daily and 29 received topical aciclovir 3% five times daily for an average of 16 months. Patients were followed for an average of 24 months. Patients on oral aciclovir experienced a significant reduction in the number of recurrences at one and two years compared with patients on topical aciclovir (12% vs 55%). Recurrences of HSK in the oral aciclovir group occurred only in the first-year post-surgery. This suggests that either there is a protective effect after ceasing the prophylaxis in the second year or most of the recurrences occur in the first-year post-surgery. [23, 90]

Another retrospective review compared the outcomes of prophylactic valaciclovir and oral aciclovir in patients having PK. Twenty patients received valaciclovir 500 mg 2 to 3 times daily for four months and tapered to 250 mg twice daily for up to 30 months according to clinical response. Nineteen patients received aciclovir 800 mg 3 to 5 times daily for four months and tapered to at least 400 mg twice daily until 11 months postop and up to 36 months if needed. The authors concluded that valaciclovir is at least as effective as oral aciclovir in preventing recurrences in patients who had a PK. [23, 91] An interventional case series of 13 patients evaluated the efficacy of long term oral aciclovir therapy in reducing recurrences of epithelial HSK at different doses. Recurrences occurred more in patients with lower doses of aciclovir (less than 800 mg daily) and in those who underwent ocular surgery within 6 weeks. Patients who had a recent ocular surgery had fewer recurrences if they received higher doses of aciclovir (average 1321 mg daily) compared with other receiving less than 1000 mg daily (See Table 1 - 9, page 69). [23, 92]

In summary, the use of long-term (one year) and low-dose antiviral agents (aciclovir 400 mg twice daily or valaciclovir 500 mg once daily) reduces the incidence of recurrences of HSK. There is no available evidence of famciclovir for prevention of

HSK. However, extrapolation of data from genital herpes studies suggests that famciclovir 250 mg twice daily could be an alternative to aciclovir and valaciclovir for HSK prophylaxis. [23]

Table 1 - 3: Summary of randomised clinical trials in epithelial HSK.

Key: ACV = aciclovir, BVDU = bromovinyldeoxyuridine, GCV = ganciclovir, HSK = Herpes simplex keratitis, IDU = idoxuridine, Occ = ointment, RCT = randomised clinical trial, TFT = trifluridine, x5 = five times daily.

First Author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
La Lau (1982)	Acyclovir and trifluorothymidine in herpetic keratitis: a multicenter trial	Leiden, Rotterdam, The Hague and Maastricht, The Netherlands	Occ ACV 3% vs Occ TFT 2% for dendritic HSK	Double-blind RCT. Clinical progress measured by examination and retrospective photographic evaluation.	59 patients: 31 received ACV 3% 28 received TFT 2%	87% ACV patients and 82% TFT patients healed after 2 weeks of treatment. No significant difference in the rate of healing between groups.	ACV and TFT are safe, have high therapeutic efficacy against dendritic HSK and low toxicity.

Table 1 – 3 (continued)

First Author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Hovding (1989)	A comparison between acyclovir and trifluorothymidine ophthalmic ointment in the treatment of epithelial dendritic keratitis. A double blind, randomized parallel group trial	Bergen, Norway	Occ ACV 3% vs Occ TFT 2% for epithelial HSK	Double blind RCT	50 patients: 25 received ACV 3%; 25 received TFT 2%.	Mean duration of treatment in both groups was 6.7 days and 5.9 days, respectively. No statistically significant difference.	Efficacy of ACV and TFT is similar. Both are highly effective and well tolerated. They are the drug of choice in the treatment of epithelial HSK.
Panda (1995)	Efficacy of four antiviral agents in the treatment of uncomplicated herpetic keratitis	New Delhi, India	Occ IDU 1% (group 1) vs Occ TFT 2% (group 2), Occ ACV 3% (group 3) and Occ BVDU 1% (group 4)	Double blind RCT	80 HSK patients with recent onset with no previous antiviral treatment.	Cure rates of 60%, 90%, 90% and 95% in groups 1, 2, 3 and 4 respectively. The average healing time was 13.4, 8.9, 8.5 and 7.5 days respectively.	BVDU has a more pronounced therapeutic effect than idoxuridine, TFT and ACV in these patients.

Table 1 – 3 (continued)

First Author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Colin (1997)	Ganciclovir ophthalmic gel (Virgan; 0.15%) in the treatment of herpes simplex keratitis.	Africa (Mali, and Tunisia) (Trial 1) Europe (The United Kingdom, Switzerland and France) (Trial 2)	Trial 1: 3 groups: GCV 0.05% GCV 0.15% Occ ACV 3% Trial 2: 2 groups GCV 0.15% Occ ACV 3% for epithelial HSK.	Two unmasked multicenter RCT	67 patients (Trial 1) 37 patients (Trial 2)	Healing rates 85% (Trial 1), 83% (Trial 2) for GCV 0.15% vs 72% (Trial 1), 71% (Trial 2) for Occ ACV. No statistically significant difference between groups. Few complaints of burning, stinging or blurred vision	GCV efficacy similar to Occ ACV with superior local tolerance
Hoh (1996)	Randomised trial of ganciclovir and acyclovir in the treatment of herpes simplex dendritic keratitis: a multicenter study.	London, the United Kingdom and Dublin, Ireland	GCV 0.15% gel vs Occ ACV 3% for dendritic HSK of less than 7 days	Unmasked RCT The rate of healing of the dendritic ulceration assessed on days 2, 7, 10, and 14	46 patients included. 24 received GCV 22 received Occ ACV Both medications given x5.	By day 14, all GCV patients had healed. 20 patients in ACV group healed. No statistically significant difference in the rate of healing between groups	Both medications are equally effective for dendritic HSK. GCV less effect on blurring vision.

Table 1 – 3 (continued)

First Author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Collum (1986)	Oral acyclovir (Zovirax) in herpes simplex dendritic corneal ulceration.	Dublin, Ireland	ACV 400mg vs Occ ACV 3% for simple dendritic corneal ulceration	Double blind placebo-controlled RCT.	60 patients: 24 received Occ ACV 3% and placebo tablets, 21 received aciclovir 400 mg and placebo ointment. All medication taken five times a day.	Median healing time was 5 days in both groups. No significant difference in the proportions of patients healed in each group (88.9% on PO ACV and 96.6% on Occ ACV).	ACV 400 mg five times daily may be an effective alternative to topical therapy in selected patients.
Collum (1985)	Oral acyclovir in herpetic keratitis.	Dublin, Ireland	ACV 400mg vs Occ ACV 3% for dendritic corneal ulceration	Double blind placebo-controlled RCT.	29 patients: 14 received Occ ACV 15 received ACV 400 mg	All Occ ACV patients and 14/15 PO ACV patients healed. Mean healing time of 5.6 days for both groups. No significant systemic or local side effects in either group.	Either medication is effective to treat dendritic corneal ulceration.

Table 1 - 4: Summary of systematic reviews in HSK.

Key: x5 = five times daily, x8 = eight times daily, ACV = aciclovir, BD = twice daily, HSK = Herpes simplex keratitis, Occ = ointment, PO = Oral, q2h = every two hours, RCT = randomised clinical trial, TDS = three times daily, TFT = trifluridine.

First Author (Year)	Name of study	Aims	Selection Criteria	Number studies/ Participants	Results	Recommendations
Wilhelmus (2015)	Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis	Compare the relative effectiveness of antiviral agents, interferon, and corneal debridement in the treatment of epithelial HSK.	RCT and quasi-randomised trials of epithelial HSK included reporting proportion of eyes healed at one week, two weeks, or both after enrolment.	137 studies involving 8333 eyes included	Vidarabine, TFT, ACV and brivudine were more effective than idoxuridine. TFT and ACV more effective than vidarabine. No significant differences in healing among TFT, ACV, brivudine, and foscarnet.	PO ACV or the combination of PO ACV with a topical antiviral appeared as effective as a single topical antiviral agent.

Table 1- 4 (continued)

First Author (Year)	Name of study	Aims	Selection Criteria	Number studies/ Participants	Results	Recommendations
Guess (2007)	Evidence-based treatment of Herpes Simplex Virus Keratitis: a systematic review	Establish rational evidence-based foundation for treatment of epithelial and stromal HSK	Double-blinded RCT for HSV epithelial and stromal keratitis	30 studies for epithelial HSK. 7 studies for stromal HSK	Epithelial HSK: Studies supported use of topical TFT and ACV, and PO ACV. Stromal HSK: Studies supported use of topical corticosteroids given with prophylactic antiviral to shorten the duration of stromal HSK, and the use of long-term suppressive PO ACV to reduce recurrent episodes	Epithelial HSK: Occ ACV 3% x5 TFT 1% x8 PO ACV 400mg TDS-x5 Stromal HSK: Topical corticosteroid: e.g. prednisolone 1% drops q2h with prophylactic antiviral (TFT or PO ACV 400mg BD) Corticosteroid drops are tapered every 1 or 2 weeks depending on clinical improvement

Table 1 - 5: Summary of randomised clinical trials in stromal HSK.

Key: ACV = aciclovir, BCVA = best corrected visual acuity, HSK = Herpes simplex keratitis, Occ = ointment, RCT = randomised clinical trial, TFT = trifluridine.

First Author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Wilhelmus (1994)	Herpetic Eye Disease Study II. A controlled trial of topical corticosteroids for herpes simplex stromal keratitis.	The USA	Evaluate efficacy of topical corticosteroids in stromal HSK	RCT, double-masked, placebo-multicenter trial.	106 patients: 49 received topical placebo plus TFT. 57 received topical prednisolone phosphate plus TFT. Both regimens tapered over 10 weeks.	Median time to treatment failure was 98 days for steroid group and 17 for placebo group. 26% patients in steroid group failed treatment vs 73% in placebo group before 10-week course.	Topical corticosteroids were significantly better in reducing persistence or progression of stromal inflammation, and healing time of stromal HSK

Table 1 – 5 (continued)

First Author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Barron (1994)	Herpetic Eye Disease Study I. A controlled trial of oral acyclovir for herpes simplex stromal keratitis	The USA	Evaluate the efficacy of oral acyclovir in treating stromal HSK in patients receiving concomitant topical corticosteroids and TFT.	RCT, double-masked, placebo-multicenter trial.	104 patients with stromal HSK without epithelial ulcer. 51 received oral aciclovir 400 mg 5 times daily, 53 received placebo. All patients also received standard regimen of topical prednisolone phosphate and TFT.	Median time to treatment failure was 84 days for ACV group and 62 for placebo group. By 10 weeks, 38% in ACV group and 49% in placebo group failed treatment. By 16 weeks, 75% in the ACV group and 74% in the placebo group failed treatment.	No statistically clinically significant benefit of adding ACV to the regimen of topical corticosteroids and TFT for reducing the time to treatment failure.

Table 1 - 6: Summary of randomised clinical trials in endothelial HSK.

Key: ACV = aciclovir, HSK = Herpes simplex keratitis, Occ = ointment, PO = oral, RCT = randomised clinical trial, VA = visual acuity.

First author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Collum (1987)	A double-blind comparative trial of acyclovir and adenine arabinoside in combination with dilute betamethasone in the management of herpetic disciform keratitis	Dublin, Ireland	Occ ACV vs adenine arabinoside Both groups received dilute betamethasone	Double-blind RCT	30 patients	Mean time of healing was 22.5 days for 86.7% patients of ACV group vs 26.7 days for 76.9% of Ara-A group. Proportion of patients developing SPK significantly greater in the Ara-A group.	No statistical difference between the two treatment groups for efficacy

Table 1 – 6 (continued)

First author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Collum (1983)	Acyclovir (Zovirax) in herpetic disciform keratitis	Dublin, Ireland	Betamethasone 0.01% drops vs placebo. Both groups received Occ ACV 3%	Double-blind RCT	40 patients. 21 received Occ ACV 3% and betamethasone drops 0.01%, 19 received Occ ACV 3% plus placebo.	All patients in the combination group healed in a median time of 21 days, 11 of 19 in the placebo group withdrawn. Combination group had a faster healing (p = 0.004).	ACV and steroid drops are effective in the treatment of disciform HSK
Porter (1990)	A comparison of local and systemic acyclovir in the management of herpetic disciform keratitis.	Liverpool, the United Kingdom	Occ ACV 3% to PO ACV 400 mg 5 times daily for endothelial HSK Both groups received topical prednisolone 0.05%	Open label RCT	43 patients 19 received Occ ACV 20 ACV 400mg 5 times daily.	Mean healing time was 25.9 days in the oral group vs 25.3 days in the topical group. Resolution of lacrimation significantly faster in the oral group (12.1 vs 27.6 days). Oral group patients showed greater improvement in VA.	Oral ACV is an effective alternative to topical ACV in the management of disciform HSK

Table 1 – 6 (continued)

First author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Power (1992)	Acyclovir ointment plus topical betamethasone or placebo in first episode disciform keratitis	Dublin, Ireland	Betamethasone 0.1% drops vs placebo for first episode of disciform HSK and with no previous steroid exposure. Both groups received Occ ACV 3%.	Double-blind RCT	30 patients. 15 received Occ ACV 3% and betamethasone 0.1% drops. 15 received Occ ACV and placebo	Mean healing time for steroid group was 21.8 days vs 34.5 for placebo group. Significant difference in healing time (p = 0.05).	ACV combined with 0.1% betamethasone produced a more rapid response with significantly fewer treatment failures than ACV and placebo.

Table 1 - 7: Summary of randomised clinical trials in herpes simplex virus iridocyclitis.

Key: x5 = five times daily, ACV = aciclovir, HSV = Herpes simplex virus, PO = oral, RCT = randomised clinical trial, TFT = trifluridine.

First Author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Herpetic Eye Disease Study Group (1996)	Herpetic Eye Disease Study III. A controlled trial of oral acyclovir for iridocyclitis caused by herpes simplex virus.	The USA	Assess benefit of PO ACV to regimen of topical prednisolone phosphate and TFT in HSV iridocyclitis.	RCT, double-masked, placebo-multicenter trial.	50 patients. 22 received ACV 400mg x5 57 received placebo. Both regimens for 10 weeks.	Treatment failure in 50% in ACV group vs 68% in placebo group. Adjusted rate ratio for treatment failure was 0.43 (10 weeks) and 0.60 (16 weeks) Small sample to achieve statistically conclusive results.	There is a benefit of PO ACV in a regimen of topical steroids and TFT in the treatment of iridocyclitis.

Table 1 - 8: Summary of randomised clinical trials in prophylaxis for HSK.

Key: x5 = five times daily, ACV = aciclovir, BD= twice daily, HSK = Herpes simplex keratitis, HSV = herpes simplex virus, Occ = ointment, PO = oral, RCT = randomised clinical trial, TFT= trifluridine, VLC = valaciclovir.

First author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Herpetic Eye Disease Study Group (1998)	Herpetic Eye Disease Study V. Acyclovir for the prevention of recurrent herpes simplex virus eye disease.	The USA	ACV 400 mg twice daily for one year would prevent ocular recurrences who had an episode of ocular HSV within the preceding year.	RCT, double-masked, placebo-multicenter trial.	703 patients 357 patients received PO ACV 400mg BD, 346 received placebo. Follow up during 12-month period and a 6- month observation period.	Cumulative probability of recurrence was 19% in ACV group and 32% in placebo group. Among 337 patients with history of stromal HSK, cumulative probability was 14% ACV group and 28% placebo group (*P*= 0.005).	Long-term antiviral prophylaxis is effective for patients with history of stromal HSK.

Table 1 – 8 (continued)

First author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Herpetic Eye Disease Study Group (1997)	Herpetic Eye Disease Study IV A controlled trial of oral acyclovir for the prevention of stromal keratitis or iritis in patients with herpes simplex virus epithelial keratitis. The Epithelial Keratitis Trial.	The USA	Evaluate the efficacy of PO ACV in preventing stromal keratitis or iritis in patients with epithelial HSK	Prospective, double-masked and placebo-controlled RCT.	287 patients with epithelial HSK treated with TFT and received 3-week course of PO ACV, 400mg x5 or placebo. 153 received PO ACV, 134 received placebo. Development of stromal HSK or iritis was assessed during 12 months.	Stromal HSK developed in 11% patients on the ACV group vs 10% in placebo group. Development of stromal HSK more frequent in patients with history of stromal HSK (23% vs 9%, *P*= 0.01)	No apparent benefit of adding PO ACV to topical TFT to prevent stromal HSK or iritis

Table 1 – 8 (continued)

First author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Miserocchi (2007)	Efficacy of valacyclovir vs acyclovir for the prevention of recurrent herpes simplex virus eye disease: a pilot study	Milan, Italy	Compare the efficacy of one-year treatment with VLC vs PO ACV in preventing recurrence of ocular HSV	Prospective pilot RCT	52 patients with a history of recurrent ocular HSV. 26 received VLC 500mg daily, 26 ACV 400mg BD. Recurrence rate of ocular HSV disease during 12 months of treatment.	Recurrence rate of 23.1% in both groups. No difference in nature, frequency or severity adverse events for both groups.	Therapy with VLC as effective and as well tolerated as PO ACV in reducing the rate of recurrent ocular HSV

Table 1 - 9: Summary of studies in prophylaxis for HSK.

Key: x5 = five times daily, x6 = six times daily, ACV = aciclovir, BCVA = best corrected visual acuity, BD = twice daily, HSK = Herpes simplex keratitis, HSV = herpes simplex virus, logMAR = logarithm of minimum angle resolution, Occ = ointment, PO = oral, PK= penetrating keratoplasty, QID = four times daily, RCT = randomised clinical trial, TDS = three times daily, TFT = trifluridine, VLC = valaciclovir.

First author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Ghosh (2008)	Acyclovir therapy in prevention of recurrent herpetic keratitis following penetrating keratoplasty	Melbourne, Australia	PO ACV vs Occ ACV for the prevention of recurrence of HSK following PK. All cases received prednisolone sodium phosphate 1% x 6, chloramphenicol 0.5% QID and cycloplegic.	Retrospective observational study between 1995 and 2005.	55 patients underwent PK for ocular HSV and received prophylactic antiviral therapy for at least one year postoperatively. 26 received PO ACV 400mg BD. 29 received Occ ACV 3% x5. Patients followed for one year.	Mean duration of prophylaxis was 16.1 months for systemic group vs 15.1 for topical group. Recurrence episodes in 12% in systemic group vs 55% in topical group. Clear graft survival rate was 96.2% in systemic group vs 86.2% in topical group.	PO ACV is more effective than Occ ACV in achieving better graft outcomes after PK. Recurrences only happened in the first year in the PO ACV group.

Table 1 – 9 (continued)

First author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Goldblum (2008)	Comparison of oral antiviral therapy with valacyclovir or acyclovir after penetrating keratoplasty for herpetic keratitis.	Bern, Switzerland	Compare the outcome of prophylactic VLC or PO ACV treatment in patients having undergone PK for HSK. All patients received topical steroids and antibiotics.	Retrospective review from 12/97 to 3/06 and 5/92 to 9/96.	39 patients. 20 received VLC 500 mg BD-TDS for four months, tapered to 250 mg BD up to 30 months. 19 received ACV 800 mg TDS- x 5d tapered to 400mg BD for 11 to 36 months.	2 patients from both groups presented graft failure. BCVA improved in both groups from logMAR 1.97 (VLC), 1.47 (ACV) to 0.85 and 0.72, respectively.	Prophylactic VLC at least as effective as ACV in preventing recurrences of HSK in patients who underwent PK.

Table 1 – 9 (continued)

First author (Year)	Name of study	Location	Aims	Study Design	Participants	Results	Recommendations
Simon (1996)	Long term oral acyclovir therapy. Effect on recurrent infectious herpes simplex keratitis in patients with and without grafts.	Boston, The USA	Evaluate efficacy of long- term PO ACV in reducing recurrences of epithelial HSK.	Retrospective and prospective trial.	13 patients with history of recurrent HSK followed before (27 months average) and during long term PO ACV. 8 were followed after ACV discontinued	Mean duration treatment was 34 months. Number of recurrences per month decreased from 0.15 to 0.03 and average duration of relapses from 12.6 to 7.8 days. Recurrences more likely in patients on doses less than 800 mg daily and with recent (6 weeks) ocular surgery.	Long-term prophylactic PO ACV is effective for preventing recurrent epithelial HSK. Therapeutic doses of PO ACV reduce rate and duration of recurrences.

1.4.4.8.3.6 Aciclovir resistance

Van Velzen et al. investigated whether long-term aciclovir prophylaxis is an important risk factor for aciclovir-refractory recurrent HSK due to aciclovir resistant HSV. [93] They found that 44% (34/76 eyes) of HSV-1 isolates from patients with HSK recurrence who received aciclovir prophylaxis for over a year, were aciclovir resistant. The authors recommended rationalising the long-term use of aciclovir for prevention of recurrent HSK. [93] Indeed, the risk of aciclovir resistance should be considered, especially for patients with history of stromal HSK who tend to have long-term antiviral and topical corticosteroid therapies. If the eye is not at risk, aciclovir prophylaxis may be stopped after a year of treatment and an aggressive treatment given in case of a subsequent recurrence. A combination therapy with topical and systemic antiviral medications may contribute to shorten disease duration and might lower the risk of emergence of drug-resistant viruses during therapy, as seen in other viral infections. [93] However, there is not sufficient good quality evidence to support this suggestion at present. For patients with resistant HSK and recurrent disease, an antiviral drug sensitivity testing with corneal swab is indicated to guide antiviral therapy. [93] However antiviral resistance testing may not be readily accessible in all locations.

1.4.4.8.3.7 Side effects of oral antiviral agents

Aciclovir and valaciclovir are well-tolerated medications. Side effects include nausea, vomiting, headache and gastro-intestinal discomfort. Dosage modification is required for patients with renal impairment as there is a risk of nephrotoxicity. [8] An animal study suggested that lower peak plasma concentrations of valaciclovir treatment may reduce the risk of renal side effects compared with aciclovir. [8]

Other side effects are thrombotic thrombocytopenic purpura/haemolytic uremia syndrome in severe immunocompromised patients. [23]

1.4.4.8.3.8 Consideration of antiviral medications in children

Young children tend to cry when receiving topical medications. The increased tear volume can dilute the medication reaching to the point that it is no longer effective.

Children present a stronger inflammatory reaction to HSV, more recurrences and higher incidence of stromal HSK increasing the risk of vision loss. Therefore, it is necessary to treat children with oral antiviral medications to ensure adequate therapeutic levels to avoid complications. [29] Safety and efficacy has been established for aciclovir in children (suspension presentation available in the USA). [23] Valaciclovir is indicated in children aged over 12 years as there is no data on its safety in children under the age of 12. [94]

See recommended antiviral doses on Appendix B, page 318, which were taken from the Australian Medical Handbook Children's Dosing Companion [95] and the British National Formulary for Children. [96]

1.4.4.8.3.9 Consideration of antiviral medications in pregnancy

Aciclovir, valaciclovir, and famciclovir belong to Pregnancy category B. [23, 97] Data on the safety of these antiviral medications during pregnancy is scarce. A nationwide registry-based cohort study was conducted in Denmark to determine any association between the use of these oral antiviral medications in the first trimester of pregnancy and major birth defects. The study concluded that women on aciclovir and valaciclovir in the first trimester of pregnancy do not have a higher risk of having children with major birth defects compared to the population. The authors did not comment on the safety of famciclovir as few women were treated with this medication. Aciclovir has been more extensively studied and should therefore be the first option during pregnancy. [97]

1.4.4.8.3.10 Consideration of antiviral medications in elderly patients

The AAO HSK treatment guideline recommended famciclovir over aciclovir or valaciclovir in patients aged over 65 with or without reduced renal function. [23] Famciclovir is a third-generation prodrug of the oral antiviral agent penciclovir. [98] The drug is a well-tolerated alterative to aciclovir and valaciclovir due to its efficacious pharmacokinetic profile. [99] It is an acyclic guanosine analogue, which is converted to penciclovir in the liver via deacetylation and oxidation, and mainly excreted by the kidneys. [98, 99] The absolute bioavailability of famciclovir is 77%, greater than

valaciclovir (55%) and oral aciclovir (15%-30%). The time to maximum observed plasma concentration is 0.9 hours for famciclovir compared to 1.71 hours for valaciclovir and 1.5 to 2.5 for oral aciclovir. The plasma elimination half-life ($t_{1/2}$) of penciclovir after oral administration of famciclovir is 2.3 hours similar to $t_{1/2}$ of aciclovir after oral administration of valaciclovir (2.6 hours) and $t_{1/2}$ of aciclovir of 3 hours after oral administration of aciclovir. [98]

Famciclovir may be preferred over valaciclovir or aciclovir due to its lower potential toxicity. [98] In patients over 65 years; aciclovir and valaciclovir can cause central nervous system adverse events such as agitation, hallucinations, confusion, and encephalopathy, and higher risk of acute renal failure compared to patients under 65 years of age. [23]

Despite the excellent pharmacokinetic profile and low toxicity of famciclovir over valaciclovir, a study found no significant differences between famciclovir and valaciclovir for the treatment of herpes zoster in immunocompetent patients over 50 years of age. [98, 100] Therefore, the ultimate choice among these two medications depends on their availability, tolerance, clinician's awareness, compliance and costs. In Australia, valaciclovir is still preferred over famciclovir for the treatment of HSK.

1.4.4.8.3.11 Consideration of antiviral medications in immunocompromised patients (HIV, transplant)

Three randomised clinical trials reported the efficacy and safety of aciclovir and valaciclovir in patients with HIV. Both medications were well-tolerated, and their safety profile was similar. However, there is a prescribing information warning for both antiviral medications: 'Valaciclovir has an increased risk of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in patients with HIV and in transplant (bone marrow and renal) recipients' and; 'Aciclovir has an increased risk thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in immunocompromised patients for any reason'. [23]

Solid organ transplant (SOT) recipients usually receive antiviral agents (ganciclovir, aciclovir, valaciclovir, or valganciclovir) for CMV prevention which also cover HSV. The only randomised clinical trials of HSV prophylaxis in SOT recipients were conducted in the 1980s and recommended aciclovir 200 mg, 3 to 4 times daily. A less frequent and higher dose of aciclovir, 400 mg to 800 mg twice daily, have been shown to be safe and effective in other immunocompromised patients (HIV and haematopoietic stem cell transplant) and is recommended due to their safety and easy administration. As there no specific studies for SOT recipients, this level of evidence was extrapolated from studies conducted to patients with similar level of immunosuppression. [25, 101, 102]

Moreover, patients with multiple HSV recurrences prior to the transplant should receive higher antiviral doses. Valaciclovir 500 mg twice daily was found to be superior to once daily when used as prophylaxis in this setting. Renal dosage adjustment for renal insufficiency is needed if the glomerular filtration rate (GFR) is less than 50 mL/min. As the majority of HSV disease occurs within the first month after transplantation, the antiviral prophylaxis should last for at least a month. For the treatment of HSK in the setting of solid organ transplantation, topical and oral antiviral agents can be used with topical corticosteroids for stromal and endothelial HSK. Valaciclovir and famciclovir can be used but there are no comparative or dose finding studies available. [25]

The available evidence supports for prevention of HSK in solid transplant recipients: [25]

- Aciclovir 400-800 mg twice daily.
- Valaciclovir 500 mg twice daily.

Recommendations for treatment of HSK in solid transplant recipients: [25]

- Topical:
    - Ganciclovir 0.15% 5 times daily until healing then three times daily for 1 week.

- Trifluridine: one drop, every 2 hours for 2 weeks. (Limited by epithelial toxicity)

- Oral:
  - Aciclovir 400 mg 5 times daily
  - Topical corticosteroids should be considered for stromal and endothelial HSK along with oral antiviral

1.4.4.8.3.12 Considerations for the use of antiviral medications in patients with impaired renal function

Oral antiviral medications must be used with caution in patients with impaired renal function and in this setting dose adjustment is required (See Table 1 - 10, page 76). [23]

Table 1 - 10: Adult renal dosing for oral antiviral medications (adapted from White and Chodosh [23]).

Key: CrCl=creatinine clearance, BD= twice daily, TDS=three times daily.

CrCl (mL/min)	Dose	Frequency
Normal dosage Valaciclovir 500mg ONCE a day		
<30	500 mg	Every 48 hours
Normal dosage Valaciclovir 500mg BD		
<30	500 mg	Every 24 hours
Normal dosage Valaciclovir 1g TDS		
30-49	1g	Every 12 hours
10-29	1g	Every 24 hours
<10	500 mg	Every 24 hours
Normal dosage Aciclovir 400mg BD		
0-10	200 mg	Every 12 hours

1.4.4.8.3.13 Use of antiviral medications for the treatment of HSK in clinical practice

The HEDS trials provided invaluable evidence to guide clinicians in the management of HSK. As new antiviral medications have been introduced into the market since the publication of these trials, current practice no longer aligns with evidence from the HEDS trials.

A study in New Zealand analysed the prescribing behaviour of ophthalmologists in the management of infectious keratitis. [103] A postal questionnaire with 23 multiple choice questions was sent to all ophthalmologists in the country. The response rate was 81% (75 of 93 ophthalmologists). The results were derived from 64 practitioners as 5 were no longer in regular clinical practice and 6 did not treat corneal or conjunctival disease. Treatment habits for epithelial HSK included debridement in 9.4% (n = 6) of respondents, topical aciclovir in 100% (n = 64), corticosteroid in 1.6% (n = 1), and antibiotic in 1.6% (n = 1). There were 63 respondents for endothelial HSK. Topical aciclovir was prescribed in 96.8% (n = 61) of respondents, corticosteroids in 98.4% (n = 62), antibiotic in 1.6% (n = 1), and cycloplegic in 9.7% (n = 6). [103]

Labetoulle et al. reported the incidence and clinical characteristics of HSK in France. During a 3-month period (September to December 2002), 412 ophthalmologists, representative of the 5471 French ophthalmologists, participated in the multicentre prospective study. Practitioners reported all HSK cases and completed an 18-item online questionnaire. Three hundred and fifty-seven events were reported by 160 ophthalmologists. The remaining ophthalmologists did not see patients with the inclusion criteria. Of 357 events, 349 (97.8%) received an antiviral treatment. The treatment was only topical in 57% of cases (n = 199) with either aciclovir, ganciclovir or trifluridine; only oral in 2.6% (n = 9) with either aciclovir or valaciclovir; and combined with topical and oral agents in 40.4% (n = 141) of cases. Thirty events of 357 (8%) were treated with a prophylactic dose of aciclovir or valaciclovir. [56]

These studies showed that the HEDS trials recommendations have been partially followed in different countries in the last two decades. These studies have limitations and their results are partially comparable among them. The respondents from New Zealand followed adequately the HEDS recommendations for epithelial HSK; but they prescribed topical aciclovir for endothelial HSK. It is not clear whether endothelial HSK also encompassed stromal HSK. Indeed, the HEDS clinical trials did not study endothelial HSK cases. The French study reported a diverse range of antiviral therapies given; but not the antiviral therapy per type of HSK. However, one could assume that, since 57% of cases received topical treatment and 56% of cases were diagnosed with dendritic keratitis, it is likely the topical treatment was given to dendritic cases. On the other hand, 2.6% of cases received only oral therapy and 40% combined oral and local agents. Stromal HSK was diagnosed in 29.5% of cases. Thus, respondents may have treated stromal HSK with a combination of agents, which is not recommended by the HEDS trials.

As shown in the above studies and seen anecdotally in the Sydney Eye Hospital, there is a gap in implementing clinical trials of HSK into everyday practice. Therefore, standardised updated treatment guidelines for HSK are warranted to improve health outcomes and reduce medical costs and adverse events.

1.4.4.9 Complications of HSK

Recurrent episodes of HSK, especially stromal, can lead to corneal scarring, thinning and perforation resulting in vision impairment and blindness.

1.4.4.9.1 Corneal scarring and vascularisation

The pathogenesis of corneal scarring and vascularisation is still uncertain. After the HSV infection, there is an inflammatory response as the polymorphonuclear leucocytes (PMN) invade the cornea secreting cytokines and angiogenic factors. This response clears the virus but allows the entry to various cytokines and angiogenic factors secreted by PMN. Co-ordinated-phenotypic changes, extracellular matrix deposition and remodeling are essential for corneal scarring. Several cytokines and growth factors play

a role in this process with epidermal growth factor and transforming growth factor beta being the most important. Angiogenesis has been demonstrated as early as 24 hours post-infection supporting the role of corneal vascularisation in the severity of HSK. HSV infection may alter the balance between angiogenic and anti-angiogenic stimuli leading to an ‘angiogenic switch’ initiating angiogenesis. HSV infection can produce many angiogenic factors including thrombospondins 1 and 2, vascular endothelial growth factor and fibrosing growth factor. Hypoxia due to corneal oedema may also trigger angiogenesis. PMN may be the main producers of these factors but vascular endothelial growth factor is also expressed in the cells of all corneal layers. The angiogenesis cascade seems to involve cytokine mediated and other paracrine effects. These findings support the hypothesis of the alteration of the normal balance between angiogenic and anti-angiogenic responses leading to corneal vascularization. [8, 22]

1.4.4.9.2 Neurotrophic keratopathy

Neurotrophic keratopathy relates to a persistent epithelial defect that progresses from punctate epithelial erosions, characterised by shallow smooth borders of grey, elevated, thickened and rolled epithelium in absence of infection or trauma. Ocular HSV disease is a major cause of neurotrophic keratopathy. Patients present with decreased corneal sensation, blink reflex and tear production due to the damage to the sensory fibres innervating the cornea. Corneal sensation is reduced during HSV infection through unclear mechanisms but probably involving the immune system and events that emerge within the sensory ganglion. After the infection is resolved, the cornea reinnervates with a different organisation of its fibres, peptidergic content or function. If the breakdown of the epithelium is not appropriately treated as soon it is diagnosed, it may lead to corneal scarring, thinning, vascularisation, perforation, or secondary corneal infection resulting in vision impairment or blindness. [8]

Treatments to promote epithelial growth include ocular lubricants, tarsorrhaphy, botulinum toxin-induced ptosis, growth factors and autologous plasma for early to moderate cases; and collagenase inhibitors, tissue adhesives, conjunctival flap, amniotic

membrane use and penetrating or lamellar keratoplasty for more severe and complicated cases. [8]

1.4.4.9.3 Microbial keratitis

Corneal abscesses are a major cause of monocular blindness worldwide. [104] Microbial keratitis accounts for 10% of preventable visual impairment in developing countries. [12] The annual incidence of corneal abscess in India has been reported to be 10 times the annual incidence in the USA. [104] Risk factors for microbial keratitis include contact lens wear (especially overnight wear), ocular trauma, ocular surgery, ocular surface disease (HSK, exposure, corneal anaesthesia, bullous keratopathy). [105-107] Contact lens wear is more common in developed countries; whereas ocular trauma during agricultural work is more common in developing countries. [12] Further, infection must be considered in immunocompromised patients or in patients with topical corticosteroid use. [105]

Signs and symptoms of microbial keratitis include redness, tearing, pain, sensitivity to light, decreased vision, discharge and white corneal infiltrate. Some signs have been described as unique to fungal keratitis or keratitis caused by specific bacteria. [108] Microbial keratitis due to bacteria (bacterial keratitis) typically presents with a corneal epithelial defect and stromal infiltrate. Stromal HSK with ulceration can be misdiagnosed as bacterial keratitis as they present with similar signs and symptoms. [23] Microbial keratitis and HSK can present together. An epithelial defect caused by HSV may predispose the cornea to a bacterial infection. In SHSK+U, severe inflammatory response may result in destructive inflammation leading to thinning and perforation especially where there is an associated bacterial infection. [8] Predisposing factors, causal organisms and outcomes of patients with microbial keratitis have been well described in the literature. [12] However, little is known about patients presenting with a concomitant microbial keratitis and HSK. Therefore, we aimed to describe this cohort from the Sydney Eye Hospital to elicit the predisposing factors, causal organisms, anti-microbial therapies and outcomes of these patients and compare these findings with other microbial keratitis case series.

Adequate diagnosis is essential for selecting the best anti-microbial therapy. Gram stain and culture of corneal scrapings are performed, despite their limited sensitivity before commencing empiric antibiotics. Gram stain is valuable as it provides fast results detecting the causal organism in 60% to 75% of bacterial cases and 35% to 90% of fungal cases. [12] Culture of corneal scrapings detects the causal organism in 50% to 65% of cases. [107, 109-116]

Selection of antibiotics depends on the typical organisms according to climate and geographic region. [117] Empiric antibiotics may be replaced by other antimicrobials depending on the results of the culture. The current recommendations for the initial treatment of bacterial keratitis in Australia, according to Therapeutic Guidelines – Antibiotic, Version 15, 2014 are: ciprofloxacin 0.3% (Ciloxan, Alcon, Australia) or ofloxacin 0.3% (Ocuflox, Allergan, Australia) or fortified cefalotin 5% plus gentamicin 0.9%. [118]

1.4.5 Summary

Herpes simplex virus can infect the cornea producing a 'keratitis'. Evidence-based management of HSK involves prescription of antiviral medications and in some cases anti-inflammatories. Anecdotally, there was a gap in implementing the treatment recommendations from RCTs into clinical practice at the hospital prior to 2013. Furthermore, there were studies reporting the lack of recent information on HSK treatment in clinical practice and a large variety of antiviral regimes. [56] We used the RNAO Toolkit "Implementation of Best Practice Guidelines" to evaluate current practice, develop and implement treatment guidelines for HSK in the Sydney Eye Hospital.

Herpes simplex virus is a double-stranded DNA virus belonging to the Herpes viridae family. The virus is transmitted through direct contact with oro-labial lesions or infected secretions or the saliva of asymptomatic individuals. Ocular manifestations of primary infection include conjunctivitis, blepharitis and corneal epithelial keratitis. The virus becomes latent in the ganglia which can re-emerge later in life. Studies have suggested that most middle-aged people and 100% of people over 60 years will harbor

the virus. One fifth of people with ocular HSV develop stromal HSK which can lead to corneal scarring and blindness.

The most important epidemiological study of ocular HSV disease was conducted in Rochester, Minnesota in 1982. The study reported that the overall incidence of all cases of HSK was 18.2 per 100,000 person-years (15.6 for new and recurrent epithelial HSK cases and 2.6 for new and recurrent stromal HSK cases) and 2.5 per 100,000 person-years for HSV uveitis. A more recent study conducted in France reported that the estimated the combined incidence of epithelial and stromal HSK was 31.2 per 100,000 person-years (22 for epithelial HSK and 9.2 for stromal HSK). Farooq and Shukla estimated the incidence of HSK at 23.3 per 100,000 person-years extrapolating data from the studies from the USA and France. Despite the increase of HSK incidence, the visual burden in developed countries apparently remains stable and is uncertain in developing countries due to lack of surveillance. [1] In addition, Farooq and Shukla estimated that at least 1.5% of HSK leads to vision worse than 20/200. Therefore, the estimated worldwide incidence of HSK in 2012 was about 1.5 million, with 40,000 new cases of severe monocular visual impairment or blindness each year. [18]

Ocular HSV disease is an important public health issue with limited therapeutic interventions. About 500,000 people have ocular HSV in the USA and the treatment of new and recurrent cases costs US$17.7 million per year. Patients with epithelial HSK need on average four follow up visits with an ophthalmologist and a patient with stromal HSK requires six. A doctor's visit causes a loss of one full day of work or leisure. An estimated 58 million days of work (444,000 in the USA) are lost treating ocular HSV worldwide. [18]

The Herpetic Eye Disease Study Group was a series of randomised clinical trials conducted in the USA in the 1990's that contributed to establishing evidence-based therapy for HSK. Subsequent clinical trials and a Cochrane review have added to the evidence base. Up to March 2014, when this project started, the evidence-base recommendations included the following. For epithelial HSK, the use of topical aciclovir 3% five times daily, topical trifluridine 1% 8 times daily, or oral aciclovir 400 mg three

to five times daily were recommended. [1, 7] For stromal HSK without ulceration, the use of a prophylactic antiviral medication such as topical trifluridine or oral aciclovir 400 mg twice daily given with 1% prednisolone eye drops (or equivalent topical therapy) every 2 hours, then tapered every 1 to 2 weeks, was supported by evidence. [1, 3] For endothelial HSK, there was insufficient clinical trial evidence and/or guidelines to recommend an appropriate antiviral dosage. However, we used the evidence from Porter et al. which supported the use of an antiviral agent such as aciclovir 400 mg five times daily plus a topical corticosteroid five times daily as a guide in our study. [88] To prevent episodes of HSK, aciclovir 400 mg twice daily for at least a year can reduce the rate of epithelial and stromal HSK episodes. [6]

Currently, there are other antiviral medications such as valaciclovir, ganciclovir, and famciclovir in the market used as an alternative to aciclovir and trifluridine for the treatment of active viral infections or for prophylaxis. However, except for ganciclovir gel for epithelial HSK, no clinical trials have been conducted to evaluate the appropriate dosage, frequency and safety in the treatment of HSK. Ganciclovir ophthalmic gel 0.15% has been first line therapy for epithelial HSK in the USA; but it is only available in Australia through the Therapeutics Goods Administration (TGA) Special Access Scheme. The cost of aciclovir tablets, aciclovir ointment and valaciclovir at the Sydney Eye Hospital is less than in a community pharmacy due to a hospital contract with the pharmaceutical company. Moreover, the cost of a valaciclovir tablet has decreased in the last two years coinciding with the expiry of the patent for a commercial brand Valtrex.

The AAO released in June 2014 a treatment guideline for HSK. The guideline included a complete guide to treat the different types of HSK, except keratouveitis, and recommendations to treat special groups of patients, for instance children, pregnant women, elderly and immunosuppressed patients. [23] This guideline was based on published clinical trial evidence and was centered on therapies available in the USA. Ganciclovir five times daily and trifluridine nine times daily were the recommended topical antiviral medications for epithelial HSK. Aciclovir, valaciclovir and famciclovir were the recommended oral agents for epithelial, SHSK+/-U, and endothelial HSK.

Aciclovir doses ranged from 400-800 mg twice to five times daily, valaciclovir from 500 mg to 1 g once to three times daily and famciclovir 250-500 mg twice daily.

Chapter 2 - Clinical translation of recommendations from randomised trials for the management of herpes simplex keratitis

2.1 Introduction

Herpes simplex keratitis is an important cause of unilateral infectious blindness in developed countries due to corneal opacification. [18] One fifth of people with ocular HSV infection develop corneal stromal disease with the attendant risk of blindness [1]. Despite HSK being an important public health issue, there are still limited therapeutic interventions available to reduce these complications and little is known of its treatment in the 'real world'.

The HEDS clinical trials, published in the 1990s, contributed significantly to determining regimens for the treatment and prevention of HSK (See Table 1 - 5, page 60; Table 1 - 7, page 65; and Table 1 - 8, page 66). [2-6] Since then, several randomised clinical trials (RCTs), a Cochrane review for the treatment of epithelial HSK and a systematic review for epithelial and stromal HSK have added to the evidence base (See Table 1 - 4, page 58). [1, 7] Treatment regimens differ for 'therapeutic' and 'prophylactic' use of antiviral therapy in HSK. As epithelial HSK is the manifestation of active replication of the virus in the epithelium, only antiviral agents are indicated. [19, 21] Stromal HSK +/- U, endothelial HSK and keratouveitis present as secondary infection. They are caused either from the reactivation of latent virus in the trigeminal ganglion or within the stroma, or from direct invasion from the epithelium along with a marked immune response. [22] Randomised clinical trials have supported the use of a prophylactic antiviral medication such as topical trifluridine or oral aciclovir given with topical corticosteroids for the management of stromal HSK without ulceration. [1, 3] For endothelial HSK, there is limited evidence; with only one clinical trial which has supported the use of an antiviral agent plus a topical corticosteroid in the management of HSK. [88]

As multiple episodes of stromal HSK may lead to corneal scarring and blindness; preventing future episodes is essential to avoid these complications. The HEDS research

group studied the effect of previous ocular HSV disease, demographic and other predictors in recurrent episodes. The study concluded that previous stromal HSK increases the risk of future episodes ten-fold, contrary to the risk of epithelial HSK. This was comparable among patients with and without previous epithelial HSK. Age, sex, ethnicity and non-ocular herpes were not significantly associated with recurrences. [119] Evidence supported that aciclovir 400 mg twice daily for at least a year can reduce the rate of epithelial and stromal HSK episodes. [6]

Anecdotally, diverse prescribing trends were seen at the Sydney Eye Hospital in 2013. Studies in France [56] and New Zealand [103] supported this, showing the translation of these recommendations have not been successful into clinical practice. It was proposed that this may be as the available evidence was outdated or not matched with newer available antiviral medications, and dosages not understood among clinicians. Further, little has been published on the management of HSK outside clinical trials. Therefore, the prescribing patterns for HSK will be reported in this chapter and whether the available evidence for the use of antiviral medication in HSK was appropriately translated into clinical practice at the Sydney Eye Hospital by clinicians with different levels of ophthalmology training.

2.2 Aim

The aim of the retrospective cohort study was to evaluate the treatment trends for HSK at the Sydney Eye Hospital in 2012 and 2013, and to compare these trends to treatment recommendations from published randomised clinical trials up to 2013.

2.3 Hypothesis

We hypothesised that the management of HSK was not evidence-based at the Sydney Eye Hospital up to 2013.

2.4 Methods

2.4.1 Study design

A retrospective cohort study was conducted. This design was chosen as a prospective study would have had the potential of influencing prescribing habits and would not have been achievable within the timeframe of the thesis. This project was conceived for a part-time Master of Philosophy degree for 3 to 4 years. After 5 semesters, the master was converted to full-time doctorate project and the work expanded.

This study was conducted at the Sydney Eye Hospital, a quaternary referral eye centre located in the central business district of Sydney, Australia that receives patients from across the state of New South Wales as inpatients and outpatients. Anecdotally, around 5 patients with HSK are seen and treated at the hospital weekly. To our knowledge, there have been no studies in Australia to date examining prescribing for HSK and only limited studies worldwide. [56, 103, 120]

A literature review was conducted and consensus between two corneal specialists reached to identify widely accepted clinical features of HSK and its sub-types. The diagnosis of HSK was then made using clinical features [1, 21, 60, 89] (See Table 2 - 1, page 87) documented in the medical records and when available positive laboratory tests.

Table 2 - 1: Clinical features of the sub-types of herpes simplex keratitis. [1, 21, 60, 89]

Type of keratitis	Clinical features
Epithelial	Dendritic or geographical ulcer
Stromal	Corneal stromal vascularisation, opacity, lipid keratopathy and/or ulceration
Endothelial	Stromal oedema and keratic precipitates
Keratouveitis	Corneal oedema, stromal keratitis, keratic precipitates, and anterior chamber cells.

2.4.2 Study population

The population of interest was patients prescribed antiviral therapy (See Table 2 - 2, page 88) for the treatment or prophylaxis of HSK. Patients were identified via a retrospective audit from 1 January 2012 to 31 December 2013 at the Sydney/Sydney Eye Hospital.

Table 2 - 2: Topical and oral antiviral medications prescribed to patients for HSK at the Sydney Eye Hospital.

Antiviral medication
Topical
Aciclovir
Trifluridine
Ganciclovir
Oral
Aciclovir
Valaciclovir
Famciclovir

2.4.2.1 Patient selection

Herpes simplex keratitis cases were identified via one of the following three methods:

(i) The South Eastern Area Laboratory Services (SEALS) microbiology dataset. This dataset contained records of patients who had a corneal swab or scrape taken for HSV PCR in 2012 and 2013 regardless of the test outcome.

(ii) The Sydney/Sydney Eye Hospital's pharmacy dataset. This dataset contained records of all out- and in-patients who were dispensed oral and topical antiviral medications listed above in Table 2 - 2, page 88.

(iii) The Sydney/Sydney Eye Hospital coding department's ICD-10 coding dataset. This dataset contained records of all admitted patients in 2012 and 2013 with a primary or additional diagnosis coded as Herpes viral ocular disease (B00.5) and Herpes viral keratitis and keratoconjunctivitis (H19.1).

A final database was derived from the above three datasets after cross-referencing to avoid duplication.

2.4.2.2 Inclusion and exclusion criteria

The medical records of all patients identified using the above methods were reviewed retrospectively. Patients were included if they fulfilled the following criteria;

(i) Age of 18 years or older and,

(ii) Antiviral therapy prescribed for the treatment or prevention of HSK.

Patients were excluded if they had an immunological corneal condition such as peripheral ulcerative keratitis (which is mainly associated with rheumatoid arthritis), an active bacterial co-infection or herpes zoster keratitis (HZK), to avoid confounding the diagnosis of HSK.

2.4.2.3 Patient subgroups

Patients were sub-grouped into those where the indication for the antiviral was treatment ('therapeutic') vs those receiving therapy for prophylaxis ('prophylactic') as follows;

- A 'therapeutic' indication for antiviral therapy was recorded when the patient presented with an active HSK episode. A guideline with signs of each type of HSK was made to help the primary investigator to classify the cases (See Table 2 - 1, page 87).

When the clinical findings documented on the medical notes did not match the signs above, the primary investigator confirmed with either the main or the associate investigator the type of keratitis.

- A 'prophylactic' indication for antiviral was recorded in the following scenarios:
  - There was no active HSK; or
  - The patient has undergone a surgery (e.g. cornea transplant or phacoemulsification) and had a history of HSK; or
  - The patient had a history of multiple HSK episodes and has been prescribed antiviral therapy to prevent recurrences.

2.4.3 Clinical trial evidence in Herpes Simplex Keratitis

A review of the literature, at the time of study commencement (March 2014) identified available evidence for the management of HSK from RCTs. The following 'guidelines' were determined to compare with the findings of our retrospective case series:

- For epithelial HSK: topical aciclovir 3% five times daily, topical trifluridine 1% 8 times daily, or oral aciclovir 400 mg three to five times daily. [1, 7]
- For stromal HSK without ulceration: prophylactic antiviral doses such as topical trifluridine or oral aciclovir 400mg twice daily given together with a topical steroid such as 1% prednisolone eye drops every 2 hours. Topical corticosteroids were then tapered every 1 to 2 weeks. [1, 3]
- For endothelial HSK: aciclovir 400 mg 5 times daily plus a topical corticosteroid five times daily. [88]
- For prophylaxis: aciclovir 400 mg twice daily for at least a year reduced the rate of epithelial and stromal HSK episodes. [6]

Because available randomised clinical trials did not evaluate valaciclovir; an equivalent dose to aciclovir was used. For therapeutic indications, the equivalent valaciclovir dose for aciclovir 400 mg 3 to 5 times daily was valaciclovir 500 mg 2 to 3

times daily. [8, 9] For prophylaxis, the equivalent valaciclovir dose was 500 mg once daily (See Table 2 - 3, page 91). [10]

Table 2 - 3: Summary of treatment recommendations for HSK from randomised clinical trials

Key: x5 = five times daily, x8 = eight times daily, BD = twice daily, TDS = three times daily, q2h = every two hours.

Indication	Antiviral therapy	Topical corticosteroid therapy
Epithelial HSK [1, 7]	Topical aciclovir 3% x5 Oral aciclovir 400mg x5 Topical trifluridine 1% x8 Valaciclovir 500mg BD-TDS	
SHSK-U [1, 3]	Oral aciclovir 400mg BD Valaciclovir 500mg OD Topical trifluridine 1% x8	Prednisolone acetate 1% q2h, drops tapered every 1-2 weeks depending on clinical improvement
Endothelial HSK [88]	Oral aciclovir 400mg x5 Valaciclovir 500mg BD-TDS	Prednisolone acetate 1% q2h, drops tapered every 1-2 weeks depending on clinical improvement
Prophylaxis [6]	Aciclovir 400mg BD Valaciclovir 500mg OD	

2.4.4 Data collection

2.4.4.1 Database design

Study data were collected and managed using REDCap (Research Electronic Data Capture), an electronic data capture tool hosted at The University of Sydney. REDCap is a secure, web-based application designed to support data capture for

research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. [121]

The REDCap database was set up based on the primary and secondary variables of interest at inclusion and primary and secondary outcome measures defined for the study (see below). Data was recorded directly into REDcap from the clinical case notes.

2.4.4.2 Data

2.4.4.2.1 Primary variables of interest at inclusion

Primary variables of interest were collected from the first recorded visit within the study inclusion period. These included the type, form, and dosage of antiviral prescribed. The clinical indication for the chosen antiviral (whether therapeutic or prophylactic), and the specific clinical diagnosis based on clinical features (See Table 2 - 1, page 87), were also documented (See Appendix C, page 321).

2.4.4.2.2 Secondary variables of interest at inclusion

These included basic demographic characteristics for each participant (date of birth, gender, country of birth and place of residence,[122] as well as relevant medical and ocular history and type of prescriber (See Appendix C, page 321).

2.4.4.2.3 Primary outcome measures

The main study outcomes were the initial antiviral therapy prescribed and proportion of patients receiving initial antiviral therapy in line with the ‘guidelines’ (See Appendix C, page 321).

2.4.5 Definitions

a) Postcode

Postcodes were not recorded as four-digit numbers due to ethics committee advice that when combined with the date of birth, gender, and country of birth a patient could potentially be identified. Area codes were therefore used (See Appendix D, page 330). The 22 codes were postcode clusters (PCC) each containing a number of adjacent postcodes defined by The Department of Environment, Climate Change and Water (DECCW). [123] Two codes were added for overseas (code 23) and interstate patients (code 24).

b) Types of prescriber

Sydney Eye Hospital is a teaching hospital and quaternary referral eye care centre which employs medical practitioners at different levels of ophthalmologic training/career. The medical practitioners were therefore grouped into four categories: consultant, fellow, registrar, and resident.

A ‘consultant’ was a medical practitioner who had completed their training in ophthalmology and had been awarded fellowship of the Royal Australian and New Zealand College of Ophthalmologists (RANZCO). At the Sydney Eye Hospital, consultants have generally also undertaken sub-specialty training in ophthalmology. A ‘fellow’ was a doctor who completed their training in ophthalmology either here in Australia with RANZCO or equivalent training overseas and was undertaking a fellowship (sub-specialty training). A ‘registrar’ was a doctor undertaking ophthalmic training with the RANZCO training program. A ‘resident’ was a doctor undertaking a year of prevocational training. Prevocational training refers to the first three years of training after graduating from university.

2.4.6 Data analysis

Descriptive statistics will be used to summarise all continuous and categorical variables. Clinicians who followed the ‘guidelines’ were compared with clinicians who

did not follow the guidelines for epithelial HSK, SHSK-U, endothelial HSK and HSK prophylaxis, using tests of proportions (Fisher's Exact or Chi-square tests). A *p*-value < 0.05 was considered as evidence of statistical significance. The statistical software used was IBM SPSS Statistics Desktop Version 22 (IBMCorp, Armork, NY).

2.4.7 Human research ethics

Ethics approval for this research was sought and granted from the South Eastern Sydney Local Health District Human Research Ethics Committee (approval number HREC 13/296) shown on Appendix E, page 334. Data are reported in line with the STROBE statement for observational data. [124] The research adhered to the Tenets of the Declaration of Helsinki. All research was conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

A first amendment to ethics was granted approving REDCap online application as the study database (See Appendix F, page 336) in October 2014. A second amendment to ethics was granted in July 2015. This amendment sought the approval to send a letter to the private rooms of some ophthalmologists. Many patients were only admitted at the hospital for one-day surgery and there was missing information in the hospital's medical records for some of the variables in our study. A letter was sent with a form requesting the missing data for the doctors to complete if they had the corresponding information (See Appendix G, page 338).

2.5 Results

After cross-referencing the datasets, 1765 medical records were identified and reviewed to determine their eligibility for the study. (See Figure 2 - 1, page 95).

Most of the reviewed medical records (83%) were excluded from the study as the initial diagnosis was not HSK, despite having an HSV PCR test performed or being treated with antiviral medications. PCR was requested at our institution not only in patients with presumed HSK diagnoses but also for several other eye conditions including blepharitis, conjunctivitis, non-infective keratitis, punctate epithelial erosions,

epithelial defect, corneal abrasion, episcleritis, anterior uveitis, herpetic neuralgia and HSV-like skin lesions.

Moreover, antiviral medications were not only prescribed for HSK but also for other ocular viral infections. From the pharmacy records, patients with HZV and CMV infections, as well as HSK with associated bacterial infection were identified. These were excluded from the study.

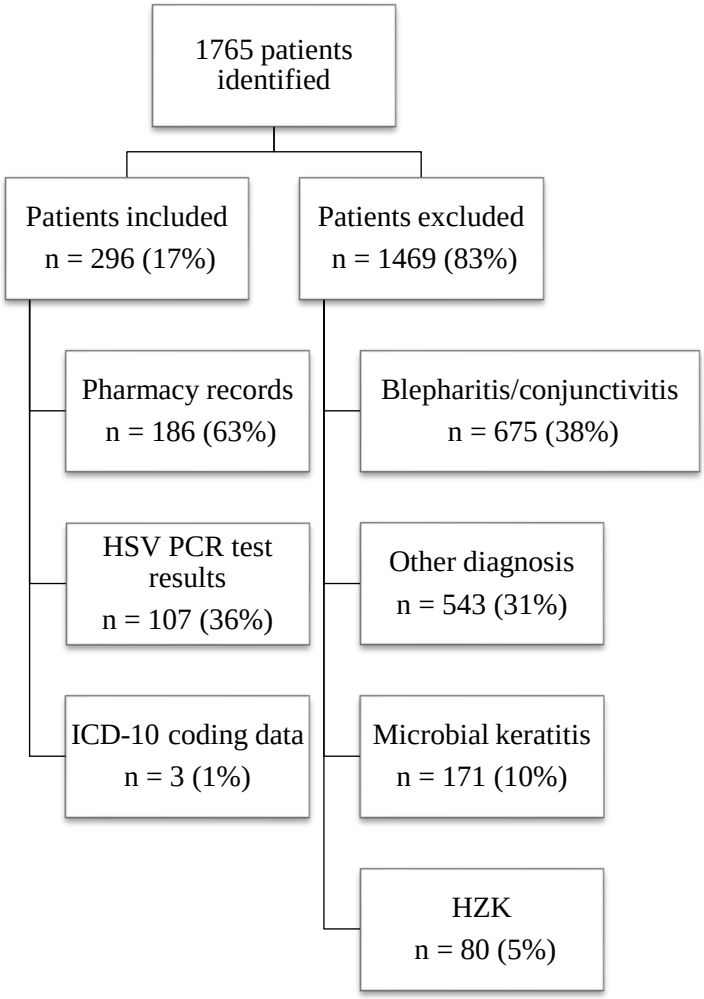


Figure 2 - 1: Eligibility for inclusion of patients in the study.

Key: n = number of patients, HSV = herpes simplex virus, HZK = herpes zoster keratitis, ICD-10 = international classification of diseases 10th revision, PCR = polymerase chain reaction.

2.5.1 Demographics

Included in the study were 301 eyes from 296 patients. Of these, 256 (85%) eyes received antiviral therapy for therapeutic indications and 45 (15%) eyes for prophylaxis. The demographics of the patients are shown in Table 2 - 4, page 96. Five patients were diagnosed with bilateral HSK at presentation.

Table 2 - 4: Socio-demographic characteristics of patients treated for HSK per antiviral indication (n = 296).

Key: n = number of patients, NSW = New South Wales, SD = standard deviation.

	Indication	
	Therapeutic	**Prophylactic**
n (%)	252 (85)	44 (15)
Age in years		
Mean (SD)	52 ±19	65±17
Range	19 to 89	25 to 94
Gender, Male [n, (%)]	153 (61)	22 (50)
Residence [n, (%)]		
Within greater Sydney	228 (90.5)	29 (66)
Outside greater Sydney but within NSW	21 (8.3)	15 (34)
Victoria	2 (0.80)	0
Overseas	1 (0.4)	0

The postcode clusters for the included patients are shown in Table 2 - 5, page 97. Patients with a therapeutic indication mainly resided in Sydney city, north, north coast clusters (n = 137, 54%); while, patients with a prophylactic indication mainly resided in west central, city, north coast and south west (n = 20, 45%) Sydney. Fifty-six countries were identified as country of birth of the patients with therapeutic and prophylactic

indication (See Table 2 - 6, page 98). Overall for both indications, 151 of 296 patients (51%) were born in Australia.

Table 2 - 5: Postcode clusters of patients treated for HSK per antiviral indication (n = 296).

Key: n = number of patients.

The numbers in bold represent most common postcode clusters.

Postcode cluster	Indication	
	Therapeutic n (%)	Prophylactic n (%)
Central Coast	3 (1.2)	2 (4.5)
Central West	1 (0.4)	2 (4.5)
Hunter	3 (1.2)	1 (2.3)
Mid North Coast	2 (0.8)	1 (2.3)
Murrumbidgee	0 (0)	1 (2.3)
Newcastle	2 (0.8)	0 (0)
North West	0 (0)	1 (2.3)
Northern	1 (0.4)	3 (6.8)
Overseas	2 (0.8)	0 (0)
South Coast	3 (1.2)	1 (2.3)
South East	3 (1.2)	2 (4.5)
Sydney city	**76 (30.2)**	**5 (11.4)**
Sydney Hills	8 (3.2)	1 (2.3)
Sydney Inner West	24 (9.5)	3 (6.8)
Sydney North	**33 (13.1)**	3 (6.8)
Sydney North Coast	**28 (11.1)**	**5 (11.4)**
Sydney North West	11 (4.4)	0 (0)
Sydney South	18 (7.1)	2 (4.5)

Table 2 - 5 (continued)

Postcode cluster	Indication	
	Therapeutic n (%)	**Prophylactic n (%)**
Sydney South West	12 (4.8)	**4 (9.1)**
Sydney West Central	18 (7.1)	**6 (13.6)**
Victoria	1 (0.4)	0 (0)
Wollongong	3 (1.2)	1 (2.3)
Total	**252 (100)**	**44 (100)**

Table 2 - 6: Country of birth of patients treated for HSK per antiviral indication (n = 296).

Key: n = number of patients.

Numbers in bold represent most common countries of birth.

Country of birth	Indication	
	Therapeutic n (%)	**Prophylactic n (%)**
Australia	**125 (49.6)**	**26 (59.1)**
Brazil	3 (1.2)	0 (0)
Canada	2 (0.8)	0 (0)
Chile	3 (1.2)	0 (0)
China	**12 (4.8)**	1 (2.3)
Colombia	2 (0.8)	0 (0)
Cyprus	2 (0.8)	0 (0)
Egypt	3 (1.2)	0 (0)
Federal Republic of Yugoslavia	2 (0.8)	1 (2.3)
Fiji	2 (0.8)	1 (2.3)
Germany	5 (2)	1 (2.3)

Table 2 – 6 (continued)

Country of birth	Indication	
	Therapeutic n (%)	**Prophylactic n (%)**
Greece	4 (1.6)	3 (6.8)
Hong Kong	2 (0.8)	1 (2.3)
Hungary	1 (0.4)	1 (2.3)
India	6 (2.4)	1 (2.3)
Indonesia	2 (0.8)	0 (0)
Iraq	2 (0.8)	1 (2.3)
Ireland	3 (1.2)	1 (2.3)
Italy	5 (2)	0 (0)
Lebanon	2 (0.8)	0 (0)
Malaysia	2 (0.8)	0 (0)
Malta	2 (0.8)	0 (0)
The Netherlands	3 (1.2)	0 (0)
New Zealand	**11 (4.4)**	1 (2.3)
The Philippines	2 (0.8)	0 (0)
Poland	2 (0.8)	0 (0)
Portugal	3 (1.2)	0 (0)
South Africa	2 (0.8)	0 (0)
The United Kingdom	**16 (6.3)**	2 (4.5)
Other	21 (8.3)	3 (6.8)
Total	**252 (100)**	**44 (100)**

Other therapeutic: Bangladesh (1), Cote D'Ivoire (1), Czech Republic (1), Former Republic of Macedonia (1), Japan (1), Mauritius (1), Norway (1), Pakistan (1), Papua New Guinea (1), Russian Federation (1), Samoa (1), Senegal (1), Singapore (1), Sri Lanka (1), Switzerland (1), Syria (1), Thailand (1), Tonga (1), The USA (1), Unknown (1), Vietnam (1).

Other prophylactic: Belgium (1), Iran (1), Slovenia (1)

2.5.2 Therapeutic indication

2.5.2.1 Prescribing trends

Of the 256 eyes (252 patients) treated with antiviral medications for a therapeutic indication, 141 (55%), 22 (9%), 22 (9%), 18 (7%) and 53 (21%) eyes were diagnosed with epithelial, SHSK+U, SHSK-U, endothelial HSK or herpetic keratouveitis, respectively. There were 4 patients with bilateral HSK; two were diagnosed with epithelial HSK and one of these patients was treated with valaciclovir 1 g three times and the other with topical aciclovir five times daily on each eye; 1 had SHSK+U treated with valaciclovir 500 mg twice daily; and 1 with keratouveitis treated with valaciclovir 1 g three times daily. Only the patient diagnosed with SHSK+U was immunosuppressed as they had a history of oral prednisone use for systemic lupus erythematosus. We excluded one eye of each bilateral case for analysis to avoid confounding.

2.5.2.1.1 Prescribing trends for epithelial HSK

Of the 139 patients with epithelial HSK, 112 (80.6%) received topical aciclovir five times daily. The remaining 27 (19.4%) were either given an oral antiviral medication or a combination of oral and topical antiviral medications (See Table 2 - 7, page 104). Valaciclovir was the most commonly prescribed oral antiviral medication, with doses ranging from 500 mg to 1g, once to three times daily.

Topical corticosteroids are not part of a first line of treatment for epithelial HSK. Topical corticosteroids were prescribed with antiviral agents in 13 of the 139 (9.4%) patients (See Table 2 - 8, page 106). Preserved dexamethasone 0.1% ophthalmic suspension (Maxidex, Alcon, The USA) (n = 3), preserved prednisolone acetate 1%, and phenylephrine hydrochloride 0.12% ophthalmic suspension (Prednefrin Forte, Allergan, Australia) (n = 3) and unpreserved dexamethasone sodium phosphate 0.1% ophthalmic solution (Minims dexamethasone sodium phosphate) (n = 3), were the preferred agents. Topical corticosteroids were prescribed at varying frequencies, including once, twice, three times, four times per day, once at night, or every one or two hours.

Reasons for prescribing topical corticosteroids included a history of previous HSK [n = 3 (2%)] and history of a corneal graft [n = 7 (5%)]. Other reasons were as follows: one patient (0.7%) had a history of recent cataract surgery and was on current topical corticosteroid therapy. One patient (0.7%) was diagnosed with uveitis one month prior to presentation and had been on topical corticosteroid therapy once daily. One patient (0.7%) with a history of laser *in situ* keratomileusis surgery was diagnosed with epithelial HSK two days prior to the presentation and was treated with topical aciclovir elsewhere. He developed ocular toxicity and presented to Sydney Eye Hospital where topical corticosteroids and oral valaciclovir were commenced.

Adherence to the 'guidelines' was found in 124 of the 139 (89%) patients with epithelial HSK. Eight patients who also received topical corticosteroids were included in this group, if they had received the antiviral medication according to the 'guidelines' for antiviral medication.

2.5.2.1.2 Prescribing trends for stromal HSK with ulceration

For SHSK+U, 9 of 21 (42.9%) patients received topical aciclovir five times daily. Oral valaciclovir was given to 7 (33.3%) patients in doses ranging 500 mg to 1g twice to three times daily. One patient received valaciclovir, but the dosage was not documented on the medical records. The remaining 4 patients (19%) received a combination of oral valaciclovir and topical aciclovir 5 times daily (See Table 2 - 7, page 104). In addition, 5 (23.8%) patients received topical corticosteroids (See Table 2 - 8, page 106). Preserved prednisolone acetate 1% (n = 2) and unpreserved prednisolone sodium phosphate ophthalmic suspensions (n = 2), both given twice daily were the most frequently prescribed topical corticosteroids. A comparison to guidelines for this type of keratitis could not be made, as no treatment recommendations for this condition were found in the literature at study commencement.

2.5.2.1.3 Prescribing trends for stromal HSK without ulceration

For SHSK-U, 9 of the 22 patients (40.9%) patients received topical aciclovir five times daily and 5 (22.7%) patients received valaciclovir 500 mg twice daily. Oral, topical or a combination of topical and oral antiviral agents was given to 8 patients (36.4%) (See Table 2 - 7, page 104). Further, 10 (45.5%) patients received topical corticosteroids (See Table 2 - 8, page 106). Preserved dexamethasone 0.1% (n = 3) four times daily was the most common prescribed topical corticosteroid.

Adherence to the 'guidelines' for antiviral therapy was found in 2 of 22 (9.1%) patients with SHSK-U.

2.5.2.1.4 Prescribing trends for endothelial HSK

For endothelial HSK, 14 (77.8%) patients received valaciclovir in doses ranging from 500 mg twice daily to 1 g twice or three times daily. Two of 18 (11.1%) patients received topical aciclovir five times daily and the remaining 2 (11.1%) patients, oral aciclovir twice or five times daily (See Table 2 - 7, page 104). Seventeen of the 18 (94%) patients also received topical corticosteroids (See Table 2 - 8, page 106). Preserved prednisolone acetate 1% and phenylephrine hydrochloride 0.12% ophthalmic suspension was the most common topical corticosteroid; it was prescribed in 8 patients at a frequency of four times, six times or every hour daily.

Adherence to the 'guidelines' was found in 6 of 18 (33%) patients with endothelial HSK.

2.5.2.1.5 Prescribing trends for keratouveitis

For keratouveitis, 29 of 52 (55.8%) patients received valaciclovir in doses ranging from 500 mg to 1 g once, twice or three times daily. Five (9.6%) patients received oral aciclovir in doses ranging from 200 to 400 mg five times daily. Eleven (21.2%) patients received topical aciclovir five times daily and the remaining 7 (13.5%) combined oral and topical antiviral medication (See Table 2 - 7, page 104). Topical corticosteroids were also given in 32 patients (61.5%) (See Table 2 - 8, page 106).

Preserved prednisolone acetate 1% and phenylephrine hydrochloride 0.12% ophthalmic suspension was the most common medication (n = 20 eyes), prescribed at frequencies including four and six times, every hour and every two hours.

A comparison to guidelines for keratouveitis could not be made, as no treatment recommendations for this condition were found in the literature at study commencement. However, diverse prescribing was noted.

Table 2 - 7: Antiviral therapies prescribed for therapeutic indication per type of HSK.

Key: x5 = five times daily, ACV = aciclovir, BD = twice daily, HSK = herpes simplex keratitis, n = number of patients, Occ = topical, od = once daily, q2h = every 2 hours, QID = four times daily, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration, TDS = three times daily, TFT = trifluridine, VLC = valaciclovir.

Numbers in bold represent dosages aligned to the 'guidelines'

Antiviral therapy	**Type of HSK**					
	Epithelial n (%) †	**SHSK+U n (%) †**	**SHSK-U n (%) †**	**Endothelial n (%) †**	**Keratouveitis n (%) †**	**Total n (%)**
Oral						
VLC 500 mg od	1 (0.7)		**2 (9.1)**		1 (1.9)	4 (1.6)
VLC 500 mg BD	**9 (6.5)**	2 (9.5)	5 (22.7)	**5 (27.8)**	5 (9.6)	26 (10.3)
VLC 500 mg TDS	**3 (2.2)**	2 (9.5)	1 (4.5)		7 (13.5)	13 (5.2)
VLC 1g BD		1 (4.8)	1 (4.5)	1 (5.6)		3 (1.2)
VLC 1g TDS	2 (1.4)	2 (9.5)	1 (4.5)	8 (44.4)	16 (30.8)	29 (11.5)
ACV 200 mg x5					1 (1.9)	1 (0.4)
ACV 400 mg BD				1 (5.6)		1 (0.4)
ACV 400 mg x5				**1 (5.6)**	4 (7.7)	5 (2)

Table 2 – 7 (continued)

Antiviral therapy	Epithelial n (%) †	SHSK+U n (%) †	SHSK-U n (%) †	Endothelial n (%) †	Keratouveitis n (%) †	Total n (%)
VLC no dose specified		1 (4.8)				1 (0.4)
Topical						
Occ ACV BD	1 (0.7)		1 (4.5)			2 (0.8)
Occ ACV TDS	1 (0.7)					1 (0.4)
Occ ACV QID	3 (2.2)					3 (1.2)
Occ ACV x5	**112 (80.6)**	9 (42.9)	9 (40.9)	2 (11.1)	11 (21.2)	143 (56.7)
Combinations						
VLC 500 mg BD + Occ ACV TDS					1 (1.9)	1 (0.4)
VLC 500 mg BD + Occ ACV x5	1 (0.7)	1 (4.8)	1 (4.5)			3 (1.2)
VLC 500 mg TDS + Occ ACV QID	1 (0.7)					1 (0.4)
VLC 500 mg TDS + Occ ACV x5					1 (1.9)	1 (0.4)
VLC 1g BD + Occ ACV x5	1 (0.7)		1 (4.5)			2 (0.8)
VLC 1g TDS + Occ ACV x5	2 (1.4)	3 (14.3)			5 (9.6)	10 (4)
VLC 1g TDS + TFT q2h	1 (0.7)					1 (0.4)
ACV 400 mg x5 + Occ ACV x5	1 (0.7)					1 (0.4)
Grand total	139 (100)	21 (100)	22 (100)	18 (100)	52 (100)	252 (100)

† (%) percentage calculated from total cases of each type of keratitis

Table 2 - 8: Topical corticosteroids prescribed per antiviral therapy indication.

Key: BD = twice daily, HSK= herpes simplex keratitis, n = number of patients, od = once daily, q1h = every hour, q2h = every 2 hours, QID = four times daily, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration, TDS = three times daily.

Topical corticosteroid and dosage regimen	**Epithelial HSK (n = 139)**	**SHSK+U (n = 21)**	**SHSK-U (n = 22)**	**Endothelial HSK (n = 18)**	**Kerato-uveitis (n = 52)**	**HSK prophylaxis (n = 44)**	**Total patients (n = 296)**
Preserved fluorometholone acetate 0.1% [n, %)] †							
BD						1 (2.3)	1 (0.3)
Preserved fluorometholone 0.1% [n, (%)] †							
od	1 (0.7)		1 (4.5)			7 (15.9)	9 (3)
BD	1 (0.7)					3 (6.8)	4 (1.4)
QID			1 (4.5)	1 (5.6)			2 (0.7)
Six times daily					1 (1.9)		1 (0.3)
Every other day od						3 (6.8)	3 (1)
Preserved dexamethasone 0.1% [n, (%)] †							
OD	2 (1.4)					2 (4.5)	4 (1.4)

Table 2 – 8 (continued)

Topical corticosteroid and dosage regimen	Epithelial HSK (n = 139)	SHSK+U (n = 21)	SHSK-U (n = 22)	Endothelial HSK (n = 18)	Kerato-uveitis (n = 52)	HSK prophylaxis (n = 44)	Total patients (n = 296)
BD			1 (4.5)			5 (11.4)	6 (2)
TDS	1 (0.7)		1 (4.5)	1 (5.6)		1 (2.3)	4 (1.4)
QID			3 (13.6)	5 (27.8)	5 (9.6)	4 (9.1)	17 (5.7)
q1h					1 (1.9)		1 (0.3)
q2h			1 (4.5)		1 (1.9)		2 (0.7)
Six times daily				1 (5.6)	2 (3.8)		3 (1)
Preserved prednisolone acetate 1% [n, (%)] †							
od						1 (2.3)	1 (0.3)
BD		2 (9.5)				1 (2.3)	3 (1)
TDS	1 (0.7)						1 (0.3)
QID	1 (0.7)		1 (4.5)	4 (22.2)	10 (19.2)		16 (5.4)
q1h		1 (4.8)		2 (11.1)	5 (9.6)		8 (2.7)
q2h	1 (0.7)				4 (7.7)		5 (1.7)
Six times daily				2 (11.1)	1 (1.9)		3 (1)
Every other day OD						1 (2.3)	1 (0.3)

Table 2 – 8 (continued)

Topical corticosteroid and dosage regimen	Epithelial HSK (n = 139)	SHSK+U (n = 21)	SHSK-U (n = 22)	Endothelial HSK (n = 18)	Kerato-uveitis (n = 52)	HSK prophylaxis (n = 44)	Total patients (n = 296)
Unpreserved prednisolone sodium phosphate [n, (%)] †							
BD		2 (9.5)				3 (6.8)	5 (1.7)
TDS						1 (2.3)	1 (0.3)
QID	1 (0.7)					1 (2.3)	2 (0.7)
Unpreserved dexamethasone sodium phosphate [n, (%)] †							
BD						1 (2.3)	1 (0.3)
TDS	1 (0.7)						1 (0.3)
QID	1 (0.7)					1 (2.3)	2 (0.7)
q1h	1 (0.7)			1 (5.6)	1 (1.9)		3 (1)
q2h					1 (1.9)	1 (2.3)	2 (0.7)
Hydrocortisone ointment [n, (%)] †							0 (0)
od			1 (4.5)				1 (0.3)
Night	1 (0.7)					1 (2.3)	2 (0.7)
Total	13 (9.4)	5 (23.8)	10 (45.5)	17 (94.4)	32 (61.5)	38 (86.4)	115 (38.9)

Table 2 – 8 (continued)

† (%) percentage calculated from total cases of each indication shown on column header

Topical steroids were prescribed daily.

2.5.2.2 Type of prescribers for therapeutic indications

One hundred and sixty-one of 252 (63.9%) patients were treated by a registrar and 91 (36.1%) by another medical practitioner (consultant, fellow or resident). The number of treated patients per prescriber is shown in Figure 2 - 2, page 110

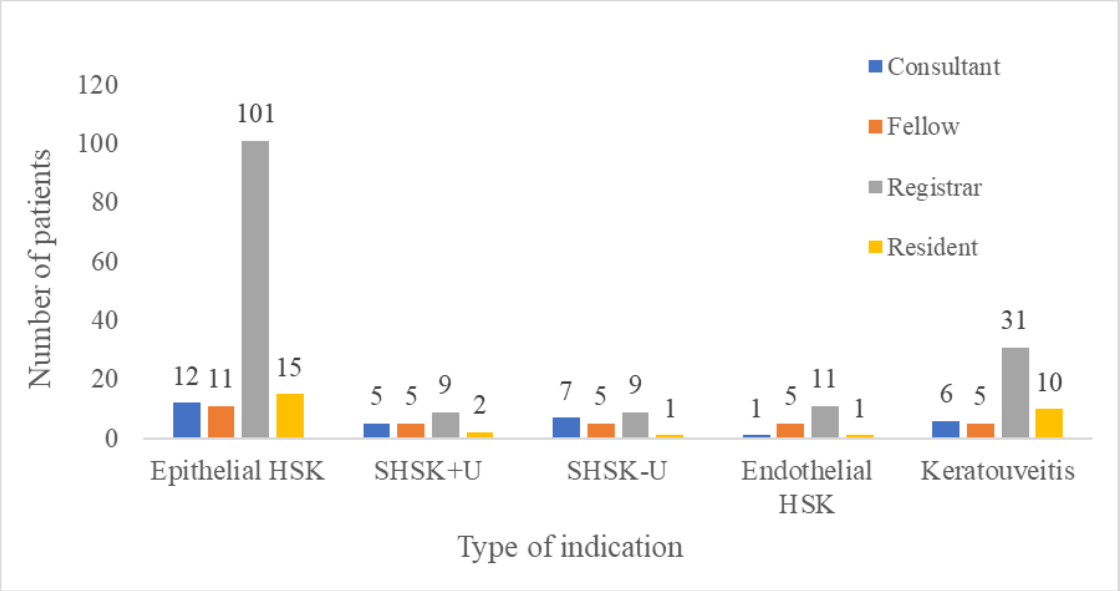


Figure 2 - 2: Number of treated patients by prescriber type.

2.5.2.2.1 Type of prescribers for epithelial HSK

One hundred and twenty four of 139 patients (89%) with epithelial HSK received an antiviral therapy aligned with the ‘guidelines’. All prescribers treated most of their patients in accordance to the ‘guidelines’ as follows: 9 of 12 patients (75%) by consultants, 8 of 11 (72%) by fellows, 92 of 101 (91%) by registrars, and 15 of 15 (100%) by residents (p = 0.05) (See Table 2 - 9, page 111).

Table 2 - 9: Antiviral therapy vs type of prescriber for epithelial HSK patients.

Key: x5 = five times daily, n = number of patients, ACV = aciclovir, BD = twice daily, Occ = ointment, od = once daily, q2h = every two hours, QID = four times daily, TDS = three times daily, VLC = valaciclovir.

Antiviral therapy	Consultant	Fellow	Registrar	Resident	Total
	[n, (%)]	[n, (%)]	[n, (%)]	[n, (%)]	[n, (%)]
Oral					
VLC 500 mg od		1 (9.1)			1 (0.7)
VLC 500 mg BD	**3 (25)**	**2 (18.2)**	**3 (3)**	**1 (6.7)**	**9 (6.5)**
VLC 500 mg TDS	**2 (16.7)**		**1 (1)**		**3 (2.2)**
VLC 1g TDS		1 (9.1)	1 (1)		2 (1.4)
Topical					
Occ ACV BD			1 (1)		1 (0.7)
Occ ACV TDS			1 (1)		1 (0.7)
Occ ACV QID	1 (8.3)		2 (2)		3 (2.2)
Occ ACV x5	**4 (33.3)**	**6 (54.5)**	**88 (87.1)**	**14 (93.3)**	**112 (80.6)**
Combinations					
VLC 500 mg BD + Occ ACV x5			1 (1)		1 (0.7)
VLC 500 mg TDS + Occ ACV QID			1 (1)		1 (0.7)
VLC 1g BD + Occ ACV x5			1 (1)		1 (0.7)
VLC 1g TDS + Occ ACV x5	1 (8.3)		1 (1)		2 (1.4)
VLC 1g TDS + TFT q2h	1 (8.3)				1 (0.7)
ACV 400 mg x5 + Occ ACV x5		1 (9.1)			1 (0.7)
Total	**12 (100)**	**11 (100)**	**101 (100)**	**15 (100)**	**139 (100)**

Bold figures represent patients that met the ‘guidelines’

% calculated based on total number of patients treated by each prescriber.

2.5.2.2.2 Type of prescribers for stromal HSK with ulceration

A comparison with the ‘guidelines’ was not made as there were no available recommendations in the literature for this condition. However, the antiviral therapy was diverse with seven different regimens identified. Registrars prescribed mainly topical aciclovir five times daily (77.8%); while consultants prescribed valaciclovir 500 mg

three times daily (40%), and fellows, valaciclovir 1 g three times daily (40%) or a combination of valaciclovir 1g three times daily and topical aciclovir five times daily (40%) (See Table 2 - 10, page 112).

Table 2 - 10: Antiviral therapy vs type of prescriber for stromal HSK with ulceration patients.

Key: x5 = five times daily, n = number of patients, ACV = aciclovir, BD = twice daily, Occ = ointment, BD = twice daily, TDS = three times daily, VLC = valaciclovir.

Antiviral therapy	**Consultant**	**Fellow**	**Registrar**	**Resident**	**Total**
	[n, (%)]	[n, %)]	[n, (%)]	[n, (%)]	[n, (%)]
Oral					
VLC 500mg BD	1 (20)		1 (11.1)		2 (9.5)
VLC 500mg TDS	2 (40)				2 (9.5)
VLC 1g BD	1 (20)				1 (4.8)
VLC 1g TDS		2 (40)			2 (9.5)
VLC no dose specified			1 (11.1)		1 (4.8)
Topical					0 (0)
Occ ACV x5		1 (20)	7 (77.8)	1 (11.1)	9 (42.9)
Combinations					0 (0)
VLC 500mg BD + Occ ACV x5	1 (20)				1 (4.8)
VLC 1g TDS + Occ ACV x5		2 (40)		1 (11.1)	3 (14.3)
Total	5 (100)	5 (100)	9 (100)	2 (22.2)	21 (100)

% calculated based on total number of patients treated by each prescriber.

2.5.2.2.3 Type of prescribers for stromal HSK without ulceration

Two of 22 patients (9%) with SHSK-U received an antiviral therapy aligned with the ‘guidelines’. One consultant (14%) and one registrar (11%) prescribed valaciclovir 500 mg once daily as recommended per the ‘guidelines’ (p = 0.832) (See Table 2 - 11, page 113).

Table 2 - 11: Antiviral therapy vs type of prescriber for stromal HSK without ulceration patients.

Key: x5 = five times daily, n = number of patients, ACV = aciclovir, BD = twice daily, Occ = ointment, od = once daily, TDS = three times daily, VLC = valaciclovir.

Antiviral therapy	Consultant	Fellow	Registrar	Resident	Total
	[n, (%)]	[n, (%)]	[n, (%)]	[n, (%)]	[n, (%)]
Oral					
VLC 500mg od	**1 (14.3)**		**1 (11.1)**		**2 (9.1)**
VLC 500mg BD	2 (28.6)	2 (40)		1 (11.1)	5 (22.7)
VLC 500mg TDS			1 (11.1)		1 (4.5)
VLC 1g BD	1 (14.3)				1 (4.5)
VLC 1g TDS	1 (14.3)				1 (4.5)
Topical					
Occ ACV BD			1 (11.1)		1 (4.5)
Occ ACV x5	1 (14.3)	3 (60)	5 (55.6)		9 (40.9)
Combinations					
VLC 500mg BD + Occ ACV x5	1 (14.3)				1 (4.5)
VLC 1g BD + Occ ACV x5			1 (11.1)		1 (4.5)
Total	**7 (100)**	**5 (100)**	**9 (100)**	**1 (11.1)**	**22 (100)**

Bold figures represent patients that met the ‘guidelines’

% calculated based on total number of patients treated by each prescriber.

2.5.2.2.4 Type of prescribers for endothelial HSK

Six of 18 patients (33%) with endothelial HSK received an antiviral therapy aligned with the ‘guidelines’. One consultant (100%), two fellows (40%) and two registrars (18.2%) prescribed valaciclovir 500 mg twice daily; and one registrar (9.1%) aciclovir 400 mg five times daily, as recommended per the ‘guidelines’ (p = 0.427) (See Table 2 - 12, page 114).

Table 2 - 12: Antiviral therapy vs type of prescriber for endothelial HSK patients.

Key: x5 = five times daily, n = number of patients, ACV = aciclovir, BD = twice daily, Occ = ointment, TDS = three times daily, VLC = valaciclovir.

Antiviral therapy	Consultant	Fellow	Registrar	Resident	Total
	[n, (%)]	[n, (%)]	[n, (%)]	[n, (%)]	[n, (%)]
Oral					
VLC 500 mg BD	**1 (100)**	**2 (40)**	**2 (18.2)**		**5 (27.8)**
VLC 1g BD			1 (9.1)		1 (5.6)
VLC 1 g TDS		1 (20)	6 (54.5)	1 (100)	8 (44.4)
ACV 400 mg BD		1 (20)			1 (5.6)
ACV 400mg x5			**1 (9.1)**		**1 (5.6)**
Topical					0 (0)
Occ ACV x5		1 (20)	1 (9.1)		2 (11.1)
Total	1 (100)	5 (100)	11 (100)	1 (100)	18 (100)

Bold figures represent patients that met the ‘guidelines’

% calculated based on total number of patients treated by each prescriber.

2.5.2.2.5 Type of prescribers for keratouveitis

A comparison with the ‘guidelines’ was not made as there were no available recommendations in the literature for this condition. Ten different regimens to treat patients with keratouveitis were identified. Registrars prescribed mainly topical aciclovir five times daily (32.3%) and valaciclovir 1 g three times daily (29%); while consultants prescribed valaciclovir 500 mg twice daily (50%), fellows, valaciclovir 500 g three times daily (60%), and residents valaciclovir 1 g three times daily (See Table 2 - 13, page 115).

Table 2 - 13: Antiviral therapy vs type of prescriber for keratouveitis patients.

Key: x5 = five times daily, n = number of patients, ACV = aciclovir, BD = twice daily, Occ = ointment, od = once daily, TDS = three times daily, VLC = valaciclovir.

Antiviral therapy	Consultant	Fellow	Registrar	Resident	Total
	[n, (%)]	[n, (%)]	[n, (%)]	[n, (%)]	[n, (%)]
Oral					
VLC 500 mg od				1 (10)	1 (1.9)
VLC 500 mg BD	3 (50)		1 (3.2)	1 (10)	5 (9.6)
VLC 500 mg TDS	1 (16.7)	3 (60)	1 (3.2)	2 (20)	7 (13.5)
VLC 1g TDS	2 (33.3)	1 (20)	9 (29)	4 (40)	16 (30.8)
ACV 200 mg x5			1 (3.2)		1 (1.9)
ACV 400 mg x5			4 (12.9)		4 (7.7)
Topical					0 (0)
Occ ACV x5		1 (20)	10 (32.3)		11 (21.2)
Combinations					0 (0)
VLC 500 mg BD + Occ ACV TDS			1 (3.2)		1 (1.9)
VLC 500 mg TDS + Occ ACV x5			1 (3.2)		1 (1.9)
VLC 1g TDS + Occ ACV x5			3 (9.7)	2 (20)	5 (9.6)
Total	6 (100)	5 (100)	31 (100)	10 (100)	52 (100)

% calculated based on total number of patients treated by each prescriber.

2.5.3 Prophylactic indication

2.5.3.1 Prescribing trends for prophylactic indication

Forty-four patients received an antiviral therapy for a prophylactic indication. Indications included, prior stromal HSK (n = 10), prior keratouveitis (n = 17), prior corneal graft (n = 6), prior stromal HSK and corneal graft (n = 7) and prior keratouveitis and corneal graft (n = 3). In one case the reason for prophylactic therapy was not available from the medical records (See Table 2 - 14, page 117).

Valaciclovir 500 mg once daily was the most commonly prescribed antiviral agent in 29 (66%) patients followed by valaciclovir 500 mg twice daily in 5 (11%) patients. Six (14%) patients received oral aciclovir in doses ranging from 200 to 400 mg once to three times daily. Topical antiviral medications were given in 2 patients. One patient (2%) received topical aciclovir 5 times daily and another (2%) trifluridine as needed. Two (4%) patients received a combination of oral and topical antiviral medications (See Table 2 - 14, page 117). Thirty-eight of the 44 (86%) patients also received a topical corticosteroid as initial therapy (See Table 2 - 8, page 106). One patient received two topical corticosteroids, hydrocortisone ointment and preserved prednisolone acetate 1%. The most common topical corticosteroid agents were preserved fluorometholone 0.1% ophthalmic suspension (FML, Allergan, Australia) and preserved dexamethasone 0.1% ophthalmic suspension prescribed at frequencies of once, twice, three, four, six times, every two hours or every other day.

Adherence to the ‘guidelines’ was found in 31 of the 44 (70%) patients receiving either valaciclovir 500 mg once daily or aciclovir 400mg twice daily. Eight of 10 (80%) patients with prior stromal HSK, 12 of 17 (70.6%) with prior keratouveitis, 2 of 6 (33.3%) with prior corneal graft, 4 of 7 (57.1%) with prior stromal HSK and corneal graft, and 3 of 3 (100%) with prior keratouveitis and corneal graft followed the ‘guidelines’.

Table 2 - 14: Number of prophylactic indications per antiviral therapy for 44 patients.

Key: x5 = five times daily, n = number of indications, ACV = aciclovir, BD = twice daily, HSK = herpes simplex keratitis, Occ = topical, od = once daily, PRN = use when necessary, TDS = three times daily, TFT = trifluridine, VLC = valaciclovir.

Bold figures represent patients that met the 'guidelines'

Antiviral therapy	**Type of prophylactic indication**						
	Stromal HSK n (%) †	**Keratouveitis n (%) †**	**Corneal graft n (%) †**	**Stromal HSK and corneal graft n (%) †**	**Keratouveitis and corneal graft n (%) †**	**Unclear n (%) †**	**Total n (%)**
Oral							
VLC 500 mg od	**8 (80)**	**12 (70.6)**	**2 (33.3)**	**4 (57.1)**	**3 (100)**		**29 (65.9)**
VLC 500 mg BD	0 (0)	1 (5.9)	2 (33.3)	2 (28.6)			5 (11.4)
ACV 200 mg BD		1 (5.9)					1 (2.3)
ACV 400 mg od	1 (10)						1 (2.3)
ACV 400 mg BD		**2 (11.8)**					**2 (4.5)**
ACV 400 mg TDS			2 (33.3)				2 (4.5)
Topical							
Occ ACV x5						1 (100)	1 (2.3)
TFT PRN	1 (10)						1 (2.3)

Table 2 – 14 (continued)

Antiviral therapy	Type of prophylactic indication						
	Stromal HSK n (%) †	**Keratouveitis n (%) †**	**Corneal graft n (%) †**	**Stromal HSK and corneal graft n (%) †**	**Keratouveitis and corneal graft n (%) †**	**Unclear n (%) †**	**Total n (%)**
Combinations							
VLC 500 mg BD + Occ ACV od				1 (14.3)			1 (2.3)
ACV 400 mg BD + Occ ACV TDS		1 (5.9)					1 (2.3)
Total	10 (100)	17 (100)	6 (100)	7 (100)	3 (100)	1 (100)	44 (100)

† (%) percentage calculated from total cases of each type of indication

2.5.3.2 Type of prescribers for prophylactic indication

Thirty-one of 44 patients (70%) received a prophylactic antiviral therapy aligned with the 'guidelines' All prescribers treated most of their patients in accord to the 'guidelines' as follows: 10 of 13 patients (77%) by consultants, 7 of 11 (64%) by fellows, and 14 of 20 (70%) by registrars (*p = 0.8)* (See Table 2 - 15, page 119).

Table 2 - 15: Antiviral therapy vs type of prescriber for HSK prophylaxis.

Key: x5 = five times daily, n = number of patients, ACV = aciclovir, BD = twice daily, Occ = topical, od = once daily, PRN = use when necessary, TDS = three times daily, TFT = trifluridine, VLC = valaciclovir.

Bold figures represent patients that met the 'guidelines'

Antiviral therapy	Consultant n, (%)	Fellow n, (%)	Registrar n, (%)	Total n, (%)
Oral				
VLC 500 mg od	**9 (69.2)**	**7 (63.6)**	**13 (65)**	**29 (65.9)**
VLC 500 mg BD	1 (7.7)	1 (9.1)	3 (15)	5 (11.4)
ACV 400 mg BD	**1 (7.7)**		**1 (5)**	**2 (4.5)**
ACV 400 mg TDS		2 (18.2)		2 (4.5)
ACV 400 mg od			1 (5)	1 (2.3)
ACV 200 mg BD			1 (5)	1 (2.3)
Topical				
Occ ACV x5		1 (9.1)		1 (2.3)
TFT PRN	1 (7.7)			1 (2.3)
Combinations				
VLC 500 mg BD + Occ ACV od			1 (5)	1 (2.3)
ACV 400 mg BD + OCC ACV TDS	1 (7.7)			1 (2.3)
Total	13 (100)	11 (100)	20 (100)	44 (100)

% calculated based on total number of patients treated by each prescriber.

2.6 Discussion

Contemporary local data on HSK is needed to highlight trends, assist diagnosis and management. In this chapter, we reported whether the evidence from randomised clinical trials and systematic reviews for HSK available up to December 2013 had been translated into clinical practice for over a 2-year period at Sydney/Sydney Eye Hospital, in Sydney, Australia. In this retrospective case review, patients resided mainly in the greater Sydney area and were born in Australia. One hundred and thirty-two of 179 (73%) patients with a therapeutic indication and 31 of 44 (70%) patients with a prophylactic indication were prescribed the recommended antiviral agents for HSK in 296 patients. Overall, 163 of 223 patients (73%) had antiviral therapy prescribed that followed the evidence-based recommendations which we summarized as 'the guidelines'. A comparison to 'the guidelines' was not made for patients with SHSK+U and keratouveitis, as there were no treatment recommendations available in the literature when the study started. Prescribing patterns for antiviral therapy to treat and prevent recurrence of HSK were diverse in this study. Overall, seven antiviral treatments were identified including topical aciclovir, trifluridine, oral aciclovir, valaciclovir, oral aciclovir and topical aciclovir, valaciclovir and topical aciclovir, and valaciclovir and trifluridine. Frequencies of the antiviral medications varied according to the type of keratitis. Registrars were the main treating doctors in this study (181 of 296, 61%). Overall, they followed the 'guidelines' in 91% (92/101) of patients with epithelial HSK, 11.1% (1/9) with SHSK-U, 27.3 % (3/11) with endothelial HSK, and 70% (14/20) of patients with a prophylactic indication.

A study conducted in France also reported a wide variety of therapeutic interventions for new and recurrent HSK suggesting a lack of consensus regarding appropriate antiviral therapy. [56] In France, 18 antiviral therapies were identified including one or two local agents (aciclovir, trifluridine, ganciclovir, idoxuridine); oral agents (valaciclovir and aciclovir); or a combination of one or two oral and one or two local agents for 357 patients. Notable therapies included 31% local therapy with one agent (aciclovir or trifluridine), 13% oral therapy (aciclovir or valaciclovir), and 20% oral therapy and topical aciclovir. [56] In contrast, in our study, 51% of the patients

received local therapy (aciclovir or trifluridine), 41.2% oral therapy (aciclovir or valaciclovir), and 8% a combination of oral therapy and topical aciclovir. Valaciclovir was preferred as oral therapy and topical aciclovir as local treatment at the Sydney Eye Hospital contrary to the study in France where ophthalmologists used a myriad of treatments, many of which are not available in Australia. The use of valaciclovir in our study probably reflects its availability and the prescribing clinician's preference to increase compliance with reduced frequency of dosing compared to aciclovir.

The wide disparity in initial antiviral therapy found in this study indicates that the 'guidelines', especially for stromal HSK, have not been translated easily into routine clinical practice. Adherence to the 'guidelines' was found in 89% of epithelial HSK cases, 9% of SHSK-U cases, 33% of endothelial HSK cases and 70% of HSK prophylaxis cases. The higher adherence to the 'guidelines' for epithelial HSK and HSK prophylaxis may relate to the diagnosis of epithelial HSK being simpler compared to the other types of HSK, and the indications for prophylaxis are well-described in the literature. The diversity in the initial antiviral therapy may be related to several factors. Existing 'guidelines' included medications such as oral aciclovir and trifluridine, which are not routinely prescribed for HSK in Australia. Since the release of HEDS recommendations in 1990s, other medications such as valaciclovir and ganciclovir have become widely available in some parts of the world. Indeed, since our study was initiated, the AAO has released a guideline for HSK management. [23] Although ganciclovir and trifluridine are recommended in the USA, they are not easily accessible in Australia. Further, there are no studies evaluating the efficacy of valaciclovir, which is widely used these days for treating HSK. Valaciclovir is an aciclovir pro-drug and, although the equivalent dose to aciclovir has been determined, it is not clearly understood by clinicians, as they prescribe various valaciclovir dosages for HSK and often follow treatment regimens learnt during their training, some of which may have become superseded by newer drugs. [125] Additionally, strong clinical evidence is not available to guide antiviral therapy for SHSK+U, endothelial HSK and keratouveitis. These types of HSK would benefit from local guidelines to prevent side effects from therapy and hopefully improve outcomes.

In the present study, of concern was that doctors prescribed higher doses of antiviral medications than recommended or a combination of oral and topical antiviral medications. These regimens can cause side effects, increase costs for patients, and have not been shown to improve outcomes in HEDS clinical trials. Most common side-effects of valaciclovir include gastrointestinal discomfort (vomiting, nausea, diarrhea, constipation, abdominal pain, indigestion) and headache. [69, 70] Rare side effects for valaciclovir include sensitivity to ultraviolet light presenting as rash or sunburn after short exposure, dizziness, confusion, drowsiness, damage to kidney and liver. [70] The risk of side-effects increases if the patient has renal impairment. For instance, half of patients with SHSK-U received higher doses of valaciclovir ranging from 500 mg to 1 g twice to three times daily; when 'the guidelines' recommended valaciclovir 500 mg once daily. This may reflect the clinician's uncertainty as to whether they are prescribing for treatment or prophylaxis. Further, 21 of 296 patients (7%) received a combination of oral and topical antiviral medications mainly for epithelial HSK and keratouveitis, which is not recommended in the literature. [3] Included patients were also elderly and ranged up to 89 years in the therapeutic group and 94 years for prophylactic; this increased the likelihood of a systemic side-effect and/or interaction with another medication. Potential reasons of higher doses of valaciclovir for epithelial HSK and for keratouveitis included a history of HSK, prior corneal graft and autoimmune disease managed with mycophenolate mofetil and prednisone.

Adherence to the 'guidelines' differed according to the clinician seniority and type of HSK. The rate of adherence to the 'guidelines' was over 70% for all types of clinicians for epithelial HSK. The rate was significant better for registrars (91%) and residents (100%) (p =0.05). Consultants and fellows may have prescribed other regimens as they tend to see more complex patients who may have needed an alternate therapy. Similarly, the rate of adherence was over 60% for HSK prophylaxis for all types of clinicians except residents who did not initiate any patient needing HSK prophylaxis. This may have occurred as residents generally only attended patients in the emergency rooms and therefore with initial presentations of HSK rather than those in clinics who typically come for follow up. Perhaps, another reason is that the residents did see these patients but were not identified for this study; because the residents did not request an

HSV PCR or prescribed HSK prophylaxis. The residents might be missing these cases or the decision to initiate prophylaxis was left to a more senior colleague. Consultants had a better adherence rate (77%) vs fellows (64%) and registrars (70%) but it was not statistically significant (p = 0.8). The trainees may have not remembered the recommended dose.

On the other hand; clinicians, regardless their seniority, failed to follow the 'guidelines' for SHSK-U and for endothelial HSK. The rates were better for endothelial HSK (33%, n = 6/18) than for SHSK-U (9%, n = 2/22). For endothelial HSK; only one consultant (100%, n = 1), two fellows (40%, n= 2/5) and three registrars (27%, n = 3/11) followed the 'guidelines'. The reason for this may be that there were no clear guidelines from published evidence to treat this type of HSK and trainees may have prescribed what their seniors do.

For SHSK-U, most of clinicians inadequately prescribed antiviral medications. The trainees may have failed to diagnose correctly the patients or may not have understood the antiviral treatment for SHSK-U. Some clinicians may prescribe valaciclovir 500 mg twice daily rather than once daily for SHSK-U as they are worried that the patient may be undertreated, especially if they take the tablets at different times every day or if they forget the dose one day. This reflects the lack of knowledge of the pharmacokinetic profile of valaciclovir and the recommended dose of antivirals for SHSK-U among clinicians. The plasma elimination half-life of aciclovir after oral administration of valaciclovir is 2.6 hours [98] comparable to the half-life of aciclovir after administration of oral aciclovir (3 hours [126]). However, the absolute bioavailability of valaciclovir is 54% [127] compared to 15-30% of oral aciclovir. [126] The greater bioavailability of valaciclovir makes it a better choice to treat patients with HSK as patients can take the medication less frequently with a better chance of adherence to the treatment. A prophylactic antiviral dosage along with a topical corticosteroid are recommended for SHSK-U according to published evidence. [1] In SHSK-U, the mainstay of treatment is a topical corticosteroid as the pathogenesis of this type of keratitis is immune-mediated. [8] Emphasising these concepts to new trainees is essential to improve the prescribing behaviour for this type of keratitis.

Another point of interest in this study was the prescription of topical aciclovir in stromal HSK, endothelial HSK, and keratouveitis. The 'guidelines' based on the available literature recommended an oral antiviral for the treatment of these conditions. [1, 3] Thirty-two of 113 (28%) patients with stromal HSK, endothelial HSK and keratouveitis received topical aciclovir five times daily. Of these, 24 (75%) patients received this regimen from a registrar. Registrars prescribed it in 45% of patients with SHSK+U, 43% of patients with SHSK-U, 11% of patients with endothelial HSK and 21% of patients with keratouveitis. These findings indicate that registrars need further education and closer supervision when diagnosing cases of HSK along with local treatment guidelines for initial therapy to assist them in making the correct diagnosis and initiating treatment.

A myriad of topical corticosteroid preparations and their frequencies were prescribed in this study. Topical corticosteroids were prescribed with antiviral agents in 13 of 139 (9%) patients with epithelial HSK and 64 of 113 (56%) patients with stromal HSK, endothelial HSK or keratouveitis; and 38 of 44 (86%) patients on antiviral prophylaxis. Although topical corticosteroids are not initially recommended for epithelial HSK; they may be used in patients with ocular comorbidities such as prior HSK episode, prior corneal graft, recent cataract surgery and prior uveitis. Topical corticosteroids are the mainstay of treatment for stromal HSK and endothelial HSK, and keratouveitis. Reasons for the reluctance to prescribe topical corticosteroids may include lack of confidence or knowledge in diagnosing HSK, insufficient senior supervision, and concerns regarding adequate follow up of patients. Stromal HSK, specifically, can mimic bacterial or fungal keratitis with presence of dense corneal infiltration and ulceration, and rarely hypopyon. [128] Additionally, bacterial superinfection is not uncommon in this group (paper in preparation) and may have been suspected although this group was excluded from this study.

Identifying HSK prescribing trends highlights the need for and can contribute to the development of local treatment guidelines as well as adding to the international literature on real world HSK management. Standardised initial antiviral therapy based on clinical evidence has the potential to reduce side effects from therapy, complications

and HSK recurrences, and reduce expensive HSK treatment costs. [13] In Australia, at the time of this thesis aciclovir was available in tablets of 200 mg and in 3% ointment (Zovirax, GlaxoSmithKline, Australia), and valaciclovir in tablets of 500 mg. The combination of favourable supply contracts with pharmaceutical companies and valaciclovir coming off patent recently means this drug is now available at a lower cost. The advantages of valaciclovir over aciclovir include less frequent dosing (2 to 3 times compared to 5 times for acute therapy and once daily compared to twice for prophylaxis), a lactose-free generic formulation, and a reduction in stomach discomfort and nausea in those with lactose intolerance. [125] Further studies can utilise the results of this study to assist the development and implementation of a local HSK treatment guideline. [23] Indeed, the need for education on the implications of 'over-dosing' antiviral therapy and the appropriate use of topical steroids could be highlighted. Nonetheless, randomized controlled trials are needed to compare dosages and frequencies of aciclovir vs valaciclovir for stromal HSK, endothelial HSK and keratouveitis.

The major limitation of the present study was its retrospective nature. There was documentation bias as the study relied on the completeness of the medical records. This type of study is prone to misclassification bias as the investigators may have classified the type of HSK in patients with HSK differently to the ophthalmologist managing the patient. However, in most cases the type and diagnosis of HSK was recorded in the medical notes. There was more ambiguity of terms for patients diagnosed with stromal HSK and endothelial HSK. This study design however was appropriate to evaluate the prescribing trends of HSK as it documented prescriber behaviour in a quaternary hospital setting and was a starting point to generate hypotheses to be tested in future studies. Additionally, the study was based at a single site; however, the Sydney Eye Hospital is a quaternary eye referral centre, which receives on average 5 patients per week with HSK from different regions of NSW. Currently, there are 6 corneal specialists, 2 fellows, 12 registrars and 15 residents at the Sydney Eye Hospital. Fellows are changed every year in January and registrars and residents rotate from centres across NSW every quarter. With similar numbers of clinicians present during our study in 2012 and 2013, around 35 different doctors were included.

In conclusion, there was a large diversity of initial antiviral therapy for HSK prescribed by consultant and trainee ophthalmologists in the quaternary referral eye hospital. Overall, 73% (163/223) of patients received the recommended therapy from the ‘guidelines’. One hundred and ten patients received the recommended therapy from registrars (67%), 21 from consultants (13%), 17 from fellows (10%) and 15 from residents (9%). Registrars and residents had a significant better adherence rate for prescribing antiviral therapy. The study highlights the moderate clinical implementation of the ‘guidelines’, lack of up-to-date studies evaluating new treatments for HSK and the importance of developing Australian guidelines for the management of HSK based on clinical evidence to improve patient care and rationalise health resources.

In the next chapter, the predisposing factors for HSK, laboratory investigations, and clinical outcomes of these patients will be reported. These results and the trends described in this chapter will add to the evidence from the literature, listed in the Chapter 1, and aid in developing and implementing the local HSK treatment guideline at the Sydney Eye Hospital.

Chapter 3 - Medical and ocular history, diagnostic tests, and clinical outcomes for herpes simplex keratitis

3.1 Introduction

Ocular herpes simplex virus (HSV) infection is a common cause of visual morbidity worldwide. [8] Almost 100% of people over 60 years of age harbor HSV in their trigeminal ganglia at autopsy. [1] After the primary infection, HSV remains latent in the trigeminal ganglia and can be reactivated as either adnexal infection or HSK. [23] About one fifth of patients with ocular HSV develop stromal HSK, an important cause of unilateral blindness in the developed world. [1, 18] Recurrent ocular HSV infection may be determined by the general and corneal susceptibility of the individual. General susceptibility includes any conditions that depress cell mediated immunity for example diabetes mellitus, organ transplant recipient and HIV infection. Further, corneal susceptibility may increase on topical corticosteroid use, local trauma and post ocular surgery. [23] .

For epithelial HSK, several clinical trials reported that patients healed at a median time of between 5 and 14 days with either topical aciclovir, ganciclovir or trifluridine. [79, 80, 83, 84] . For stromal HSK, in HEDS I, patients received topical corticosteroid and trifluridine and either placebo or oral aciclovir. The median time to treatment failure was 84 days [95% confidence interval (CI), 69-93] for the aciclovir group vs 62 days (95% CI, 57-90) for the placebo group. In HEDS II, patients received trifluridine and either placebo or topical corticosteroids. There was a statistically significant difference in time of treatment failure between steroid and placebo group (98 days vs 17 days, p <0.001). Long term prophylactic dose of oral aciclovir prevents recurrence of epithelial and stromal HSK. [59] The cumulative probability of recurrence for any ocular HSV disease was 19% in the aciclovir group compared with 32% in the placebo group.

More recent data is needed to add to the evidence base for the predisposing factors and management of HSK to improve patient outcomes, particularly since the

introduction of new antiviral medications such as ganciclovir, valaciclovir, and famciclovir and with the variable drug accessibility in various geographical locations. [129]

3.2 Aim

This chapter aimed to report the predisposing factors, diagnostic tests and outcomes for patients with an active HSK episode (epithelial, stromal, endothelial, keratouveitis) and for those receiving antiviral medications to prevent HSK recurrence in a quaternary eye centre in Sydney, Australia.

3.3 Hypothesis

We hypothesised that, in the Sydney Eye Hospital:

1. Prior topical corticosteroid use was the most common predisposing factor for patients with HSK, and
2. Diverse initial antiviral therapy was more associated to poor clinical outcomes in patients with HSK.

3.4 Methods

A retrospective case study of patients prescribed antiviral medications for HSK from 1st January 2012 to 31st December 2013 was performed at the Sydney Eye Hospital, Sydney Australia. Pharmacy, hospital coding and pathology results databases were used to identify potential patients. Medical records of patients identified were reviewed and included in the study if they were 18 years of age or older and had antiviral therapy prescribed for the treatment or prevention of HSK. For bilateral HSK cases, one eye was excluded to avoid confounding. For bilateral HSK cases, the eye with better vision was excluded to avoid confounding. Methods have been described in section 2.4, page 87. [129]

Study data were collected and managed using REDCap (Research Electronic Data Capture, Nashville, TN, The USA) hosted at The University of Sydney. [121] Ethics approval was gained from the South Eastern Sydney Local Health District Human Resources Ethics Committee (approval number: HREC 13/296) shown in Appendix E,

page 334. Data were reported in line with the STROBE statement for observational data. [124] The research adhered to the Tenets of the Declaration of Helsinki.

3.4.1 Herpes simplex keratitis classification

As discussed in Chapter 2, the indication for the chosen initial antiviral therapy (whether therapeutic or prophylactic) and type of HSK was determined based on the clinical findings and medical history documented in the medical notes.

For therapeutic indications, the type of HSK was divided into six subgroups: 'epithelial', 'stromal with ulceration', 'stromal without ulceration', 'endothelial', 'keratouveitis' and 'active HSK with prior corneal graft'. A group with patients with 'an active HSK with prior corneal graft' was determined as the infection in these patients may have a different outcome compared with patients with the same type of keratitis without corneal graft.

3.4.2 Polymerase chain reaction test for herpes simplex virus

Herpes Simplex Virus type 1 and type 2 (HSV-1, HSV-2) were detected using the VZV R-gene kit, a Real-Time PCR on DNA extracted from human clinical samples (Argene, Australia) according to manufacturer's instructions. [130] The PCR testing was performed by the attending medical practitioner. The tests were performed using a Roche LC480 thermal cycler for real time amplification and results reported as viral genome copies/ml and calculated log10 copies/ml. Positive and negative controls were used as standard.

3.4.3 Outcomes

The outcome of the HSK episode was determined when the initial antiviral therapy was stopped or changed to indicate a change in clinical status. For therapeutic indication, the outcomes were classified depending on clinical response as 'resolved', 'partially resolved', and 'worsened'. 'Resolved' outcome was recorded when the dendritic ulcer healed or there were no signs of active HSK. 'Partially resolved' outcome was recorded when there were still signs of active HSK but improving from the

presentation date. ‘Worsened’ outcome was recorded when there were signs of non-resolving HSK. For prophylactic indication, ‘success’ was recorded when an eye had no further HSK episodes and ‘failure’ as an eye with an occurrence of an HSK episode (Appendix C, page 321).

Patients excluded from the data analysis included those classified as ‘lost to follow up’, ‘not HSK’ and ‘ongoing therapy’. ‘Lost to follow up’ referred to the patients who did not attend the Sydney Eye Hospital for follow up visits after their initial visit. The patients categorised as ‘Not HSK’ were those with an initial HSK diagnosis who were found not to have had HSK when the outcome was measured during follow up visits. ‘Ongoing antiviral therapy’ referred to a patient with no information of change or cessation of initial antiviral therapy in their medical records (Appendix C, page 321).

3.4.4 Visual acuity

Initial visual acuity (VA) was defined as the VA at first presentation and final VA as the VA at the visit when the antiviral treatment was stopped or changed. The Snellen fractions in combination with any letters incorrectly identified or any letters correctly identified on smaller lines were converted to the logarithm of the minimum angle of resolution (logMAR) for analysis. The following logMAR values were allocated for non-numeric visual acuities to enable graphical representation and numerical analysis: counting fingers 1.7 logMAR, hand movement 2.0 logMAR, light perception 2.3 logMAR and no light perception 3.0 logMAR. [131]

3.4.5 Outpatient visits

For the therapeutic indication, the number of visits was counted until the HSK episode was resolved or worsened.

For prophylactic indication, the number of visits was counted until the patient presented with a recurrence.

3.4.6 Statistical analysis

Descriptive statistics were used to summarise all continuous and categorical variables. Change in visual acuity (logMAR) was investigated using a Wilcoxon test. A p-value < 0.05 was considered as evidence of statistical significance. The statistical software used was IBM SPSS Statistics Desktop Version 22 (IBM Corp, Armonk, NY).

3.5 Results

Two hundred and ninety-six patients were included in the study. Two hundred and fifty-two (85%) and 44 (15%) patients received antiviral therapy for therapeutic and prophylactic indications, respectively.

3.5.1 Therapeutic indication

The mean age of the patients in the therapeutic group was 52 years (standard deviation (SD) ± 19) and two-thirds were male (See Table 3 - 1, page 132). Most patients were from the greater Sydney Metropolitan area (90.5%). The right eye (43%) was affected in 108 patients, the left eye in 140 patients (56%), and both eyes in 4 patients (2%). In the 4 cases with bilateral HSK, each eye had the same therapeutic indication for HSK therapy.

One hundred and twenty-three of 252 patients (49%) were diagnosed with epithelial HSK, 21 (8%) with SHSK+U, 22 (9%) with SHSK-U, 14 (6%) with endothelial HSK, 49 (19%) with keratouveitis, and 25 (10%) had active HSK with a prior corneal graft. Topical agents were the most commonly prescribed antiviral therapy for epithelial and stromal HSK patients while oral agents were for the other types of HSK. Seventy-six of 252 (30%) patients with HSK were prescribed with topical corticosteroids in addition to antiviral therapy. Most of patients with endothelial HSK, keratouveitis, and patients with active HSK with prior corneal graft received topical corticosteroid therapy (See Table 3 - 2, page 133).

Table 3 - 1: Socio-demographic characteristics of patients with for herpes simplex keratitis per antiviral indication (n = 296).

Key: SD = standard deviation, NSW = New South Wales, n = number of patients.

	Antiviral indication	
	Therapeutic	**Prophylactic**
n (%)	252 (85)	44 (15)
Age in years		
Mean (SD)	52 ± 19	65 ± 17
Range	19 to 89	25 to 94
Gender, Male [n, (%)]	153 (61)	22 (50)
Residence [n, (%)]		
Within greater Sydney	228 (90.5)	29 (66)
Outside greater Sydney but within NSW	21 (8.3)	15 (34)
Victoria	2 (0.80)	0
Overseas	1 (0.4)	0

Table 3 - 2: Number of initial antiviral and topical corticosteroid therapies per antiviral indication for 296 patients with HSK.

Key: n = number of patients, SHSK+U = stromal with ulceration, SHSK-U = stromal without ulceration.

Therapy	Indication of antiviral therapy							
	Epithelial HSK n = 123	**SHSK+U n = 19**	**SHSK -U n = 22**	**Endothelial HSK n = 14**	**Keratouveitis n = 49**	**Prior corneal graft n = 25**	**Prophylactic n = 44**	**Total patients n = 296**
Antiviral								
Oral	7 (5.7)	8 (38.1)	10 (45.5)	12 (85.7)	31 (63.3)	17 (68)	40 (90.9)	125 (42.2)
Topical	112 (91.1)	9 (42.9)	10 (45.5)	2 (14.3)	11 (22.4)	5 (20)	2 (4.5)	151 (51)
Combined	4 (3.3)	4 (19)	2 (9.1)	0 (0)	7 (14.3)	3 (12)	2 (4.5)	22 (7.4)
Topical corticosteroid	6 (4.9)	3 (14.3)	10 (45.5)	13 (92.9)	29 (59.2)	15 (60)	38 (86.4)	114 (38.5)

3.5.1.1 Medical and ocular history

Twenty-six of 252 patients (10%) had a prior immunosuppressive condition including diabetes mellitus (n = 20), HIV (n = 1), solid organ transplant (n = 2), steroid-sparing medication use (n = 3), and oral steroid use (n = 11). Six patients had more than one immunosuppressive condition. Half of these patients presented with epithelial HSK (13 of 26), 6 with keratouveitis, 3 with SHSK+U, 3 with SHSK-U, and 1 with endothelial HSK. Seven patients used oral steroids for autoimmune conditions (Systemic lupus erythematosus, Sjogren syndrome, polymyalgia rheumatica, and arthropathy), one for a prior solid organ transplant and 3 for ocular disease. Nineteen patients were contact lens wearers, of these, 11 presented with epithelial HSK, one with endothelial HSK, 6 with keratouveitis and another with stromal HSK who had a prior corneal graft.

Eighty-three of 252 patients (33%) had a pre-existing eye condition limiting visual acuity; most commonly corneal pathology aside from HSK (n = 28) and glaucoma (n = 22). Ninety-six (38%) patients had a prior HSK episode. Half of these patients did not report the form of their prior episode(s) HSK (epithelial, stromal, endothelial or keratouveitis). Fifteen patients (6%) had a prior ocular trauma. Forty-six patients (18%) were using a topical corticosteroid at initial presentation. The most common agents were preserved dexamethasone 0.1% (Maxidex) (n = 15) and preserved prednisolone acetate 1% (Prednefrin forte) (n = 13). Sixteen patients with epithelial HSK were on topical corticosteroid use at initial presentation (See Table 3 - 3, page 135). Of these, 3 also were using a topical aciclovir and one taking oral valaciclovir.

Sixteen of 25 (64%) patients from the prior cornea graft group had had penetrating keratoplasty (PK); one (4%), lamellar keratoplasty (LK); one (4%), a deep anterior lamellar keratoplasty (DALK); 8 (32%) Descemet stripping endothelial keratoplasty (DSEK); and one (4%), Descemet membrane endothelial keratoplasty (DMEK). Three patients had a history of two corneal transplants. About two-thirds of patients with a prior corneal graft (60%, n = 15/25) were on topical corticosteroid therapy at initial presentation.

Table 3 - 3: Ocular history per therapeutic group for 252 patients with HSK.

Key: n = number of patients, HSK = herpes simplex keratitis, VA = visual acuity.

Note: percentages do not add to 100% most cases had > 1 risk factor, percentages calculated from total patients of each type of HSK, the ocular history was recorded only for the eye with HSK.

Ocular history	Epithelial HSK (n = 123)	SHSK+U (n = 19)	SHSK-U (n = 22)	Endothelial HSK (n = 14)	Keratouveitis (n = 49)	Prior corneal graft (n = 25)	Total patients (n = 252)
Pre-existing eye condition limiting VA [n (%)]	35 (28)	3 (15)	7 (32)	4 (29)	12 (24)	20 (80)	83 (33)
Corneal pathology	5	1	3	0	3	16	28
Glaucoma	11	2	1	1	3	4	22
Other†	6	0	0	0	2	3	22
Retinal pathology	8	1	1	2	1	1	14
Uveitis	4	1	1	0	4	1	11
Amblyopia	3	0	0	0	1	1	5
Cataract	0	0	1	1	1	0	3
Macular degeneration	0	0	1	0	0	0	1
Previous HSK [n (%)]	35 (28)	11 (58)	13 (59)	5 (36)	23 (47)	9 (36)	96 (38)
Unclear	20	7	6	2	8	5	48

Table 3 – 3 (continued)

Ocular history	Epithelial HSK (n = 123)	SHSK+U (n = 19)	SHSK-U (n = 22)	Endothelial HSK (n = 14)	Keratouveitis (n = 49)	Prior corneal graft (n = 25)	Total patients (n = 252)
Keratouveitis	7	1	2	2	11	1	24
Stromal	4	3	4	0	0	1	12
Epithelial	3	3	3	0	1	0	10
Endothelial/Disciform	1	1	0	2	3	3	10
Previous ocular trauma [n (%)]	7 (6)	3 (16)	1 (5)	1 (7)	1 (2)	2 (8)	15 (6)
Non-penetrating	6	2	1	1	1	0	11
Abrasion	3	1	0	0	1	0	5
Chemical	2	0	0	1	0	0	3
Blunt	1	0	1	0	0	0	2
Thermal	0	1	0	0	0	0	1
Penetrating	1	1	0	0	0	1	3
Unknown	0	0	0	0	0	1	1
Current topical steroid use [n, (%)]	16 (13)	5 (26)	4 (18)	2 (14)	4 (8)	15 (60)	46 (18)
Preserved dexamethasone 0.1%	6	1	1	0	2	5	15
Preserved prednisolone acetate 1%	4	1	2	1	2	3	13
Preserved fluorometholone 0.1%	3	3	1	1	0	1	9

Table 3 – 3 (continued)

Ocular history	Epithelial HSK (n = 123)	SHSK+U (n = 19)	SHSK-U (n = 22)	Endothelial HSK (n = 14)	Keratouveitis (n = 49)	Prior corneal graft (n = 25)	Total patients (n = 252)
Unpreserved dexamethasone sodium phosphate 0.1%	3	0	0	0	0	4	7
Unpreserved prednisolone sodium phosphate 0.5%	0	0	0	0	0	1	1
Unknown	0	0	0	0	0	1	1

† **Epithelial HSK**: ocular hypertension (2), aphakia (1), strabismus (1), thyroid eye disease (1), Posner-Schlossman syndrome (1), **Keratouveitis:** ocular hypertension (1), pigment dispersion syndrome (1). Prior corneal graft: ectodermal dysplasia (1), limbal stem cell failure (1), ptosis (1)

3.5.1.2 Diagnostic tests

One hundred and ninety-four of 252 patients had a PCR test performed for HSV before or at the initial presentation. Of these, 166 (86%) had the PCR test at initial visit (See Table 3 - 4, page 139). The test was mainly requested on patients with epithelial HSK (94 of 123, 76%), with SHSK+U (14 of 19, 77%) and keratouveitis (33 of 49, 67%), and active HSK with prior corneal graft (11 of 25, 44%). Overall, the rate of positive PCR test was 27% (45 of 166). Similarly, the positive rates were 34% for epithelial HSK, 29% for SHSK+U and 27% for active HSK with prior corneal graft. Of the patients with prior corneal graft, two were diagnosed with epithelial HSK and one with SHSK+U. 0% (0 of 3) of the patients with endothelial HSK and 0% (0 of 11) of patients with SHSK-U had a positive PCR for HSV-1 (See Table 3 - 4, page 139).

3.5.1.3 Clinical outcomes

An outcome (resolved, partially resolved or worsened) was determined for 174 patients (69%). The remaining 78 (31%) patients were excluded from further analysis as they were either lost to follow up (n = 61), found not to have HSK on a subsequent review (n = 16), or on ongoing antiviral therapy (n = 1) (See Figure 3 - 1, page 142). For the ‘not HSK’ group, the most common final diagnoses were HZK and corneal erosion (See Table 3 - 5, page 140).

The number of visits at the hospital was documented for 140 of 174 (80%) patients with a determined outcome. The median number of visits was 3 (range 1 - 9) for all groups except for SHSK+U which had a median number of 5 visits (range 3 - 12). Endothelial HSK patients had at least 2 visits and SHSK+U patients had at least 3 visits. The patients in the remaining groups had at least one visit (See Table 3 - 6, page 141).

Table 3 - 4: Number of HSV PCR tests in the HSK patients with a therapeutic indication (n = 252).

Key: n = number of patients, PCR = polymerase chain reaction.

PCR result	Epithelial HSK (n=123)	SHSK+U (n = 19)	SHSK-U (n = 22)	Endothelial HSK (n = 14)	Keratouveitis (n = 49)	Prior corneal graft (n = 25)	Total cases (n = 252)
Never performed	20	3	5	10	8	12	58
Prior positive	4	0	3	0	2	1	10
Prior negative	5	2	3	1	6	1	18
Current positive	32	4	0	0	6	3	45
Current negative	62	10	11	3	27	8	121
Rate of current positive	32/94 (34%)	4/14 (29%)	0/11 (0%)	0/3 (0%)	6/33 (18%)	3/11 (27%)	45/166 (27%)

Table 3 - 5: Final diagnosis of determined not to have HSK on follow up in patients initially diagnosed with HSK and prescribed antiviral medication.

Key: CMV = cytomegalovirus, EHSK = epithelial HSK, ENHSK = endothelial HSK, HSK= herpes simplex keratitis, HZK = Herpes zoster keratitis, IOP= intraocular pressure, KU = keratouveitis, No dx = final diagnosis not found on medical notes, OVD = ophthalmic viscosurgical device, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration.

Case No	Initial HSK diagnosis	Final diagnosis
1	EHSK	HZK
2	EHSK	Corneal erosion
3	EHSK	HZK
4	EHSK	Corneal erosion
5	EHSK	No dx
6	SHSK + U	Bacterial keratitis
7	SHSK + U	Corneal erosion
8	SHSK - U	HZK
9	SHSK - U	Marginal keratitis
10	SHSK - U	Marginal keratitis
11	ENHSK	Uveitis
12	KU	CMV
13	KU	No dx
14	KU	No dx
15	Prior graft + ENHSK	Corneal graft rejection
16	Prior graft + KU	retained OVD and increased IOP

Table 3 - 6: Median number of outpatient visits in patients with HSK per therapeutic indication group.

Key: n = number of patients, HSK= herpes simplex keratitis, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration.

	Epithelial HSK (n = 83)	**SHSK+U (n = 11)**	**SHSK-U (n = 15)**	**Endothelial HSK (n = 11)**	**Keratouveitis (n = 36)**	**Prior corneal graft (n = 18)**
n (%)	67 (80.7)	11 (100)	10 (66.7)	10 (90.9)	29 (80.6)	13 (72.2)
Mean visits (range)	3 (1-9)	5 (3-12)	3 (1-6)	3 (2-7)	3 (1-7)	3 (1-9)

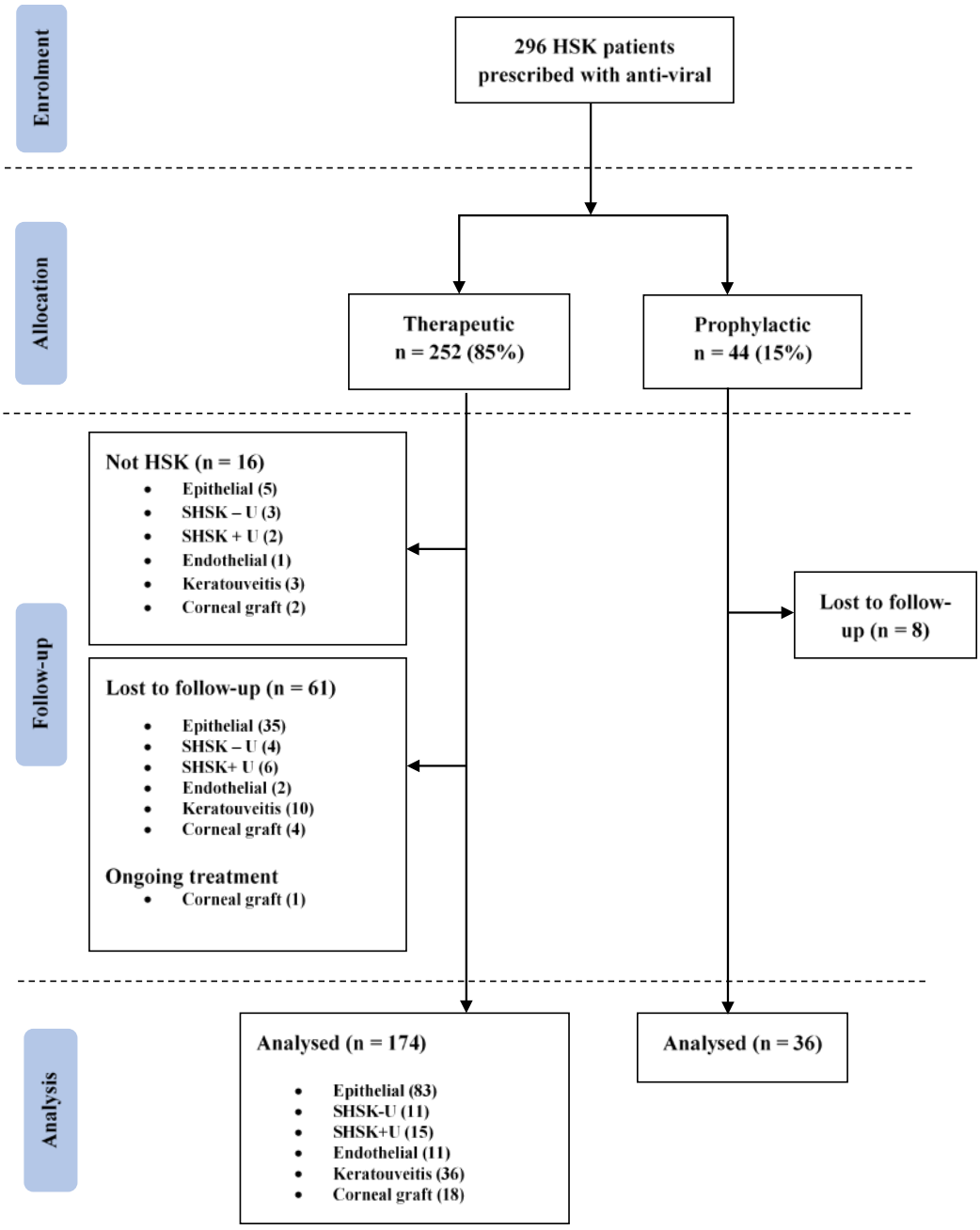


Figure 3 - 1: Inclusion and exclusion flow chart for analysis of herpes simplex keratitis outcomes.

Key: HSK = herpes simplex keratitis, n = number of patients, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration.

The outcome was able to be classified as resolved, partially resolved or worsened in 83 of 123 (67%) patients with epithelial HSK, 11 of 19 (57%) patients with SHSK+U, 15 of 22 (68%) patients with SHSK-U, 11 of 14 (78.6 %) patients with endothelial HSK, 36 of 49 (73%) patients with keratouveitis, and 18 of 25 (72%) patients with active HSK and a prior corneal graft.

Most of the patients with epithelial HSK (80/83, 97%) either resolved or partially resolved. The preferred antiviral therapy, topical aciclovir five times daily, was given to 71 of 83 (86%) patients. Of these, 35 partially resolved at a median time of 7 days, 33 resolved in 6 days, and 3 worsened in 8 days (See Table 3 - 7, page 145). Topical corticosteroids were also given to 6 of 83 patients (7%) for a median duration of 22 days (range 4 - 531). Indications included a prior episode of HSK (n = 2), prior episode of uveitis (n = 1), and recent ocular surgery either cataract surgery (n = 1), DALK (n = 1) or laser *in situ* keratomileusis (n = 1).

For SHSK+U, the most common antiviral therapy was topical aciclovir five times daily, which was prescribed in 5 patients. Of these, 3 partially resolved at a median time of 6 days, and the remaining worsened at day 9. Two patients resolved after receiving valaciclovir (See Table 3 - 8, page 146). Three of 11 patients (27%) also received topical corticosteroids for a median time of 29 days (range 2 - 56).

For SHSK-U, the preferred antiviral therapies were topical aciclovir five times daily, in 7 patients and valaciclovir 500 mg twice daily, in 4 patients. Four patients on topical aciclovir partially resolved at day 5, and 3 worsened at day 12. Four patients resolved after receiving valaciclovir. Of these, 3 received valaciclovir 500 mg twice daily, resolving at a median time of 14 days and one on valaciclovir 1 g three times daily, resolved at day 7 (See Table 3 - 9, page 147). Five of 15 eyes (33%) also received topical corticosteroids for a median duration of 6 days (range 4 - 28).

Three of 11 (27%) patients with endothelial HSK resolved, and 8 patients (73%) partially resolved. Valaciclovir 1 g three times daily was given to 6 patients. Of these, 5 partially resolved at a median time of 8 days and one resolved at day 15 (See Table 3 -

10, page 148). Topical corticosteroids were also given to 8 of 11 patients (72%) for a median duration of 14 days (range 8 - 42).

Similarly, most of the eyes with keratouveitis either resolved (n = 9, 25%) or partially resolved (n = 21, 58%). The preferred antiviral therapies were topical aciclovir five times daily, in 9 patients and valaciclovir 1 g three times daily, in 8. Of the patients on topical aciclovir, 6 partially resolved at a median time of 6 days. Of the patients on valaciclovir 1 g three times daily, 5 partially resolved at a median time of 5 days (See Table 3 - 11, page 149). About half of these patients (19 of 36) were also given topical corticosteroids for a median time of 7 days (range 2 - 89).

Seven of 18 (39%) patients with a prior corneal graft resolved and 8 patients (44%) partially resolved. The preferred antiviral therapies were valaciclovir 500 mg twice daily in 6 patients; three of these patients resolved at a median time of 15 days, one partially resolved at day 11; and 2 worsened at day 5. (See Table 3 - 12, page 150). A topical corticosteroid was also given to 10 of 18 eyes (55.6%) for a median time of 11.5 days (range 1 - 35).

Table 3 - 7: Outcomes of patients with epithelial HSK associated with seven antiviral treatments.

Key: x5 = five times daily, ACV = aciclovir, BD = twice daily, HSK = herpes simplex keratitis, n = number of patients, Occ = ointment, QID = four times daily, TDS = three times daily, Time = median duration in days until outcome was measured, VLC = valaciclovir.

	Outcome of epithelial HSK						
Antiviral therapy	**Resolved**		**Partial resolution**		**Worsened**		**Total patients**
	[n, (%)]	Time (range)	[n, (%)]	Time (range)	[n, (%)]	Time (range)	[n, (%)]
Topical							
Occ ACV x5	33 (40)	6 (2 - 27)	35 (42)	7 (2 - 25)	3 (4)	8 (2 - 26)	71 (86)
Occ ACV BD	1 (1)	5					1 (1)
Occ ACV QID	1 (1)	2	1 (1)	14			2 (2)
Oral							
VLC 500 mg BD	4 (5)	19.5 (14 - 24)					4 (5)
VLC 500 mg TDS	1 (1)	7	1 (1)	18			2 (2)
Combined							
VLC 1g BD + Occ ACV x5	1 (1)	6					1 (1)
VLC 1g TDS + Occ ACV x5			2 (2)	2.5 (2 - 3)			2 (2)
Total	**41 (49)**	**6 (2 - 27)**	**39 (47)**	**3 (1 - 18)**	**3 (4)**	**8 (2 - 26)**	**83 (100)**

(%) percentage calculated from total cases of each outcome

Table 3 - 8: Outcomes of patients with SHSK+U associated with five antiviral treatments.

Key: x5 = five times daily, ACV = aciclovir, BD = twice daily, HSK = herpes simplex keratitis, n = number of patients, Occ = ointment, SHSK+U = stromal HSK with ulceration, TDS = three times daily, Time = median duration until outcome was measured, VLC = valaciclovir.

	Outcome of SHSK+U						
Antiviral therapy	**Resolved**		**Partial resolution**		**Worsened**		**Total patients**
	[n, (%)]	Time (range)	[n, (%)]	Time (range)	[n, (%)]	Time (range)	[n, (%)]
Topical							
Occ ACV x5			3 (27)	6 (2 - 9)	2 (18)	9 (5 - 12)	5 (45)
Oral							
VLC 500 mg BD	1 (9)	56					1 (9)
VLC 1g TDS			1 (9)	7			1 (9)
VLC dose not specified	1 (9)	6					1 (9)
Combined							
VLC 1 g TDS + Occ ACV x5			2 (18)	8 (7 - 9)	1 (9)	3	3 (27)
Total	**2 (18)**	**31 (6-56)**	**6 (55)**	**5 (2 - 9)**	**3 (27)**	**5 (3 - 12)**	**11 (100)**

(%) percentage calculated from total cases of each outcome

Table 3 - 9: Outcomes of patients with SHSK-U associated with six antiviral treatments.

Key: x5 = five times daily, ACV = aciclovir, BD = twice daily, HSK = herpes simplex keratitis, n = number of patients, Occ = ointment, SHSK-U = stromal HSK without ulceration, TDS = three times daily, Time = median duration in days until outcome was measured, VLC = valaciclovir.

	Outcome of SHSK-U						
Antiviral therapy	**Resolved**		**Partial resolution**		**Worsened**		**Total patients**
	[n, (%)]	Time (range)	[n, (%)]	Time (range)	[n, (%)]	Time (range)	[n, (%)]
Topical							
Occ ACV x5			4 (27)	5 (3 - 8)	3 (20)	12 (3 - 14)	7 (47)
Oral							
VLC 500 mg BD	3 (20)	14 (12 - 154)	1 (7)	38			4 (27)
VLC 500 mg TDS			1 (7)	4			1 (7)
VLC 1 g TDS	1 (7)	7					1 (7)
Combined							
VLC 500 mg BD + Occ ACV x5			1 (7)	8			1 (7)
VLC 1 g TDS + Occ ACV x5			1 (7)	6			1 (7)
Total	**4 (27)**	**13 (7 - 154)**	**8 (53)**	**7 (3 - 38)**	**3 (20)**	**12 (3 - 14)**	**15 (100)**

(%) percentage calculated from total cases of each outcome

Table 3 - 10: Outcomes of patients with endothelial HSK associated with four antiviral treatments.

Key: x5 = five times daily, ACV = aciclovir, BD = twice daily, HSK = herpes simplex keratitis, n = number of patients, Occ = ointment, TDS = three times daily, Time = median duration in days until outcome was measured, VLC = valaciclovir.

Antiviral therapy	**Outcome of Endothelial HSK**				
	Resolved		**Partial resolution**		**Total patients**
	[n, (%)]	Time (range)	[n, (%)]	Time (range)	[n, (%)]
Oral					
VLC 1 g TDS	1 (9)	15	5 (45)	8 (3 - 11)	6 (55)
VLC 500 mg BD	2 (18)	39 (36 - 42)			2 (18)
VLC 1 g BD			1 (9)	6	1 (9)
Topical					
Occ ACV x5			2 (18)	7.5 (3 - 12)	2 (18)
Total	**3 (27)**	**36 (15 - 42)**	**8 (73)**	**8 (3 - 12)**	**11 (100)**

(%) percentage calculated from total cases of each outcome

Table 3 - 11: Outcomes of patients with keratouveitis associated with nine antiviral treatments.

Key: x5 = five times daily, BD = twice daily, HSV = herpes simplex virus, n = number of patients, Occ = ointment, od = once daily, TDS = three times daily, Time = median duration in days until outcome was measured, VLC = valaciclovir.

Antiviral therapy	Outcomes of Keratouveitis						
	Resolved		Partial resolution		Worsened		Total patients
	[n, (%)]	Time (range)	[n, (%)]	Time (range)	[n, (%)]	Time (range)	[n, (%)]
Topical							
Occ ACV x5	1 (3)	3	6 (17)	4.5 (2 - 13)	2 (6)	2 (0)	9 (25)
Oral							
VLC 1 g TDS	2 (6)	11 (10 - 12)	5 (14)	3 (2 - 10)	1 (3)	15	8 (22)
VLC 500 mg TDS	1 (3)	32	4 (11)	8.5 (1 - 11)	1 (3)	43	6 (17)
VLC 500 mg BD	1 (3)	8	1 (3)	3	1 (3)	6	3 (8)
ACV 400 mg x5	1 (3)	7	1 (3)	2	1 (3)	49	3 (8)
VLC 500 mg od	1 (3)	7					1 (3)
ACV 200 mg x5	1 (3)	6					1 (3)
Combined							
VLC 1g TDS + Occ ACV x5	1 (3)	8	3 (8)	11 (3 - 12)			4 (11)
VLC 500 mg TDS + Occ ACV x5			1 (3)	4			1 (3)
Total	**9 (25)**	**8 (3 - 32)**	**21 (58)**	**4 (1 - 13)**	**6 (17)**	**10.5 (2 - 49)**	**36 (100)**

(%) percentage calculated from total cases of each outcome

Table 3 - 12: Outcomes of patients with an active HSK with prior corneal graft associated with seven antiviral treatments.

Key: q2h = every two hours, x5 = five times daily, BD= twice daily, HSK = herpes simplex keratitis, n = number of patients, Occ = ointment, QID = four times daily, TDS = three times daily, Time = median duration in days until outcome was measured, TFT = trifluridine, VLC = valaciclovir.

	Outcome of active HSK in a corneal graft						
Antiviral therapy	**Resolved**		**Partial resolution**		**Worsened**		**Total patients**
	[n, (%)]	Time (range)	[n, (%)]	Time (range)	[n, (%)]	Time (range)	[n, (%)]
Oral							
VLC 500 mg BD	3 (17)	15 (9 - 245)	1 (6)	11	2 (11)	4.5 (3 - 6)	6 (33)
VLC 1g TDS	1 (6)	8	3 (17)	5 (2 - 14)			4 (22)
VLC 500 mg TDS			1 (6)	3			1 (6)
ACV 400 mg BD	1 (6)	42					1 (6)
Topical							
Occ ACV x5			2 (11)	5.5 (2 - 9)	1 (6)	13	3 (17)
Occ ACV QID	1 (6)	14					1 (6)
Combined							
VLC 500 mg TDS + Occ ACV QID			1 (6)	7			1 (6)
VLC 1g TDS + TFT q2h	1 (6)	6					1 (6)
Total	**7 (39)**	**14 (6 - 245)**	**8 (44)**	**6 (2 - 14)**	**3 (100)**	**6 (3 - 13)**	**18 (100)**

(%) percentage calculated from total cases of each outcome

3.5.1.3.1 Outcomes in patients with diabetes mellitus in the therapeutic group

Twenty of 252 patients (8%) with therapeutic indication suffered from diabetes mellitus. Nine patients were diagnosed with epithelial HSK, 6 with keratouveitis, 2 with SHSK+U, 1 with SHSK-U ulceration, 1 with endothelial HSK, and 1 with epithelial HSK with a prior corneal graft.

Of the 9 patients with epithelial HSK, an outcome was determined for three patients; two partially resolved and one worsened. Patient 1 partially resolved with an initial antiviral therapy of valaciclovir 1 g three times daily and topical aciclovir five times daily. The treatment was changed at day 2. The reason for this prescription may have been that the patient had history of Ig G4-related disease treated with prednisone and mycophenolic acid (MMF). Patient 2 partially resolved at day 18 with valaciclovir 500 mg three times daily. Patient 3 worsened at day 26 with topical aciclovir five times daily. Topical aciclovir was changed for trifluridine.

An outcome was determined for 9 of the remaining 11 patients from the other HSK disease therapeutic groups. Five patients, 4 with keratouveitis and 1 with SHSK-U, partially resolved between 3 and 13 days with either only oral medications, valaciclovir 500 mg twice daily or valaciclovir 1 g three times daily, or only topical aciclovir five times daily, or a combination of topical and oral agents. Two patients also received topical corticosteroids.

Four patients worsened between 3 to 43 days. Patient 1 with SHSK+U was treated with valaciclovir 1 g three times daily in combination with topical aciclovir five times daily worsened at day 3 due to a corneal perforation. Patient 2 with keratouveitis was treated with topical aciclovir five times daily, worsened at day 2 as the patient did not respond to the treatment. Patient 3 with keratouveitis was treated with valaciclovir 500 mg three times daily, worsened at day 43 due to corneal perforation. Patient 4 with epithelial HSK and corneal graft was treated with topical aciclovir 5 times daily, worsened at day 13 due to developing stromal HSK.

3.5.1.3.2 Outcomes vs HSV PCR result

An outcome was determined for 112 of 166 patients (67%) tested with HSV-PCR. HSV-PCR was positive in 33 of 112 patients (30%), of which 30 (91%) improved. HSV-PCR was negative in 79 of 112 patients, of which 67 (85%) improved (See Table 3 - 13, page 152). There was no association between outcome and HSV PCR result (p = 0.5). For epithelial HSK, SHSK+U, keratouveitis and active HSK with prior corneal groups, over two-thirds of the patients improved having either a positive or negative HSV PCR.

Table 3 - 13: Outcomes of HSK vs HSV PCR result per type of therapeutic indication.

Key: HSV = herpes simplex virus, HSK = herpes simplex keratitis, PCR = polymerase chain reaction test, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration.

	Epithelial HSK (n = 60)	**SHSK+U (n = 9)**	**SHSK-U (n = 7)**	**Endothelial HSK (n = 3)**	**Keratouveitis (n = 23)**	**Prior corneal graft (n = 10)**	**Total (n = 112)**
HSV PCR positive	21	3	0	0	6	3	33
Improved (n, %) †	21 (100)	2 (66.7)	0	0	5 (83.3)	2 (66.7)	30 (90.9)
Worsened (n, %) †	0 (0)	1 (33.3)	0	0	1 (16.7)	1 (33.3)	3 (9.1)
HSV PCR negative	39	6	8	3	17	7	79
Improved (n, %) ‡	37 (94.9)	4 (66.7)	4 (57.1)	3 (100)	13 (76.5)	6 (85.7)	67 (84.8)
Worsened (n, %) ‡	2 (5.1)	2 (33.3)	3 (42.9)	0 (0)	4 (23.5)	1 (14.3)	12 (15.2)

† (%) percentage calculated from total cases of positive HSV PCR.

‡ (%) percentage calculated from total cases of negative HSV PCR.

3.5.1.4 Visual acuity

Initial and final VA was recorded for 161 of 174 (93%) patients with an outcome: 80 patients with epithelial HSK, 10 with SHSK+U, 14 with SHSK-U, 11 with endothelial HSK, 35 with keratouveitis, and 11 with prior corneal graft. LogMAR of 0 is equivalent to 6/6, and a logMAR of 1 is equivalent to 6/60. For epithelial HSK, the median initial VA was similar to the final VA (0.22 vs to 0.18 logMAR; p = 0.27). Fifty-five of 80 patients (68.8%) had a final VA better than 6/12, and 18 patients (22.6%) improved more than 2 lines. For SHSK+U, the median initial VA improved from 0.95 to 0.58 logMAR (p = 0.018). Eight (80%) patients had a final VA better than 6/60. Six patients (60%) improved more than 2 lines. For SHSK-U, the median initial VA improved from 0.59 to 0.36 logMAR (p = 0.1). Half of the patients had a final VA better than 6/12. There was no improvement in final VA for 50% of patients (See Figure 3 - 2, page 154 and Table 3 - 14, page 155).

For endothelial HSK, the median initial VA was similar to the final VA (0.42 vs 0.4 logMAR; p = 0.39). Five patients (45.5%) had a final VA better than 6/12. For keratouveitis, the median initial VA worsened from 0.34 to 0.48 logMAR (p = 0.34). The final VA either remained stable or worsened compared to the initial VA in 25 patients (71%). For patients with a prior corneal graft, there was no change from the median initial VA of 1.0 to the final median VA of 0.9 logMAR (p= 0.36). Eight patients (72.7%) had a final VA between 6/15 and 6/60. Despite the moderate visual outcome, four patients (36.4%) improved more than 2 lines (See Figure 3 - 2, page 154 and Table 3 - 14, page 155).

3.5.1.5 Adverse events

Thirty-six of 252 patients (14%) with HSK had 42 adverse events recorded including corneal perforation [n = 8 (3%)]; secondary bacterial keratitis requiring intensive topical antibiotics [n = 7, (3%)]; non-healing ulcer [n = 6, (2%)]; ocular toxicity due to topical aciclovir [n = 6, (2%)]; and systemic side effects due to antiviral medications [n = 4, (2%)] such as constipation, dizziness, stomach pain due to valaciclovir (See Table 3 - 15, page 156)

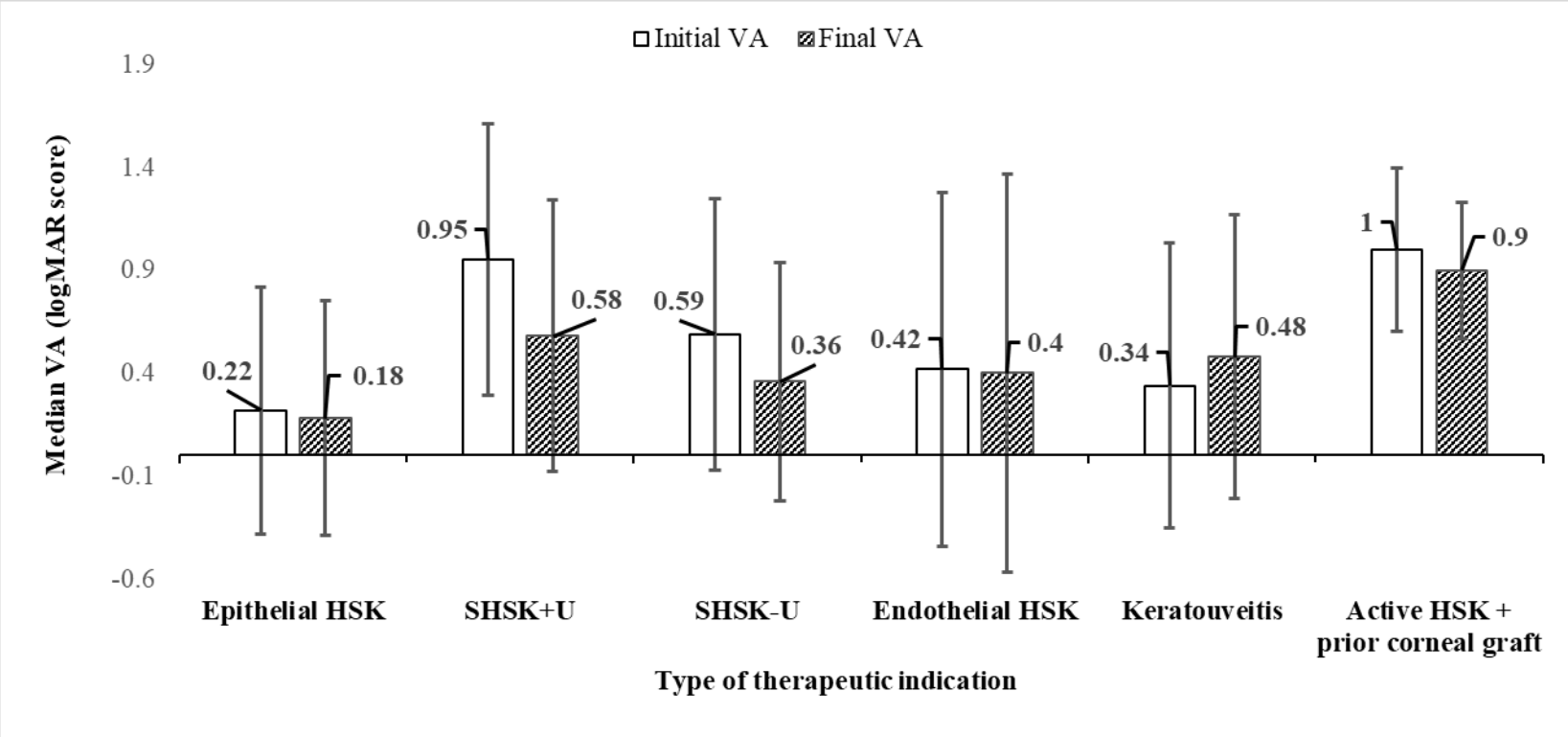


Figure 3 - 2: Median initial VA and final VA in logMAR for the different therapeutic indication for antiviral therapy.

Key: HSK = herpes simplex keratitis, logMAR= logarithm of the minimum angle of resolution, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration, VA = visual acuity.

Table 3 - 14: Visual outcomes associated with different antiviral therapy indications and classification.

Key: HSK = herpes simplex keratitis, HSV = herpes simplex virus, n = number of patients, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration, VA = visual acuity.

Visual acuity	Type of antiviral indication						
	Epithelial HSK (n = 80)	**SHSK+U (n = 10)**	**SHSK-U (n = 14)**	**Endothelial HSK (n = 11)**	**Keratouveitis (n = 35)**	**Prior corneal graft (n = 11)**	**Prophylaxis (n = 35)**
Final VA							
6/12 or better	55 (68.8)	4 (40)	7 (50)	5 (45.5)	14 (40)	0 (0)	6 (17.1)
6/15 - 6/60	17 (21.3)	4 (40)	5 (35.7)	4 (36.4)	15 (42.9)	8 (72.7)	18 (51.4)
6/75 or worse	8 (10)	2 (20)	2 (14.3)	2 (18.2)	7 (20)	3 (27.3)	10 (28.6)
Change in VA from presentation							
Worsened	27 (33.8)	0 (0)	2 (14.3)	4 (36.4)	12 (34.3)	2 (18.2)	16 (45.7)
No improvement	20 (25)	3 (30)	7 (50)	2 (18.2)	13 (37.1)	3 (27.3)	6 (17.1)
Improvement							
2 - 3 lines	11 (13.8)	4 (40)	1 (7.1)	4 (36.4)	2 (5.7)	1 (9.1)	6 (17.1)
4 - 5 lines	3 (3.8)	0 (0)	0 (0)	1 (9.1)	1 (2.9)	2 (18.2)	0 (0)
> 6 lines	4 (5)	2 (20)	4 (28.6)	0 (0)	1 (2.9)	1 (9.1)	2 (5.7)

Table 3- 15: Adverse events observed in 36 patients as a proportion of eyes affected (n=252 patients), stratified by therapeutic group.

Key: n = number of patients, IOP = intraocular pressure, PEE = punctuate epithelial erosions, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration.

Type of adverse event	Type of therapeutic indication						
	Epithelial HSK (n = 123)	**SHSK+U (n = 19)**	**SHSK-U (n = 22)**	**Endothelial HSK (n = 14)**	**Keratouveitis (n = 49)**	**Prior corneal graft (n = 25)**	**Total patients (n = 252)**
Corneal perforation [n, %]	1 (0.8)	2 (10.5)	3 (13.6)	0 (0)	1 (2)	1 (4)	8 (3.2)
Secondary microbial keratitis requiring intensive topical antibiotics [n, %]	3 (2.4)	2 (10.5)	0 (0)	0 (0)	1 (2)	1 (4)	7 (2.8)
Non-healing ulcer	2 (1.6)	0 (0)	1 (4.5)	0 (0)	1 (2)	2 (8)	6 (2.4)
Ocular toxicity (due to topical aciclovir) [n, %]	5 (4.1)	0 (0)	0 (0)	1 (7.1)	0 (0)	0 (0)	6 (2.4)
Side effect to antiviral [n, %]	1 (0.8)	0 (0)	0 (0)	0 (0)	3 (6.1)	0 (0)	4 (1.6)
Allergy to antiviral [n, %]	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	2 (0.8)
Other † [n, %]	2 (1.6)	3 (15.8)	2 (9.1)	0 (0)	1 (2)	1 (4)	9 (3.6)

Table 3 – 15 (continued)

Type of adverse event	Type of therapeutic indication						
	Epithelial HSK (n = 125)	**SHSK+U (n = 19)**	**SHSK-U (n = 22)**	**Endothelial HSK (n = 14)**	**Keratouveitis (n = 49)**	**Prior corneal graft (n = 25)**	**Total patients (n = 252)**
Total	15 (12.2)	7 (36.8)	6 (27.3)	1 (7.1)	8 (16.3)	5 (20)	42 (16.7)

Note: Six patients had more than one complication. Hence 42 adverse events were documented.

† Other adverse events per type of therapeutic indication:

Epithelial HSK: Keratouveitis (n = 1), PEE (n = 1), SHSK-U: descemetocele (n = 1), PEE (n = 1), SHSK+U: Evisceration due to corneal perforation secondary to severe microbial keratitis (n = 1), conjunctivitis (n = 1), persistent stromal oedema (n = 1), Keratouveitis: IOP elevation (n = 1), Prior corneal graft: Episcleritis (n = 1).

3.5.1.6 Admission of patients with therapeutic indication

Twenty-four of 252 patients (10%) with a therapeutic indication were admitted to the Sydney Eye Hospital. The indications for admission included the treatment of HSK or the management of complications after commencing the antiviral therapy for HSK. The median length of stay at the hospital was 7 days [interquartile range (IQR) 4 - 14 days, range 1 - 45 days]. Patients diagnosed with stromal HSK, and those with active HSK with prior corneal graft were most frequently admitted. The number of admissions per group was as follows: 10 of 25 patients (40%) with an active HSK and prior corneal graft, 5 of 22 patients (23) with SHSK-U, 4 of 19 (21%) patients with SHSK+U, 2 of 49 patients (4%) with keratouveitis, and 3 of 123 patients (2%) with epithelial HSK. Patients with endothelial HSK were not admitted for their treatment.

3.5.1.6.1 Reasons for admission

Fifteen of 24 patients (62.5%) were admitted for the management of HSK. Of these, 10 (66%) had a history of corneal graft. The most common indication of admission was corneal perforation in 5 patients. Of these, 3 were diagnosed with SHSK-U, 1 with SHSK+U, and 1 with keratouveitis. Other indications included graft rejection (n = 2), stromal HSK (n = 2), prior corneal graft (n = 2) and history of immunosuppressive conditions (n = 2), persistent epithelial defect and prior corneal graft (n = 1), and ptosis surgery and history of corneal graft (n = 1) (See Table 3 - 16, page 159).

Five of 24 patients (21%) had the admission after commencing the antiviral therapy at a median time of 5 days. Indications for these admissions included development of stromal HSK, corneal perforation, persistent epithelial ulcer, episcleritis and corneal abscess. One of 24 patients (4%) had the admission 129 days after commencing antiviral therapy for a superficial keratectomy. The remaining 3 of 24 patients (12.5%) were admitted to the hospital due to a corneal graft operation, persistent corneal ulcer, and a retained OVD and increased intraocular pressure. These three patients presented the HSK episode at a median time of 4 days during the admission.

Table 3 - 16: Causes of admission for patients with a therapeutic indication.

Key: AMT = amniotic membrane transplant, DALK = deep anterior lamellar keratoplasty, EHSK = epithelial HSK, ENHSK = endothelial HSK, HSK = herpes simplex keratitis, IOP = intraocular pressure, KU = keratouveitis, LSCF = limbal stem cell failure, MMF = mycophenolate, OVD = ophthalmic viscosurgical device, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration.

Case No	Initial diagnosis	History of HSK	Indication of admission	Length of stay	Admission on date of presentation
1	EHSK	Yes	Ig G4-related disease, use of MMF and oral prednisone	5	Yes
2	EHSK	No	Developed stromal HSK	9	No
3	EHSK	No	For DALK. History of keratoconus. Presented epithelial ulcer during admission. Extended admission due to non-healing ulcer and secondary bacterial keratitis.	45	No
4	SHSK+U	Yes	Developed corneal perforation	5	No
5	SHSK+U	Yes	Corneal perforation	16	Yes
6	SHSK+U	Yes	Stromal thinning, central defect, vascularised neurotrophic ulcer	4	Yes
7	SHSK+U	No	Stromal HSK vs microbial keratitis	7	Yes
8	SHSK-U	Yes	Corneal perforation	14	Yes

Table 3 – 16 (continued)

Case No	Initial diagnosis	History of HSK	Indication of admission	Length of stay	Admission on date of presentation
9	SHSK-U	Yes	Corneal perforation	9	Yes
10	SHSK-U	Yes	Superficial keratectomy and vessel cautery	5	No
11	SHSK-U	Yes	Polymyalgia rheumatica, use of oral prednisone	15	Yes
12	SHSK-U	Yes	Corneal perforation	7	Yes
13	KU	No	Non-healing ulcer. History of LSCF	20	No
14	KU	Yes	Corneal perforation	9	Yes
15	ENHSK	No	Prior corneal transplant	6	Yes
16	EHSK	Yes	Prior corneal transplant	6	Yes
17	EHSK	No	Prior corneal transplant and keratoconus. Non-healing ulcer	27	No
18	EHSK	Yes	Prior corneal transplant. Admission for ptosis surgery. Presented epithelial ulcer during admission	1	Yes
19	EHSK	No	Prior corneal transplant. Graft rejection	4	Yes
20	EHSK	Yes	Prior corneal transplant. Episcleritis	3	No
21	EHSK	No	Prior corneal transplant. Developed corneal abscess	13	No
22	EHSK	No	Prior corneal transplant. Persistent epithelial defect for AMT	4	Yes

Case No	Initial diagnosis	History of HSK	Indication of admission	Length of stay	Admission on date of presentation
23	KU	No	Prior corneal transplant. Retained OVD and increased IOP	12	No
24	SHSK+U	No	Prior corneal transplant. Graft rejection	2	Yes

3.5.1.6.2 Outcomes of patients with admissions

The outcomes for these patients were diverse. The most common outcome was 'partially resolved' in 8 of 24 patients (33%); 4 with a prior corneal graft, 2 with SHSK-U, 1 with SHSK+U and 1 with epithelial HSK. Six patients (25%) had a 'resolved' outcome and 6 patients (25%) a 'worsened' outcome. The initial diagnosis of HSK changed in two patients (8.3%). One patient had an initial diagnosis of SHSK+U, but the diagnosis was changed to bacterial keratitis after *Staphylococcus warneri* was isolated in the broth culture of corneal scrapings. The other patient was initially diagnosed with keratouveitis and had a prior corneal graft. The patient, with a history of keratoconus, was admitted post-operatively due to a retained optical viscosurgical device (OVD) and elevated intraocular pressure. As the patient did not have a history of HSK and the HSV PCR was negative, clinicians treated the inflammation (possible non-HSV uveitis) with topical corticosteroids and oral prednisone. Two patients were lost to follow up (See Table 3 - 17, page 162).

Table 3 - 17: Outcomes of 24 patients with HSK admitted at the Sydney Eye Hospital.

Key: n = number of patients, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration.

Outcome	**Type of therapeutic indication**					
	Epithelial HSK n = 123	**SHSK+U n = 19**	**SHSK-U n = 22**	**Keratouveitis n = 49**	**Prior corneal graft n = 25**	**Total n = 252**
Resolved	1 (4.2)		3 (12.5)		2 (8.3)	6 (25)
Partially resolved	1 (4.2)	1 (4.2)	2 (8.3)		4 (16.7)	8 (33.3)
Worsened	1 (4.2)	1 (4.2)		2 (8.3)	2 (8.3)	6 (25)
Lost to follow up		1 (4.2)			1 (4.2)	2 (8.3)
Not HSK		1 (4.2)			1 (4.2)	2 (8.3)
Total	3 (12.5)	4 (16.7)	5 (20.8)	2 (8.3)	10 (41.7)	24 (100)

3.5.2 Prophylactic indication

The mean age in the prophylactic group was 65 years ± 17 and half were male. Approximately two-thirds resided in the Sydney greater metropolitan area (See Table 3 - 1, page 132). There were 17 right eyes (39%), 26 left eyes (59%) and one (2%) bilateral case.

At initial presentation, 36 of 44 patients (81%) were on oral antiviral prophylaxis with aciclovir (n = 8), valaciclovir (n = 27), or famciclovir (n = 1). Another 3 of the 44 patients (7%) were on topical antiviral medications and 30 (68%) were on topical corticosteroid therapy. Oral antiviral agents were initially prescribed to 40 of 44 patients (90%) with a prophylactic indication with 86% (38 of 44) of patients also receiving topical corticosteroids (See Table 3 - 2, page 133).

3.5.2.1 Medical and ocular history

Four patients suffered from diabetes mellitus, one from HIV syndrome, and one had a prior use of oral steroids. Fourteen of 44 patients (31%) had had a prior corneal graft; with penetrating keratoplasty the most common graft (n = 12). Forty-eight previous HSK episodes were reported in 44 patients. The most common types of 'prior' HSK were keratouveitis (n = 23) and stromal (n = 13). Twenty of 44 (45%) patients had a non-HSV related pre-existing eye condition limiting their visual acuity in the affected eye with HSK. Corneal pathology (n = 7) and glaucoma (n = 6) were the most common conditions. None of the patients on prophylaxis was a contact lens wearer.

3.5.2.2 Diagnostic tests

Twenty-three of 44 patients (52%) with prophylactic indication had an HSV PCR test performed at any point in time. Of these, only one patient had the test performed at the initial visit, the result of which was positive for HSV-1. The remaining 22 patients (48%) had the test performed prior to the initial visit. Of these, 12 were positive for HSV-1 and 10 were negative (See Table 3 -18, page 164).

Table 3 -18: Number of HSV PCR tests in 44 patients on prophylaxis for HSK.

Key: n = number of patients, PCR = polymerase chain reaction.

PCR result	n (%)
Never performed	21
Previous positive	12
Previous negative	10
Current positive	1
Current negative	0
Rate of current positivity	1/1 (100%)

3.5.2.3 Clinical outcomes

An outcome was determined in 36 of 44 (82%) patients on prophylaxis. The remaining 8 (18%) were lost to follow up (See Figure 3 - 1, page 142). Valaciclovir 500 mg once daily was the most common antiviral therapy in 27 (75%) patients. Twenty-six of 36 patients (72%) had a 'success' outcome with a median duration of 528 days (IQR 215 - 829, range 14 - 938), or the equivalent of 19 months. Of these, 18 received the most common treatment, valaciclovir 500 mg once daily, with median duration of 714 days (IQR 314 - 844, range 55 - 938). Ten of 36 patients (28%) presented with an HSK recurrence after a median duration of 70 days (IQR 23 – 242, range 11 - 610). Of these, 9 patients had received valaciclovir 500 mg once daily, for a median duration of 90 days (IQR 22 – 345, range 11 - 610) (See Table 3 - 19, page 165). Three patients received valaciclovir 500 mg twice daily. All three patients had a 'success' outcome at a median time of 182 days or equivalent of 6.5 months. There was a no significant difference in the outcomes between valaciclovir 500 mg once daily vs valaciclovir 500 mg twice daily ($p = 0.53$)

Thirty-one of 36 patients (86%) with a known outcome received topical corticosteroid therapy and of these, 11 had a corneal graft. The median duration of this

therapy was 221 days (range 1 - 861). Twenty-one (68%) patients had a 'success' outcome.

Table 3 - 19: Outcomes of patients on prophylaxis for HSK associated with eight antiviral treatments.

Key: ACV = aciclovir, BD = twice daily, failure = recurrence of HSK, HSK = herpes simplex keratitis, n = number of patients, Occ = ointment, od = once daily, PRN = per necessary, Success = no recurrence, TDS = three times daily, time = median duration in days until outcome was measured, TFT = trifluridine, VLC = valaciclovir.

Prophylactic antiviral therapy	**Success**		**Failure**		**Total patients n, (%)**
	n, (%)	Time (range)	n, (%)	Time (range)	
VLC 500 mg od	18 (50)	714 (55-938)	9 (25)	90 (11-610)	27 (75)
VLC 500 mg BD	3 (8)	182 (42-521)			3 (8)
ACV 200 mg BD			1 (3)	26	1 (3)
ACV 400 mg od	1 (3)	462			1 (3)
ACV 400 mg BD	1 (3)	861			1 (3)
ACV 400 mg TDS	1 (3)	70			1 (3)
Occ ACV x5	1 (3)	14			1 (3)
TFT PRN	1 (3)	791			1 (3)
Total	26 (72)	528 (14-938)	10 (28)	70 (11-610)	36 (100)

3.5.2.3.1 Outcomes in patients with immunosuppressive conditions in the prophylactic group

The most common immunosuppressive condition was diabetes mellitus in 4 of 36 (11%) patients. Of these, 3 had a 'success' outcome. Patient 1 received valaciclovir 500 mg once daily for 24 months. Patient 2 also received valaciclovir 500 mg once daily for 19 months. Patient 3 received aciclovir 400 mg twice daily for 30 months. One patient had a failure outcome as presented with a recurrence of the infection at day 14.

One patient with HIV had received trifluridine as per necessary for 28 months without experiencing any recurrence. The patient had a history of epithelial HSK and stromal HSK. One patient on oral prednisone for recurrent uveitis received aciclovir 200 mg twice daily for prophylaxis. The patient presented with a recurrence at day 26.

3.5.2.4 Visual outcome

Initial and final VA were recorded in 35 eyes following prophylaxis. The median VA improved from 0.86 logMAR (range 0.10 - 2.30) at presentation to 0.83 logMAR (range 0.10 - 2.3), $p = 0.47$. Half of the patients had a final VA between 6/15 and 6/60. About a third of patients (n = 10, 29%) had a final VA of 6/75 or worse and 6 patients (17%) a final VA of 6/12 or better. Eight patients (23%) improved more than 2 lines from initial presentation.

3.5.2.5 Adverse events

Four of 36 (11%) patients on HSK prophylaxis had adverse events during the initial antiviral therapy. These included side effects due to valaciclovir (stomach pain), a descemetocele, band keratopathy, and a recurrence of HSK with a secondary bacterial keratitis

3.5.2.6 Admission of patients with prophylactic indication

Seven of 44 patients (16%) had an admission to hospital. The median time of length of stay in hospital was 3 days (IQR 1 - 5, range 1 - 10). The most common indication of admission was corneal transplantation in 4 patients. Other indications included corneal graft repair (n = 1), management of open angle closure glaucoma (n = 1) and management of endophthalmitis (n = 1). The prophylactic antiviral therapy was started at different stages in 5 patients admitted for a corneal transplantation or repair graft rupture surgery. The prophylaxis was started on the day of admission before the surgery in 2 patients and one day after the surgery in other 2 patients. The remaining patient had a PK performed 3 months after the prophylactic therapy was started due to history of stromal HSK and LK (See Table 3 - 20, page 167).

In terms of outcomes, prophylactic antiviral therapy was successful in 3 of 7 patients. One patient had a 'failure' outcome as he was admitted for endophthalmitis after repeat graft and the corneal button result showed an HSV crystalline keratopathy An outcome could not be determined for 3 patients as they only had the surgeries performed at the hospital and were followed up by the treating ophthalmologist in their private rooms.

Table 3 - 20: Indications of admission for 7 patients with prophylactic indication for antiviral therapy in HSK.

Key: DALK = Deep anterior lamellar keratoplasty, PK= penetrating keratoplasty.

Case No	Indication of admission	Length of stay	Current medications at initial presentation
1	DALK	1	Oral valaciclovir
2	Developed endophthalmitis one month after repeat PK	10	Topical corticosteroid
3	PK	4	No
4	DALK	1	No
5	Repair graft rupture	5	Oral valaciclovir and topical corticosteroid
6	PK and cataract surgery	3	No
7	Open angle closure glaucoma	1	Oral famciclovir and topical aciclovir

3.6 Discussion

In this chapter, the medical and ocular history, diagnostic tests and clinical outcomes of HSK in adults presenting to the Sydney Eye Hospital in 2012 - 2013 have been reported. Two-hundred and ninety-six patients were included, of these, 252 patients (85%) received antiviral medications for a therapeutic and 44 (15%) for a prophylactic indication. For the therapeutic indication, the most common immunosuppressant condition was diabetes mellitus in 20 patients (8%). The most common ocular pre-existing eye conditions limiting visual acuity were corneal pathology aside HSK (n = 28) and glaucoma (n = 22). Ninety-six (38%) patients had a prior HSK episode and 46 (18%) patients were on topical corticosteroid use at initial presentation. Twenty-five (10%) patients had a prior corneal transplant. Half of the patients from the therapeutic group were diagnosed with epithelial HSK. Topical aciclovir was the most common antiviral medication given for epithelial and SHSK+U. Valaciclovir was the most common oral antiviral medication for all types of HSK. Most patients with endothelial HSK; two-thirds of the patients with keratouveitis, and two-thirds with a prior corneal graft received topical corticosteroids in addition to antiviral therapy for one to two weeks. Half of the patients with a therapeutic indication partially resolved with the initial antiviral therapy given. Adverse events occurred approximately in 1 out of 5 patients with a therapeutic indication. The most common adverse events were ocular toxicity due to topical aciclovir, for epithelial HSK; and corneal perforation, for stromal HSK. Over half of patients with any type of indication except epithelial HSK had a final VA worse than 6/15.There was a trend towards improvement in the final VA of the patients with SHSK+U and with SHSK-U. The difference was statistically significant only for patients with SHSK+U.

For the prophylactic indication, corneal pathology (n = 7) and glaucoma (n = 6) were the most common conditions limiting vision acuity; and diabetes mellitus the most common systemic condition (4 of 44, 9%). Fourteen of 44 patients (31%) had a prior corneal graft. Most of the patients in the prophylactic group received an oral antiviral medication and a topical corticosteroid as initial therapy, due to previous stromal HSK or herpetic keratouveitis. Valaciclovir 500 mg once daily was the most common antiviral

prescribed (n= 27, 75%) for prophylaxis. The prophylactic therapy prevented HSK recurrence in 72% of patients. Half of the patients had a final VA between 6/15 and 6/60. One of 10 patients presented an adverse event.

Differential diagnosis

The differential diagnosis of HSK includes other infectious (acanthamoeba, HZV, Epstein-Barr virus, adenovirus, bacteria, fungi) and non-infectious conditions (epithelial regeneration lines after abrasion, neurotrophic keratopathy, recurrent epithelial erosion, persistent epithelial defect, exposure keratopathy). [23] In our study, 5% of patients (16 of 296) were misdiagnosed as HSK. Epithelial HSK (n = 5) and stromal HSK (n = 5) were the most misdiagnosed conditions. After the initial antiviral therapy and a negative HSV PCR result, the diagnosis was changed in 4 patients to either HZK (n = 2) or corneal erosion (n = 2). The final diagnosis was not specified on the medical notes for another patient. The diagnosis for 2 patients with SHSK+U was changed to bacterial keratitis and corneal erosion and for 3 patients with SHSK-U to marginal keratitis (n=2) and HZK (n=1). These final diagnoses were among the most common probable diagnoses for the clinical presentation of HSK. HZK presents with small, fine pseudodendrites with similar branching pattern to dendrites seen in epithelial HSK. [132] Corneal erosion syndrome symptoms are similar to HSK (pain, redness, photophobia and tearing). Corneal epithelial defects, stromal infiltrates and opacities may be present. [133] All these clinical features may resemble epithelial HSK or stromal HSK. Further, acanthamoeba keratitis can be easily confused with HSK in early stages and with bacterial or fungal keratitis in late stages. [134] There was only one final diagnosis of bacterial keratitis and no diagnosis of acanthamoeba keratitis.

Medical and ocular predisposing factors

<u>Diabetes mellitus</u>

Any immunosuppressive condition increases the risk of frequent recurrence of HSK or severe HSV disease. [23] Diabetes mellitus was the most common immunosuppressive condition in our study. Diabetes mellitus is a condition

characterised by elevated blood glucose levels due to deficiencies in insulin secretion, insulin action, or both. [135] Patients with long standing diabetes may have an impaired cell immunity affecting their response to infections. [23] There is conflicting evidence about a possible association of diabetes mellitus and HSK. In our therapeutic group, 8% of patients (20 of 252) had a history of diabetes mellitus which compares with the prevalence of diabetes in the general Australian population (6%). [136] The proportion of patients in our study was comparable to the proportion found in a prospective, observational study in New Zealand which was 4.8% (6/125). [137] Unfortunately, we could not correlate diabetes mellitus and ethnicity in our study as ethnicity data was not collected. Further, the New Zealand study found no association between HSK and diabetes mellitus ($p = 0.62$). [137]

About half of our patients (9 of 20) with diabetes mellitus presented with epithelial HSK. An outcome was determined for 3 of these patients, 2 partially resolved and 1 worsened. One patient on valaciclovir 500 mg three times daily, partially resolved almost three weeks after presentation, much longer than the usual healing time (7 - 14 days). [81, 83-85] Another patient on valaciclovir 1 g three times daily and topical aciclovir five times daily, partially resolved at day 2. Another patient treated with topical aciclovir 5 times daily, worsened at day 26 of treatment. The long healing time of the first patient and the prolonged topical therapy of the third patient may have been due to diabetes mellitus. Patients with diabetes mellitus apparently have impaired cell mediated immunity and have higher risk of presenting with more severe infections. [26] Eleven of 20 patients with diabetes mellitus presented with other types of HSK. An outcome was determined for 9 of 11 patients. Of these, 5 of 9 (55%) patients partially resolved within 2 weeks. Of these, 2 received topical corticosteroids in addition to antiviral therapy. On the other hand, 3 of 9 patients worsened within 2 weeks and one worsened at day 43; none of these patients received topical corticosteroids. The lack of topical corticosteroid therapy in these patients may have caused the poor outcomes rather than the comorbidity with the diabetes mellitus.

Corticosteroid use

Corticosteroid use may have a possible association with HSV reactivation. However, the impact of chronic corticosteroid use on HSK had not been investigated. [137] A New Zealand study reported that 20% (25 of 125) of HSK patients were corticosteroid users. This proportion encompassed the use of topical creams (n = 8), asthma inhalers (n = 8), nasal sprays (n = 4), oral medication (n = 4), and intramuscular injections (n = 1). Moreover, 89% of corticosteroid users were diagnosed with epithelial HSK. [137] It was difficult to compare our proportion of corticosteroid use with that in the New Zealand study as we only collected data on oral corticosteroid use. Nevertheless, we can comment that a similar proportion of oral corticosteroid use was found in our case series (3.2% [4/125] vs 4% [11/252]).

Previous HSK

Reactivation of HSV may occur after initial HSV infection. The New Zealand study reported that 52% of HSK patients had history of HSK. The study demonstrated a 3-fold increase in odds of HSK in patients with a history of HSK than in those without previous episodes. [137] In our study, 38% of the patients had a history of HSK, lower than the New Zealand study. The immune system may provide some defense to reactivation, but it may occur in periods of immunocompromise such as stress, medications or illness. [137]

Polymerase chain reaction test

Polymerase chain reaction test is a highly sensitive diagnostic test for HSK. [19, 63] Its diagnostic power varies depending on the type of HSK, previous aciclovir therapy, use of topical anaesthetics or dyes, and viral load in the specimen. [138] PCR most likely identifies patients with a typical lesion as it is a manifestation of active viral infection. [19] In our study, clinicians requested most of the PCR tests in patients with a provisional diagnosis of epithelial HSK (76%), SHSK+U (74%) and keratouveitis (67%). The positivity rate was 36% in the epithelial HSK group, 29% in the SHSK+U group and 18% in the keratouveitis group. Stromal HSK is thought to occur due to an immune

response to the virus rather than via viral infection. [19] It is also assumed that stromal HSK and endothelial HSK are recurrent episodes [1] and the patients may have a previous positive PCR result. Due to the absence of an epithelial defect, it is not possible to access the stroma and therefore to obtain a sample of the area affected. This may explain the negative PCR results for this type of HSK. [19] This may be the reason why clinicians did not request as many PCR tests on patients with SHSK-U (50%) and endothelial HSK (21%) as they did for patients with epithelial HSK (76%) and SHSK+U (74%). The positivity rate for both, SHSK-U and endothelial HSK was 0% coinciding with the above hypothesis.

Further, another factor may be the cost of the PCR. A PCR test is an expensive test requiring skilled technicians and costly equipment. [23] The positivity rate for patients with active HSK with prior corneal graft may depend on the type of HSK that they manifest. Clinicians requested a PCR test in 40% of these patients. The positivity rate was 27% (3 of 11 patients) as two patients presented with epithelial HSK and one patient with SHSK+U. This confirms that the PCR test tends to be positive in patients with epithelial HSK. In summary, reasons for the low positivity rate may include previous or current antiviral therapy, low viral load, use of fluorescein or topical anaesthetics leading to false negative results or the immune response of keratouveitis. In addition, for herpetic keratitis without ulceration including endotheliitis a swab of the superficial cornea may not have accessed the corneal layers with viral activity.

Similarly, the mechanism of recurrent infection is unclear. In our patients with a prophylactic indication for antiviral therapy, only one had a PCR test requested for which the result was positive. This patient had a history of keratouveitis, was receiving topical corticosteroids but no antiviral medications at the initial presentation. A PCR test is not usually requested to these patients during review visits to the ophthalmologists. It is unclear the reason that a PCR was performed in this patient. It may have simply been that a new trainee doctor requested the test.

Outcomes

Antiviral therapy for epithelial HSK has been widely investigated. Currently, there are several agents available to treat this condition. [23] The choice of antiviral therapy depends on the likely efficacy and the availability of the product, patient's tolerance of the medication and the previous response to the medication. In Australia, topical aciclovir is the preferred topical agent, and valaciclovir the preferred oral agent, both being readily available. In our study, 50% (123/252) of the patients with a therapeutic indication were diagnosed with epithelial HSK. Of these patients, 112 (91%) received topical aciclovir five times daily, as recommended by different clinical trials and systematic reviews. [1, 7, 79-81, 84] Most of the patients either resolved or partially resolved within a week. This is similar to the results of RCTs which have reported healing times within 14 days. [7, 79-81, 84, 85] In summary, our findings support the use of topical aciclovir as a an effective and safe for epithelial HSK. [7, 82, 83]

The HEDS clinical trials provided significant evidence for the management of stromal HSK, specifically for SHSK-U. [3] A prophylactic dose of an oral antiviral medication and topical corticosteroid for at least 10 weeks were recommended for the management of stromal HSK. In our study, a third of the patients with stromal HSK (13/41) received topical corticosteroids in addition to antiviral medication. An outcome was determined for 7 of 13 patients. Of these, one (14%) had a 'worsened' outcome. The remaining 28 patients with stromal HSK did not receive adjuvant topical corticosteroids. An outcome was determined for 19 of 28 patients (68%). Of these, 5 (26%) patients had a 'worsened' outcome. There was no statistically difference between prescription of topical corticosteroids and outcomes (p = 0.8). Although, the number of patients with stromal HSK was small to achieve statistically conclusions; these findings support the HEDS trial data suggesting that patients receiving topical corticosteroid medication in addition to antiviral medication may have a better outcome

With respect to the initial antiviral therapies for stromal HSK, we found 6 different regimes with topical aciclovir five times daily the most prescribed (19 of 41 patients, 46%). [23] For SHSK+U, half of the patients (n = 5, 45.5%) received topical

aciclovir five times daily. Of these, 3 partially resolved within a week and two worsened in 9 days. Another 3 patients received oral valaciclovir. Two patients resolved at a median time of 31 days and one partially resolved in 7 days. There was no statistically significant difference between the outcomes of topical vs systemic antiviral medications (p = 0.09). For SHSK-U, half of the patients (n = 7, 46.7%) received topical aciclovir five times daily. Of these, 4 partially resolved in 5 days and 3 worsened in 12 days. Four patients on valaciclovir resolved within 2 weeks. There was statistically significant difference between the outcomes of topical vs systemic antiviral medications (p = 0.02). This significant difference between the outcomes and types of antiviral agents is not conclusive due to small number of patients. Reasons for the low proportion of resolved outcomes may be due to the use of topical aciclovir therapy or to the lack of topical corticosteroid therapy. Oral antiviral agents are preferred over topical agents for their higher safety for long periods of time and for better corneal penetration. [23] Our initial antiviral regimens clearly differed from the evidence-based recommendations. [1-3]

The diverse prescribing behaviour for stromal HSK in our series may reflect that clinicians at our institution were not referring to published medical literature when prescribing for stromal HSK and/or were concerned of worsening the condition with topical steroids in case it was microbial keratitis. Notably, our study was conducted prior to publication of the results of the Steroids for Corneal Ulcers Trial (SCUT). In fact, 2% (1 of 41) of patients initially diagnosed with stromal HSK were found to eventually have a diagnosis of bacterial keratitis. One third of our patients (13 of 41) with stromal HSK had an adverse event, being corneal perforation and microbial keratitis the most common. This differs from the HEDS I clinical trials where the adverse reactions were infrequent and more numerous in the placebo group (treatment with trifluridine and topical corticosteroids). [3] It appears that raising clinician awareness of the benefits of topical corticosteroids in HSK will likely be an important step in improving outcomes.

A few studies have provided evidence for the management of endothelial HSK. [87, 88, 139] In our study, about a quarter of patients (n = 3/11, 27%) with endothelial HSK resolved at a median time of 36 days. All the patients received in addition a topical

corticosteroid. Previous studies have reported healing times of endothelial HSK at 22 and 26 days. [88, 139]

The median initial and final VA were similar for patients with endothelial HSK. This differs from the results from Porter where there was a significant improvement between initial and final VA for the group receiving oral aciclovir five times daily and a topical corticosteroid (mean change in VA 0.28 logMAR, $p = 0.28$). [88] This could reflect the heterogenous nature of HSK endotheliitis, with patients in our series having disease sparing the visual axis or other conditions affecting vision, such as cataract (n = 1) and retinal pathology (n = 2).

There is a lack of studies investigating clinical outcomes of herpetic keratouveitis. The HEDS III clinical trial was used to compare the results of our keratouveitis group. This trial investigated the role of oral aciclovir in treating HSV iridocyclitis. The number of patients recruited was too small to show statistically significant results, but the results suggested the benefit of adding oral aciclovir to a regimen of trifluridine and a topical corticosteroid for this condition. [4] In our study, 6 of 36 (17%) patients with keratouveitis, treated with different dosages of topical and oral antiviral medications, 'worsened' at a median time of 10.5 days. Of these, two patients received concurrent topical corticosteroids. Our proportion of failed treatment is lower than the proportions found in the HEDS III clinical trial: 50% for the aciclovir group and 68% for the placebo group. [4] Further, most of our patients (84%) either resolved or partially resolved. Nine patients (25%) resolved at a median time of one week and of these, 6 also received a topical corticosteroid. The remaining 21 patients (58%) partially resolved at a median time of 4 days and 12 patients received corticosteroids. There was no statistically difference between type of antiviral therapy (topical, oral or combination) and outcomes ($p = 0.6$). The high proportion of partially resolved patients may be due to low doses of valaciclovir (500 mg twice or three times daily), use of topical aciclovir, and/or lack of topical corticosteroid therapy in our series. Clinicians may therefore consider antiviral doses of valaciclovir of 1 g three times daily, or equivalent along with topical corticosteroids as suggested by Cunningham. [89]

To our knowledge, there are no studies reporting the clinical outcomes of patients with a history of corneal grafting and an active HSK episode. A third of the patients (n = 6) received valaciclovir 500 mg twice daily which was the most common prescription. Of these, 3 resolved at a median time of two weeks. Further, about two-thirds of patients (15 of 25) received topical corticosteroids. The topical corticosteroids were given for a median time of 11 days (range of 1-35 days). Three of 15 patients (20%) on topical corticosteroids presented with graft rejection compared with one of 10 patients (10%) who did not receive topical corticosteroids. There was no statistically significant difference (p = 0.6). Despite the variety of initial antiviral therapies, 83% of patients (n = 15) with an HSK episode resolved or partially resolved within 2 weeks. The higher rate of resolution could have been due to the concomitant use of topical corticosteroids. Treatment recommendations are needed to standardise initial antiviral therapy for these cases to improve outcomes as recurrent disease may lead to graft failure. [47]

Permanent visual loss is associated with recurrent HSK episodes and typically occurs due to corneal scarring. In our study, most of the patients with a prophylactic indication had a history of either stromal HSK or keratouveitis, and a third of the patients had had a previous corneal transplant. The overall recurrence rate for patients given antiviral therapy to prophylactic against HSK recurrence (n = 36) was 28%; the 10 whom presented with a recurrence at a median time of 70 days. Notably, there was a small cohort on HSK prophylaxis in our study. Twenty-six of the remaining 36 patients on HSK prophylaxis had a successful antiviral therapy. The most common therapy overall was valaciclovir 500 mg once daily (n = 18, 69%) as recommended by the published evidence, [1, 23, 59] with a median duration of 18 months (range 0.5 - 34 months). The duration of the prophylactic therapy in our cohort compares with other studies which reported that a therapy of at least one year decreases the recurrence rate of HSK episodes. [10, 90, 92]

Diverse antiviral therapy regimens were used for therapeutic and prophylactic indications in our study. The most common medications were topical aciclovir and oral valaciclovir. These agents were not studied in the HEDS clinical trials which provided

the main recommendations to treat this condition more than 20 years ago. The main antiviral therapy prescribed for epithelial HSK in our patients was topical aciclovir, as recommended widely in the literature, with a median healing time of 7 days. However, the initial antiviral therapy for stromal HSK did not match published evidence as most of the patients did not receive a prophylactic dose of oral antiviral and topical corticosteroids. Yet, half of the patients with stromal HSK partially resolved at a median time of 7 days. For endothelial HSK, patients resolved or partially resolved within 15 days. Most of the patients were treated with oral valaciclovir and topical corticosteroids. The dosage and frequency of valaciclovir varied in our study as there was no standard recommendations in the literature. For keratouveitis, the initial antiviral therapy was diverse as it was mainly based on clinical experience due to the lack of published evidence, with two-thirds of the patients partially resolved. Our finding that prescribing patterns were diverse may also reflect the heterogeneity of HSK, as the clinical manifestations of HSK depend on the interaction between the virus and the host. [23] Future therapies are needed to tailor treatments in order to minimize ocular damage from the interaction between the virus and the host. Nonetheless, until novel therapies are found treatment recommendations are needed to ensure the efficacy of therapies in the majority of cases with maximum safety.

A combined antiviral therapy for the treatment of stromal HSK is not recommended by HEDS studies. [3] Nevertheless, 22 of 296 (7%) patients in our study were found with this regimen, 20 patients with a therapeutic indication and 2 with a prophylactic indication. The most common regimen was valaciclovir 1 g three times daily with topical aciclovir five times daily in 9 patients (3 with epithelial HSK, 2 with SHSK+U, 1 with SHSK-U, and 3 with keratouveitis). An outcome was determined only for 15 of 20 patients with therapeutic indication. Of these, 11 partially resolved between 3 to 12 days; 3 resolved in a week, and 1 worsened at day 3 presenting with corneal perforation that was managed with glue. There was no clear benefit of prescribing a combination of oral and topical antiviral therapy. Three of 15 patients (30%) had a resolved outcome. These patients were diagnosed with epithelial HSK and one had prior corneal graft, with a healing time within a week. This healing time was similar to the

healing time of patients diagnosed with epithelial of HSK who received either only oral or topical antiviral medications in this study.

Patients diagnosed with HSK are typically treated as outpatients. Eighty percent (n = 140) of our patients with an outcome returned to the hospital for follow-up. The median number of visits for all groups except for SHSK+U was 3 (range 1-12), comparable to the average number of follow-up visits (2 visits, range 1 - 6 visits) in a retrospective chart review study in New York. [140] SHSK+U patients had a median number of 5 visits (range 3 - 12). These patients may have needed more visits as this type of HSK is caused by active viral replication and a marked immune response. Reasons for limited outpatient visits may include patients preferring to have follow-up visits with a private ophthalmologist and/or the patient feeling that they do not need medical attention as their symptoms had improved.

Ten percent of our patients (n = 24) were admitted to the hospital for the management of HSK or its complications. Most of the admitted patients (80%) had a prior corneal graft or stromal HSK. The most common indication for admission was corneal perforation. Other indications may have been due to their comorbidities which could worsen the infection, living outside the Sydney area (7 of 24, 30%), being elderly (15 of 24, 63%) or been unable to manage eye drop regimens at home if they are frequent. Six patients were admitted into hospital to receive treatment for complications of HSK such as stromal HSK, corneal perforation, persistent epithelial disease and corneal abscess. To our knowledge, there are no studies reporting the length of hospital stay for patients with HSK. The median length of admission in our group was 7 days which is comparable to a microbial keratitis case series in Brisbane, Australia (7 days); [110] and in Amsterdam, the Netherlands (7 days). [141] Overall, admission of patients to hospital with HSK is infrequent. Therefore, these findings are valuable as they will inform measures aimed at reducing the need for hospital admission, such as timelier recognition, or prediction of the common complications that are associated with admission.

Our findings contribute to the literature as there is a lack of studies reporting predisposing factors and investigating clinical outcomes of HSK, particularly for SHSK+U, endothelial HSK, herpetic keratouveitis, and patients with corneal grafts. Future studies are needed to compare the outcomes of different doses of antiviral agents for the treatment of these conditions as there are no standard initial dosages. The results of this study have contributed to the development and implementation of local guidelines for the management of HSK at the Sydney Eye Hospital (refer to Chapter 5). [129] These guidelines have been already implemented at the hospital. A future study may report the impact of these guidelines at the hospital.

Limitations

The main limitation of the present study is its retrospective nature. This introduced risks of documentation bias and misclassification bias as the investigators depended on the quality of the medical records and may have not recorded potentially important risk factors and categorised HSK cases differently to the patient's treating doctor, if the diagnosis was not explicitly documented. Another limitation was the small number of patients in certain groups such as SHSK+U, SHSK-U, endothelial HSK and active HSK with prior corneal graft to ascertain conclusions after comparing type of antiviral therapy and the outcomes. Despite this, we analysed the data and draw some conclusions suggesting certain trends. Certainly, further studies with larger sample sizes are needed to determine significant conclusions. This study design is appropriate to describe predisposing factor, diagnostic tests and outcomes of patients with HSK in a quaternary hospital.

In conclusion, for all types of HSK, topical aciclovir five times daily, alone or in combination with valaciclovir in doses ranging from 500 mg to 1 g once to three times daily, were the preferred antiviral agents in our study. Half of patients with stromal HSK, endothelial HSK and herpetic keratouveitis received topical corticosteroid therapy. Half of the patients with a therapeutic indication partially resolved between 3 and 8 days. Diabetes mellitus was the most common immunosuppressive condition in both antiviral therapy indication groups. In the therapeutic group, 38% of patients had had a

previous HSK episode, 18% prior topical corticosteroid use, 11% corneal pathology aside from HSK, and 10% a corneal graft. The HSV PCR positivity rate was 27%. Positive results were mainly for patients with epithelial HSK and SHSK+U. Ten percent of patients had an admission to hospital, which was due to either corneal perforation, corneal graft rejection, persistent epithelial defect or history of corneal graft. The final visual acuity only significantly improved for the patients with SHSK+U (0.95 to 0.58 logMAR, $p = 0.018$). Prophylactic therapy was successful in two-thirds of patients over 18 months of treatment. Fifteen percent of the patients had an admission to the hospital for a corneal graft or repair of corneal graft. Overall, most of the patients had good clinical and visual outcomes with a low proportion of adverse events.

This study highlights the lack of evidence for initial antiviral therapy for HSK resulting in a myriad of therapies found in our study. First, we hypothesized that prior topical corticosteroid use was the most common predisposing factor for HSK. Indeed, 18% (n = 45 of 252) of patients had a prior topical corticosteroid use at initial presentation. One third of these patients were diagnosed with epithelial HSK. The development of secondary ocular infections in long-term users of topical corticosteroids has been described. [142] Further, we hypothesized that diverse initial antiviral therapy was more often associated with poor clinical outcomes. However, our study showed that most of our patients (83%, 176/210) had an ‘improved’ or ‘partially improved’ or ‘success’ outcome with different antiviral regimens where oral valaciclovir and topical aciclovir were the most common prescribed agents. Nonetheless 1 in 5 patients still ‘worsened’, standardization of initial therapy may improve outcomes in this group but also reduce disease duration. Topical aciclovir is not a new antiviral medication but it was not studied in the HEDS clinical trials.

Microbial keratitis can develop after an episode of HSK, present simultaneously with HSK, or be misdiagnosed as SHSK+U. In the next chapter, the clinical features and outcomes of a cohort of patients with presumed microbial and HSK will be reported. Furthermore, the findings of this retrospective study will be compared with other microbial keratitis series.

Chapter 4 - Risk factors, microbiological features and outcomes of patients with concomitant microbial keratitis and herpes simplex keratitis.

4.1 Introduction

Corneal blindness is the second cause of blindness worldwide after cataract. [104] As traditional causes of blindness in resource limited settings (trachoma, leprosy and onchocerciasis) have decreased due to successful public health programs, microbial keratitis has become a significant cause of avoidable monocular blindness. [104] Microbial keratitis is an ophthalmic emergency needing immediate treatment. [104, 105, 143] Risk factors and the causal organisms vary according to climate and geographic region. [117] Contact lens wear is most associated with microbial keratitis in the USA; and other developed nations; [105, 106] whereas ocular trauma sustained during agricultural works predisposes to microbial keratitis in developing countries. [12] Individuals infected with ocular HSV have a 20% risk of developing stromal HSK with the attendant risk of blindness. [1] Differential diagnoses of SHSK+U are all forms of microbial keratitis and HZK. [23] Moreover, microbial keratitis can occur with HSK.

Several studies have described HSK as a predisposing factor in patients with microbial keratitis. [105, 111, 115, 116, 141, 144-147] Microbial keratitis has been described as a 'superinfection' or 'secondary infection' complicating HSK. [148] Some case reports have indicated that antiviral medications and/or topical corticosteroids used in the management of HSK might predispose to secondary bacterial keratitis. [149, 150] Case series of patients with HSK and secondary microbial keratitis are scarce. Two case series conducted in the USA had a limited patient numbers (n = 9 [151] and 15 [152]), and another case series conducted in London included a greater number of patients (n = 85). [148] These studies reported that factors to increase risk of superinfection included presence of epithelial defect, history of keratouveitis and of corneal graft, and topical corticosteroid use. [148, 151, 152] Gram-positive cocci were mostly isolated in these studies. [148, 151] Almost half of the patients had a final VA of less than 6/60 in the London study. [148] Although predisposing factors and microbiology patterns found in these studies may be still

relevant these days, the antibiotics used in these studies (penicillin and methicillin) and the recommendations given for prophylactic antibiotic therapy; to patients with damaged corneal epithelium with erythromycin, bacitracin, neomycin-polymyxin B combination, or chloramphenicol; are no longer first line therapies for microbial keratitis. [148, 151, 152]

Many case series worldwide have described the risk factors, clinical features, microbiology spectrum and outcomes of microbial keratitis alone; however, little is known whether these features vary in cases with presumed concomitant microbial keratitis and HSK. We will review clinically presumed cases with this condition to identify the abovementioned features. This study will add evidence to the literature and potentially guide clinicians to identify early these cases for an appropriate anti-microbial treatment to avoid complications and significant loss of vision.

4.2 Aim

The aims of this retrospective cohort study were to add to the knowledge based of concomitant microbial keratitis and HSK. Specifically, to report the predisposing factors, clinical features, microbiology spectrum, antibiotic resistance, anti-microbial therapy and outcomes over 5 years from 2012 to 2016 at a quaternary eye centre in Sydney, Australia.

4.3 Hypothesis

We hypothesised that patients with concomitant microbial keratitis and HSK would form a unique cohort compared to those with microbial keratitis alone, with the demographic, clinical and microbiological features, and outcomes identified.

4.4 Methods

A retrospective case series over the five years, 2012-2016 was conducted at the Sydney Eye Hospital, a quaternary referral unit for eye diseases located in the central business district of Sydney, Australia that treats patients from across the state of New South Wales. All patients with microbial keratitis at the Sydney Eye Hospital were identified from the following International Classification of Disease (ICD-10) codes:

corneal ulcer (H16.0), other superficial keratitis without conjunctivitis (H16.1), keratoconjunctivitis (H16.2), interstitial and deep keratitis (H16.3), other keratitis (H16.8) and keratitis, unspecified (H16.9); and by querying the laboratory information system containing pathology results. Patients were included if their clinical presentation was consistent with a presumed concomitant microbial keratitis and HSK, a corneal scrape was performed, and an antiviral medication were commenced as part of the initial treatment, and their age was 18 years or greater.

A presumed concomitant microbial keratitis and HSK case was determined by the investigators when:

- Clinical features associated with microbial keratitis (corneal ulcer, infiltrates, hypopyon, corneal thinning, or corneal perforation) were present, and
- Antiviral therapy was commenced meaning that the treating clinician considered HSV as a potential causative organism of the infection.

Each separate episode of keratitis suffered by a patient during the period was interpreted as an individual case. A new episode was considered to be another individual case when it occurred more than three months after the previous episode healed and, was unrelated to the first episode of microbial keratitis.

Patients were excluded if they had a corneal scrape performed in another hospital, or if the initial diagnosis was an auto-immune related non-infectious keratitis, neurotrophic corneal ulcer, corneal perforation needing corneal transplant immediately after admission, or trauma.

Ethics approval was obtained from the South Eastern Sydney Local Health District Human Resources Ethics Committee (approval number: HREC 14/282) (Appendix I, page 343). Data are reported in line with the STROBE statement for observational data. [124] Study data were collected and managed using REDCap (Research Electronic Data Capture, Nashville, TN, The USA) hosted at The University of Sydney. [121]

Medical records were reviewed, and the following data extracted: socio-demographic information, clinical presentation, management, and outcomes (Appendix J, page 346). The clinical history was reviewed to determine the date of symptom onset; date of initial presentation, whether the patient sought care elsewhere; and the date of presentation to Sydney Eye Hospital. These dates were used to calculate delays in presentation (days) and to categorise the event as a primary presentation or a referral from elsewhere. Relevant systemic comorbidities and medications were noted based on known associations with keratitis. [23, 105]

Data relating to ocular trauma, ocular surgery, corneal disease, ocular surface disease, ocular medications prescribed both prior to presentation and those prescribed at Sydney Eye Hospital, the duration of the antimicrobials (days), the diagnostic work-up, and associated results were extracted. The clinical presentation was described in terms of the presence and size of the epithelial defect and infiltrates, hypopyon, satellite lesions, ring infiltrates, and/or corneal thinning.

4.4.1 Diagnostic tests

Corneal scrapes and specimens for HSV PCR were taken in accordance with local protocols, from patients with a clinical diagnosis of concomitant microbial and HSK at presentation at the Sydney Eye Hospital. [153] Specimens were smeared onto a glass slide, and a Gram-stain was performed to guide empiric treatment. For bacterial cultures the following solid media were inoculated and incubated at 35° C in different conditions: Horse blood Columbia agar incubated anaerobically; Chocolate Columbia agar, incubated in 5% CO_2; and Saponin lysed horse blood Columbia agar, incubated in air. The agar plates were examined for growth at 24 and 48 hours. In addition, an enrichment liquid medium was inoculated and incubated at 35° C. After 48 hours the liquid media was sub-cultured onto Horse blood Columbia agar (incubated anaerobically), Chocolate Columbia agar (incubated in 5% CO_2), and MacConkey agar (incubated in air). All plates were examined for growth at 24 and 48 hours. A positive culture was defined as any bacterial and/or fungal growth present on the solid media. Bacteria were identified by matrix assisted laser desorption ionization-time of flight

(MALDI-TOF) mass spectrometry using an Ultraflex LT with v 3.0 software (Bruker Daltonics® Germany). Antibiotic susceptibilities were determined by the Calibrated Dichotomous Susceptibility (CDS) method [154] and the breakpoints for resistance were in accord with those specified in the CDS method for systemic isolates. Methods have been described elsewhere. [155]

In cases where a corneal biopsy was performed it was done according to methods described elsewhere [156] and processed for histopathology (described below) and microbiology (as above). An anterior chamber (AC) tap, when performed, was with a 25G needle on a 1 ml syringe using a sterile technique in the operating theatre.

Corneal biopsy specimens were fixed in 10% neutral buffered formalin, macroscopically described and processed in automated processors on a routine overnight cycle (Tissue-Tek VIP 6, Olympus, Australia). Briefly, processing included further fixation, progressive dehydration in alcohol and clearing with xylol then infiltration with wax before wax (Paraplast) embedding. Three-micron sections were cut on microtomes for routine haematoxylin and eosin (H&E) staining, as well as Gram, methenamine silver (MethAg), diastase periodic acid Schiff (DPAS), Ziehl Neelsen (ZN) and Fite special stains, and the auramine fluorescent stain, using routine protocols.

Herpes Simplex Virus type 1 and type 2 (HSV1, HSV2) were detected using the VZV R-gene kit, a Real-Time PCR on DNA extracted from human clinical samples (Argene, Australia) according to manufacturer's instructions. [130] The tests were performed using a Roche LC480 thermal cycler for real time amplification and results reported as viral genome copies/ml and calculated to log10 copies/ml. Positive and negative controls were used as standard.

Confocal microscopy was performed with a Nidek ConfoScan 3 Corneal Confocal Microscope, as follows. Anaesthesia was achieved with tetracaine. A drop of optical coupling medium (for example Genteal gel) was first placed on the objective lens prior to approaching the eye. The confocal microscope was approximated to the corneal region of interest. The image was focused manually and then a series of volume scans taken. Each volume scan had a z-stack of 40 sections, each section measuring 400

microns by 400 microns (384 X 384 pixels) with an optical thickness of 2 microns. The scan images were read by the trained technician and images with any positive findings (such as hyphae or *Acanthamoeba* cysts) were provided to the treating clinician for confirmation of the findings.

The confocal microscopy results were determined as 'probable hyphae or *Acanthamoeba* cysts', 'possible hyphae or *Acanthamoeba'* or 'negative'. 'Probable' referred to high probability of the confocal findings being hyphae or *Acanthamoeba* cyst-like structures as previously described. [157, 158] 'Possible' referred to low probability of the confocal findings being hyphae or *Acanthamoeba* cyst-like structures. 'Negative' referred to no identification of hyphae or *Acanthamoeba* cyst-like structures.

4.4.2 Visual acuity

Vision acuity (VA) at the presentation to the hospital and at discharge or at the last outpatient visit was recorded. The VA was measured using Snellen projector charts in the hospital unaided or aided with their usual means of correction (glasses or contact lens). The Snellen fractions in combination with any letters incorrectly identified or any letters correctly identified on smaller lines were converted to the logarithm of the minimum angle of resolution (logMAR) for further analysis. The following logMAR values were allocated for non-numeric visual acuities: counting fingers 1.7 logMAR, hand movement 2.0 logMAR, light perception 2.3 logMAR and no light perception 3.0 logMAR. [131]

4.4.3 Outcomes

Following a review of the literature, these outcomes were chosen to enable comparison of our results with a similar case series conducted in Brisbane. [159] Further, the data needed to create these outcome groups was easily available in our medical notes. Outcomes were grouped as follows: [159]

1. Good outcome: final VA of 6/12 or better, and no complications or surgical intervention, and no decrease in VA during treatment.

2. Moderate outcome: final VA 6/15–6/60, and no complications or surgical intervention, and no decrease in VA during treatment.

3. Poor outcome: final VA worse than 6/60 or decrease in VA during treatment; or complication of infection (perforation or endophthalmitis), or requiring surgical intervention (penetrating keratoplasty, enucleation or evisceration).

4.4.4 Statistical analysis

Descriptive statistics were used to summarise all continuous and categorical variables for this case series. Sociodemographic, predisposing factors and clinical feature data were compared among outcomes and statistical significance assessed using the chi-square test for proportions and Kruskal-Wallis test for non-parametric distributed variables (age, symptom duration and ulcer size). Epithelial defect and infiltrates size were defined as the geometric mean of the longest diameter of the lesion and its perpendicular diameter. Change in visual acuity (logMAR) was investigated using a Wilcoxon test. A p-value < 0.05 was considered as evidence of statistical significance. The statistical software used was IBM SPSS Statistics Desktop Version 25 (IBM Corp, Armonk, NY).

4.5 Results

4.5.1 Demographics

After cross-referencing the datasets, 1581 medical records were identified and reviewed, and of these, 1052 episodes of microbial keratitis were identified. After applying the inclusion and exclusion criteria, 126 episodes from 121 patients were included. There were 118 patients with 1 episode of presumed concomitant keratitis, 2 patients with 2 episodes (one patient presented with bilateral infection), and 1 patient with 4 episodes. The patient with bilateral infection had a history of atopic keratoconjunctivitis and hepatitis C. The patient's vision acuity was $6/30^{-2}$ on right eye and 6/45 on left eye. The right eye presented with an epithelial defect of 3.6 x 2.3 mm and infiltrates of 1x1 mm. The left eye presented with an epithelial defect of 4.6 mm x 3.5 mm, infiltrates and corneal perforation with negative Seidel test. Cultures of corneal

scrapings from both eyes and an HSV PCR test were negative. The patient developed a descemetocele in left eye requiring bandage contact lenses in both eyes. Both epithelial ulcers resolved in a week. Antibiotics were ceased at 3 months in both eyes.

The median age of all patients was 70 years (IQR 44 - 84, range 18 - 96, mean 64 ± 21), 56% were male and right eyes (n = 75; 59.5%) were more often cultured than left eyes (n = 51; 40.5%). The majority of patients were from greater metropolitan Sydney (n = 77, 64%) with other regional centres and rural parts of New South Wales (n = 40, 32%) (See Table 4 - 1, page 188).

Table 4 - 1: Socio-demographic characteristics and systemic factors for 121 patients treated for concomitant microbial and herpes simplex keratitis.

Key: ACT = Australian Capital Territory, COPD = Chronic Obstructive Pulmonary Disease, IQR = interquartile range, NSW = New South Wales, n = number of patients.

Age (years)	Mean 64 ± 21, median 70, IQR 44 - 84, range 18 - 96
Gender (male) [n, %]	68 (56)
Residence [n, %]	
Within greater Sydney	77 (64)
Outside greater Sydney but within NSW	40 (33)
Interstate (ACT)	2 (2)
Overseas	2 (2)
Systemic disease [n, %]	34 (28)
Diabetes Mellitus	15 (12)
Asthma/COPD	15 (12)
Rheumatoid arthritis	4 (3)
Thyrotoxicosis	2 (2)
Systemic medication [n, %]	6 (5)
Prednisone	5 (4)
Methotrexate	4 (3)
Leflunomide	2 (2)

4.5.2 Presentation to hospital

The date of onset of symptoms was recorded for 105 of 126 (83%) episodes. The median duration was 5 days (IQR 2 - 13, range 0 - 139). One hundred and eleven of 126 episodes (88%) were treated as inpatients and 15 (12%) as outpatients. The median length of stay for in-patients was 9 days (IQR 5 - 13, range 0 - 83) including one episode which was admitted and discharged from hospital on the same day. Twelve patients required readmission to the hospital to continue the treatment for the keratitis episode; of these one required a second admission. The median length of stay of the first readmission was 3.5 days (IQR 1 - 9.25, range 0 - 17) including one episode which was admitted and discharged from hospital on the same day.

Most of the cases [(n = 96 of 126), 76%] were assessed elsewhere first, including by another ophthalmologist [(n = 79 of 96), 82%], general practitioner [(n = 18 of 96), 19%), and/or optometrist [(n = 6 of 96), 6%]. The large proportion of cases seen initially by different health professionals reflects that these cases of microbial keratitis were initially managed elsewhere and then referred to the hospital

Within the 14 days prior to presentation, antimicrobials were used in 65 of 126 (52%) episodes. Thirty-six glaucoma eye drops, mainly prostaglandin analogues, were given in 27 episodes (21%) (See Table 4 - 2, page 190).

4.5.3 Predisposing factors

A predisposing factor for microbial keratitis was found in 115 of 126 episodes (91%), and of these, a single risk factor was found in 35 (30%) and 2 or more risk factors in 80 episodes (70%). Diabetes mellitus was identified in 15 patients (12%) (See Table 4 - 1, page 188). The use of topical corticosteroids was found in 48 episodes (38%); a history of previous HSK episodes in 46 (37%); ocular surface disease in 43 (34%); and other corneal disease in 39 (31%). The most common ocular surface diseases included blepharitis (n = 20), dry eye (n = 8) and lid malposition (n = 8). The most common corneal conditions included previous corneal transplantation (n = 19) and degenerative diseases such as keratoconus and keratopathy (n = 12). Corneal

transplantation was performed within three months of presentation in 3 episodes. Soft contact lens wear was identified in 17 episodes (13%) with overnight wear (8), water-related activities such as swimming or bathing with contact lens or washing contact lens with tap water (4), and poor compliance (1) as risk factors (See Table 4 - 3, page 191).

Table 4 - 2: Number of medications given during 14 days prior to presentation for 126 episodes diagnosed with concomitant microbial keratitis and HSK.

Topical antibiotics	Ofloxacin (26), chloramphenicol (18), chloramphenicol ointment (15), ciprofloxacin (8), tobramycin ointment (4), gentamicin (2), cefalotin (1), tobramycin (1), not specified (1)
Oral antibiotics	Ciprofloxacin (1)
Antiviral medications	Topical aciclovir (30), oral valaciclovir (17), oral aciclovir (6), topical trifluridine (1)
Topical Antifungals	Natamycin (1)
Topical antiamoebic agents	Polyhexanide (1), chlorhexidine (1)
Topical anti-inflammatories	Ketorolac trometamol (3), ciclosporin (2)
Topical glaucoma agents	Brimonidine + timolol (6), latanoprost (5), brimonidine (5), timolol (5), brinzolamide (3), travaprost (3), bimatoprost + timolol (3), bimatoprost (2), latanoprost + timolol (1), travaprost + timolol (1), dorzolamide + timolol (1), not specified (1)
Note: multiple medications may have been used within 14 days prior presentation	

Table 4 - 3: Ocular predisposing factors for 126 episodes with concomitant microbial keratitis and HSK.

Key: BCL = bandage contact lens, DSEK = Descemet's stripping endothelial keratoplasty, HSV = herpes simplex virus, N = overall number of patients per ocular factor, PK = penetrating keratoplasty, RCES = recurrent corneal erosion, RGP = Rigid gas permeable.

Percentages do not add to 100% as 79 of 121 patients had > 1 risk factor.

Ocular factor	N (%)	Sub-categories
Topical corticosteroid use	48 (38%)	Dexamethasone 0.1% (25), prednisolone acetate 1% (11), prednisolone sodium phosphate 0.5% (2), fluorometholone 0.1% (10), fluorometholone acetate 0.1% (3), hydrocortisone ointment 1% (1)
Previous herpetic keratitis	46 (37%)	
Ocular surface disease	43 (34%)	Blepharitis (20), trichiasis (2), ocular rosacea (2), Sjogren syndrome (1), neurotrophic cornea (9) atopic/vernal keratoconjunctivitis (2), dry eye (8), lid malposition (8), lagophthalmos (2), other † (2)
Corneal disease	38 (30%)	Dystrophy (2), Previous corneal transplant (18), degenerative (12), RCES (5), band keratopathy (2), HSV keratopathy (2), ectasia (2), other ‡ (3)
Contact lens wear	17 (14%)	Daily disposables (1), weekly/monthly (5), RGP (2), BCL (7), not recorded (2)
Recent ocular surgery	11 (9%)	Cataract (3), PK (2), retinal (1), corneal gluing (2), other§ (3)
Corneal trauma	8 (6%)	Foreign body: organic (1), not specified (1), penetrating (2), blunt (4)

† Nodular Scleritis (1), Bilateral blocked tear ducts (1)

‡Troutman wedge (1), Gundersen flap (1), DSEK+IOL exchange (1)

§ Pterygium (1), corneal melting (1), corneal decompensation (1)

4.5.4 Clinical findings

An epithelial defect was identified in 107 of 126 episodes (85%) and measured in 82 of 107 episodes (77%). Of these, 57 (70%) epithelial defects measured over 2 mm. The median area of epithelial defect was 8.2 mm^2 (IQR 2.2 - 18, range 0.04 - 121) for 75 episodes with available information regarding major and minor diameters of the defect. Infiltrate was present in 81 of 126 episodes (64%) and measured on 44 of 81 (54%). The median area of the infiltrate was 3.5 mm^2 (IQR 1 - 10.9 mm^2, range 0.04 - 100).

Other findings included hypopyon in 33 episodes (26%); corneal thinning in 25 (20%); satellite lesions in 16 (13%); ring infiltrates in 9 (7%); and a perforation that was Seidel negative in 4 (3%), and positive in 6 (5%).

4.5.5 Microbiological data

One hundred and thirty-seven corneal scrapes were performed in 126 episodes. Gram staining was positive for Gram-positive organisms in 11 of 126 (9%) episodes, and for Gram-negative organisms in 5 episodes (4%). Pus cells were identified in 53 episodes (42%). Gram staining was negative in 50 (40%) episodes. Results were unavailable in 7 episodes (6%) and there was insufficient material for staining in 1 (1%) episode. All episodes with Gram staining positive for either Gram-positive or Gram-negative organisms also had a positive culture of the corneal scrapings. Of the episodes with no micro-organisms seen on Gram staining, 30 had a positive culture (60%)

Culture was positive in 92 of 137 scrapes (67%), with 116 organisms identified. Of the 137 scrapes, 11 were repeat scrapes. In 10 of these 11 episodes, the culture from the initial scrape was positive. Three of 11 repeat scrapes had a positive culture. In all three, the organisms isolated from the repeat scrapes, *Moraxella* spp., *Staphylococcus epidermidis* and *Acanthamoeba* cysts, were different than the organisms isolated from the first scrapes, *Streptococcus pneumoniae* (n = 2) and *Staphylococcus epidermidis*, respectively. A repeat scrape was performed as the episode of microbial keratitis was not resolving despite the antibiotic therapy.

Bacterial keratitis accounted for 110 of the positive growths (95% of all isolates). Fungal isolates accounted for 4% (n = 5) and *Acanthamoeba* species accounted for the remaining 1% (n = 1) (See Table 4 - 4, page 194). The total number of Gram-positive and Gram-negative isolates was 83 (75%) and 27 (25%), respectively. Thirty-seven of 83 (45%) Gram-positive organisms were isolated in broth culture. The predominant Gram-positive, Gram-negative and fungi organisms were the coagulase-negative staphylococci (CoNS) group [(51 of 83), 61%) with *Staphylococcus epidermidis* as the major species (n = 35), *Pseudomonas aeruginosa* [(11 of 27, 41%], and *Candida parapsilosis* [(2 of 5), 40%], respectively (See Table 4 - 4, page 194).

Polymicrobial infection was detected in 20 of 137 scrapes (15%) with 44 organisms isolated. Most of these scrapes isolated two organisms (80%, n = 16). Three organisms were isolated from 4 scrapes. More than 50% of the following organisms were involved in a polymicrobial infection: *Curvularia* spp. (100%, 1 of 1), *Acinetobacter* spp. (100%, 3 of 3), *Neisseria mucosa* (100%, 1 of 1), *Branhamella catarrhalis* (100%, 1 of 1), *Capnocytophaga sputigena* (100%, 1 of 1), *Streptococcus* spp. (57%, 4 of 7), *Micrococcus luteus* (50%, 2 of 4).

Of the CoNS, 18% (9 of 51) were resistant to cefalotin, 14% (7 of 51) resistant to chloramphenicol, 12% (6 of 51) resistant to gentamicin, and 8% (4 of 51) resistant to ciprofloxacin. Of the methicillin-sensitive *Staphylococcus aureus* (MSSA) isolates identified, 37.5% (3 of 8) were resistant to ciprofloxacin and 12.5% (1 of 8) resistant to gentamicin (See Table 4 - 5, page 195). All Gram-positive isolates were susceptible to vancomycin. All *Pseudomonas aeruginosa* isolates were susceptible to ciprofloxacin, gentamicin and tobramycin.

Table 4 - 4: Distribution of organisms cultured in 137 corneal scrapes from 126 episodes of presumed concomitant microbial keratitis and HSK.

Key: n = number of isolates, spp. = species.

Note: Percentage is percentage of 116 organisms.

Name of organism	Total organisms		Polymicrobial infection	
	n	%	n	%
Gram-positive				
Coagulase-negative S*taphylococci*	51	44	21	41
Staphylococcus aureus	11	9	3	27
Corynebacterium spp.	7	6	2	29
Streptococcus spp.	7	6	4	57
Micrococcus luteus	4	3	2	50
Other Gram-positive†	3	3	0	0
Total Gram-positive	83	72	32	39
Gram-negative				
Pseudomonas aeruginosa	11	9	3	27
Moraxella spp.	4	3	1	25
Serratia spp.	3	3	1	33
Acinetobacter spp.	3	3	3	100
Proteus mirabilis	2	2	0	0
Other Gram-negative ‡	4	3	3	75
Total Gram-negative	27	23	11	41
Fungi				
Candida parapsilosis	2	2	0	0
Fungi not specified	1	1	0	0
Chaetomium spp.	1	1	0	0

Table 4 – 4 (continued)

Name of organism	Total organisms		Polymicrobial infection	
	n	%	n	%
Curvularia spp.	1	1	1	100
Total fungi	5	4	1	20
***Acanthamoeba* cysts**	1	1	0	0
Total	116	100	44	38

† Other Gram-positive: *Bacillus cereus* (1), *Diphtheroids* (1), *Mycobacterium chelonae* (1)

‡ Other Gram-negative: *Haemophilus influenza (*1), *Capnocytophaga sputigena* (1), *Neisseria mucosa* (1), *Branhamella catarrhalis* (1).

Table 4 - 5: The total numbers of isolates (n), number tested for each antibiotic and percentage (%) of resistance to antibiotics for most common organisms isolated from 137 corneal scrapes from 126 episodes with presumed concomitant microbial keratitis and HSK.

Key: CoNS = coagulase-negative *Staphylococcus* spp., MSSA = methicillin-sensitive *Staphylococcus aureus*, MRSA = methicillin-resistant *Staphylococcus aureus*.

Organism	Antibiotic							
	Cefalotin		Chloramphenicol		Ciprofloxacin		Gentamicin	
	n	%	n	%	n	%	n	%
CoNS	9 (51)	18	7 (51)	14	4 (51)	8	6 (51)	12
MSSA	0 (8)	0	0 (8)	0	3 (8)	37.5	1 (8)	12.5
MRSA	3 (3)	100	0 (3)	0	0 (2)	0	0 (2)	0

Numbers shown are number of resistant isolates (total tested).

Percentages are percentage of resistant isolates.

4.5.6 Other pathology tests

4.5.6.1 Corneal biopsy

A corneal biopsy was performed in 10 of 126 episodes (8%) with culture positivity in 6 of the 10 (60%). The corneal biopsy was performed at a median time of 19 days (IQR 9 - 32, range 5 - 145). Corneal biopsy was performed as the infection was not resolving despite the appropriate antibiotic treatment in accordance to the corneal scrape's culture result. Organisms isolated included *Staphylococcus epidermidis* (n = 2), *Acanthamoeba* cysts (n = 2), *Serratia ureilytica* (n = 1), and a fungus that was not specified (n = 1). A second corneal biopsy was required in two episodes, as the infection was progressing. The culture was negative in these two repeat biopsies (See Table 4 - 6, page 197). Further, one episode had an anterior chamber (AC) tap performed with a subsequent negative culture result.

4.5.6.2 In vivo confocal microscopy

In vivo confocal microscopy was performed on 15 of 126 episodes (12%) with the following results: 'probable hyphae' (n = 1) and 'possible *Acanthamoeba'* (n = 4). *In vivo* confocal microscopy was performed at a median time of 2 days (IQR 0 - 5, range 0 - 57). Eventual PCR results for fungi and for Acanthamoeba were negative for these episodes. For the episode with a 'probable hyphae' result, *Staphylococci pasteuri* had been isolated from the initial corneal scrape. The confocal result was not confirmed by any culture. Despite having a negative fungal culture, anti-fungal medications were given to the patient. For the four episodes with the 'possible Acanthamoeba' result, only one was confirmed with a corneal biopsy (134 days after the confocal). *Staphylococcus epidermidis* had been isolated from the initial corneal scrape. Despite these results, three of 4 episodes with 'possible Acanthamoeba' were treated with topical anti-amoebic medications.

Table 4 - 6: Results of diagnostic tests performed to 10 of 126 episodes with presumed microbial and HSK which needed a corneal biopsy.

Key: NA = not applicable

ID	Corneal scrape	Date	Second corneal scrape	Date	First corneal biopsy	Date	Second corneal biopsy	Date
1	*Serratia ureilytica*	31/12/2012	NA		*Serratia ureilytica*	31/12/2012	NA	
2	Fungus	26/11/2013	NA		Fungus	26/11/2013	NA	
3	No growth	5/03/2013	NA		*Staphylococcus epidermidis*	5/03/2013	NA	
4	*Staphylococcus capitis*	9/06/2012	NA		Scarce Acanthamoeba cysts	9/06/2012	No growth	13/12/2012
5	*Pseudomonas aeruginosa*	12/09/2013	No growth	11/10/2013	Growth from broth: *Staphylococcus epidermidis*	12/09/2013	NA	
6	*Micrococcus luteus*	22/05/2014	NA		Stromal melt, no growth	22/05/2014	Few pus cells, no growth	4/06/2014
7	*Staphylococcus pasteuri*	27/02/2013	No growth	21/03/2013	No growth	27/02/2013	NA	
8	*Staphylococcus epidermidis*	8/09/2014	Acanthamoeba cysts	25/09/2014	Acanthamoeba cysts (water agar culture)	8/09/2014	NA	
9	*Pseudomonas aeruginosa* and *Acinetobacter Iwoffii*	18/02/2015	NA		No growth	18/02/2015	NA	
10	*Chaetomium* spp.	14/11/2014	No growth	28/11/2014	No growth	14/11/2014	NA	

4.5.6.3 Polymerase chain reaction test for herpes simplex virus

Herpes simplex virus PCR was performed in 115 of 126 (91%) episodes. The test was positive in 31 (27%) cases. Of these, 16 (52%) had no previous history of HSK and 12 (39%) were culture negative for bacteria. No results were available for 2 cases.

4.5.7 Antimicrobial therapy

The preferred initial therapy was a combination of two topical antibiotics, an antiviral and a cycloplegic medications. The most commonly used topical antibiotics were cefalotin (81 of 126, 64%), gentamicin (68 of 126, 54%) and ofloxacin (41 of 126, 33%). The most common topical cycloplegic was homatropine (60 of 126, 48%). The preferred antiviral was valaciclovir in 109 of 126 episodes (87%) (See Figure 4- 1, page 201) The most common topical antibiotic combination was cefalotin and gentamicin in 65 episodes followed by cefalotin and ofloxacin in 14 episodes. (See Table 4 - 7, page 199).

Upon receipt of microbiology results, anti-microbial therapy was changed in 119 of 126 episodes (94%) (See Table 4 - 7, page 199). Of these, 83 (70%) had a positive culture and 36 (30%) had a negative culture from corneal scrape. The initial anti-microbial therapy was switched mostly to chloramphenicol eye drops, ofloxacin eye drops, tobramycin ointment and/or chloramphenicol ointment (See Figure 4- 1, page 201).

Figure 4- 1 (see page 201) shows the pattern of anti-microbial prescription for these episodes. Initial therapy consisted mainly of a combination of cefalotin, gentamicin and valaciclovir (n = 57 episodes)

Table 4 - 7: Number of medications given at initial presentation and number of medications introduced upon receipt of corneal scrape results for 126 cases diagnosed with presumed concomitant microbial keratitis and HSK.

Note: multiple medications used as initial therapy and revised therapy.

Therapy	Initial medication	Revised medication	Variation
	n (%)	n (%)	
Antibiotics			
Eye drops			
Cefalotin	81 (64)	7 (6)	↓
Gentamicin	68 (54)	5 (4)	↓
Ofloxacin	41 (33)	47 (37)	↑
Ciprofloxacin	6 (5)	3 (2)	↓
Chloramphenicol	5 (4)	49 (39)	↑
Cephazolin	4 (3)	1 (1)	↓
Penicillin	1 (1)	1 (1)	-
Vancomycin	0 (0)	1 (1)	↑
Amikacin	0 (0)	3 (2)	↑
Moxifloxacin	0 (0)	4 (3)	↑
Ointment			
Chloramphenicol	5 (4)	41 (33)	↑
Tobramycin	1 (1)	45 (36)	↑
Oral			
Doxycycline	23 (18)	30 (24)	↑
Ciprofloxacin	6 (5)	8 (6)	↑
Clarithromycin	0 (0)	2 (2)	↑
Antiviral			
Topical			
Aciclovir	13 (10)	5 (4)	↓
Ganciclovir	0 (0)	3 (2)	↑
Oral			
Valaciclovir	109 (87)	5 (4)	↓

Table 4 – 7 (continued)

Therapy	Initial medication	Revised medication	Variation
	n (%)	n (%)	
Aciclovir	9 (7)	2 (2)	↓
Famciclovir	1 (1)	0 (0)	↓
Cycloplegic			
Homatropine	60 (48)	9 (7)	↓
Atropine	14 (11)	14 (11)	↓
Cyclopentolate	1 (1)	3 (2)	↑
Anti-fungal			
Topical			
Natamycin	1 (1)	2 (2)	↑
Voriconazole	0 (0)	2 (2)	↑
Amphotericin	0 (0)	1 (1)	↑
Oral			
Voriconazole	0 (0)	3 (2)	↑
Fluconazole	0 (0)	1 (1)	↑
Intrastromal			
Voriconazole	0 (0)	1 (1)	↑
Anti-amoebic			
Polyhexanide	2 (2)	3 (2)	↑
Chlorhexidine	2 (2)	2 (2)	-
Propamidine	2 (2)	2 (2)	-
Anti-inflammatories			
Topical			
Prednisolone sodium phosphate 0.5%	3 (2)	1 (1)	↓
Dexamethasone 0.1%	2 (2)	5 (4)	↑
Prednisolone acetate 1%	1 (1)	2 (2)	↑
Fluorometholone 0.1%	1 (1)	8 (6)	↑
Dexamethasone sodium phosphate 0.1%	0 (0)	3 (2)	↑
Ciclosporin	1 (1)	0 (0)	↓

Table 4 – 7 (continued)

Therapy	Initial medication n (%)	Revised medication n (%)	Variation
Ointment			
Hydrocortisone	0 (0)	1 (1)	↑
Oral			
Prednisolone	5 (4)	0 (0)	↓

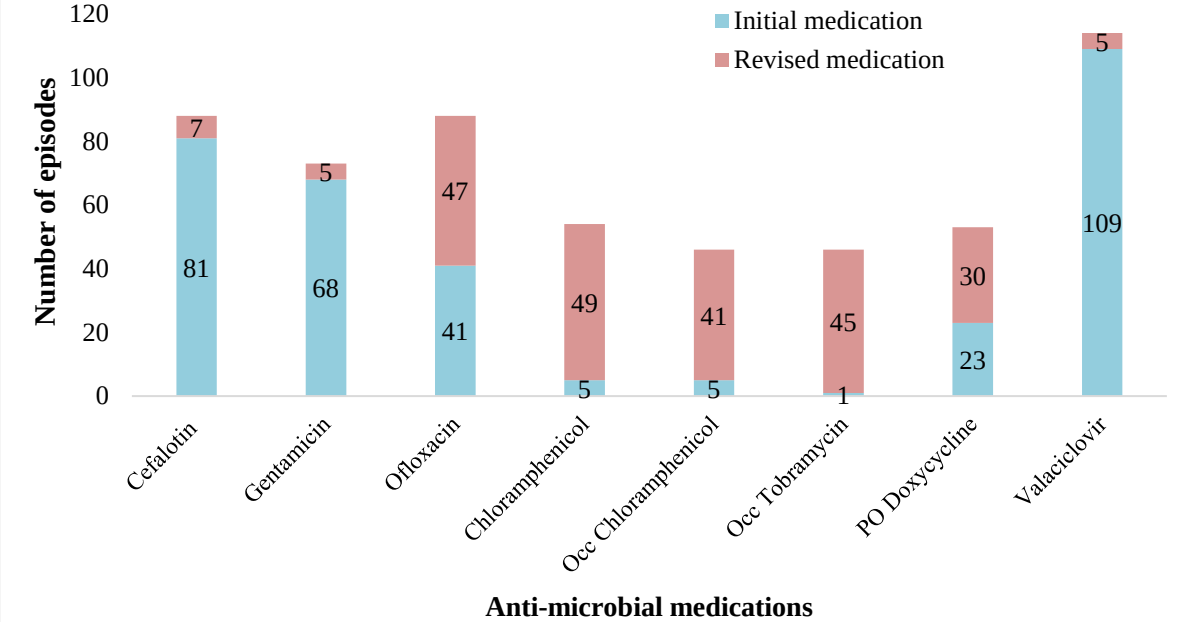


Figure 4- 1: Number of most common anti-microbial medications given at initial presentation and upon receipt of culture results of corneal scrapes.

Key: Occ = ointment, PO = oral medication.

4.5.8 Anti-inflammatory treatment

Eighty-one of 126 episodes (64%) received topical corticosteroids at some point during their treatment. Topical corticosteroids were only used as part of the initial therapy in seven episodes. For the rest of the episodes, topical corticosteroids were commenced at a median time of 5 days (IQR 3 - 6, range 0 - 124) after initial presentation at the hospital. The date of cessation of topical corticosteroids was only available for 19 episodes. For these cases, the median duration of topical corticosteroid therapy was 11 days (IQR 3 - 88, range 1 - 114). Table 4 - 8, on page 202 illustrates the list of anti-inflammatory medications given to 126 episodes.

Table 4 - 8: Anti-inflammatory medications given to 126 episodes of presumed concomitant microbial keratitis and HSK.

Key: n = number of episodes.

Anti-inflammatory therapy	n	%
Unpreserved prednisolone sodium phosphate 0.5%	50	40
Unpreserved dexamethasone sodium phosphate 0.1%	10	8
Preserved dexamethasone 0.1%	7	6
Preserved prednisolone acetate 1% and phenylephrine hydrochloride 0.12%	6	5
Preserved fluorometholone 0.1%	6	5
Preserved fluorometholone acetate 0.1%	1	1
Oral prednisolone	15	12
Ciclosporin	5	4
Intravenous methyl prednisolone	1	1

4.5.9 Outcomes

The median time of follow up was 39 days (IQR 16 - 100, range 1 - 526 days) for 71 of 126 episodes (56%) that had follow-up visits at the Sydney Eye Hospital. Of these, 12 were lost to follow up after attending at least one appointment at the hospital and 30

episodes continued their follow up elsewhere. The median number of clinic visits at the hospital was 3 (IQR 2 - 5, range 1 - 35). Furthermore, 55 of 126 (43%) episodes did not have follow up with a corneal specialist at the hospital post-discharge from hospital. Of these, 47 visited a private ophthalmologist to continue their treatment, 4 were considered lost to follow up, and 4 visited other ophthalmologists at the hospital, typically oculoplastic specialists, to follow up after their evisceration procedure.

An outcome was determined in 75 of 126 episodes (60%). The remaining 51 episodes were lost to follow up, followed up by private ophthalmologists or had missing information on their medical records, including missing VA. Of the episodes with known outcomes, 16 (21.3%) had a good outcome, 13 (17.3%) had a moderate outcome, and 46 (61%) had a poor outcome. Moderate and poor outcomes occurred mainly in patients over 60 years of age (See Figure 4- 2, page 204). Patients with a poor outcome were significantly older (75 years vs 66 years in moderate outcome vs 47 years in good outcome, $p = 0.005$), and presented with worse visual acuity at initial presentation (median 2 logMAR vs 1.3 logMAR in moderate outcome vs 0.8 logMAR in good outcome, $p < 0.001$); and larger ulcers (median stromal infiltrate size 6 mm^2 vs 5.46 mm^2 vs 1.06 mm^2, $p = 0.04$). There was no significant statistically association between ocular history and the outcomes (See Table 4 - 9, page 205).

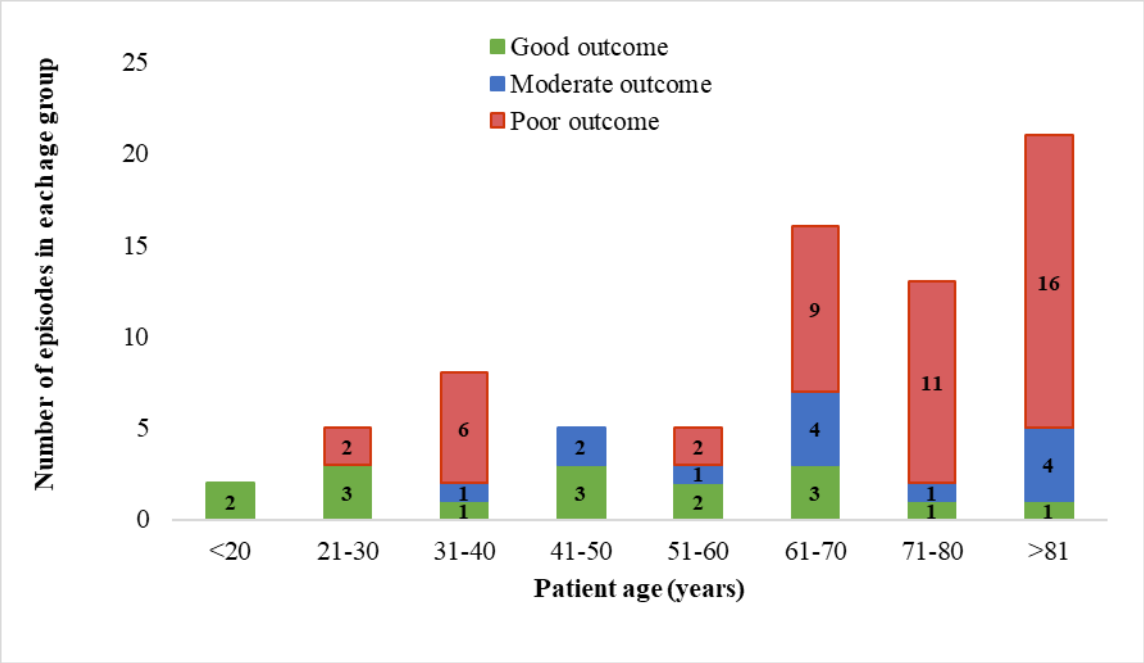


Figure 4- 2: Outcomes in 75 episodes with concomitant microbial keratitis and HSK correlated with age groups.

Table 4 - 9: Predisposing factors associated with clinical outcomes.

Predisposing factor	Outcome			*p* - value
	Good (n = 16)	**Moderate (n = 13)**	**Poor (n = 46)**	
Age, years (median, IQR)	47 (30-65)	66 (48-83)	75 (63-85)	**0.005**
History				
Symptom duration, days (median, range)	4 (0-26)	2 (0-9)	7 (0-139)	0.066
Topical corticosteroid	5 (31.3)	3 (23.1)	23 (50)	0.144
Previous HSK	2 (12.5)	4 (30.8)	20 (43.5)	0.077
Ocular surface disease	6 (37.5)	2 (15.4)	18 (39.1)	0.273
Corneal disease	4 (25)	4 (30.8)	14 (30.4)	0.912
Contact lens wear	1 (6.3)	1 (7.7)	8 (17.4)	0.426
Recent ocular surgery	0 (0)	2 (15.4)	4 (8.7)	0.303
Corneal trauma	1 (6.3)	0 (0)	5 (10.9)	0.425
Clinical features				
Best corrected visual acuity- affected eye (median logMAR, IQR)	0.8 (0.4-1.5)	1.3 (0.69-1.7)	2 (1.7-2.3)	**<0.001**
Stromal infiltrate size, mm^2 (median, IQR)	1.06 (0.52-2.14)	5.46 (0.83-8.7)	6 (2.1-36)	**0.04**

† Note: groups compared with chi-square test for proportions and Kruskall-Wallis for continuous non-parametrically distributed variables

4.5.9.1 Visual outcomes

Vision acuity in the affected eye was recorded at the initial presentation for 74 of 75 episodes (99%) and at a final visit for 58 episodes (77%). Of these, 18 (31%) had a final VA of 6/12 or better, 15 (26%) had a final VA between 6/12 and 6/60, and 25 (43%) had final VA of 6/60 or worse. Overall, the median VA at presentation improved from 1.7 to 0.7 logMAR ($p < 0.05$), where logMAR of 0 is equivalent to 6/6, and a logMAR of 1 is equivalent to 6/60.

4.5.9.2 Final clinical findings

The epithelial defect healed in 65 of 120 episodes (54%) with a median healing time of 11 days (IQR 7 - 26, range 1 - 153). Corneal thinning, neovascularisation and scarring were present in 9%, 11% and 33% of episodes, respectively (See Table 4 - 10, page 206). The date at which the anti-infective agent was ceased was documented in 43 of 126 episodes (34%) with a median time to cessation of 35 days in these patients (IQR 22 - 55, range 8 - 327).

Table 4 - 10: Final clinical findings for 120 cases with concomitant microbial keratitis and HSK.

Note: 6 eyes were removed from this analysis as they underwent evisceration.
† Median number of quadrants with new vascularisation: 1 (IQR 1 - 2, range 1 - 4).

Clinical feature	[n, (%)]
Epithelial defect healing	
Healed	65 (54)
No healed	8 (7)
Unknown	47 (39)
Corneal thinning	
Yes	11 (9)
No	68 (57)
Unknown	41 (34)
New vascularisation	
Yes†	13 (11)
Not specified	12
Deep	1
No	71 (59)
Unknown	35 (29)
Scar	
Yes	39 (33)
No	26 (22)
Unknown	55 (46)

4.5.9.3 Complications

Seventy of 126 episodes (55%) experienced complications. The most common complications were persistent epithelial defect [(n = 38), 30.2%], intraocular pressure elevation necessitating either topical or oral management [(n = 15), 12%], and corneal perforation [(n = 13), 10%] (See Table 4 - 11, page 208).

4.5.9.4 Surgical management

Penetrating keratoplasty (PK) was required in 8 episodes, 5 due to corneal perforation and 3 to non-resolving infection. The median time from presentation until PK was performed was 8 days (IQR 5 - 14, range 4 - 21). *Chaetomium* spp (n = 1), unspecified fungi (n = 1) and *Corynebacterium propinquum* (n = 1) were isolated in the non-resolving infection cases. Lamellar keratoplasty (LK) was required in one episode for a non-resolving infection. The patient had a history of keratoconus and corneal transplant. The patient developed a descemetocele managed with LK. The cultures of two corneal scrapes were negative. Of the 38 episodes with persistent epithelial defect, tarsorrhaphy was performed in 18 episodes and amniotic membrane grafting (AMT) in one. Evisceration was performed in 5 episodes with causal organisms isolated in 4 episodes including *Serratia ureilytica, Staphylococcus epidermidis, Pseudomonas aeruginosa and Moraxella nonliquefaciens.* Enucleation was required in one episode caused by *Pseudomonas aeruginosa.*

Table 4 - 11: Number of complications observed in 70 episodes with concomitant microbial and HSK as a proportion of all episodes (n = 126).

Key: n = number of complications, IOP = intraocular pressure, LSCF = limbal stem cell failure.

Type of complication	n (%)
Persistent epithelial defect	38 (30)
IOP elevation needing	15 (12)
topical management	10 (8)
oral management	5 (4)
Corneal perforation needing	13 (10)
transplantation	5 (4)
gluing	8 (6)
Non resolving infection managed with	10 (8)
transplantation	4 (3)
evisceration	5 (4)
enucleation	1 (1)
Descemetocele	9 (7)
Progressive infection needing intravitreal, intracameral, subconjunctival antifungal/antibiotics	5 (4)
Eye drops toxicity	3 (2)
Scleritis	2 (2)
Recurrence epithelial defect	2 (2)
Other†	7 (6)

† Hyphaema (1), LSCF (1), epithelial hypertrophy with filamentary keratitis (1), dehiscence Gundersen flap (1), trabeculitis (1), resuturing corneal graft (1), ectasia (1).

4.6 Discussion

This study reported demographics, predisposing factors, clinical findings, microbiological patterns, anti-microbial therapy and outcomes of cases with presumed concomitant microbial keratitis and HSK in adults presenting to the Sydney Eye Hospital over a 5-year period. There are a few outdated case reports and a retrospective study describing secondary microbial keratitis in HSK from 1980's. The inclusion criteria of our cohort were similar to these historical reports. [148, 151, 152] Clinicians in practice however are interested to know if patients with concomitant microbial keratitis and HSK are different to those with microbial keratitis alone, as this data could be used to assist diagnosis and management. Furthermore, keratitis features vary with geographic location and patient demographics.

In our study, 126 episodes of 121 patients were included, 56% of patients were male and 64% resided within the greater Sydney area. The most common predisposing factors were topical corticosteroid use, ocular surface disease including prior HSK and prior corneal transplant. Presentation was delayed by 5 days from the onset of symptoms, with half of the episodes receiving anti-microbial and/or topical corticosteroids during these days. Half of the episodes on glaucoma eye drops (15/27) received prostaglandin analogues which can trigger epithelial HSK. [23] It is recommended to avoid this class of medication in patients with a known history of HSK. [23]

Most of the episodes (88%) were admitted to the hospital for management of their keratitis with a median length of stay of 9 days. Admission of patients with microbial keratitis in our institution is frequent as most of our patients tend to be elderly, from regional NSW or from interstate, are not able to manage the hourly eye drop regimen or were referred by private ophthalmologists who had already started antibiotic therapy but the infection was not resolving. Investigation via corneal scraping and/or HSV PCR was used to support the clinical diagnosis. When there was a progressing infection or slow-healing ulcer, a corneal scrape was repeated, and/or corneal biopsy performed. Culture positivity rate was 67% (92 of 137 samples) for corneal scrapes.

Coagulase-negative staphylococci (51 of 116, 44%), predominantly *Staphylococcus epidermidis*, *Staphylococcus aureus* (11 of 116, 9.5%) and *Pseudomonas aeruginosa* (11 of 116, 9.5%) were the most common isolated microorganisms.

For CoNS, the resistance to cefalotin was 18% (9 of 51), chloramphenicol 14% (7 of 51), ciprofloxacin 8% (4 of 51) and gentamicin 12% (6 of 51). For MSSA, the resistance to ciprofloxacin was 37.5% (3 of 8) and to gentamicin 12.5% (1 of 8). The HSV PCR positivity rate was 27% (31 of 115 episodes). The most common initial therapy was a standard regimen of fortified antibiotics, cefalotin 5% and gentamicin 0.9%, and oral valaciclovir. Oral valaciclovir was preferred as the patients were already receiving multiple topical medications and a topical antiviral ointment might affect the penetration of the antibiotics, produce additional toxicity or cause issues with drop compliance. Further, most of these cases presented with signs of stromal keratitis and an oral antiviral is the recommended therapy for this type of keratitis. [23] The initial antibiotic therapy was changed in most of the episodes (n = 119/126, 94%). Initial antibiotics were mainly switched according to the culture results (n = 83/119, 70%). The empiric therapy with broad-spectrum fortified antibiotics was altered in the episodes with a negative culture (30%) probably due to the antibiotic toxicity which could affect healing. [12, 105] The empiric therapy tended to be changed to chloramphenicol eye drops or ointment, tobramycin ointment or ofloxacin which are readily available in community pharmacies. Therefore, clinicians change initial antibiotics to something the patient will easily be able to obtain after discharge. Corneal biopsy was performed in one episode isolating *Staphylococcus epidermidis* and a rescrape in another episode with a negative culture.

A ‘poor outcome’ was determined for 61% (46 of 75) of patients. Patients with poor outcomes were likely to be older, presenting with poor vision acuity and larger ulcers. Further intervention was required in 5 episodes with antifungal/antibiotic injections given to the vitreous, anterior chamber and/or subconjunctival space, corneal transplantation in 8 episodes, evisceration in 5 episodes and enucleation in one episode.

Correct initial diagnosis of microbial keratitis based only on clinical features is challenging. Hence the need of a good medical history and diagnostic tests such as corneal scrape and viral or acanthamoeba PCR to guide the appropriate therapy. As the infection may worsen rapidly, empiric therapy is started. Severe keratitis, patient age, poor visual acuity at presentation, herpetic keratitis, ocular surface disease and systematic disease have been associated with poor outcomes in a previous microbial keratitis study in Brisbane, Australia.[159] There are many case series of microbial keratitis worldwide reporting risk factors, including previous HSK, clinical patterns and outcomes. [116, 141] Due to the lack of published cohorts of patients with both microbial keratitis and HSK and the need to understand if patients with both infections differ from those with microbial keratitis alone, we have compared our findings to published series of cases diagnosed with microbial keratitis.

Age

The proportion of patients over 60 years in our study was 65% suggesting that this condition may occur more frequently in the elderly. Our mean age was higher than the mean age of a study conducted in London which also included patients with suppurative keratitis with previous HSK (64 years vs 55 years). [148] The comparison of the mean age in our study with other microbial keratitis case series was variable. Our mean age was greater than other microbial keratitis case series from Australia. [109, 110, 145, 146]

Predisposing factors

Microbial keratitis most often occurs in patients with identified risk factors. [105] Most of our patients (91%) had at least one risk factor as found in other studies in Sydney (94%), [116] Perth (94%), [146] Melbourne (92%) in Australia; [111] and Ehime, Japan (81%). [160] Previous ocular disease and surgery, topical corticosteroid use, immunosuppressive conditions and medications have been reported as the main predisposing factors among the elderly with microbial keratitis, [110, 116, 141] and among patients with HSK and secondary microbial keratitis. [148, 151, 152] The importance of these predisposing factors was comparable to our study as our main risk factors were topical

corticosteroid use (48 of 126 episodes, 38%), previous HSK (46 of 126 episodes, 37%), blepharitis/dry eye (28 of 126 episodes, 22%). Our overall results were similar to a case series in the Netherlands where the use of topical corticosteroids (26%), dry eye/blepharitis (21%) and prior HSK (29%) were prevalent in the group of patients over 60 years of age. [141] This Dutch study included all cases of microbial keratitis but divided the patients into two groups for analysis (under 60 years vs over 60 years) to elicit any differences regarding risk factors, clinical features and outcomes of infectious keratitis between younger and elder patients. [141] Our main predisposing factors were also the most common in a case series of patients with HSK and secondary microbial keratitis; however, this case series reported greater proportions of patients with previous HSK (66%, n = 10/15), [152] and topical corticosteroid use (87%, n = 13/15). [152] These proportions may not be comparable to our findings due to their limited number of patients.

Moreover, previous ocular surgery was an important risk factor in microbial keratitis studies with elderly populations (23% to 46%). [116, 141, 160-163] The proportion of patients with previous ocular surgery in our group was 22% (27 of 121 of patients) which was lower than in the other microbial keratitis studies with elderly patients. Our most common previous ocular surgery was a corneal transplant in 15% of patients (18/121). This proportion of patients with previous corneal graft was also lower than in two case series of patients with HSK and secondary microbial keratitis which reported high proportions of this procedure (40%, 16/40 [148] and 100%, 9/9 [151]). The outcomes from corneal grafting in the setting of HSK can be poor such that in the presence of HSK grafting may often be avoided. [47] Surprisingly, common risk factors in the elderly population such as systemic conditions and immunosuppressive medication use were uncommon in our group; however, other factors including previous herpetic disease, previous corneal disease, topical corticosteroid use and blepharitis/dry eye were present. Microbial keratitis often arises from a disturbance in the corneal epithelium. As HSK can disturb the corneal epithelium, other risk factors that can disturb the epithelium such as prior surgery would not have to have been present as frequently in our cohort. The risk factor pattern in the elderly population matches with the age of our patients as two-thirds of our patients were over 60 years.

Contact lens use, and ocular trauma are common risk factors among the younger population. [110, 111, 116, 141] Low proportions of these risk factors were found in our study; 14% were contact lens wearers (17 of 126 episodes), and 6% (8 of 126 episodes) had prior ocular trauma. This compares with previous results reported by Butler in elderly patients [116] but differs from results from Brisbane [110] and Melbourne [111] and Sydney [145] where contact lens wear and trauma were the main two risk factors. Prior HSK can be a contra-indication to contact lens wear due to the increased risk for HSK recurrence (0.4 episodes/year in CLW vs 0.2 episodes/year in non-CLW, $p = 0.02$). [164]

Clinical features

Generally, microbial keratitis manifests with a corneal ulcer. [105] Moreover, there are some relevant features described in keratitis caused by Gram-positive and Gram-negative bacteria, fungi and acanthamoeba cysts. Gram-positive bacteria manifest as localised round or oval ulceration, greyish -white stromal infiltrates, distinct borders and minimal stromal haze. Gram-negative bacteria manifest with dense stromal suppuration, and a hazy surrounding corneal 'immune ring'. Filamentous fungi manifest with dry elevated slough, stromal infiltrate with hyphate margins, satellite lesions and thick endothelial exudate. Acanthamoeba cysts manifest with single or multiple stromal infiltrates, ring-shape configuration, and epithelial irregularities. [108] Simultaneous diagnostic tests are needed to rule out other causal organisms due to these non-specific signs. [108] For example, in our cohort, satellite lesions were identified in 16 episodes, but filamentary fungi, *Chaetomium* species, was only isolated in one episode. Other bacteria isolated in these episodes included CoNS (n = 4), *Staphylococcus aureus* (n = 3), *Streptococcus* spp. (n = 2), *Micrococcus luteus* (n = 2), *Pseudomonas aeruginosa* (n = 1), and *Acinetobacter calcoaceticus var lwoffii* (n = 1). Ring infiltrates were identified in 9 episodes, but A*canthamoeba* cysts were not isolated in any episode. Organisms isolated included CoNS (n = 1), *Staphylococcus aureus* (n = 1), *Pseudomonas aeruginosa* (n = 1), *Moraxella nonliquefaciens* (n = 1), *Proteus mirabilis* (n = 1), and *Candida parapsilosis* (n = 1). Our findings highlight that clinical signs in our cohort could not be used to predict the infecting organism, supporting the continued need for corneal scrape and, if needed, biopsy for diagnosis.

Microbiology patterns

Our culture positive rate was 67% comparable to previous Australian microbial keratitis series, [109, 110, 146] and a Brazilian microbial keratitis series. [161] This is not surprising as similar techniques were used to isolate and culture the organisms across our and the reported studies. Gram-positive isolates were identified in 72% of all organisms in our study being comparable with microbial keratitis studies in Perth, [146] Adelaide, [109] Melbourne [111] and Sydney, [145] and to studies with elderly patients in Australia, [116] India, [161, 163] Brazil, [162] Japan,[160] and the Netherlands.[141] Further, our findings were comparable to the study of patients with HSK and secondary microbial keratitis from London where Gram-positive organisms were identified in 70% of the cases. [148]

The most frequent organisms in our group were CoNS, *Staphylococcus aureus* and *Pseudomonas aeruginosa.* CoNS were also the most frequent organisms reported in case series by Australia, [116] India, [163] Brazil,[162] the United Kingdom, [148] and the USA; [151] while *Staphylococcus aureus* was most frequently reported in the Netherlands, [141] and *Pseudomonas aeruginosa* in Japan. [160] *Streptococcus pneumoniae* was the fourth most isolated organism in our study (6%) contrasting to the study from India [161] where this organism was the most common isolated (16%). Filamentous fungi were the second most cultured organism in a study from India (25.7%) [163] differing from our study where fungi was identified in 3% of all organisms. Notably, this illustrates the higher prevalence of fungal keratitis in patients with ocular trauma in the developing world. This guides the choice of the empiric therapy and demonstrates that the spectrum was the same in the presumed concomitant infection cases in our study and in microbial keratitis series.

Antimicrobial resistance patterns

The antimicrobial resistance patterns were analysed for the most common microorganisms: CoNS, *Staphylococcus aureus,* and *Pseudomonas aeruginosa.* All organisms were susceptible to at least one tested antibiotic. There was no reported resistance in our group for *Pseudomonas aeruginosa* isolates as in other Australian

previous studies. [110, 111, 116, 145, 146] There are reports of increasing resistance to fluoroquinolones particularly for CoNS [15.3% (22/144) to 38.9% (7/18)] and *Staphylococcus aureus* [5.8% (5/86) to 35% (7/20)] in the USA for the period 1993 to 1997. [116, 165] In contrast to the USA, the resistance trend was considerably lower for *Staphylococcus aureus* in Australia with 9% (n = 2/22) and 6% (1/16) for CoNS, and 5% (1/19) and 17% (2/12) in Brisbane [110] and in Sydney, [116] respectively in early 2000's. In our study, the resistance to fluoroquinolones was 37.5% (3/8) for *Staphylococcus aureus* isolates and 8% (4/51) for CoNS. Our proportion of *Staphylococcus aureus* resistance was much higher (37.5%) than in the study conducted in USA (13.9%). [165] It should be noted that the number of *Staphylococcus aureus* isolates in our study was small; and may therefore not be representative of the population. One possible explanation for the higher levels of resistance in this study may relate to the HSK patients' eyelid and ocular surface flora having been exposed to antibiotics prior to the initial presentation to hospital. Our proportion of CoNS resistance to fluoroquinolone (8%) was lower than the proportion found in the study from Pennsylvania (18.7%, 72/386). [165] Resistance to ciprofloxacin for CoNS was comparable between our study [8% (4/51)] and a prior Sydney study [6% (1/16)]. [116]

Further, the resistance to cefalotin (18%) for CoNS and MSSA (0%) in our study was comparable to the resistance found in a previous microbial keratitis study in Sydney (18% and 0%) in the period 1998-2002. [116] However, our resistance was much lower than previously reported proportions in Adelaide (35%) [109] and Brisbane (34%). [110] The resistance to gentamicin for CoNS and MSSA differed from the previous Sydney study [116] as the proportions decreased from 33% and 75% to 12% and 12.5%, respectively. These data support the empiric therapy with fortified antibiotics, cefalotin and gentamicin, or with fluoroquinolones as monotherapy for the treatment of presumed concomitant microbial keratitis and HSK.

Diagnostic tests

A corneal biopsy is a valuable diagnostic test for microbial keratitis cases unresponsive to regular initial antimicrobial therapy. [156] Broad indications in our

institution include clinical worsening, despite broad-spectrum antibiotics, and persistent negative cultures on repeat corneal scrapings; or clinical worsening, despite broad-spectrum antibiotics, in cases with a positive culture on corneal scrapings but other organisms are suspected but not growing on repeat scrapings. [156] However, in our cohort a cornea biopsy was performed along with a corneal scraping at initial presentation in 8% (n = 10/121) of patients with 60% of culture positivity from the corneal biopsies. Of patients who underwent corneal biopsy, 90% (n = 9/10) were referred by private ophthalmologists and 70% (n = 7/10) were on antibiotic therapy when the corneal biopsy was performed at initial presentation. Four repeat scrapings were performed in the patients who had a corneal biopsy. Of these, 3 had negative cultures. The remaining culture confirmed the isolation of A*canthamoeba* cysts which was also reported in the corneal biopsy. Therefore, a repeat scraping did not contribute to the final diagnosis. Two repeat corneal biopsies were performed in patients who did not have any repeat scrapings. The cultures from the repeat corneal biopsies were negative.

Notably, there was a case of *Serratia ureilytica* isolated in the corneal scraping and biopsy cultures. The patient was an 85-year-old male with a history of HSK, glaucoma, corneal gluing due to corneal perforation two months prior the initial presentation, and BCL wear. He resided in Sydney metropolitan area with no history of recent travel. The patient was receiving the following eye drops: brimonidine tartrate, ketorolac tromethamine, chloramphenicol, and preserved dexamethasone 0.1%; and topical aciclovir. Initial visual acuity was light perception. Clinical features included an epithelial ulcer of 5.5 x 3.5 mm with no infiltrates, hypopyon, corneal thinning or corneal perforation. Despite initial management with cefalotin, gentamicin, and oral valaciclovir, the patient worsened and eventually underwent an evisceration. This case was an exceptional finding as *Serratia ureilytica* is an unusual organism, first isolated in river water in India in 2005; and had not been previously reported as a human pathogen. [166]

Outcomes

The Steroids for Corneal Ulcers Trial reported that the median time of reepithelialisation was 7 days. [167] Similarly, Green et al. reported a median time of 9 days in a microbial keratitis study, [110] however, in our study, the reepithelialisation occurred later at a median time of 11 days. Over half of the episodes (55%) in our series had at least one complication, being comparable to a previous study with elderly patients with microbial keratitis in Australia (50%); [116] however, our proportion was double that of the proportion reported in India which also included elderly patients with microbial keratitis. [161] A surgical intervention was required in 31% of our patients. This proportion was lower than in a previous studies with elderly patients with microbial keratitis from Australia (43.7%), [116] The Netherlands (57.1%), [141] and India (41%). [163] Our rate of corneal perforation was 10% (13 of 126) similar to a previous study with elderly patients with microbial keratitis in Sydney (12%), [116] but lower than in a study with patients from any age with HSK and secondary microbial keratitis in London (28%). [148] Our patients with a corneal perforation were mainly treated with gluing (8 of 13, 60%). Our rate of PK [6% (8 of 126)] was much lower than the rates reported in previous series of microbial keratitis in the elderly by Kunimoto (10.8%), [163] Butler (17.9%), [116] and van der Meulen; (27.6%) [141] and a case series with patients with HSK and secondary microbial keratitis by Wilhelmus (48%). [148] Perhaps, the clinicians at our institution intended to avoid PK in eyes with history of HSK and persisted with a conservative approach for longer. This may have left some patients with poorer final VA from scarring, or glue or an eccentric LK; nevertheless, it would have been a better outcome than a PK.

The proportion of evisceration/enucleation has varied in previous microbial keratitis studies worldwide. Our proportion of eyes requiring evisceration/enucleation [6 of 126 eyes (5%)] was lower than the proportions reported by previous studies with elderly population with microbial keratitis from Hyderabad, India (14.7%) [163] and Sydney, Australia (8.9%). [116] On the other hand, our proportion was comparable with the proportion found in the studies with elderly patients with microbial keratitis from Amsterdam and Rotterdam in the Netherlands (4%) [141] and from Tiruchirappalli, India

(4%), [161] and in the study with patients with HSK and secondary microbial keratitis from London (3%). [148] In our study, the associated organisms associated with evisceration included *Serratia ureilytica* (n = 1), *Staphylococcus epidermidis* (n = 1), *Pseudomonas aeruginosa* and MRSA (n = 1), *Moraxella nonliquefaciens* (n = 1), and no isolated bacteria, but HSV PCR positive (n = 1). The organism associated with the enucleation case was *Pseudomonas aeruginosa*.

Our patients had a poor presenting median VA of 1.7 logMAR (count fingers) and final visual outcome of 0.7 logMAR (6/30) with 43% (25 of 58) with a VA worse than 6/60 and 7% (4 of 58) with LP or worse. The poorer initial vision was likely due to prior ocular disease, including HSK. In a study with elderly patients with microbial keratitis, Butler et al. [116] reported poor initial VA (6/300) with over 40% of patients with a final VA worse than 6/60 and about 20% with LP or worse. Our proportion of final VA worse than 6/60 (43%) was also comparable to a study with elderly patients with microbial keratitis from Tiruchirapalli, India (38%); [161] but much lower than the final VA of a study from Hyderabad, India (88%). [163] On the other hand, Wilhelmus reported a similar proportion of patients with final VA worse than 6/60 [45% (18 of 40)] to our proportion. [148] Similarly, Gebauer reported that 39% (14 of 53) of patients with severe microbial keratitis had a final VA poorer than 6/60. [146] Among various microbial keratitis studies, VA at presentation is poor regardless of the age group; but it is noted that older patients consistently seem to achieve poorer final VA. [141, 161, 163]

Limitations

The main limitation of this study is its retrospective nature introducing risks of selection bias and misclassification. Clinical data collected was only that recorded. Nonetheless, this is a recent large series of cases with presumed concomitant microbial keratitis and HSK over 5 years to be reported from Australia.

We considered that our cases of presumed concomitant microbial keratitis and HSK correlate more closely to the microbial keratitis in the elderly. Our cases of presumed concomitant microbial keratitis and HSK were likely to present with poor vision and severe disease (large ulcers) in patients over 60 years of age with at least one

predisposing factor. The predisposing factors were highlighted, including corneal or ocular surface disease, history of prior HSK, and topical corticosteroid use. Clinicians should be aware of these risks to assist them in making a prompt diagnosis. The microbiological spectrum was comparable to microbial keratitis series with Gram-positive isolates being the most common culprit of the infection. One-fifth of CoNS isolates were resistant to cefalotin; and a third of MSSA were resistant to ciprofloxacin. Despite these resistance rates, the empiric treatment with cefalotin and gentamicin or monotherapy with ofloxacin was still relevant. The outcomes of our patients were comparable to the poor outcomes reported in several studies in elderly patients with microbial keratitis. In our study, 1 out of 3 episodes resulted with a poor final VA worse than 6/60 and/or a need of a surgery (PK, evisceration, enucleation, LK, AMT and glueing). Clinicians might further consider this for guiding their treatment duration in the future. This series adds to worldwide data on keratitis and will assist with local diagnosis and management. To improve outcomes for patients with mixed infection, there is a need for earlier diagnosis via increased suspicion in patients with risk factors and rapid diagnostic techniques.

In the next chapter, the development, implementation and evaluation of HSK treatment guidelines will be described.

Chapter 5 - Development, implementation and evaluation of treatment guidelines for Herpes Simplex Keratitis

5.1 Introduction

Translating results from research to everyday clinical practice is an important challenge in medicine. [11, 14] Despite the resources invested in research that uncover new knowledge or lead to changes in practice, implementing the outcomes from research is often a slow process. Researchers from the USA and the Netherlands have found that 30% to 45% of patients are not receiving evidence-based care (whether acute, chronic, or preventive), and 20% to 25% receive unnecessary or potentially harmful care. [11, 14] To close the gap between knowledge and action, a systematic approach is needed involving a range of stakeholders. [11]

Herpes simplex keratitis is an important cause of unilateral infectious blindness in developed countries due to stromal opacification. [18] The incidence worldwide of HSK in 2012 was estimated at about 1.5 million, with 40,000 new cases of severe monocular visual impairment or blindness every year. [18] Antiviral and topical corticosteroid therapies are the mainstay of treatment. The dosage and frequency of these medications are dependent on whether the indication for their use is to treat or prevent the infection. Despite the wide availability of these medications, complications such as corneal scarring and blindness still occur.

The Herpetic Eye Disease Study group clinical trials, conducted in the 1990s, provided recommendations for the treatment of HSK. [2-6] Subsequent clinical trials and a Cochrane review have added to the evidence base. [1, 7] The HEDS studies however were performed some time ago and did not include antiviral medications used in Australia. Furthermore, since the HEDS trials other antivirals such as ganciclovir and valaciclovir have been introduced into the market and are now widely used across the globe. A study in France in 2012 reported a wide variety of therapeutic interventions for new and recurrent HSK suggesting a lack of consensus regarding appropriate antiviral therapy. [56] Eighteen antiviral therapies were identified in that study, including topical agents

(aciclovir, trifluridine, ganciclovir, idoxuridine); oral agents (valaciclovir and aciclovir); and a combination of 1-2 oral and 1-2 local agents. Until recently, there was no consensus as to the antiviral and topical corticosteroid medication, or to the dosage that should be prescribed for the treatment and prophylaxis of HSK. The AAO released a treatment guideline for HSK in 2014. [23] Although this reviewed the available evidence for HSK treatment and prophylaxis and provided general guidance, it was not entirely applicable to Australia. As occurred with the HEDS recommendations, 'The AAO HSK treatment guideline' did not include topical aciclovir for epithelial HSK and made no recommendations on the treatment of keratouveitis.

A diverse prescribing trend for HSK was reported in the Sydney Eye Hospital, Sydney, Australia in 2012 and 2013. [129] As the recommendations from HEDS clinical trials and other studies were not relevant to Australia and had not translated to clinical practice, the Save Sight Institute in collaboration with the Sydney Eye Hospital developed a local guideline to standardise initial therapy with their subsequent implementation and evaluation. The necessary steps for this process were determined through using *The RNAO Toolkit: 'Implementation of Best Practice Guidelines'*. [15]

5.1.1 The Registered Nurses Association of Ontario Toolkit: 'Implementation of Best Practice Guidelines'

The RNAO Toolkit: 'Implementation of Best Guidelines' was used as a guide for developing, monitoring and evaluating a local HSK treatment guideline. [15] The primary focus of this Toolkit is the implementation of the best practice guidelines at an organisational or departmental level through a systematic and well-planned process. This Toolkit was originally developed in 2002 by an expert panel of nurses, allied health professionals and researchers in guideline implementation. A consensus was achieved for the scope of the Toolkit, a model of guidelines implementation was informed by the best available evidence and specific recommendations regarding each phase of the implementation process were based on published evidence. A revision was conducted in 2012 by a Review Panel of expert nurses and researchers from the original panel and other people with experience in guideline implementation at the organisational level

through the RNAO Best Practice Spotlight Organisation initiative. Research in best practice guidelines has constantly evolved to include important structures and processes to influence practice and patient outcomes. The nature of knowledge translation is context specific. Therefore, any effort to present a systematic process must be approached carefully when contextualising to local culture. [15] The RNAO Toolkit has been used to create multiple guidelines mainly for nurses in diverse topics including mental health, respiratory conditions, administration of insulin in diabetes mellitus, establishing therapeutic relationships, breastfeeding, chronic kidney disease, management venous leg ulcers; but also, for interprofessional teams in adopting e-Health solutions, pain management, assessment and management of venous leg ulcers, integrating tobacco interventions into daily practice among others.

This Toolkit was created based on the 'Knowledge-to-Action' Framework. [14] The 'Knowledge-to-Action Framework' is divided in two parts: **knowledge creation process**, and **the action cycle**. This framework is iterative, dynamic and involves all stakeholders (patients, health care providers, managers and policy makers) (See Figure 1 - 1, page 7).

5.1.1.1 Knowledge creation

Knowledge creation comprises three types of knowledge or research that can be used in health care: knowledge inquiry, knowledge synthesis, and creation of knowledge tools/products. As knowledge moves from one of these phases to the next, it becomes more refined and useful to the researchers.

5.1.1.1.1 Knowledge inquiry

The first phase, 'knowledge inquiry', represents the immense number of primary studies or information of variable quality in their natural state, unrefined which may or may not be easily accessible. [14]

5.1.1.1.2 Knowledge synthesis

The second phase, ‘knowledge synthesis’, represents the aggregation of existing knowledge. The process consists of the application of reproducible methods to identify, appraise and synthesise studies relevant to a specific question. This type of knowledge is represented by systematic reviews, including meta-analysis and meta-synthesis. [14]

5.1.1.1.3 Knowledge tools/products

The purpose of the third phase, ‘creation of knowledge tools/products’ is to present knowledge in a clear, concise and user-friendly format as a tool or product. The tool or product aims to provide explicit recommendations to different stakeholders and meet their needs facilitating the uptake and use of the new knowledge. [14]

5.1.1.2 Action cycle

The action cycle aims to implement or apply new knowledge in clinical care. This is a dynamic and iterative process illustrated by seven components (See Figure 1 - 1, page 7). [15]

5.1.1.2.1 Step 1: Identify problem, review and select knowledge

Best practice guidelines are used by health professionals and organisations to provide the best quality, safe and ethical health care. The aim is to ensure that the approaches used in daily practice to achieve quality outcomes are based on the best evidence. There are two ways to trigger practice change. One way is that a new guideline is made available and leads to a practice review and potentially adoption of the new guideline. The other way is that a clinical issue, problem or challenge arises which then encourages the need for a solution. [15]

5.1.1.2.2 Step 2A: Adapt knowledge to local context

Most clinical guidelines need some modification to fit into different contexts. Sometimes guideline adaptation may be challenging due to cultural differences, organisational priorities, available resources, scopes of practice and regional legislation.

[15] Nevertheless, adapting high-quality guidelines into local settings reduces the need to fully develop local specific clinical practice guidelines and supports the implementation of evidence-based recommendations to the specific site. Guideline adaptation requires the determination of what knowledge from the original source will suit local conditions. [15] The ADAPTE Collaboration [168] created a systematic framework to guideline adaptation recommended on The Toolkit (See Figure 5 - 1, page 224). [15] An implementation team must tailor this knowledge to the local context through the implementation activities. The main objective is to guarantee that the implemented guidelines and recommendations are recognised by all stakeholders to address the problem, suit the local setting and represent the best available evidence. [15]

Phases	Tasks	Associated modules
Set up phase	Prepare for ADAPTE framework	Preparation
Adaption phase	Define Health Questions	Scope and purpose
	Search and Screen Guidelines	Search and screen
	Assess Guidelines	Assesement
	Decide and Select	Decision and selcetion
	Draft Guideline Report	Customization
Finalization phase	Extrenal Review	External Review
	Plan for future review and update	Aftercare planning
	Produce final guideline	Final procution

Figure 5 - 1: The ADAPTE process framework (adapted from RNAO [15]).

5.1.1.2.3 Step 2B: Stakeholders

Stakeholders are individuals, groups and organisations who are interested in, are affected by or can affect a practice change. [15] Stakeholders play a key role supporting,

opposing or being neutral during the implementation process. The implementation team must understand well the implementation process before considering the potential stakeholders. [15] A variety of stakeholders must be considered including client/patient/resident, staff nurses, physicians, allied health professionals, senior and middle management staff and front-line employees. Stakeholders can also be categorised as external, internal or interface. [15]

- External stakeholders: accreditation bodies or consumer interest groups.
- Internal stakeholders: nurses, physicians and allied health professionals.
- Interface stakeholders: board members and staff with cross appointments.

An early stakeholder involvement is essential for a successful implementation. [15] A stakeholder analysis should consider the qualities of the stakeholder, such as their knowledge of the topic, their perspectives, experience with team and decision-making skills. [15] Moreover, the stakeholder involvement requires a regular revision as new stakeholders may appear in the scenario and others may change their positions or leave the organisation. [15]

Two variables should be considered when conducting the stakeholder analysis: the potential for support of the change initiative and the potential for threat or the degree of influence to the adoption of the change. As a result, four combinations can occur: [15]

- **High influence and highly supportive**: this group most positively influence dissemination and adoption of the guidelines. These stakeholders need a lot of attention for ongoing support of the initiative and must be regularly informed.
- **High influence and low in support**: this group needs a great deal of attention to have them on board of the initiative.
- **Low influence and highly supportive**: this group needs some attention to prevent them from becoming neutral or negative towards the implementation

and can provide enough assistance.

- **Low influence and low in support**: this group is the most negative combination for the adoption of guidelines. Nevertheless, it is essential to neutralise them before they influence negatively towards the initiative.

5.1.1.2.4 Step 2C: Resources

An indispensable component of the implementation plan is the assessment and acquisition of the resources required to execute the plan. Understanding the availability of resources will guarantee a successful implementation in a local setting. The availability of resources may be an important barrier or facilitator of the implementation plan. [15]

5.1.1.2.5 Step 3: Assess facilitators and barriers

Identifying the facilitators will allow the implementation team to obtain the maximum support for this process. Understanding the barriers will assist the team to create strategies to overcome them early. New barriers may emerge as new stakeholders are involved in the process. [15] Factors that influence guideline implementation can be facilitators, in other situations may be barriers, or sometimes they are both. Unanticipated events such as staff changes, organisational restructure, funding changes, illness or corporate direction shifts can facilitate new opportunities or present new barriers. Therefore, the assessment of facilitators and barriers is an ongoing process itself. [15] These factors can be classified as those related to:

- The evidence (guideline)
- The target audience for the change (individuals and teams)
- The resources
- The organisation

5.1.1.2.6 Step 4: Select and tailor implement interventions and strategies

Selecting an implementation strategy to easily translate the new knowledge into practice is fundamental in the knowledge-to-action process. Recognising the barriers for translating the new knowledge can provide an initial picture for creating the strategy. Implementation strategies are different depending on the care delivery models, for medical practice, nursing and interdisciplinary health teams. [15] The evidence suggests that one single intervention will not make a difference in implementing guidelines; therefore, different combinations of interventions can effectively change practices. [15]

Changing health care provider behaviour is difficult. Effective strategies encompass various elements targeting the identified barriers. Strategies may include education, audit and feedback, local opinion leaders, patient-mediated interventions, interventions at the organisational level and integrated recommendations into organisational process. **Education strategies** should be interactive or combined with other interventions. A presentation is categorised as passive dissemination of information. It is often used as part of a multifaceted education strategy, as passive education on its own will probably not change complex behaviour. [15] Interactive or multimedia educational interventions, for example role plays and practising skills are generally more effective than passive dissemination of information. As the pharmaceutical industry knows well, one-on-one visits to a health provider or in combination with other strategies have a small, but consistent effect on prescribing behaviour. Printed education materials have a small positive effect on professional practice. [15] When educational strategies are combined with interaction between educator and practitioner (audit and feedback, reminders or interaction with opinion leaders), they are more likely to change the behaviour.

Strategies related to **audit and feedback** have been shown to influence health professional practice. They are more effective when the difference between baseline, pre-guideline implementation practice, and the recommended practice is large. Audit and feedback are more effective when they are personalised, intensive and repetitive over a long period of time. Strategies related to **local opinion leaders** involve the leader

influencing their colleagues' knowledge and practice. Strategies related to **patient mediated interventions** may be effective as part of a multifaceted strategy. These interventions include educating patients about research evidence relevant to their medical condition and treatment. The evidence about the effectiveness of strategies related to the organisational level is mixed. [15] These strategies may influence the organisational processes

Integrating recommendations into organisational processes, for example automated reminders, clinical decision support systems or restructuring patient records can also be effective. Strategies closer to the end user and integrated into the health care delivery process probably work better. [15] Reminders can significantly improve practice and are successful if they are part of the normal workflow at the time and location of the decision-making, for example as part of electronic charting or order entry; if they provide a specific recommendation with a reason and if they are provided via computer-based support. [15]

5.1.1.2.7 Step 5: Monitor knowledge use

Monitoring and evaluation of knowledge use are a critical part of the knowledge-to-action process. [14, 15] Monitoring indicates the extent to which the best practice guidelines are known, accepted and applied; the extent to which the implementation intervention was successful in changing clinical practice; information about knowledge, attitudes, skills; and adherence to recommendations, and the rationale for subsequent changes in the already implemented strategies. [15]

Evaluating the outcomes of the knowledge use provides an indication of the impact of the guideline's implementation in different levels: patient/client, health care provider and health care unit or organisation. This step answers the question: 'what difference, if any, does applying the recommendations make in clinical practice, in particular to my patient's health and clinical outcomes?' [14, 15]

The strategies for monitoring depend on the type of knowledge use and which stakeholders will be using the knowledge (public or health-consumers, health care

professionals, managers and administrators and policymakers). [15] Monitoring strategies include interviews, surveys, audits and analysis of administrative databases for clinicians; and interviews and document analysis for policymakers.

Knowledge is an essential component in the clinician adherence to evidence-based practice recommendations. Three types of knowledge have to be considered to effectively monitor the adherence of the practice recommendations: [15]

- **Conceptual knowledge use:** illustrates the understanding, acceptance and internalisation of the knowledge. Strategies include tests to assess the extent to which clinicians acquired the knowledge and skills taught in the training sessions, for example surveys of attitudes and intentions, measures of attitudes towards a specific practice and perceptions of self-efficacy while performing a specific practice or intending to perform a practice to perform practices. [15]

- **Behavioural or instrumental knowledge use:** represents the knowledge that influences actions and behaviours. It illustrates the real application of knowledge in clinical practice and alignment with the new guidelines that should result in the excepted outcomes. Most of knowledge utilisation tools measure this type of knowledge use. These tools include measures of adherence to recommendations or quality indicators by using administrative databases or chart audits, observation of the service user and clinician encounter, and direct questioning of patients about their health-care encounter. [15] These measures rely on self-reporting and are thus subject to recall bias and social response bias. Recall bias occurs when a person may not accurately remember what they have learned, and social response bias occurs when a person gives an answer that they think the questioner wants to hear. [15]

- **Symbolic knowledge use:** represents the use of the chosen data to convince others to do something or stop doing something. [15]

5.1.1.2.8 Step 6: Evaluate outcomes

The following elements must be considered when evaluating the impact of knowledge use: [15]

- Type of knowledge (conceptual, behavioural or instrumental and symbolic)
- Focus of evaluation (patient, health care provider, organisational level)
    - Patient: measures of an actual change in health status such as mortality, morbidity, quality of life and adverse events. Other measures of impact unrelated to health status (patient satisfaction).
    - Health care provider: measures of provider satisfaction.
    - Organisational level: measures of change in the health care system (wait time, length of stay, health care visits, readmissions) or expenditures.
- Type of indicator (structure, process, outcome)
    - Structural indicators focus on organisational aspects of service provision, such as endorsement of guidelines, introduction of policies that clearly identified the required practice, and forms that prompt adherence to guideline.
    - Process indicators focus on patient care delivery processes, for example a plan tailored for each patient.
    - Outcome indicators focus on improving patient health outcomes, for example prevalence of pain according to severity (mild, moderate, severe).

There are different aspects to consider when measuring outcomes: [15]

- ‘Direct aspect’ measures an outcome that can be directly observed or measured, for example observing a nurse conducting a pain assessment or measuring

conceptual knowledge after an education session by administering a multiple-choice test assessing knowledge of the content taught in that session

- 'Indirect aspect' measures the outcome of a behaviour or action, for example chart audit of documentation by nurses of a pain assessment

- 'Subjective aspect' is the subjective experience of the person, and maybe measured for example by a self-reporting tool, patient interview, and/or focus groups

- 'Objective aspect' is data that does not have subjective bias or recall, for example the number of self-administered doses of pain medication a patient received via a computerized pain pump including tracking of the number of attempts and doses given.

5.1.1.2.9 Step 7: Sustain knowledge use

The interest in sustainability of knowledge use is recent such that there is little research on the subject. [14] Sustainability is defined as the degree to which an innovation continues to be used after initial efforts to secure its adoption are completed. [15] This final step in the knowledge-to-action plan is key to guaranteeing that the practice changes will be incorporated in the current and future health-care flow. Sustainability planning must be also considered early in the implementation process. [15]

Nine factors facilitate practice change and bring a realistic sustainability monitoring to the health-care setting. These nine factors, derived from evidence and from experience of implementing health-care guidelines, include: relevance of the topic, benefits, attitudes, networks, leadership, policy articulation and integration, financial, and political issues. [15] Further, the following three strategies were found to promote more sustainable evidence-based practice;

- **Developing a 'yes we can' attitude:** despite the presence of ongoing barriers, a positive approach to overcome these barriers will be beneficial for an ongoing project. [15]

- **Interprofessional reflective practice:** stakeholders need to individually and collectively reflect on what is required to sustain the knowledge use long-term. They must understand the continuous challenges faced daily by providers, patients and their families. Team meetings, unit councils and family forums have been reported to provide adequate opportunities for administrators and care providers to discuss evidence-informed decision-making processes in order to match future care with best practice recommendations. [15]

- **Leadership:** it is essential to sustain knowledge use. Successful leadership strategies include facilitating individual staff to use guidelines, creating a positive environment for best practices, and influencing organisational structures and processes. [15]

Indicators to monitor sustainability must be identified to interconnect the **micro, meso and macro levels of health-care delivery**. Micro level refers to the individual area of practice including the use of unit protocols and patient/family education tools. Meso level refers to clinical units and/or departments within the same institution that require consultation and collaboration for example looking for synergies among multiple departments. Macro level refers to the sustainability planning that external organisations must consider to guarantee the continuous knowledge use. [15] Several mechanisms are used to ensure transparency of quality improvement processes at different levels. Some examples of balance scorecard indicators include tracking of specific health-care delivery outcomes, quality assurance committee, specific performance audits and public health campaigns. [15]

5.2 Aim

The aim of this chapter was to utilise *The RNAO Toolkit: 'Implementation of Best Practice Guidelines'* [15] for the development, implementation and evaluation of treatment guidelines for the management of HSK at the Sydney Eye Hospital

5.3 Hypothesis

We hypothesised that treatment guidelines for the management of HSK could be successfully implemented into practice at the Sydney Eye Hospital.

5.4 Methods

5.4.1 Step 1: Identify problem

The RNAO Toolkit recommended carrying out a gap analysis to confirm the evidence-to-practice gap. The evidence-to-practice gap is the gap between the current practice in the hospital and evidence from high quality best practice guidelines or systematic reviews. [15]

The terms ‘Unmet’, ‘Partially met’ and ‘Met’ were used for the gap analysis and determined as: [15]

- ‘Unmet’: adherence to ‘guidelines’ in 0% to 60% of patients.
- ‘Partially met’: adherence to ‘guidelines’ in 60% to 90% of patients.
- ‘Met’: adherence to ‘guidelines’ in 90% to 100% of patients.

In addition, the RNAO Toolkit recommended assessing the available knowledge tools (‘The AAO HSK treatment guideline’) which may be used to resolve the problem. The knowledge tools are assessed with the Appraisal of Guidelines for Research & Evaluation (AGREE) II Instrument. [15] The AGREE II instrument was developed by AGREE Collaboration [169] and has six domains (See Table 5 - 1, page 234):

Table 5 - 1: Domains of AGREE II instrument.

Number	Domain
1	Scope and purpose
2	Stakeholder involvement
3	Rigour of development
4	Clarity of presentation
5	Applicability
6	Editorial independence

5.4.2 Step 2: Adapt knowledge, stakeholders and resources to local context

The ADAPTE framework (See Figure 5 - 1, page 224) was utilised to adapt 'The AAO HSK treatment guideline' to our local context at the Sydney Eye Hospital.

The main investigator and supervisors considered a variety of individuals to form the implementation team and to be part of the stakeholder group. Local corneal experts, uveitis experts, and pharmacists, as they dispense the medications at the hospital, were considered to form the implementation team. Four corneal specialists, two uveitis specialists and two pharmacists accepted the invitation to be part of the implementation team. The implementation team held a meeting where relevant stakeholders were identified including clinicians, nurses, pharmacists, and administrative hospital staff. The administrative staff consisted of the Drug and Therapeutics Committee and the Director of Clinical Services. These were chosen as the local HSK treatment guideline needed approval before implementation. A stakeholder analysis was performed utilizing the two variables (potential for support the change initiative and the degree of influence to the adoption of the change) described earlier in the chapter (See 5.1.1.2.3, page 224).

The main investigator and main supervisor created an expense worksheet to assess the availability of resources for the implementation, monitoring and evaluation of the local HSK treatment guideline (See Table 5 - 8, page 252). [15] A budget was created

for the implementation phase. Quotes for printing lanyard cards were obtained and for updating the Sydney Eye Hospital Pharmacopeia mobile application.

5.4.3 Step 3: Facilitators and barriers for implementing the local HSK guideline

The implementation team held a meeting to discuss the potential facilitators and barriers for the guideline implementation at the hospital. The team selected the facilitators and barriers based on The RNAO toolkit recommendations according to the evidence (guideline), the target (clinicians at Sydney Eye Hospital), resources (human, financial and physical) and the organisation (Sydney Eye Hospital). [15]

5.4.4 Step 4: Select, tailor and implement intervention and strategies

The implementation team selected the implementation strategies for the local HSK treatment guideline at the hospital after identifying the facilitators and barriers in the same meeting. The strategies were chosen based on experience and on published evidence (The RNAO Tooklit, [15] and previous studies [170-173]). The creation of lanyard cards was chosen as pharmacy designed lanyards cards for antibiotic use at the hospital which were widely used and positively reviewed among clinicians.

5.4.5 Step 5 and 6: Monitor knowledge use and evaluate outcomes

Evaluation of impact should start with formulating the question of interest using The PICO framework: [15]

P- population of interest

I- implementation/intervention (knowledge translation strategy)

C- comparator group (another group where strategy was not used) or if there is no comparator group, think about context

O – outcome of interest (health, provider, organisational or system)

Did the local HSK treatment guideline (I) change clinicians' (P) knowledge (O) on how to initially treat patients diagnosed with HSK at the Sydney Eye Hospital after the implementation of the local guidelines compared with those who prescribed antiviral therapy before the implementation of the guidelines (C)? The knowledge was measured with a survey and the prescribing behaviour was measured with an audit.

The implementation team chose the behavioural or instrumental knowledge use model for monitoring and evaluating the outcomes of the local HSK guideline implementation. The strategies that were used in this study for monitoring and evaluating the impact of the guideline implementation are shown in Table 5 - 2 (page 237).

Table 5 - 2: Strategies for monitoring and evaluating outcomes of the local HSK treatment guideline implementation (adapted from RNAO Toolkit [15]).

Construct	Type indicator	Description	Examples of measures	Strategy for data collection	Source of data
Knowledge use					
Conceptual	Process	Changing in knowledge levels	Knowledge, attitudes, intention to adopt practice	Self-report	Survey to clinicians
Instrumental	Process	Changes in behaviour or practice	Adherence to recommendations	Audit	Electronic clinical database
Enablers of instrumental use	Structure	Changes required to enable changes in behaviour	Organisational endorsement of guideline recommendations	Document analysis	Annual review of HSK local guidelines
Impact of knowledge use					
Provider	Outcome	Impact on providers in applying knowledge	Satisfaction with practice. Time taken to introduce new practice	Self-report	Survey to clinicians

5.4.5.1 Audit

A medical record audit was conducted to monitor and evaluate the adherence to the local HSK treatment guideline developed at the Sydney Eye Hospital. The guideline was implemented in June 2017. All HSK cases aged 18 and above presenting at the hospital from 3 June to 30 November 2017 were included. The potential patients were identified via pharmacy records, hospital coding data and from pathology results (HSV PCR).

Inclusion and exclusion criteria were the same applied to the retrospective case series with patients presenting in 2012 and 2013 (See 2.4.4.2, page 92). The primary and secondary variables of interest at inclusion and the primary outcomes were the same as in the retrospective case series (See Appendix C, page 321).

The level of adherence to the local HSK treatment guideline was determined as follows: if the patient received the recommended antiviral medication regardless of the topical corticosteroid, it was considered 'adherent' to the local HSK treatment guideline.

The outcome of the HSK episode was determined when the initial antiviral therapy was stopped or changed. For therapeutic indication, the outcomes were classified depending on clinical response as 'resolved', 'partially resolved', and 'worsened' (See 3.4.3, page 129).

Study data were collected and managed using REDCap (Research Electronic Data Capture, Nashville, TN, the USA) hosted at The University of Sydney [121] (See 2.4.4.1, page 91). [121] Data were reported in line with the STROBE statement for observational data. The research adhered to the Tenets of the Declaration of Helsinki. [124]

5.4.5.2 Web-based survey

5.4.5.2.1 Design

The implementation team reviewed and refined the initial 15-item web-based survey. A 9-item survey was peer-reviewed by researchers at the Save Sight Institute,

and a pilot version also trialed by other researchers at Save Sight Institute before review and approval by the ethics committee.

Participants were asked about the role of the clinician at the hospital; (ii) guideline awareness, (iii) guideline use; and (iv) guideline knowledge (Appendix K, page 371). The primary method of accessing and completing the survey was via an online survey company (www.surveymonkey.com). The survey company hosted and collected the survey data. Only participants who received the email invitation could access and respond the survey, via a hyperlink.

5.4.5.2.2 Participants

Inclusion criteria were consultants, fellows, registrars and residents employed at the Sydney Eye Hospital whose email addresses were included in a list managed by the senior registrar at the hospital. A request to complete the survey was emailed to a list comprising 95 clinicians on 10 December 2017.

5.4.5.2.3 Web-based survey administration

An email invitation with a hyperlink to access the survey was sent to all clinicians employed at the Sydney Eye Hospital registered in the abovementioned list. To increase the response rate, a reminder email was sent to the list of clinicians a fortnight later (7 January 2018). The survey was closed in February 2018.

5.4.6 Step 7: Sustain knowledge

The implementation team discussed the following questions regarding the factors that facilitate a realistic sustainability plan.

- What is the relevance of the topic?
- Is there a well-defined need and priority for the topic being implemented?
- Is there consensus about what knowledge needs to be sustained and what is needed to create conditions for sustainability?

- How does the new knowledge fit with current priorities?

There was a well-defined need to introduce a treatment guideline for the initial antiviral therapy for HSK. A diverse antiviral therapy was found in the retrospective case series (see Chapter 2) with 73% of patients receiving an appropriate antiviral therapy according to available evidence. There were no available guidelines for SHSK+U and for keratouveitis. The need for a guideline suited with the current priorities of the hospital as approximately 5 new patients with HSK present to the hospital weekly. Moreover, HSK is a major cause of unilateral blindness in developed countries.

Benefits

- What are the anticipated outcomes of knowledge implementation from a biological, economic, psychological, organisational, social, political or other perspective?

- How meaningful are these benefits to other stakeholders?

We hypothesised that following the local HSK treatment guideline, clinicians would have a clear idea on how to initially treat most of the HSK cases following the available evidence. It would mostly benefit the trainees as managing HSK can be very challenging. Patients would also benefit from the guidelines as they receive either oral or topical prescriptions (not both) which may reduce their treatment costs whilst still achieving a successful outcome.

Attitudes

- What attitudes (potential resistance) did major stakeholders have about the actions recommended in the guideline? Are the recommendations a major change? How?

The stakeholders (See Table 5 - 6, page 249) supported the introduction of HSK treatment guidelines at the Sydney Eye Hospital. They reached a consensus on the best

treatments for the different types of HSK. The guidelines were reviewed by other corneal specialists, pharmacy and the Drug and Therapeutics Committee. There was a positive attitude in the hospital towards our guidelines. Perhaps some consultants may not have used the guidelines as they were accustomed to their prescribing style acquired during their working experience.

Networks

- What teams/groups can be engaged to facilitate the sustainability of knowledge use?

The trainee group (registrars, residents and fellows) was able to assist in the sustainability of the project by recommending the local guidelines to new trainees and reminding their peers during consultation in the emergency department or in outpatient clinics. Pharmacy was also able to support the sustainability of the knowledge use by reminding clinicians whenever they received a prescription with an inappropriate dosage and frequency.

Leadership

- Who is responsible from a project lead perspective (short-term, long-term)?
- Are they champions and peer mentors in your setting?
- What actions can unit managers and administrators take?
- What might a senior administration do from a sustainability perspective?

The main investigator and the supervisors were the project leaders. The supervisors were targeted as the project leaders for long-term. The supervisors were mentors in the Sydney Eye Hospital as consultant ophthalmologists at the Sydney Eye Hospital: one as a professor and the other a senior lecture of the University of Sydney. Administrators and Drugs and Therapeutics Committee staff may ensure a yearly revision of these guidelines for sustainability.

Policy articulation and integration

- Does the recommendation fit with the current policies?
- What might need to change?
- Are reminder systems feasible?

There were no current policies about HSK treatment in the hospital. This was an initial guideline for HSK initial therapy with the potential to improve as more evidence appears in the literature. The clinicians' prescribing habits needed to align with the local HSK treatment guideline. Reminder systems were not feasible, but incorporation of the guidelines into electronic prescription system was considered.

Financial

- What funding is required to implement your strategies and action plan?

Funding was required for printing educational materials and the main investigator stipend. There is a need for further funding to secure ongoing training for new and current staff and for presenting our project at conferences and journals.

Political

- Who are the stakeholders and what power, or support might be leveraged?
- Who will initiate the scaling up process?

The clinical services manager and the Drug and Therapeutics Committee authorised the implementation of the guidelines.

After identifying the factors that may facilitate the sustainability of this project, some outcomes were determined. These included seeking an increase in awareness of the HSK guidelines at organisational level, obtaining higher clinician adherence to the HSK guidelines at provider level, and securing financial support for ongoing educational materials and for attendance to conferences to acquire new knowledge and disseminate

the findings of this project. The structures, processes and outcomes are shown in Table 5 - 3, page 244

Table 5 - 3: Identification of sustainability outcomes for the local HSK treatment guideline.

Category	Structure (What you need to have)	Process (How you go about it)	Outcome (What happens)
Organisation	– Mission and culture to support necessary changes – Drug and Therapeutic Committee – Interprofessional team involvement	– Engagement and accountability of leaders from administration and clinical practice – Development of policies and procedures – Guideline added to staff orientation – Continual education and availability of education	– Increase in awareness of in-house resources
Provider	– Number and qualification of staff – Roles and responsibilities multidisciplinary collaboration – Educational program	– Awareness of/attitude toward HSK guidelines – Knowledge/skills level – Leadership – Marketing of strategy to health-care recipient	– Higher adherence to HSK guidelines
Financial costs	– Cost of ongoing education	– Cost of implementation strategies – Internet and web support	– Financial support for educational materials – Financial support for staff to attend conference for knowledge acquisition and/or dissemination

5.4.7 Human research ethics

Ethics approval for this research was sought and granted from the South Eastern Sydney Local Health District Human Research Ethics Committee (approval number HREC 13/296) shown on Appendix E, page 334. A third amendment to ethics was approved to conduct the audit and the web-based survey (Appendix L, page 373).

5.4.8 Statistical analysis

Descriptive statistics will be used to summarise all continuous and categorical variables. Treatment trends post-guideline implementation were compared with trends found in a previous retrospective case series (Chapter 2) using tests of proportions (Fisher's Exact or Chi-square tests). A *p*-value < 0.05 was considered as evidence of statistical significance. The statistical software used was IBM SPSS Statistics Desktop Version 22 (IBMCorp, Armork, NY).

5.5 Results

5.5.1 Knowledge creation

5.5.1.1 Knowledge inquiry

In our study, 'knowledge enquiry' involved identifying appropriate RCT and observational studies on treatment of epithelial, stromal, iridocyclitis HSK and for the prevention of HSK. The most significant RCTs were conducted by the HEDS group (See 1.4.4.8, page 40). [2-6]

5.5.1.2 Knowledge synthesis

In our study, existing knowledge via systematic reviews including meta-analysis and meta-synthesis were identified as 'knowledge synthesis', for example the systematic review by Guess et al. [1] and the Cochrane review of treatment for epithelial HSK (See Table 1 - 4, page 58). [1, 7]

5.5.1.3 Knowledge tools/products

For our study, 'The AAO HSK treatment guideline' (See Appendix A, page 313) [23] and the recommendations for paediatric patients (See Appendix B, page 318) [95, 96] were used as knowledge tools 'The AAO HSK treatment guideline' was chosen as it is a thorough and updated guideline for the treatment and prevention of HSK. It covers the different types of HSK and recommendations for children, pregnant women and immunosuppressed patients. The paediatric recommendations from the Australian Medical Handbook (Children's dosing companion) and British National Formulary for Children were chosen as there are no other published HSK guidelines for children.

5.5.2 Action cycle

5.5.2.1 Step 1: Identify the problem

A diverse initial antiviral therapy for HSK management was observed at the Sydney Eye Hospital in 2013 was identified as a **'problem'** (See Table 5 - 4, page 246).

Table 5 - 4: How knowledge gap was identified for our study (adapted from RNAO Toolkit [15]).

Chain of events	Stakeholder involvement
What happened?	Ophthalmologist observed a diverse initial antiviral therapy for HSK at Sydney Eye Hospital.
Related 'problems' or opportunity identified	Initial antiviral therapies may have not been aligned with the evidence-based recommendations. Initial antiviral therapy may need a review. Patients may have expensive costs due to inappropriate prescriptions Unknown clinical outcomes due to diverse antiviral therapy
Other guidelines used	'AAO HSK guidelines'
Response to the problem	Conduct retrospective case series to determine initial antiviral therapy and clinical outcomes. Compare antiviral therapies with evidence-based recommendations Develop local guidelines for initial antiviral therapy for HSK at the Sydney Eye Hospital.

In 2013, there were no clinical guidelines available for the treatment of HSK at the Sydney Eye Hospital. A retrospective case series of all HSK patients presenting at the hospital in 2012 and 2013 was conducted to confirm the evidence-to-practice gap. The prescribing behaviour found in this case series was compared with the treatment recommendations from published RCTs. Evidence-based recommendations were compiled to enable comparison (See 2.4.3, page 90). Twenty-one antiviral regimens for the treatment of HSK and 10 for the prevention of HSK were identified in this case series. Only the regimens for epithelial HSK, SHSK-U, endothelial HSK and HSK prophylaxis were compared with evidence-based recommendations as there were no recommendations for SHSK+U and keratouveitis. Thus, 73% of patients had followed the evidence-based recommendations. (See 2.6, page 120).

The results of the retrospective case series were analysis using the terms ‘Unmet, partially met and met’ (See 5.4.1, page 233). Only the patients with epithelial HSK ‘met’ the evidence-based recommendations; while patients with endothelial HSK and on HSK prophylaxis ‘partially met’ the recommendations; and patients with SHSK-U ‘unmet’ the recommendations (See below Table 5 - 5).

Table 5 - 5: Gap analysis summary for HSK evidence-based recommendations.

Type of HSK	Met	Partially met	Unmet	Adherence to HSK evidence-based recommendations
Epithelial	✓			89% patients
SHSK+U				No available recommendations
SHSK-U			✓	9% patients
Endothelial		✓		33% patients
Keratouveitis				No available recommendations
HSK prophylaxis		✓		70% patients

Following ‘The RNAO Toolkit’, an appropriate evidence to address the identified ‘problem’ or ‘issue’ was sought. ‘The AAO HSK treatment guideline’ released in 2014 was assessed with AGREE II [169] (See Table 5 - 1, page 234). The score

for domain 3 (rigour of development) was 71%. As this score was over 70%, the rest of the domains were appraised. The scores were for domain 1, 100%; domain 2, 63%; domain 4, 100%; domain 5, 0%; and domain 6, 50%. The overall guideline assessment was rated with 5 out of 7 with 7 indicating the highest possible quality. The implementation team recommended 'The AAO HSK guidelines' for use (Appendix A, page 313).

5.5.2.2 Step 2A: Adapt knowledge to local context

The implementation team appraised 'The AAO HSK guidelines' using the AGREE II instrument. Despite being a high-quality guideline, it did not fit into the Australian context. 'The AAO HSK guidelines' recommended ganciclovir and trifluridine as first line therapy for epithelial HSK as topical aciclovir is not approved for epithelial HSK in the USA. However, topical aciclovir is the first line therapy in Australia as per evidence. [1] Moreover, 'The AAO HSK guideline' did not include recommendations for keratouveitis. 'The AAO HSK guideline' met the criteria for all domains except for applicability. The guidelines did not describe facilitators and barriers to the guideline's application, tools on how the recommendations can be applied in practice, potential resource implications of applying the recommendations, and monitoring and/or auditing criteria to measure the application of the recommendations.

Following the ADAPTE framework (See Figure 5 - 1, page 224), 'The AAO HSK guideline' was adapted with adjustments made to suit the local context, the Sydney Eye Hospital **(Prepare for ADAPTE framework)**. Having reviewed the available published evidence and conducted the retrospective case series **(Define health questions, search and screen guidelines)**, a committee of cornea and uveitis specialists was established to discuss their experience prescribing antiviral medications and topical corticosteroids for each type of HSK and for HSK prevention. Firstly, a meeting was organised to obtain a consensus among the consultants on the best regimens for each type of HSK **(Decide and select)**. Secondly, the implementation team (See Table 5 - 6, page 249) discussed the first draft of the HSK treatment guideline **(Draft guideline report).** Between February and June 2016, the implementation team worked on defining

the guideline with attention paid to language and design. Recommendations were included for the following types of HSK: epithelial HSK, SHSK+U, SHSK-U, endothelial HSK, keratouveitis, HSK prophylaxis, and recommendations were made for pregnancy, adult renal dosing for oral antiviral medications, and local and systemic treatment for paediatric patients (Appendix M, page 375).

The guideline was approved by the Drug and Therapeutics Committee of the Sydney Eye Hospital in December 2016 **(External review)**. Another meeting was organised with the pharmacists to approve the final version of the guidelines for printing posters and lanyard cards; for the upload into the hospital's intranet; and to schedule a meeting to review the uptake of the guideline 12 months later **(Plan for future review and update and produce final guideline)**.

5.5.2.3 Step 2B: Stakeholders

Our implementation team and stakeholders are listed below in Table 5 - 6:

Table 5 - 6: List of members of implementation team and stakeholders involved in the implementation of the local HSK treatment guideline.

Implementation team	Stakeholders
– Main investigator (PhD student) – Main supervisor (Prof. Stephanie Watson) – Auxiliary supervisor 1 (Dr. Dana Robaei) – Auxiliary supervisor 2 (Dr. Yves Kerdraon) – Corneal specialists (Dr. Chameen Samarawickrama) – Uveitic specialists (Prof. Peter McCluskey and Dr. Richard Symes) – Pharmacists (Judy Hampson and Cathy Vlouhos)	– Implementation team – Clinicians (trainees and consultants) – Pharmacists – Nurses – Drug and Therapeutics Committee – Director of Clinical Services

A stakeholder analysis was performed (See Table 5 - 7, page 251). Clinicians in training (fellows, registrars and residents) were identified as potentially positively affecting the dissemination and adoption of the guidelines as they can easily adopt clear and concise recommendations to initiate treatment to patients with HSK. If one such clinician uses the guidelines, it is more likely that their peers will use it. Similarly, pharmacists can remind other pharmacists to encourage that clinicians follow the guidelines when pharmacists dispense the medications. The Drug and Therapeutics Committee members can also support the adoption of the new guidelines and influence clinicians and pharmacists. On the other hand, consultants can negatively affect the dissemination and adoption of the guidelines as they may prefer to treat HSK based on their experience or follow the recommendations learnt as trainees in Australia or overseas.

Similarly, the Director of Clinical Services, under budgetary and other resource constraints, may consider that adopting this guideline is not a priority in the institution. A great amount of attention may be needed to obtain their support. Staff nurses can highly support clinicians in the adoption of the new guidelines and may require reminders from the implementation team to not remove the guidelines from the consulting rooms in emergency and outpatient clinic rooms in the long term. We believe that no stakeholder provided low support and low influence. Every stakeholder provided a certain amount of support or influence in the adoption of this guideline at the hospital as it had the potential to improve patients' clinical outcomes. In our scenario, the stakeholders were only internal. The extent of this guideline did not involve external or interface stakeholders.

Table 5 - 7: Stakeholder influence and support grid for implementation of HSK treatment guidelines.

Support	Influence	
	High	**Low**
High	– Trainees – Pharmacists – Drug and Therapeutics Committee	Nurses
Low	– Consultants – Director Clinical Services	NA

5.5.2.4 Step 2C: Resources

Funding for this project was initially granted by the Sydney Eye Hospital Foundation for 3 years. This funding covered the stipend for the main investigator and for implementing the guidelines at the hospital. As the project was extended to monitor and evaluate the guidelines, further funding was obtained for 3 years. The time allocated by the pharmacists, medical records staff, microbiology staff, and consultants to assist in this project was part of their research duties. Resources included in-kind contributions from staff and consultants; including uploading the guidelines on the intranet (See Table 5 - 8, page 252).

Table 5 - 8: Expense worksheet for implementing HSK treatment guidelines.

Step	Expenses
Setting the stage – Getting organized – Educational/public relations activities	– Main investigator time – Supervisor time
Guidelines identification Search and assessment activities	– Main investigator time
Stakeholders Identification, assessment and engagement activities	– Corneal and uveitic specialists meeting – Pharmacist meeting
Implementation Promotion and behaviour changing activities	– Lanyard cards printing costs – Attendance at key meetings – Poster production – Marketing (posters in each unit) – Trainees educational workshop – Main investigator time – Mobile application developer time
Evaluation Data generation, review and report production	– Medical records staff: retrieve charts – Microbiology staff: extract HSV PCR results – Pharmacy: extract antiviral medications records – Main investigator time: extraction of data from charts, data entry and analysis

5.5.2.5 Step 3: Facilitators and barriers for implementing HSK local guidelines

The implementation team identified the facilitators and barriers for implementing the HSK guidelines at the Sydney Eye Hospital listed below in Table 5 - 9.

Table 5 - 9: List of facilitators and barriers and strategies for local HSK treatment guideline implementation at the Sydney Eye Hospital.

Factors related to	Facilitators	Barriers
The evidence	– Accessibility – Understandability/complexity – Believability – Compatibility	– Ease of implementation
The target audience	– Knowledge/skills – Time – Opinion of others – Cohesiveness – Buy-in – Exchange of information processes	– Attitudes and beliefs
The resources	– Human Resources – Financial resources – Physical resources – Space	– Time as a resource
The organisation	– Leadership – Scope of practice – Change agents/opinion leaders – Existing policy and procedures	– Workload – Concurrent projects – Priorities – Organisational approval processes

5.5.2.5.1 Assessing facilitators

5.5.2.5.1.1 Facilitators relating to the evidence

Four facilitators relating to the evidence were identified: accessibility, understandability/complexity, believability and compatibility.

- **Accessibility** means the awareness of where and how to access the guidelines. [15] The HSK local guidelines were planned to be disseminated in multiple ways: as lanyard cards, as posters in the consulting rooms, as electronic documents and on the mobile application Sydney Eye Hospital-Ophthalmic Pharmacopoeia

- **Understandability/complexity** means the level of understanding and how to implement it in practice. [15] The HSK guidelines were developed in a clear and simple language.

- **Believability** means the quality of evidence on which the guideline was based, and **compatibility** means the compatibility with what is already known, believed and done. [15] The levels of believability and compatibility of the HSK local guidelines were high as they were based on 'The AAO HSK treatment guideline' and on published RCTs. The methods from The Scottish Intercollegiate Guideline Network (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) group were used to grade the strength of evidence individually. [23] Most of the main recommendations that formed 'The AAO HSK guideline' derived from the HEDS group which were RCTs rated I+ [2, 3, 5, 6] and systematic reviews rated I++. [7]

Therefore, the local HSK treatment guideline was found to be compatible with what was already known and published in the literature for HSK treatment.

5.5.2.5.1.2 Facilitators relating to the target audience

Five facilitators relating to the target audience were identified: knowledge/skills, time, opinion of others, cohesiveness and buy-in.

- **Knowledge/skills:** Training to fellows, registrars and residents was planned as part of the launch of the guidelines at the hospital. A lecture was organised to deliver a presentation about HSK, clinical manifestations, different types of HSK, diagnosis and treatment. The lanyard cards were distributed during the lecture.

- **Time** was provided to clinicians to read the guidelines and to ask questions during the lecture where the HSK local guidelines were launched.

- **The opinion and feedback of other corneal specialists** in the hospital was requested and considered for the development of the HSK local guidelines.

- **Cohesiveness**: the consultants and pharmacists have previously worked smoothly in various research projects without any issues at the hospital. They therefore did not anticipate any potential barriers to develop, implement, monitor and evaluate the guidelines with the lead of the main investigator and the implementation team.

- **Buy-in:** the implementation team considered that the local HSK treatment guideline would make a difference in the clinical outcomes at the hospital because a disparity of antiviral therapies was previously shown between the current prescribing trends and the published evidence (See 2.6, page 120)

- **Exchange of information processes:** there were several opportunities to exchange information about the local HSK treatment guideline. Firstly, this guideline was launched during a lecture. Secondly, the guideline was uploaded into the hospital intranet and on the ophthalmology registrars' Sydney Eye School website. Medical students and trainees could consult the guidelines on this website. Thirdly, lanyards cards were distributed among clinicians, especially registrars. We expected that the registrars showed the lanyards cards to each other in the clinics and emergency. Finally, the guidelines were also shared with trainees during journal clubs at the hospital, and at local and international conferences.

5.5.2.5.1.3 Facilitators relating to resources

Four facilitators relating to resources were identified: human resources, financial resources, physical resources and space.

- **Human resources**: adequate staff was ensured to develop, implement, monitor and evaluate the local HSK treatment guideline. The implementation team included a main investigator, three supervisors, one corneal specialist, two uveitis specialists and two pharmacists (See Table 5 - 6, page 249).

- **Financial resources:** these resources were also ensured through the funding initially granted for 3 years in 2014 and extended 3 more years in 2017. These resources covered the stipend for the main investigator and the activities for developing, monitoring and evaluating the local HSK treatment guideline.

- **Physical resources:** these resources were also ensured as the University of Sydney provided a workstation with a computer for the main investigator to conduct all tasks related to the project at the Save Sight Institute on the grounds of the Sydney Eye Hospital. Moreover, the online application REDCap was supplied by the University to store the dataset in their servers.

5.5.2.5.1.4 Facilitators relating to the organisation

Four facilitators relating to the organisation were identified: leadership, scope of practice and change agents/opinion leaders and existing policy and procedures.

- **Leadership:** the presence of an effective leader was ensured with the involvement of the main supervisor. She has an extensive history of successful research projects in Australia and overseas. She is a good communicator, and an accessible and effective change agent, actively involved in medical innovation research.

- **Scope of practice:** the local HSK treatment guideline was consistent with the scope of practice of the Sydney Eye Hospital, as the hospital is a quaternary

referral unit for eye diseases that treats patients from across the state of NSW and other Australian states and territories.

- **Change agents/opinion leaders:** effective change leaders or opinion leaders were also involved in this project. They included corneal and uveitis specialists, pharmacists, clinical services managers, and members of the Drugs and Therapeutics Committee.

- **Existing policy and procedures:** there were no existing policies or procedures on the management of HSK in the hospital. Hence, the local HSK treatment guideline was appropriate to be implemented as a hospital procedure.

5.5.2.5.2 Assessing barriers

5.5.2.5.2.1 Barrier relating to the evidence

One barrier relating to evidence was identified: **ease of implementation**. We anticipated that engaging with consultants may be more difficult than with the trainees in terms of demonstrating how the local HSK treatment guideline could be integrated into their current practice. Consultants may continue with their prescribing behaviour and be more hesitant to try other regimens.

5.5.2.5.2.2 Barrier relating to target audience

One barrier relating to target audience was identified: **attitudes and beliefs**. We anticipated that changing attitudes and beliefs of clinicians was a slow process. We believed that, compared to registrars and residents, consultants may be the hardest group to target as they were used to their prescribing regimens learnt in their training years or during their clinical experience.

5.5.2.5.2.3 Barrier relating to resources

Time as a resource was identified as a barrier. Time is always a concern when implementing projects as the timeline could be altered by any stakeholder affecting the entire process. A realistic timeline of three years was built to conduct the retrospective

case series study. Later, when the main investigator converted the part-time master's degree to a doctorate degree, another timeline was created for a total of 6 years. Having 6 years for this project guaranteed that all stakeholders participated in the different stages of the process and for disseminating this work at conferences and as manuscripts in medical journals.

5.5.2.5.2.4 Barriers relating to the organisation

Four barriers relating to the organisation were identified: workload, priorities, concurrent projects, and organisational approval processes.

- **Workload:** hospital clinicians face a large workload in the emergency department and outpatient clinics. We anticipated that clinicians may forget to use the local HSK treatment guideline and proceed with their regular regimens due to a hectic schedule.

- **Concurrent projects and priorities:** as Sydney Eye Hospital is a teaching hospital, many research projects may occur simultaneously. Clinicians may not remember the introduction of the local HSK treatment guideline focusing on other more relevant projects.

- **Organisational approval processes:** the hospital's approval process was at risk of delaying the implementation of the local HSK treatment guideline. When the final draft of the guideline was ready, the approval of the Clinical Services Manager was required and needed to be discussed in the Drugs and Therapeutics Committee meeting which was held every quarter. We anticipated that the approval process might have taken 6 months.

5.5.3 Step 4: Select and tailor implement interventions and strategies

The implementation team carefully chose strategies to implement the local HSK treatment guideline at the Sydney Eye Hospital considering the identified facilitators and barriers. The chosen strategies included communication of the guidelines via:

- **Educational lecture**: an educational lecture was given on 1 June 2017 presenting an update of the HSK management and the results of the retrospective case series to registrars and residents (See 2.5.2.1, page 100).

- **Lanyard card:** a lanyard card was designed with the input of the corneal and uveitis specialists and the pharmacists (See Figure 5 - 2, page 260). Two-hundred lanyard cards were printed. Thirty-five lanyard cards were distributed at the educational lecture. The senior registrar and pharmacy passed on lanyard cards to other clinicians who did not attend the lecture. Furthermore, they continued to provide the cards to new staff at the start of each term. In total, 90 lanyards were given to clinicians.

- **A4-size laminated posters:** An A4-sized laminated poster was placed in the 23 various consulting rooms of the hospital's emergency and outpatient departments (See Figure 5 - 3, page 261).

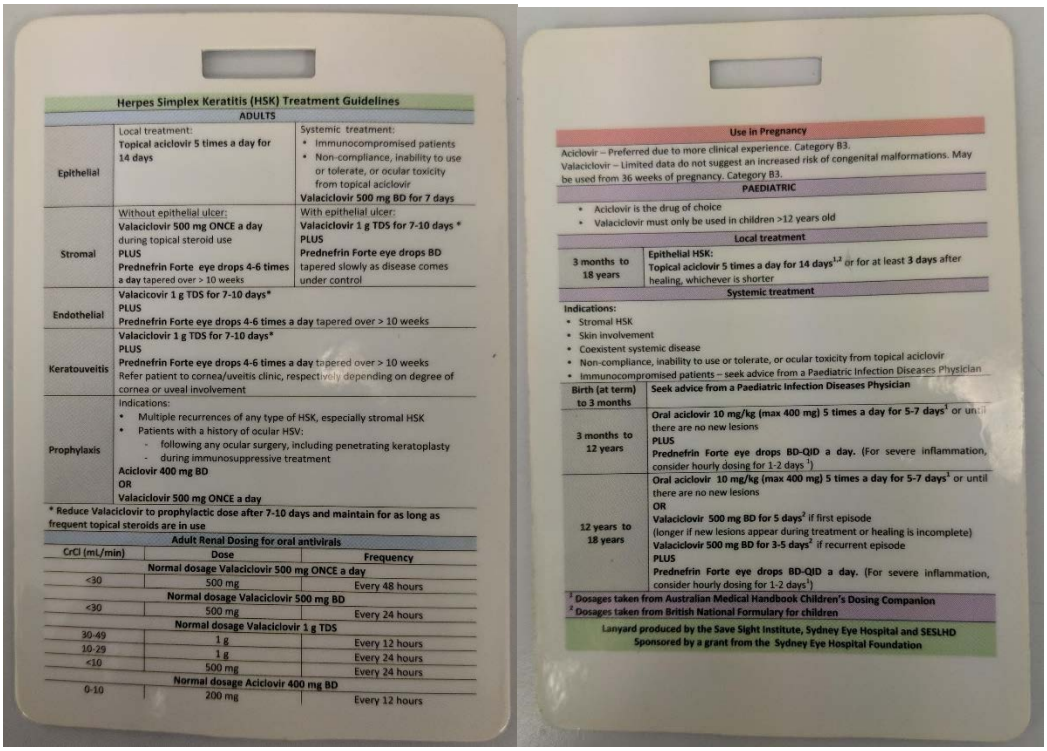
- **Email distribution:** an email was sent to all the hospital's registrars, residents, fellows and consultants with the local HSK treatment guideline as a PDF attachment.

- **A mail out to all consultants from Sydney Eye Hospital:** an envelope with an A4-size laminated poster, a lanyard card and a letter introducing the local HSK treatment guideline was sent to 30 consultants to their private rooms.

- **Hospital intranet site:** the local HSK treatment guideline was formatted in a hospital template and uploaded into the hospital's intranet. The guideline was made available on 27 July 2017 (See Appendix M, page 375).

- **Ophthalmology registars' Sydney Eye School website:** The local HSK treatment guideline was also uploaded to the Sydney Eye School website, which is an online repository for educational clinical resources, for the Sydney Eye Hospital Registrars. The site includes weekly eye school lectures and clinical resources such as these guidelines.

- **Sydney Eye Hospital Ophthalmic Pharmacopoeia mobile application:** the ophthalmology department and the pharmacy of Sydney Eye Hospital previously developed a mobile application called 'Ophthalmic Pharmacopoeia' with funding from the Sydney Eye Hospital Foundation. The mobile application is mostly used by ophthalmic trainees. We therefore considered that this application would be another excellent resource for clinicians to consult. Two meetings were held with the person in charge of maintaining the mobile application and the pharmacists to evaluate the possibility of updating the application. Afterwards, the pharmacists discussed the changes with the application's developers. As of 26 April 2019, the update is currently awaiting the availability of the programmers for implementation.



Herpes Simplex Keratitis (HSK) Treatment Guidelines

ADULTS

Epithelial	Local treatment: **Topical aciclovir 5 times a day for 14 days**	Systemic treatment: • Immunocompromised patients • Non-compliance, inability to use or tolerate, or ocular toxicity from topical aciclovir **Valaciclovir 500 mg BD for 7 days**
Stromal	Without epithelial ulcer: **Valaciclovir 500 mg ONCE a day** during topical steroid use **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over > 10 weeks	With epithelial ulcer: **Valaciclovir 1 g TDS for 7-10 days *** **PLUS** **Prednefrin Forte eye drops BD** tapered slowly as disease comes under control
Endothelial	**Valacicovir 1 g TDS for 7-10 days*** **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over > 10 weeks	
Keratouveitis	**Valaciclovir 1 g TDS for 7-10 days*** **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over > 10 weeks Refer patient to cornea/uveitis clinic, respectively depending on degree of cornea or uveal involvement	
Prophylaxis	Indications: • Multiple recurrences of any type of HSK, especially stromal HSK • Patients with a history of ocular HSV: - following any ocular surgery, including penetrating keratoplasty - during immunosuppressive treatment **Aciclovir 400 mg BD** **OR** **Valaciclovir 500 mg ONCE a day**	

* Reduce Valaciclovir to prophylactic dose after 7-10 days and maintain for as long as frequent topical steroids are in use

Adult Renal Dosing for oral antivirals

CrCl (mL/min)	Dose	Frequency
Normal dosage Valaciclovir 500 mg ONCE a day		
<30	500 mg	Every 48 hours
Normal dosage Valaciclovir 500 mg BD		
<30	500 mg	Every 24 hours
Normal dosage Valaciclovir 1 g TDS		
30-49	1 g	Every 12 hours
10-29	1 g	Every 24 hours
<10	500 mg	Every 24 hours
Normal dosage Aciclovir 400 mg BD		
0-10	200 mg	Every 12 hours

Use in Pregnancy

Aciclovir – Preferred due to more clinical experience. Category B3.
Valaciclovir – Limited data do not suggest an increased risk of congenital malformations. May be used from 36 weeks of pregnancy. Category B3.

PAEDIATRIC

- Aciclovir is the drug of choice
- Valaciclovir must only be used in children >12 years old

Local treatment

3 months to 18 years	**Epithelial HSK:** **Topical aciclovir 5 times a day for 14 days**[1,2] or for at least **3 days** after healing, whichever is shorter

Systemic treatment

Indications:
- Stromal HSK
- Skin involvement
- Coexistent systemic disease
- Non-compliance, inability to use or tolerate, or ocular toxicity from topical aciclovir
- Immunocompromised patients – seek advice from a Paediatric Infection Diseases Physician

Birth (at term) to 3 months	**Seek advice from a Paediatric Infection Diseases Physician**
3 months to 12 years	**Oral aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days**[1] or until there are no new lesions **PLUS** **Prednefrin Forte eye drops BD-QID a day.** (For severe inflammation, consider hourly dosing for 1-2 days [1])
12 years to 18 years	**Oral aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days**[1] or until there are no new lesions **OR** **Valaciclovir 500 mg BD for 5 days**[2] if first episode (longer if new lesions appear during treatment or healing is incomplete) **Valaciclovir 500 mg BD for 3-5 days**[2] if recurrent episode **PLUS** **Prednefrin Forte eye drops BD-QID a day.** (For severe inflammation, consider hourly dosing for 1-2 days [1])

[1] Dosages taken from Australian Medical Handbook Children's Dosing Companion
[2] Dosages taken from British National Formulary for children

Lanyard produced by the Save Sight Institute, Sydney Eye Hospital and SESLHD
Sponsored by a grant from the Sydney Eye Hospital Foundation

Figure 5 - 2: Local HSK treatment guideline on a lanyard card, version 1 (both sides).

Herpes Simplex Keratitis Treatment Guidelines

ADULTS		
Epithelial	Local treatment: **Topical aciclovir 5 times a day for 14 days**	Systemic treatment: • Immunocompromised patients • Non-compliance, inability to use or tolerate, or ocular toxicity from topical aciclovir **Valaciclovir 500 mg BD for 7 days**
Stromal	Without epithelial ulcer: **Valaciclovir 500 mg ONCE a day** during topical steroid use **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over >10 weeks	With epithelial ulcer: **Valaciclovir 1 g TDS for 7-10 days *** **PLUS** **Prednefrin Forte eye drops BD** tapered slowly as disease comes under control
Endothelial	**Valaciclovir 1 g TDS for 7-10 days*** **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over >10 weeks	
Keratouveitis	**Valaciclovir 1 g TDS for 7-10 days*** **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over >10 weeks Refer patient to cornea/uveitis clinic, respectively depending on degree of cornea or uveal involvement	
Prophylaxis	Indications: • Multiple recurrences of any type of HSK, especially stromal HSK • Patients with a history of ocular HSV: - following any ocular surgery, including penetrating keratoplasty - during immunosuppressive treatment **Aciclovir 400 mg BD** **OR** **Valaciclovir 500 mg ONCE a day**	

*** Reduce Valaciclovir to prophylactic dose after 7-10 days and maintain for as long as frequent topical steroids are in use**

Adult Renal Dosing for oral antivirals		
CrCl (mL/min)	**Dose**	**Frequency**
Normal dosage Valaciclovir 500 mg ONCE a day		
<30	500 mg	Every 48 hours
Normal dosage Valaciclovir 500 mg BD		
<30	500 mg	Every 24 hours
Normal dosage Valaciclovir 1 g TDS		
30-49	1 g	Every 12 hours
10-29	1 g	Every 24 hours
<10	500 mg	Every 24 hours
Normal dosage Aciclovir 400 mg BD		
0-10	200 mg	Every 12 hours

Use in Pregnancy

Aciclovir – Preferred due to more clinical experience. Category B3.
Valaciclovir – Limited data do not suggest an increased risk of congenital malformations. May be used from 36 weeks of pregnancy. Category B3.

PAEDIATRIC

- Aciclovir is the drug of choice
- Valaciclovir must only be used in children >12 years old

Local treatment	
3 months to 18 years	**Epithelial HSK:** **Topical aciclovir 5 times a day for 14 days**[1,2] or for at least **3 days** after healing, whichever is shorter

Systemic treatment

Indications:

- Stromal HSK
- Skin involvement
- Coexistent systemic disease
- Non-compliance, inability to use or tolerate, or ocular toxicity from topical aciclovir
- Immunocompromised patients – seek advice from a Paediatric Infection Diseases Physician

Birth (at term) to 3 months	**Seek advice from a Paediatric Infection Diseases Physician**
3 months to 12 years	**Oral aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days**[1] or until there are no new lesions **PLUS** **Prednefrin Forte eye drops BD-QID a day.** (For severe inflammation, consider hourly dosing for 1-2 days [1])
12 years to 18 years	**Oral aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days**[1] or until there are no new lesions **OR** **Valaciclovir 500 mg BD for 5 days**[2] if first episode (longer if new lesions appear during treatment or healing is incomplete) **Valaciclovir 500 mg BD for 3-5 days**[2] if recurrent episode **PLUS** **Prednefrin Forte eye drops BD-QID a day.** (For severe inflammation, consider hourly dosing for 1-2 days[1])

[1] **Dosages taken from Australian Medical Handbook Children's Dosing Companion**
[2] **Dosages taken from British National Formulary for children**

Lanyard produced by the Save Sight Institute, Sydney Eye Hospital and SESLHD
Sponsored by a grant from the Sydney Eye Hospital Foundation

Figure 5 - 3: Local HSK treatment guideline, version 1 - A4-size poster.

5.5.3.1 Step 5 and 6: Monitor and evaluate knowledge

5.5.3.1.1 Audit of medical records

A medical record audit was conducted to monitor and evaluate the adherence to the local HSK treatment guideline at the Sydney Eye Hospital (See 5.4.5.1, page 238). After applying the inclusion and exclusion criteria, 85 eyes of 85 patients with HSK were included. Of these, 63 (74%) patients received antiviral therapy for a therapeutic indication and 22 (26%) for a prophylactic indication. The demographics of the patients are shown in Table 5 - 10 (see page 263).

5.5.3.1.1.1 Antiviral therapy prescribing trends

For the therapeutic group, 36 (57%) patients were diagnosed with epithelial HSK, 6 (10%) with SHSK+U, 4 (6%) with SHSK-U, 3 (5%) with endothelial HSK and 14 (22%) with keratouveitis.

Of the 36 patients with epithelial HSK, 23 (64%) received topical aciclovir five times daily. Eleven patients (31%) received valaciclovir with doses ranging from 500 mg twice daily to 1 g three times daily. The remaining 2 patients (6%) received a combination of valaciclovir and topical aciclovir (See Table 5 - 11, page 265)

Table 5 - 10: Socio-demographic characteristics of patients treated for HSK per antiviral indication in the post-implementation audit (n = 85).

Key: n = number of patients, NSW = New South Wales, SD = standard deviation.

	Indication	
	Therapeutic	**Prophylactic**
n (%)	63 (74)	22 (26)
Age in years		
Mean (SD)	58 ± 19	69 ± 18
Range	21 to 91	24 to 92
Gender, Male [n, (%)]	41 (65)	12 (55)
Residence [n, (%)]		
Within greater Sydney	57 (90)	19 (86)
Outside greater Sydney but within NSW	5 (8)	3 (14)
Overseas	1 (2)	0

For the SHSK-U group, each patient received valaciclovir 500 mg but in different frequencies (once, twice and three times daily) (See Table 5 - 11, page 265). For the SHSK+U group, 5 of 7 patients (71.4%) received valaciclovir 1 g three times daily, one patient (14.3%) valaciclovir 500 mg twice daily and the remaining patient (14.3%) valaciclovir 1 g twice daily (See Table 5 - 11, page 265).

For the endothelial HSK group, 2 of 3 patients (66.7%) received valaciclovir 1 g three times daily and the remaining patient, valaciclovir 500 mg once daily (See Table 5 - 11, page 265). For the keratouveitis group, 8 of 14 (57%) patients received valaciclovir 1 g three times daily, 3 (21.4%) valaciclovir 500 mg three times daily, and one patient valaciclovir 500 mg twice daily. The remaining two patients received a combination of valaciclovir in doses ranging from 500 mg to 1 g twice to three times daily and topical aciclovir five times daily (See Table 5 - 11, page 265).

For the therapeutic group, the adherence to the local HSK treatment guideline was found in 26 of the 36 (72%) patients with epithelial HSK, 1 of the 4 (25%) patients

with SHSK-U, 4 of 6 patients with SHSK+U (66%), 2 of 3 (66%) patients with endothelial HSK, and 8 of 14 (57%) with keratouveitis.

For the prophylactic group, all 22 patients received valaciclovir 500 mg once daily (See Table 5 - 11, page 265). The adherence to the local HSK treatment guideline was found in all 22 (100%) of patients.

5.5.3.1.1.2 Topical corticosteroid prescribing trends

Overall, preserved prednisolone acetate 1% (13/38, 34%) and preserved fluorometholone 0.1% (10/38, 26%) were the preferred prescribed agents.

Four of 36 patients (11%) with epithelial HSK received topical corticosteroid therapy. Patients received different type of agents and frequencies (See Table 5 - 12, page 267). Indications for topical corticosteroid therapy included prior corneal graft and prior stromal HSK episode.

Topical corticosteroids were given to all patients with SHSK-U between three to four times daily, and to over half of patients (57%) with SHSK+U at frequencies ranging from twice to four times daily (See Table 5 - 12, page 267).

Two-thirds of patients with endothelial HSK received topical corticosteroids four times daily. Similarly, 71% of patients (10/14) with keratouveitis and 68% of patients (15/22) with prophylactic indication were prescribed topical corticosteroids (See Table 5 - 12, page 267).

Adherence to the local HSK guidelines was found in 2 of the 3 patients (66%) with SHSK-U, 2 of the 7 patients (30%) with SHSK+U, 2 of the 3 patients (66%) with endothelial HSK, and 8 of the 14 patients (57%) with keratouveitis.

Table 5 - 11: Antiviral therapies prescribed for patients diagnosed with HSK post-implementation of the local HSK treatment guideline.

Key: x5 = five times daily, ACV = aciclovir, BD = twice daily, HSK = herpes simplex keratitis, n = number of patients, Occ = topical, od = once daily, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration, TDS = three times daily, VLC = valaciclovir.

Numbers in bold represent dosages aligned to the local HSK treatment guideline.

Antiviral therapy	Epithelial HSK n (%) †	SHSK-U n (%) †	SHSK+U n (%) †	Endothelial HSK n (%) †	Keratouveitis n (%) †	HSK prophylaxis n (%) †
Topical						
Occ ACV x5	**23 (63.9)**					
Oral						
VLC 500 mg od		**1 (33.3)**		1 (33.3)		**22 (100)**
VLC 500mg BD	**3 (8.3)**	1 (33.3)	1 (14.3)		1 (7.1)	
VLC 500 mg TDS		1 (33.3)			3 (21.4)	
VLC 1 g BD	1 (2.8)		1 (14.3)			
VLC 1 g TDS	7 (19.4)		**5 (71.4)**	**2 (66.7)**	**8 (57.1)**	

Table 5 – 11 (continued)

Antiviral therapy	Epithelial HSK n (%) †	SHSK-U n (%) †	SHSK+U n (%) †	Endothelial HSK n (%) †	Keratouveitis n (%) †	HSK prophylaxis n (%) †
Combinations						
VLC 500 mg od +ACV occ x5	1 (2.8)					
VLC 500 mg BD + Occ ACV x5	1 (2.8)				1 (7.1)	
VLC 1 g TDS + ACV Occ x5					1 (7.1)	
Total	**36 (100)**	**3 (100)**	**7 (100)**	**3 (100)**	**14 (100)**	**22 (100)**

† (%) percentages calculated from total cases of each type of keratitis.

Table 5 - 12: Topical corticosteroids prescribed per antiviral therapy indication post-implementation of the local HSK treatment guideline.

Key: BD = twice daily, HSK= herpes simplex keratitis, N = number of patients, od = once daily, QID = four times daily, SHSK+U = stromal HSK with ulceration, SHSK-U = stromal HSK without ulceration, TDS = three times daily.

Numbers in bold represent dosages aligned to the local HSK treatment guideline.

Topical corticosteroid and dosage regimen	**Indication of antiviral therapy**					
	Epithelial HSK (n= 36)	**SHSK-U (n=3)**	**SHSK+U (n=7)**	**Endothelial HSK (n=3)**	**Keratouveitis (n=14)**	**Prophylaxis (n=22)**
Preserved fluorometholone acetate 0.1% [N, (%)] †						
BD						1 (4.5)
Preserved fluorometholone 0.1% [N, (%)] †						
OD						7 (31.8)
BD			**1 (14.3)**			
QID				**1 (33.3)**	**1 (7.1)**	
Preserved dexamethasone 0.1% [N, (%)] †						
OD	1 (2.8)					3 (13.6)
BD						1 (4.5)
TDS	1 (2.8)					

Table 5 – 12 (continued)

Topical corticosteroid and dosage regimen	Indication of antiviral therapy					
	Epithelial HSK (n= 36)	**SHSK-U (n=3)**	**SHSK+U (n=7)**	**Endothelial HSK (n=3)**	**Keratouveitis (n=14)**	**Prophylaxis (n=22)**
QID		**1 (33.3)**			**1 (7.1)**	
Every hour					1 (7.1)	
Preserved prednisolone acetate 1% [N, (%)] †						
BD						1 (4.5)
TDS		1 (33.3)	1 (14.3)			1 (4.5)
QID	1 (2.8)			**1 (33.3)**	**4 (28.6)**	
Six times daily					**2 (14.3)**	
Not specified	1 (2.8)					
Unpreserved prednisolone sodium phosphate [N, (%)] †						
OD						1 (4.5)
BD			**1 (14.3)**			
Unpreserved dexamethasone sodium phosphate [N, (%)] †						
QID		1 (33.3)	1 (14.3)			
Every two hours					1 (7.1)	
Total	4 (11.1)	3 (100)	4 (57.1)	2 (66.7)	10 (71.4)	15 (68.2)

† (%) percentage calculated from total cases of each indication shown on column header

5.5.3.1.1.3 Comparison of antiviral medication prescribing trends pre- and post-HSK treatment guideline implementation

Adherence to the local HSK treatment guideline was found in 36 patients (72%) with epithelial HSK, 1 of 3 patients (33%) with SHSK-U, 5 of 7 (71%) with SHSK+U, 2 of 3 (67%) with endothelial HSK, 8 of 14 patients (57%) with keratouveitis, and 22 of 22 patients (100%) on HSK prophylaxis (See Table 5 - 11, page 265). Overall, 51 of 64 patients (80%) received antiviral therapy as per the local HSK treatment guideline. The adherence of guidelines improved for all HSK indications except for epithelial HSK (See Table 5 - 13, page 270). There was a significant increase in the proportion of patients aligned with the HSK guidelines for HSK prophylaxis (p = 0.003) and a significant decrease proportion for epithelial HSK (p = 0.009) following guideline implementation. The increased proportions for SHSK-U and endothelial HSK were not statistically significant.

No comparison could be made for SHSK+U and keratouveitis as there was no evidence-based recommendations before the implementation of the local HSK treatment guideline. Therefore, these patients were not included in the overall comparison. However, for SHSK+U, 8 antiviral regimens were found before the guideline's implementation compared with 3 regimens after the guideline's implementation. The most common regimen for SHSK+U was topical aciclovir five times daily in 43% of patients before the implementation (See Table 2 - 7, page 104) compared with valaciclovir 1 g three times daily in 71% of patients, after the implementation (See Table 5 - 11, page 265). For keratouveitis, 10 antiviral regimens (See Table 2 - 7, page 104) were found before the guideline's implementation compared with 3 regimens found after guideline's implementation (See Table 5 - 11, page 265). Valaciclovir 1 g, three times daily was the preferred regimen before and after guideline's implementation. This regimen was given to 31% of patients (See Table 2 - 7, page 104) before implementation and to 57% of patients after implementation (See Table 5 - 11, page 265).

Overall, there was no significant increase in the proportion of patients receiving evidence-based recommendations for HSK treatment post-guideline implementation compared with the proportion pre-guideline implementation (**73% vs 80%, *p* = 0.331)**.

Table 5 - 13: Proportion of patients prescribed antiviral medication that was in alignment with HSK recommendations pre- and post-implementation of HSK local guidelines.

Key: SHSK-U = stromal herpes simplex keratitis without ulceration, SHSK+U = stromal herpes simplex keratitis with ulceration.

Type of antiviral therapy indication	**Pre-guideline % (n)**	**Post-guideline % (n)**	***p*-value**
Epithelial	89 (124/139)	72 (26/36)	**0.009**
SHSK-U	9 (2/22)	33 (1/3)	0.3
SHSK+U		71 (5/7)	
Endothelial	33 (6/18)	67 (2/3)	0.5
Keratouveitis		57 (8/14)	
Prophylaxis	70 (31/44)	100 (22/22)	**0.003**
Total	73 (163/223)	80 (51/64)	0.331

Note: The number of patients with SHSK+U and keratouveitis from the post-guideline audit were not analysed as there were no available treatment recommendations pre-guideline for these conditions. Therefore, the final number of patients for the comparison was 64 for post-guideline audit.

5.5.3.1.2 Outcomes of HSK cases post-implementation of HSK local guidelines

An outcome (resolved, partially resolved or worsened) was determined for 40 of 63 patients (63%) with a therapeutic indication. The remaining 23 (37%) patients were excluded from analysis as they were either lost to follow up (n = 16), found not to have HSK on a subsequent review (n = 6) or on ongoing antiviral therapy (See Figure 5 - 4, page 273). For the ‘not HSK’ group, epithelial HSK was initially misdiagnosed in patients eventually found to have allergic conjunctivitis, adenovirus conjunctivitis and

corneal erosions. An outcome (success or failure) was determined for all 22 patients with a prophylactic indication.

Overall, for the therapeutic indication group, 19 patients (48%) had an improved outcome, 19 (48%) a partially resolved outcome and 2 (5%) a worsened outcome. There was no significant association between outcomes and the adherence to evidence-based recommendations pre- and post-local HSK guideline implementation (p = 0.4). On the other hand, for the prophylactic indication group, there was a significant association between the initial antiviral therapy (valaciclovir 500 mg once daily) and outcome post-guidelines implementation (p = 0.009) (See Table 5 - 14, page 274).

5.5.3.2 Web-based survey

There were 41 respondents of 95 clinicians invited (43%). The primary email invitation was sent on in early December 2017. Twenty-eight responses were received in the fortnight following the initial survey invitation, 13 following the second invitation in early January 2018. Of the respondents, 23 (56%) were registrars. Thirty respondents (73%) had managed patients with HSK in the last 6 months. Thirty-five respondents (85%, n = 35/41) had heard about the local HSK treatment guideline mainly through the educational lecture (39%, n = 16/41), via an email with the pdf version of the guideline (27%, n = 11/41) or had seen the A4 size posters at the consultation rooms (24%, n = 10). Despite distributing the lanyard cards via several means, nearly two-thirds (63%, n = 26/41) of the clinicians claimed not to have receive it. Six (15%) clinicians received the lanyard card at the lecture. The respondents were aware of the guideline through the lanyard card (48%, n = 20/41) and the A4- size poster in the emergency (44%, n = 18/41), and outpatient consultation rooms (31%, n = 13/41). Respondents had accessed the guideline when prescribing for patients with HSK mainly through the posters in emergency consultation rooms (29%, 12/41), the lanyard card (27%, n = 11/41), and PDF version (44%, n = 18/41). Seventeen (41%) clinicians consulted the guideline once to twice monthly; and recommendations for keratouveitis (70%, n = 28/41) and stromal HSK (60%, n = 24/41) were consulted most frequently (See Table 5 - 15, page 275).

Google analytics was used to measure the number of times the local HSK treatment guideline was seen on the Sydney Eye School website. The guideline was seen 5 times of 1714 views (0.3%) of the Sydney Eye School website from 1 November 2018 to 26 May 2019. The average time spent seeing the guideline was 3.38 minutes. Most of the guideline's views (n = 3) were done in November 2018.

Unfortunately, it was not possible to access the web analytics for the PDF document on the hospital's intranet as the IT staff has not developed a code for this.

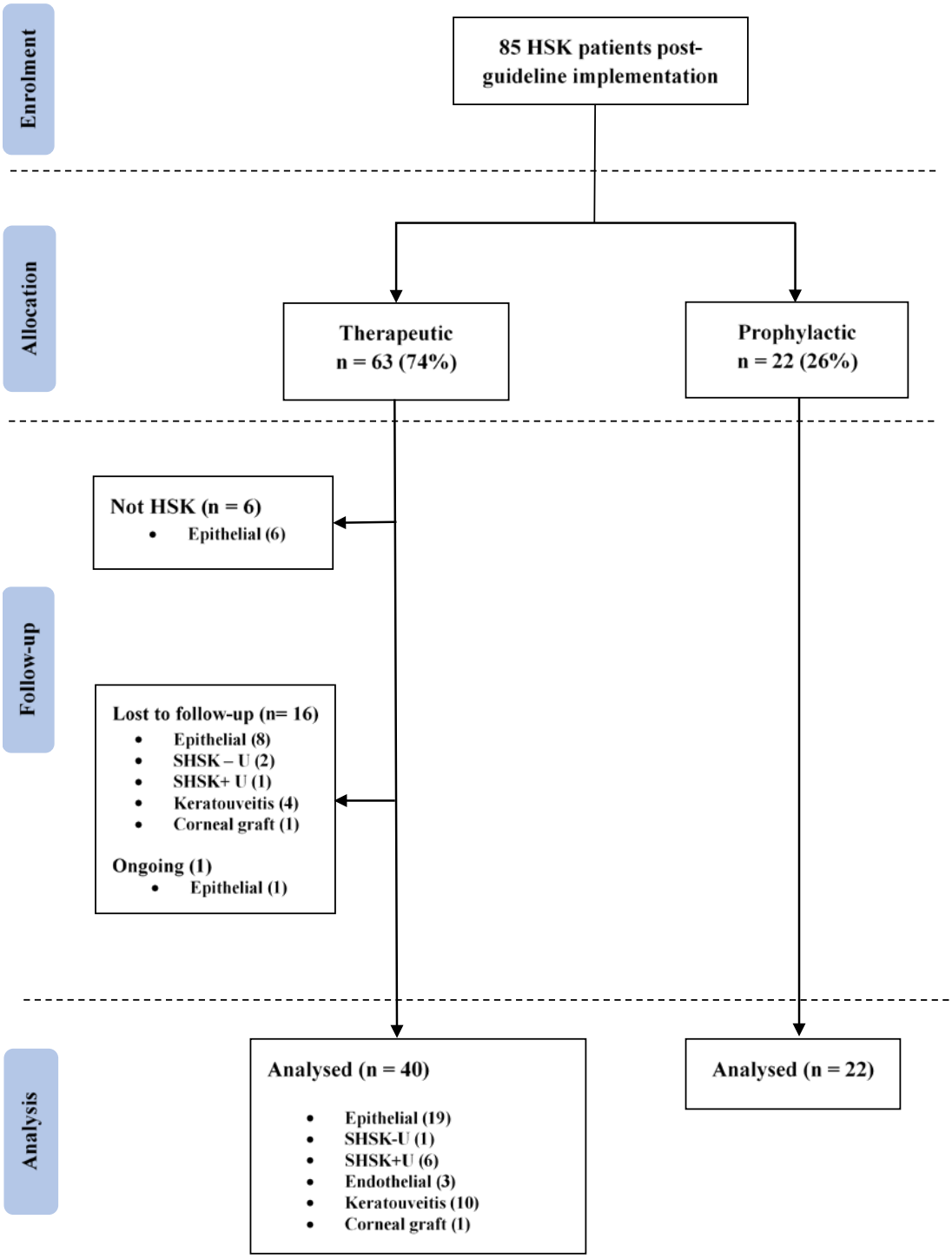


Figure 5 - 4: Inclusion and exclusion flow chart for analysis of HSK outcomes post-guideline implementation.

Table 5 - 14: Outcomes vs type of antiviral therapy indication pre- and post-HSK guideline implementation.

Key: SHSK-U = stromal herpes simplex keratitis without ulceration, SHSK+U = stromal herpes simplex keratitis with ulceration.

	Pre-guidelines [%, (n)]	**Post-guidelines [%, (n)]**	***p*-value**
Epithelial HSK			**0.5**
Resolved	49 (41/83)	63 (12/19)	
Partially resolved	47 (39/83)	32 (6/19)	
Worsened	4 (3/83)	5 (1/19)	
SHSK-U			**0.3**
Resolved	27 (4/15)	100 (1/1)	
Partially resolved	53 (8/15)	0	
Worsened	20 (3/15)	0	
SHSK+U			**0.9**
Resolved	18 (2/11)	17 (1/6)	
Partially resolved	55 (6/11)	67 (4/6)	
Worsened	27 (3/11)	17 (1/6)	
Endothelial HSK			**1**
Resolved	27 (3/11)	0	
Partially resolved	73 (8/11)	100 (3/3)	
Worsened	0	0	
Keratouveitis			**0.3**
Resolved	25 (9/36)	40 (4/10)	
Partially resolved	58 (21/36)	60 (6/10)	
Worsened	17 (6/36)	0 (0)	
Prior corneal graft			**0.5**
Resolved	39 (7/18)	100 (1/1)	
Partially resolved	44 (8/18)	0 (0)	
Worsened	17 (3 /18)	0 (0)	
HSK prophylaxis			**0.009**
Success	72 (26/36)	100 (22/22)	
Failure	28 (10/36)	0	

Table 5 - 15: Web-based survey results about the local HSK treatment guideline implementation

Key: n = number of respondents

Questions and choices	n, (%)
1. What is your role in the hospital?	
Consultant	12 (29.3)
Fellow	3 (7.3)
Registrar	23 (56.1)
Resident	3 (7.3)
2. Have you treated patients with herpes simplex keratitis (HSK) in the last 6 months (1 June to November 30, 2017)?	
Yes	30 (73.2)
No	11 (26.8)
3. How did you hear about the Sydney Eye Hospital's 'HSK treatment guidelines'?	
Have not heard	6 (14.6)
Registrar talk at Claffy theatre on 2 June 2017	16 (39)
Receive lanyard card	8 (19.5)
Word of mouth	6 (14.6)
As a PDF attachment on email	11 (26.8)
A4 posters in emergency and consultation rooms	10 (24.4)
Sydney Eye Hospital intranet	0 (0)
A4 laminated sheet, lanyard and invitation letter	3 (7.3)
4. How did you receive the Sydney Eye Hospital's 'HSK treatment guidelines' lanyard card?	
Have not received lanyard card	26 (63.4)
Registrar talk at Claffy theatre on 2 June 2017	6 (14.6)
Via post	4 (9.8)
Via pharmacist	1 (2.4)
Via registrar	4 (9.8)
Via specialist	0 (0)
Via fellow	0 (0)

Table 5 – 15 (continued)

Questions and choices	n, (%)
5. Are you aware that the Sydney Eye Hospital's 'Herpes simplex keratitis' treatment guidelines' are accessible on the following sources (Chose all that apply)?	
Lanyard card	20 (48.8)
A4 posters on emergency consultation rooms	18 (43.9)
A4 poster on consultation rooms at Bicentennial Clinic and Sydney Eye Hospital outpatient clinic	13 (31.7)
A4 poster on examination rooms at wards	10 (24.4)
Sydney Eye hospital intranet	5 (12.2)
Not aware	11 (26.8)
6. What sources do you use to review the Sydney Eye Hospital's 'HSK treatment guidelines'? (Choose all that apply)	
Lanyard card	11 (26.8)
A4 poster on emergency	12 (29.3)
A4 poster on consultation rooms at Bicentennial Clinic and Sydney Eye Hospital outpatient's clinic	8 (19.5)
A4 poster on examination rooms at wards	4 (9.8)
PDF file	18 (43.9)
Sydney Eye hospital intranet	0 (0)
Don't use the treatment guidelines	9 (22)
7. How often do you use the Sydney Eye Hospital's 'HSK treatment guidelines'?	
Never	7 (17.1)
Rarely	8 (19.5)
1-2 times a month	17 (41.5)
1-2 times a fortnight	5 (12.2)
1-2 times a week	3 (7.3)
Daily	0 (0)
8. What sections of the Sydney Eye Hospital's 'HSK treatment guidelines' have you consulted?	
Epithelial HSK	23 (56.1)
Stromal HSK	24 (58.5)
Endothelial HSK	13 (31.7)
Keratouveitis	28 (68.3)
HSK prophylaxis	12 (29.3)

Table 5 - 15 (continued)

Questions and choices	n, (%)
Renal dosing for oral antivirals	8 (19.5)
Use in pregnancy	7 (17.1)
Paediatric local treatment	1 (2.4)
Paediatric systemic treatment	3 (7.3)
None	0 (0)

5.5.4 Step 7: Sustainability

A sustainability plan was designed for 2 years (See Table 5 - 16, page 277). The local HSK treatment guideline was implemented in June 2017. A yearly meeting was held in June 2018 with the implementation team. Results of the audit and the web-based survey were presented. Two corneal specialists from Westmead Hospital were invited to discuss the findings of the audit.

Table 5 - 16: Sustainability action plan for the local HSK treatment guideline.

Key: BPG = best practice guidelines.

Year 1	BPGs	How sustained		
		Staff roles	Structures	Processes
100% registrars/residents receive education of HSK guidelines	New	Implementation team	Adherence to professional development	Distribution lanyard cards and electronic document (PDF) Access guidelines at Sydney Eye School website
90-100 % Adherence to HSK guidelines	Ongoing	Implementation team Newly hired staff	Adherence to professional development	Yearly audit

Table 5 – 16 (continued)

Year 1	BPGs	How sustained		
		Staff roles	Structures	Processes
HSK guidelines revision	Ongoing	Implementation team	Organisational practice change Stakeholder involvement	Yearly meeting

Two issues emerged during the meeting. One was the duration of the epithelial HSK local treatment and the second was the dosage and frequency of valaciclovir for endothelial HSK. The potential epithelial toxicity after a 14-day therapy with topical aciclovir was raised. The implementation team agreed on changing the duration of the topical aciclovir from 14 days to 1-2 weeks at discretion of clinician. The dosage of valaciclovir for endothelial HSK was changed to 500 mg once daily to 1 g three times daily at discretion of the clinician as there is a lack of clinical evidence (See Figure 5 - 5, page 279). The second version of the HSK guidelines was approved by the Drugs and Therapeutics Committee in October 2018. In November 2018, new lanyard cards were ordered and distributed to clinicians (See Figure 5 - 6, page 280); A4-size laminated posters were changed in the consulting rooms in the emergency department and outpatient clinics, and guidelines were updated on the Sydney Eye School website and in hospital intranet (Appendix N, page 382). When fellows, registrars and residents start their term at the hospital, they receive the lanyard card and are advised how they can access the guidelines. The second version of the guidelines was presented in a teaching session to the registrars in June 2019.

Herpes Simplex Keratitis Treatment Guidelines

ADULTS		
Epithelial	Local treatment: **Topical Aciclovir 5 times a day for 1-2 weeks**	Systemic treatment: • Immunocompromised patients • Non-compliance, inability to use or tolerate, or ocular toxicity from topical Aciclovir **Valaciclovir 500mg BD for 7 days**
Stromal	Without epithelial ulcer: **Valaciclovir 500mg ONCE a day** during topical steroid use **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over >10 weeks	With epithelial ulcer: **Valaciclovir 1g TDS for 7-10 days*** **PLUS** **Prednefrin Forte eye drops BD** tapered slowly as disease comes under control
Endothelial	Dosage at discretion of ophthalmologist **Valaciclovir 500mg ONCE a day to 1 g TDS for 7-10 days*†** **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over >10 weeks	
Keratouveitis	**Valaciclovir 1 g TDS for 7-10 days*** **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over >10 weeks Refer patient to cornea/uveitis clinic, respectively depending on degree of cornea or uveal involvement	
Prophylaxis	Indications: • Multiple recurrences of any type of HSK, especially stromal HSK • Patients with a history of ocular HSV: - following any ocular surgery, including penetrating keratoplasty - during immunosuppressive treatment **Aciclovir 400mg BD** **OR** **Valaciclovir 500mg ONCE a day**	

*** Reduce Valaciclovir to prophylactic dose after 7-10 days and maintain for as long as frequent topical steroids are in use**
† There is a lack of clinical evidence to guide dosage in this situation

Adult Renal Dosing for oral antivirals		
CrCl (mL/min)	**Dose**	**Frequency**
Normal dosage Valaciclovir 500mg ONCE a day		
<30	500mg	Every 48 hours
Normal dosage Valaciclovir 500mg BD		
<30	500mg	Every 24 hours
Normal dosage Valaciclovir 1g TDS		
30-49	1g	Every 12 hours
10-29	1g	Every 24 hours
<10	500mg	Every 24 hours
Normal dosage Aciclovir 400mg BD		
0-10	200mg	Every 12 hours

Use in Pregnancy

Aciclovir – Preferred due to more clinical experience. Category B3.
Valaciclovir – Limited data do not suggest an increased risk of congenital malformations. May be used from 36 weeks of pregnancy. Category B3.

PAEDIATRIC

- Aciclovir is the drug of choice
- Valaciclovir must only be used in children >12 years old

Paediatric local treatment	
3 months to 18 years	**Epithelial HSK:** **Topical aciclovir 5 times a day for 14 days[1,2]** or for at least **3 days** after healing, whichever is shorter

Paediatric systemic treatment	
Indications: • Stromal HSK • Skin involvement • Coexistent systemic disease • Non-compliance, inability to use or tolerate, or ocular toxicity from topical Aciclovir • Immunocompromised patients – seek advice from a Paediatric Infection Diseases Physician	
Birth (at term) to 3 months	**Seek advice from a Paediatric Infection Diseases Physician**
3 months to 12 years	**Oral Aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days[1]** or until there are no new lesions **PLUS** **Prednefrin Forte eye drops BD-QID a day.** (For severe inflammation, consider hourly dosing for 1-2 days [1])
12 years to 18 years	**Oral Aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days[1]** or until there are no new lesions **OR** **Valaciclovir 500 mg BD for 5 days[2]** if first episode (longer if new lesions appear during treatment or healing is incomplete) **Valaciclovir 500 mg BD for 3-5 days[2]** if recurrent episode **PLUS** **Prednefrin Forte eye drops BD-QID a day.** (For severe inflammation, consider hourly dosing for 1-2 days[1])

[1] Dosages taken from Australian Medical Handbook Children's Dosing Companion
[2] Dosages taken from British National Formulary for children

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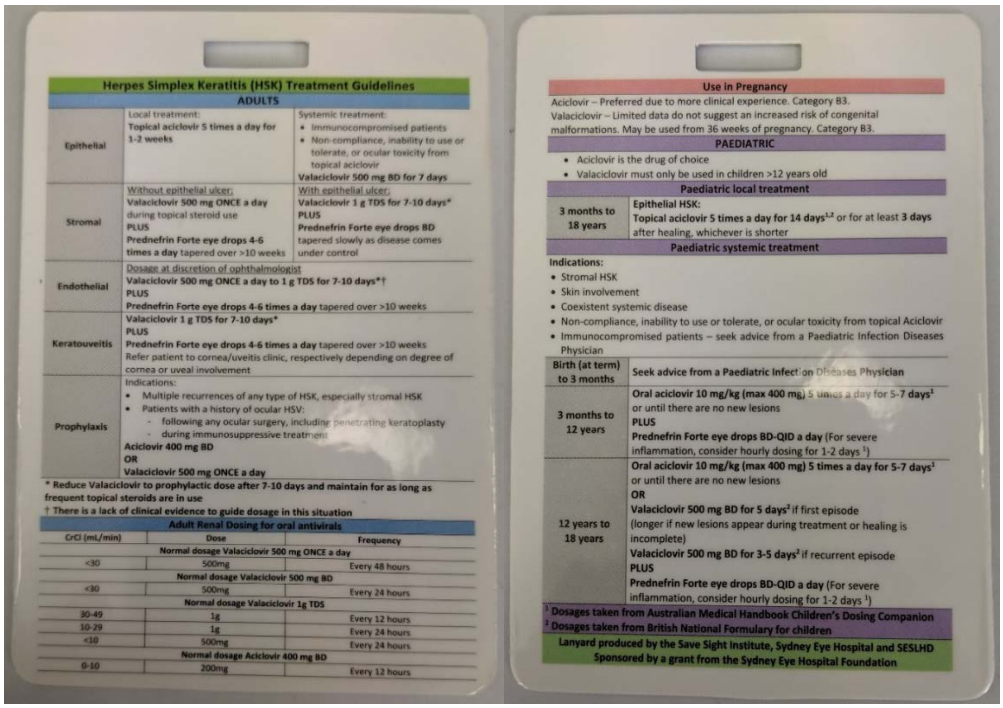
Sponsored by a grant from the Sydney Eye Hospital Foundation

Figure 5 - 5: Local HSK treatment guideline, version 2 – A4 size poster.



Herpes Simplex Keratitis (HSK) Treatment Guidelines

ADULTS

Epithelial	Local treatment: **Topical aciclovir 5 times a day for 1-2 weeks**	Systemic treatment: • Immunocompromised patients • Non-compliance, inability to use or tolerate, or ocular toxicity from topical aciclovir **Valaciclovir 500 mg BD for 7 days**
Stromal	Without epithelial ulcer: **Valaciclovir 500 mg ONCE a day** during topical steroid use **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over >10 weeks	With epithelial ulcer: **Valaciclovir 1 g TDS for 7-10 days*** **PLUS** **Prednefrin Forte eye drops BD** tapered slowly as disease comes under control
Endothelial	Dosage at discretion of ophthalmologist **Valaciclovir 500 mg ONCE a day to 1 g TDS for 7-10 days*†** **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over >10 weeks	
Keratouveitis	**Valaciclovir 1 g TDS for 7-10 days*** **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over >10 weeks Refer patient to cornea/uveitis clinic, respectively depending on degree of cornea or uveal involvement	
Prophylaxis	Indications: • Multiple recurrences of any type of HSK, especially stromal HSK • Patients with a history of ocular HSV: - following any ocular surgery, including penetrating keratoplasty - during immunosuppressive treatment **Aciclovir 400 mg BD** **OR** **Valaciclovir 500 mg ONCE a day**	

* Reduce Valaciclovir to prophylactic dose after 7-10 days and maintain for as long as frequent topical steroids are in use

† There is a lack of clinical evidence to guide dosage in this situation

Adult Renal Dosing for oral antivirals

CrCl (mL/min)	Dose	Frequency
Normal dosage Valaciclovir 500 mg ONCE a day		
<30	500mg	Every 48 hours
Normal dosage Valaciclovir 500 mg BD		
<30	500mg	Every 24 hours
Normal dosage Valaciclovir 1g TDS		
30-49	1g	Every 12 hours
10-29	1g	Every 24 hours
<10	500mg	Every 24 hours
Normal dosage Aciclovir 400 mg BD		
0-10	200mg	Every 12 hours

Use in Pregnancy

Aciclovir – Preferred due to more clinical experience. Category B3.
Valaciclovir – Limited data do not suggest an increased risk of congenital malformations. May be used from 36 weeks of pregnancy. Category B3.

PAEDIATRIC

- Aciclovir is the drug of choice
- Valaciclovir must only be used in children >12 years old

Paediatric local treatment

3 months to 18 years	**Epithelial HSK:** **Topical aciclovir 5 times a day for 14 days[1,2]** or for at least **3 days** after healing, whichever is shorter

Paediatric systemic treatment

Indications:
- Stromal HSK
- Skin involvement
- Coexistent systemic disease
- Non-compliance, inability to use or tolerate, or ocular toxicity from topical Aciclovir
- Immunocompromised patients – seek advice from a Paediatric Infection Diseases Physician

Birth (at term) to 3 months	**Seek advice from a Paediatric Infection Diseases Physician**
3 months to 12 years	**Oral aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days[1]** or until there are no new lesions **PLUS** **Prednefrin Forte eye drops BD-QID a day** (For severe inflammation, consider hourly dosing for 1-2 days [1])
12 years to 18 years	**Oral aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days[1]** or until there are no new lesions **OR** **Valaciclovir 500 mg BD for 5 days[2]** if first episode (longer if new lesions appear during treatment or healing is incomplete) **Valaciclovir 500 mg BD for 3-5 days[2]** if recurrent episode **PLUS** **Prednefrin Forte eye drops BD-QID a day** (For severe inflammation, consider hourly dosing for 1-2 days [1])

[1] **Dosages taken from Australian Medical Handbook Children's Dosing Companion**
[2] **Dosages taken from British National Formulary for children**

Lanyard produced by the Save Sight Institute, Sydney Eye Hospital and SESLHD
Sponsored by a grant from the Sydney Eye Hospital Foundation

Figure 5 - 6: Local HSK treatment guideline on a lanyard card, version 2 (both sides).

5.6 Discussion

The RNAO Toolkit: Implementation of Best Practice Guidelines was utilised to develop, implement and evaluate an HSK treatment guideline at the Sydney Eye Hospital. The RNAO Toolkit was created using the Knowledge-to-Action Framework. [14, 15] The framework comprised two elements: knowledge creation and the action cycle. Knowledge creation included 3 phases. For the first phase of the knowledge creation, knowledge enquiry, a literature review was conducted that included the landmark studies for HSK, the HEDS clinical trials, other clinical trials and observational studies. [2-5, 59] For the second phase, knowledge synthesis, a Cochrane review for epithelial HSK and an HSK systematic review were utilised. [1, 7] For the third phase, creation of knowledge tools, 'The AAO HSK guideline' was used to develop our guideline. [23]

To illustrate the action cycle in our context, a local group of ophthalmologists noticed diverse trends for initial antiviral therapy for HSK at the Sydney Eye Hospital in 2013. Some of these therapies resulted in high costs for patients and the risk of side effects. After identification of the 'problem', a retrospective case series was conducted

to determine knowledge-practice gap. All patients with HSK who presented the hospital from 1 January 2012 to 31 December 2013 and received antivirals for HSK were included. Antiviral medications and topical corticosteroids prescribing trends were identified. Simultaneously, a review of the literature was used to identify available evidence for the treatment of HSK. Some evidence-based guidelines from the clinical trials and systematic reviews were determined to compare with the results of the retrospective case series. Overall, 73% of the patients received 'evidence-based' antiviral therapy. [129] There were no available guidelines for SHSK+U and for keratouveitis. Therefore, patients with these diagnoses were not included in the analysis.

The stakeholders included the implementation team, clinicians, pharmacists, nurses, the Drug and Therapeutics Committee staff and the Director of Clinical Services. The implementation group held meetings with the hospital's cornea and uveitis specialists and pharmacy staff to reach a consensus in the dosage for each type of HSK and for HSK prophylaxis. Evidence from the literature, including 'The AAO HSK treatment guideline', and the results from the retrospective review were used to develop the local HSK treatment guideline. [129] The guidelines were approved by the hospital's cornea and uveitis teams and endorsed by the hospital's Drug and Therapeutics Committee. The implementation team identified barriers to implement the local guideline. Barriers included difficulty in engaging with consultants to integrate the new guidelines into their clinical practice. Other issues were the difficulty in changing prescribing behaviour, lack of educational opportunities, heavy workload, complexity of patients, other institutional priorities to address, concurrent projects, delay in organisational processes approval, and time constraints to participate in all stages of implementation.

Multiple implementation strategies were created including printed and online educational materials for clinicians in different formats, and educational lectures at including those held at Sydney Eye Hospital, the 2018 Australian & New Zealand Cornea Society Meeting, and 2017 and 2018 RANZCO Annual meetings. To evaluate the response to the local guidelines, a retrospective audit of all HSK cases presenting the hospital during a 6-month post-guideline implementation period was conducted.

Simultaneously, a web-based survey assessed clinician awareness, usage and level of knowledge of the guidelines. As part of the sustainability phase, the implementation team held a meeting to discuss the results of the audit and the web-based survey, one-year following guideline implementation. The guideline was revised, and a second version was approved by the Drug and Therapeutics Committee.

The main lessons from this project were:

- Clinical guidelines need to be adapted to local context
- The implementation phase is the most crucial step in the knowledge to action process.
- Change of clinician behaviour is challenging and requires a multi-faceted approach.
- Evidence can emerge daily, therefore a sustainability plan to review the guidelines is essential to continue the process

'The RNAO Toolkit' was chosen to guide our implementation process as the RNAO is one of the few organisations in the world that develops guidelines for issues related to education and policy recommendations. [15] Its major focus is in implementation and evaluation which was the main aspect in our project. 'The RNAO Toolkit' was conceptualised on the knowledge-to-action framework which has been used in other studies to assess the knowledge translation into practice of different clinical guidelines. [11] 'The RNAO Toolkit' provides a rigorous, scientific and systematic process to assist any health organisation in a smooth and successful implementation process. The RNAO's Nursing Best Practice Guidelines Program was launched 20 years ago and up to 2011 has produced 38 clinical and 9 health work environment guidelines, a toolkit to support implementation of the guidelines in health settings and another toolkit to facilitate application to curriculum and education. As 'The RNAO Toolkit' had produced clinical guidelines for different medical conditions, we believed it can also be useful in translating eye research into daily clinical practice.

Local guidelines are beneficial in improving level of care. [174] Certain barriers to guideline implementation can be avoided by having local guidelines developed by local experts. [174] These barriers include incompatibility of recommendations with local context, lack of credibility of guideline developer with users, and recommendations not well integrated in the context. [174] Approaching local experts help to better understand whether these guidelines would work in the local context. [175] Having local experts was a major facilitator in our project. The implementation team identified the knowledge gap and assessed 'The AAO HSK treatment guideline' with the AGREE tool. Unfortunately, 'The AAO HSK guideline' was unsuitable for the Australian context. Local experts produced evidence-based and easily understood guideline compatible with what was already available in the literature. Furthermore, peers at the hospital were also asked to provide their opinion which increased the local guidelines buy-in, value and cohesiveness. Involving not only the local experts but also their peers in the development of the guideline addressed the barriers of lack of attitude towards the guideline implementation.

Our recommendations for endothelial HSK and keratouveitis differ to some extent to what is available in the literature. The implementation team recommended valaciclovir 1 g, three times daily for endothelial HSK and keratouveitis based on their clinical experience, despite the AAO recommendation of valaciclovir 500 mg twice daily [23] and the recommendation of aciclovir 400 mg, 5 times daily by Porter et al. [88] However, the valaciclovir dosage for endothelial HSK was altered at the yearly meeting with the implementation team. One consultant was concerned that 1 g three times daily of valaciclovir may be a high dose considering the AAO HSK treatment guideline recommendation. As there is scarce evidence towards endothelial HSK, the implementation team agreed on a dosage at the discretion of the ophthalmologist. On the other hand, there was a complete consensus on the dose for keratouveitis since the conception of the guideline; despite the lack of evidence. This dosage was taken from the uveitis consultant's experience who considered that a high dosage of valaciclovir has been successful in his patients. Cunningham in his editorial also recommended this dosage based on previous studies. [89]

Furthermore, preserved prednisolone acetate 1% (Prednefin Forte, Allergan) was selected as the recommended topical corticosteroid for stromal HSK, endothelial HSK and keratouveitis. This choice was based on the AAO HSK treatment guideline, [23] the implementation team's clinical experience and the literature. [176] Drug-penetration studies have shown that prednisolone acetate 1% and dexamethasone alcohol 0.1% have good aqueous penetration and can be used in immune-related corneal diseases and anterior uveitis. [176] Other studies have reported that fluorometholone 0.1% was equally efficacious than prednisolone 0.1%, despite being a mild corticosteroid with lower penetration to aqueous humour. [176] Nevertheless, clinicians can certainly prescribe another type of corticosteroid depending on the initial presentation of the patient.

Implementing clinical guidelines is a challenging step in the knowledge-to-action framework. [174, 177, 178] One of the most crucial barriers in our study was the clinician's attitudes and beliefs. As reported in the literature in other contexts, clinical guidelines have not had a significant effect in changing clinician behaviour. [177] Seven general categories have been previously identified as barriers in the spheres of the clinician's knowledge (lack of awareness or lack of familiarity), attitudes (lack of agreement, lack of self-efficacy, lack of outcome expectancy, or the inertia of previous practice) and behaviour. [177] A change of on average 10% in prescriber behaviour is achievable when a well-designed intervention is used. [170] Despite the conflicting evidence that multifaceted interventions may or may not be more effective than single interventions, [173] multifaceted interventions have been recommended to disseminate clinical guidelines. [172] Evidence on professional-oriented intervention (education, reminder, feedback) has been more investigated than on those aimed to the patient or to an organisation. [170] Different strategies may be recommended for certain settings, but each project is unique. Some strategies may well work in some settings but not in others. [179] Reminders, audits and feedback have been described as the most successful strategies for change. [170, 173, 179, 180] Active strategies such as interactive sessions or one-on-one sessions are preferred to passive strategies (e.g. didactic sessions). [173, 174]

Although the evidence on the effect of educational materials is limited, their practicality and low cost, make them a frequently used component of a multifaceted

intervention. [170] Lanyard cards were created as educational materials and a reminder strategy for clinicians. An interactive educational lecture was organised to update the registrars and residents about HSK and to launch the implementation of the local HSK treatment guideline. Furthermore, the local HSK guideline has been presented to consultants and trainees at the local conferences (RANZCO and Australia & New Zealand Cornea Society). The intention of these strategies was to raise awareness of the new guideline among those trainees who tend to see most patients in the emergency department, and amongst consultants with whom the trainees discuss cases. In addition, an email was sent with a PDF document to all clinicians. Thus, they could also have the local HSK treatment guideline saved on their mobile phone, tablet or laptop computer. By having the local HSK treatment guideline on the hospital intranet, as lanyard cards, as a A4-size laminated poster in the consultation rooms, and on the mobile application, all the available means to disseminate the guideline were covered. In terms of clinician behaviour, simple strategies to avoid increasing the clinician's workload were considered. [179] Having a simple A4-size guideline located in front of patient chart was preferred by doctors, [179] and it was used as a reminder when prescribing the medications. Hence, a A4-size laminated poster was placed in the consultation rooms next to the computer's screen as clinicians sit in front of the computer to write the medical notes and prescribe the medications.

Unfortunately, the strategy of updating the Sydney Eye Hospital Ophthalmic Pharmacopoeia mobile application with the local HSK treatment guideline has not yet been completed. Meetings with stakeholders and pharmacists were held to discuss the changes to be made. Later, the leader of the mobile application project met the developers who worked on a beta application. Our implementation team had asked for updates but as of April 2019, the mobile application has yet to be updated. This issue has taught us that a process such as this, which involves diverse stakeholders, is complex and can take a long time (2.5 years). We expect that the HSK guidelines will be finally included in a broader system update of the mobile application sometime this year.

Educational outreach visits by an expert or trained facilitator is especially effective for changing prescriber behaviour. [170] Nevertheless, this strategy was not used

in our project as informing each clinician at the hospital about the local HSK treatment guideline was not feasible due to their workload at hectic outpatient clinics. Consequently, a didactic session (educational lecture) with all trainees was organised, and an envelope with a letter introducing the local HSK treatment guideline, with an A4-size laminated poster, and with a lanyard card was sent to all consultants to their private rooms.

Guideline implementation has been found to be mostly dependent on various characteristics relating to both clinicians and their organisations. [180] However, the characteristics of the guidelines themselves may also affect their adoption. [180] Compliance is higher for guidelines with a "trialability' characteristic. 'Trialability' means a guideline that could be tried out temporarily and discarded if wanted. Compliance is lower if guidelines are complex, ambiguous, incompatible with clinician's values and norms, and disruptive with their clinical practice. [180] The local HSK treatment guideline was clear, simply worded, and evidence-based to optimise chances of adoption by clinicians. First, they were written according to a hospital template. Later, a version for the lanyard card was created which subsequently was adapted for the A4-size poster. The guideline's understandability was a facilitator in our project. We aimed to develop a guideline that was easy to follow to ensure that they would be translated into practice accurately.

Feedback seems to be more effective for test ordering and prevention; however, it is recommended in combination with other strategies such as education, reminders and outreach visits. [170, 174] With the boom of the Internet and email communication in recent decades, web-based surveys offered some advantages over face-to-face or telephone interviews, with perhaps an increased response rate. The usefulness of this type of survey, however, is still debated. [181] This type of research is still relevant as it is a way to collect clinician's knowledge and attitudes, and to evaluate the translation of research into practice. [181] Overall, health care professionals belong to a professional group with variable survey response rates. [181] Several meta-analyses found that the relevance of the topic is one of the most important factors that influences response rates. [181] The 43% response rate of our study was comparable to similar studies using a web-based survey

which physician response rates ranged from 20% to 44%. [181-185] Some similarities between our study and these studies included the use of the SurveyMonkey tool, [181, 182] an initial invitation containing a link, [181, 182] a multi-choice survey with an additional question for free-text comments, [182] follow-up email reminders, [182, 185] anonymous survey, [183, 185] short length of the survey, and no incentives to complete the survey. [183] We believed that the local HSK treatment guideline drew the attention of clinicians, especially registrars who see most patients with this condition, hence the high response rate for the survey.

Some strengths of the web-based survey included its peer-reviewed design, short response time (1 to 2 minutes) and anonymity. Furthermore, sending follow-up reminders has been reported to increase response rates. The suggested optimal timing and number of such reminders vary in the literature. [181] In our study, only one reminder was sent two weeks after the initial invitation.

Audits for interventions seem variably effective with some studies showing modest results and mixed effects. [170, 173, 179, 180] A 10% change was expected as described in the literature. [170] In our study, the audit was successful. Indeed, a 10% improvement was achieved in the adherence to the HSK local guidelines pre- and post-implementation in terms of proportions (73% vs 80%, p = 0.331). Patients with SHSK+U and keratouveitis were not included in the analysis as there was no evidence-based recommendation for these conditions prior to our guideline implementation. Annual audits were included as part of the sustainability plan for the local HSK treatment guideline to determine whether this guideline has been continuously utilised by the clinicians at the hospital.

The audit showed favourable results with respect to guideline implementation. There was an increase in the adherence to the local HSK treatment guideline for all types of HSK and for HSK prophylaxis except for epithelial HSK. These changes only reached statistical significance for epithelial HSK (p = 0.009) and for HSK prophylaxis (p = 0.003). The decrease in adherence for epithelial HSK may be due to the small number of patients in the audit compared with the retrospective series conducted before

the local HSK treatment guideline implementation. The local HSK treatment guideline may have helped the clinicians, as 6 regimens for epithelial HSK were identified in the audit compared to 14 in the retrospective case series. Further, the increase was not statistically significant for SHSK-U and endothelial HSK because these groups may be too small particularly in the audit. However, a positive change was found in the prescribing behaviour in both groups. Nine antiviral regimens were identified for SHSK-U and six for endothelial HSK in the pre-implementation retrospective series, compared to three regimens for both types of HSK in the post-implementation audit. Clinicians followed the recommendations better for endothelial HSK as two-thirds of these patients received the recommended regimen (33% vs 67%, $p = 0.5$) compared to one-third of the patients in the SHSK-U group (9% vs 33%, $p = 0.3$). While, there were no comparisons to be made for SHSK+U and keratouveitis; it was nevertheless pleasing to ascertain a great uptake of the local HSK treatment guideline with 71% of patients with SHSK+U and 54% of patients with keratouveitis receiving the recommended regimens.

The outcomes of HSK were also analysed in the audit. Overall, 95% of the patients had a resolved or partially resolved outcome (39/41) compared to 90% (156/174) in the retrospective series ($p = 0.4$). A comparison was also made for each type of therapeutic indication. There was no statistically significant difference for any of the groups. A reason may be that the cohort in the audit was too small especially for patients with prior graft, SHSK-U and endothelial HSK. In contrast, there was a statistically significant difference in the recurrence rate ($p = 0.009$) for the HSK prophylaxis group. The recurrence rate was 0% in the audit compared with 28% in the retrospective series. This may be because the indications and recommended antiviral regimens for HSK prophylaxis were unambiguous to clinicians for adopting them. Moreover, the audit only included six-month data which is a short period to evaluate HSK recurrence as HSK prophylaxis is recommended for least one year. [59]

Adherence to new guidelines requires an active implementation strategy over a long period of time. [186] Even after successful implementation, it may be difficult to sustain a long-term quality improvement. [186] Health professionals tend to return to their old routine. [186] Three processes were established in our study: local HSK treatment

guideline distribution to new staff, a yearly audit and a yearly meeting with the implementation team and the consensus group. The yearly meeting in July 2018 was the only completed process where the implementation team and the consensus group reviewed the audit and results of the feedback and produced a second version of the local HSK treatment guideline. The second version was successfully implemented in November 2018. A yearly audit has not yet been scheduled as the focus shifted to the guideline's revision and subsequent implementation. A yearly audit would be advisable to monitor the guideline's sustainability. A systematic review reported that the adherence to clinical practice guidelines in medical care was sustained on average for 2.6 years after their implementation (minimum 1.5 - maximum 7). However, no definite conclusion could be drawn in this review as there was a lack of structural methods for sustainability evaluations, as well as, heterogeneity between included studies. [186]

A main limitation of our study was the use of medical record audit as a measure of practice. There was documentation bias relying on the completeness of the medical records. Furthermore, we may have categorised the type of HSK differently to what the clinician diagnosed initially. Practice observation is an alternative to auditing of medical records, but it is costly and time consuming. Another limitation of successful implementation may have been other research studies being carried out at the hospital. They may have potentially relegated the local HSK treatment guideline implementation as clinicians prioritised other studies. Clinicians may have felt confident and comfortable with their antiviral prescribing habits or not seen any advantages in following the new guidelines. Other limitations included the small number of medical notes audited (n = 85), use of single site, and lack of comparison group. Perhaps, as part of the sustainability plan, audits including patients presenting for one year or over at the hospital could be conducted to assess whether the rotation of trainees affects the adherence to the guideline. During our six-month audit, there were two groups of registrars and the same fellows at the hospital. We did not expect much difference in adherence between junior and senior registrars as they were very keen in following the guideline as shown in the survey. However, the frequent rotation of trainees could have affected the adherence to the guideline; but it was not analysed.

The methods of the web-based survey also had some limitations. Firstly, the topic may have been not relevant for respondents. The list of survey respondents included clinicians from different ophthalmic specialties, so some respondents may not have routinely managed patients with HSK. Secondly, the email invitation may have been categorised as 'spam email', with clinicians never opening it. Thirdly, clinicians may have simply forgotten to return the survey due to lack of time. It should be noted that a non-response bias was not measured as reasons for non-responses among clinicians were not explored in our study.

The results of the audit and feedback showed a successful and moderate uptake of the HSK guidelines. There are still opportunities to further improve the ongoing implementation. Future directions include the addition of the local HSK treatment guideline into the Sydney Eye Hospital Ophthalmic Pharmacopoeia mobile application, and perhaps into the hospital's Electronic Medical Records software as a reminder when antiviral medications are prescribed for HSK. Furthermore, future sustainability evaluations, audits and feedback, are needed at two and three years post initial implementation. [186] In future audits, the level of adherence among consultants and trainees could be measured to design tailored strategies for the clinicians with lower level of adherence to the guideline. Educational lectures may also be valuable for continuous educational for trainees. [170] This sustainability plan depends on securing further finance support for training new and current staff, and for disseminating these findings at local and international conferences.

Chapter 6 - Conclusions

Herpes simplex virus is an enveloped double-stranded DNA virus. [1, 8] The primary ocular infection occurs generally early in life with most of the population showing a positive serology by middle age. Most people aged over 60 years will harbor the virus in the trigeminal ganglia. [1] Herpes simplex keratitis is the ocular manifestation of the virus in the cornea. The virus can affect the different layers of the cornea, manifesting itself in clinically different ways. One fifth of the people infected with the HSV are in risk of developing stromal HSK leading to corneal scarring and potentially blindness. [1]

Translating research into clinical practice is crucial. Studies from the USA and the Netherlands have reported that nearly half of patients are not treated according to evidence-based recommendations. It is imperative to close this gap with a systematic approach. [14] The main evidence to manage HSK was provided by the HEDS studies conducted in 1990s. Nevertheless, some studies have reported that these recommendations have been inadequately translated into clinical practice. [56] Anecdotally, a diverse antiviral therapy was identified at the Sydney Eye Hospital in 2013. The preferred antiviral medication was valaciclovir prescribed at different dosages and frequencies. The price of this medication was costly, and the clinical outcomes of the patients were unknown. Furthermore, the HEDS recommendations [2-6] were outdated and not applicable to Australia as topical aciclovir, used widely for epithelial HSK in Australia, was not approved in the USA. Moreover, types of HSK such as SHSK+U, endothelial HSK and keratouveitis were no investigated in the HEDS studies.

The overall aim of this thesis study was to develop, implement and evaluate local treatment guidelines for the initial treatment and prophylaxis of HSK at the Sydney Eye Hospital. *The RNAO Toolkit 'Implementation of Best Practice Guidelines'* was utilised as a guideline for this process. This Toolkit was created based on the 'Knowledge-to-Action' framework. [14] Many guidelines have been created using this framework but not in ophthalmic care to date. [15]

The first aim of the thesis was to determine the antiviral prescribing behaviour for HSK at the Sydney Eye Hospital for the period 2012-2013, and to compare these trends to evidence-based recommendations up to 2013. This retrospective case series showed that 163 of 223 patients (73%) were given an antiviral therapy aligned with the evidence-based recommendations. Patients with SHSK+U and keratouveitis were not included in the analysis as there were no evidence-based recommendations available. There was a large variety of antiviral therapies for HSK in use, including topical aciclovir ranging from 2 to 5 times daily; oral aciclovir 200 mg to 400 mg, one to five times daily; valaciclovir 500 mg to 1 g, once to three times daily; topical trifluridine two hourly or as needed daily; or combined oral and topical antiviral medications. Sixty-four of 113 patients (57%) with stromal HSK, endothelial HSK or keratouveitis also received topical corticosteroids. Reasons for the diversity of antiviral therapy included the availability of other antiviral medications in Australia which were not studied in the HEDS clinical trials (e.g. valaciclovir) or are not approved for the treatment of HSK (e.g. topical aciclovir). Moreover, there was no clear understanding of the appropriate dosages and frequencies for SHSK+U, SHSK-U, endothelial HSK and keratouveitis.

The second aim was to report the predisposing factors, diagnostic tests and outcomes for patients with HSK at the Sydney Eye Hospital for the period 2012-2013. Half of the patients with a therapeutic indication partially resolved within a week. The best outcomes were achieved by patients with endothelial HSK (73%) and keratouveitis (58%). Overall, 27% of patients with a therapeutic indication had a positive HSV PCR result. These patients were diagnosed mainly with epithelial HSK or with SHSK+U. Most of the patients (72%) with a prophylactic indication had a successful outcome at a median time of 18 months. Thirty-six of 252 patients (14%) experienced 42 adverse events relating to HSK. The most common included corneal perforation and secondary bacterial keratitis. The relatively moderate outcomes of patients with a therapeutic indication may have been due to the diverse initial antiviral therapy and lack of appropriate corticosteroid therapy for stromal HSK, endothelial HSK and keratouveitis. On the other hand, the success of HSK prophylaxis may have been due to clinicians having a better understanding of the evidence-based recommendations for this therapy, as these were clearly defined in previous studies. [6] The low positivity rate of HSV PCR

may relate to the absence of virus replication in the lesions tested, or the prior use of antiviral medication. Half of the patients with a therapeutic indication were diagnosed with stromal HSK, endothelial HSK or keratouveitis. These types of HSK are immune responses to the virus, hence PCR is more likely to be negative. A third of patients with epithelial HSK had a positive HSV PCR. Reasons for low positivity rate in this group included previous use of antiviral medications or issues in the sample collection, as fluorescein and topical anaesthetics agents can also affect test sensitivity. [64]

The third aim of this thesis was to report the predisposing factors, clinical features, microbiology spectrum, antibiotic resistance, anti-microbial therapy and outcomes of patients with presumed concomitant microbial keratitis and HSK in the 5 years to 2016 at the Sydney Eye Hospital. Two-thirds of episodes resulted in 'poor' outcomes for the patient. As there were only a few outdated studies reporting cases of concomitant microbial keratitis and HSK, [148, 149, 151] our cohort was also compared with other microbial keratitis series conducted in Australia [109-111, 145, 146] and with microbial keratitis series of elderly patients [116, 141, 160-163] as the mean age of our study was 64 years. One hundred and twenty-six episodes of presumed concomitant microbial keratitis and HSK in 121 patients were included in our study. Main predisposing factors included blepharitis, corneal transplantation, topical corticosteroid use, and prior HSK. Gram-positive isolates, predominantly CoNS, were isolated in 70% of scrape cultures. Half of episodes presented complications including persistent epithelial defect, intraocular pressure elevation, and corneal perforation. Our episodes showed similar predisposing factors and clinical outcomes when comparing with studies on microbial keratitis in the elderly. These episodes were likely to present with poor vision and severe disease in patients over 60 years of age with at least one risk factor. Clinicians should be aware of these risks to make a prompt diagnosis and treat appropriately to avoid severe complications.

The fourth aim was to utilise *The RNAO Toolkit: 'Implementation of Best Practice Guidelines'* [15] for the development, implementation and evaluation of treatment guidelines for the management of HSK at the Sydney Eye Hospital. The post-implementation audit illustrated that most of the clinicians followed the local HSK

treatment guideline. There was no significant improvement between the adherence to evidence-based recommendations pre- and post-guideline implementation (73% vs 80%, $p = 0.331$). Similarly, there was no statistically significant increase in the proportion of patients with a resolved or partially resolved outcome from 90% pre-guideline to 95% post-guideline implementation ($p = 0.4$). In contrast, there was a statistically significant decrease in the rate of recurrence in the patients on HSK prophylaxis (28% vs 0%, $p = 0.003$). However, we acknowledge that the reduction of the recurrence rate post-guideline may have been due to the short time of the audit. A future audit for a longer period is warranted to confirm our findings. With respect to further evaluation of the implementation process, our survey response rate was 43% similar to other studies. [182-186] Most of the clinicians, especially trainees, were aware of and used the local HSK treatment guideline.

Some limitations of this thesis need to be mentioned. The major limitation was the retrospective nature of the HSK series and the concomitant microbial keratitis and HSK series. Documentation bias must be considered as we relied on completeness and accuracy of the medical records. Misclassification bias was also considered in the HSK series as the type of HSK may have been categorised differently to what the clinicians diagnosed and treated the patients for. Other limitations included the small number of medical records audited post-guideline implementation, lack of comparison group, the use of a single site, and other competing simultaneous projects relegating our local HSK treatment guideline. It could be argued that the audit should have been conducted after the guideline was implementation for a longer period as clinicians may have needed more time to adjust to the new recommendations. With respect to the web-based survey, a non-response bias was not measured.

This local HSK treatment guideline is the starting point of a standardised initial therapy for this condition at the Sydney Eye Hospital. As mentioned in Chapter 5, a plan for sustaining the implemented knowledge long-term was recommended. The local HSK treatment guideline requires an ongoing distribution to new staff and trainees via lanyard cards, electronic documents and reminders of where to access them. Moreover, a regular inspection in the consultation rooms is needed to replace missing posters. The release of

the update of the ‘Sydney Eye Hospital-Ophthalmic Pharmacopoeia’ mobile application is warranted to increase the adherence of the guideline among clinicians, especially trainees, as would the integration of the guideline into the hospital’s electronic medication prescribing software.

Yearly revisions and audits are needed to continuously monitor and evaluate the local HSK treatment guideline. Perhaps, a study to determine appropriate dosages and frequencies of antiviral medication for cases of concomitant microbial keratitis and HSK may be advisable. In addition, surveys to analyse the uptake of the guideline may be needed. Our limitations regarding the web-based survey must be considered to improve the response rate possibly including phone call reminders and personalised emails. Google Analytics may be a useful tool to measure the number of visits to the local HSK treatment guideline on the Sydney Eye School website and on the hospital’s intranet, albeit limited to the subgroup of clinicians that use this method to refer to the guidelines.

Lastly, we provide this local HSK treatment guideline for discussion and consideration as other hospitals, institutes and private practices in Australia may adopt them in the future. We intend to obtain an endorsement of RANZCO. The same strategies used at the Sydney Eye Hospital can be implemented in other teaching hospitals. On the other hand, in private practices, lanyard cards and posters along with a cover letter can be sent via post as an initial contact with the practice. Later, we can contact the practice manager or orthoptist to organise an online training session to briefly explain the guideline. We could also organise with RANZCO support, Continuing Professional Development (CPD) activities for ophthalmologists. Indeed, one CPD activity was already completed in December 2018 when the article ‘Clinical translation of recommendations from randomized trials for management of herpes simplex virus keratitis’ was published in Clinical & Experimental Ophthalmology. RANZCO fellows can claim CPD points by reading two articles which appear in each issue and answering five questions. One point is awarded for each set of five questions answered. The adoption of the guideline in private practices may be more challenging; however, if the guideline is endorsed by RANZCO, the specialists would be more inclined to change their prescribing habits. In addition, it is crucial to continue

reminding consultants and trainees in annual meetings and conferences (RANZCO, Australia & New Zealand Cornea Society, registrars' meetings) about the guideline to gradually achieve a change.

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Appendix A - American Academy of Ophthalmology Summary of herpes simplex keratitis treatment recommendations

1. Epithelial Keratitis

a. Dendritic

(Therapeutic dose of topical or oral antiviral agent)

Acyclovir (Zovirax®): 400 mg 3–5 times daily for 7–10 days **or**
Valacyclovir (Valtrex®): 500 mg twice daily for 7–10 days **or**
Famciclovir (Famvir®): 250 mg twice daily for 7–10 days **or**
Trifluridine ophthalmic solution 1% (Viroptic): instillation of 1 drop into affected eye(s) 9 times daily for 7 days; may decrease dose to 5 times daily after 7 days if ulcer is healed. Treatment should not extend beyond 21 days because of potential ocular toxicity.

or

Ganciclovir ophthalmic gel 0.15% (Zirgan®): instillation of 1 drop into affected eye(s) 5 times daily while awake until healing of corneal ulcer, followed by 1 drop 3 times a day for 7 days.

b. Geographic

(Therapeutic dose of topical or oral antiviral agent)

Acyclovir (Zovirax®): 800 mg 5 times daily for 14–21 days **or**
Valacyclovir (Valtrex®): 1 g 3 times daily for 14–21 days **or**
Famciclovir (Famvir®): 500 mg twice daily for 14–21 days **or**
Trifluridine ophthalmic solution 1% (Viroptic®): instillation of 1 drop into affected eye(s) 9 times daily for 7 days; may decrease dose to 5 times daily after 7 days if ulcer is healed. Treatment should not extend beyond 21 days because of potential ocular toxicity.

or

Ganciclovir ophthalmic gel 0.15% (Zirgan®): instillation of 1 drop into affected eye(s) 5 times daily while awake until healing of corneal ulcer, followed by 1 drop 3 times daily for 7 days.

2. Stromal Keratitis

a. Without epithelial ulceration

(Therapeutic dose of topical corticosteroid PLUS prophylactic dose of oral antiviral agent)

Prednisolone 1%: 6–8 times daily tapered over greater than 10 weeks **plus**
Acyclovir (Zovirax®): 400 mg twice daily **or**
Valacyclovir (Valtrex®): 500 mg once daily **or**
Famciclovir (Famvir®): 250 mg twice daily
As disease comes under control, prednisolone can be tapered slowly to the lowest possible dose and frequency as determined by the patient's clinical condition. The lower the dose and frequency of topical corticosteroid, the longer the interval between subsequent dose reduction. Oral antiviral agents in **prophylactic** doses (above) should be maintained during corticosteroid treatment.

b. With epithelial ulceration

(Limited dose of topical corticosteroid PLUS therapeutic dose of oral antiviral agent)

Prednisolone 1%: twice daily **plus**
Acyclovir (Zovirax®): 800 mg 3–5 times daily for 7–10 days **or**
Valacyclovir (Valtrex®): 1 g 3 times daily for 7–10 days **or**
Famciclovir (Famvir®): 500 mg twice daily for 7–10 days
The oral antiviral agent is reduced to prophylactic dose and maintained as long as topical corticosteroids are in use. As disease comes under control prednisolone can be tapered slowly. Note: there is no clinical trial data to support a specific recommendation for length of treatment.

3. Endothelial Keratitis

(Therapeutic dose of topical corticosteroid PLUS therapeutic dose of oral antiviral)

Prednisolone 1%: 6–8 times daily **plus**
Acyclovir (Zovirax®): 400 mg 3–5 times daily **or**
Valacyclovir (Valtrex®): 500 mg twice daily **or**
Famciclovir (Famvir®): 250 mg twice daily
The oral antiviral agent is reduced to prophylactic dose after 7–10 days and maintained as long as topical corticosteroids are in use. As disease comes under control, the topical corticosteroid can be tapered slowly. Note: there is no clinical trial data to support a specific recommendation for length of treatment.

Topical corticosteroid options

1. Fluorometholone 0.1% ophthalmic suspension
2. Rimexolone 1% ophthalmic suspension
3. Prednisolone Sodium Phosphate 1% ophthalmic solution
4. Prednisolone Acetate 1% ophthalmic suspension
5. Difluprednate 0.05% ophthalmic emulsion

Special circumstances

Low doses of acyclovir, valacyclovir, and famciclovir are safe for long-term prophylaxis against HSV keratitis in HIV-infected patients. Atopic patients with HSV keratitis may require prolonged treatment with oral antiviral agents.

Prophylaxis of recurrent HSV keratitis

Potential indications:

1. Multiple recurrences of any type of HSV keratitis, especially HSV stromal keratitis.
2. Recurrent inflammation with scar/vascularization approaching visual axis.
3. More than one episode of HSV keratitis with ulceration: strong stimulus for corneal vascularization and lipid deposition.
4. Post-keratoplasty performed for HSV-related scarring/astigmatism.
5. Postoperatively in patients with a history of HSV ocular disease undergoing any type of ocular surgery or laser procedure.
6. In patients with a history of ocular HSV during immunosuppressive treatment.

Prophylaxis options:

1. Acyclovir (Zovirax®): 400 mg twice daily for one year **or**
2. Valacyclovir (Valtrex®): 500 mg once daily **or**
3. Famciclovir (Famvir®): 250 mg twice daily

The optimal duration of prophylaxis is not fully established, but at least one year is recommended.

RENAL DOSING

The following tables are intended as general guidelines for renal dosing of oral antivirals. However, renal dosing is best determined in conjunction with a nephrologist.

Renal Dosing: HSV Epithelial Keratitis (Dendritic)

Oral Antiviral	Creatinine Clearance (ml/min)	Dose	Frequency
Acyclovir	Normal Dosage	400 mg	3–5 times daily
	> 25	400 mg	3–5 times daily
	10–25	400 mg	Every 8 hours
	0–10	400 mg	Every 12 hours
Famciclovir	Normal Dosage	250 mg	2–3 times daily
	≥ 40–59	250 mg	Every 12 hours
	20–39	125 mg	Every 12 hours
	< 20	125 mg	Every 24 hours
	HD	125 mg	Following each dialysis
Valacyclovir	Normal Dosage	500 mg	Twice daily
	30–49	500 mg	Every 12 hours
	10–29	500 mg	Every 24 hours
	< 10	500 mg	Every 24 hours

Renal Dosing: HSV Epithelial Keratitis (Geographic)

Oral Antiviral	Creatinine Clearance (ml/min)	Dose	Frequency
Acyclovir	Normal Dosage	800 mg	5 times daily
	> 25	800 mg	3–5 times daily
	10–25	800 mg	Every 8 hours
	0–10	800 mg	Every 12 hours
Famciclovir	Normal Dosage	500 mg	Every 8–12 hours
	≥ 40	500 mg	Every 12 hours
	20–39	500 mg	Every 24 hours
	< 20	250 mg	Every 24 hours
	HD	250 mg	Following each dialysis

Renal Dosing: HSV Epithelial Keratitis (Geographic) cont…

Oral Antiviral	Creatinine Clearance (ml/min)	Dose	Frequency
Valacyclovir	Normal Dosage	1 g	3 times daily
	30–49	1 g	Every 12 hours
	10–29	1 g	Every 24 hours
	< 10	500 mg	Every 24 hours

Renal Dosing: HSV Stromal Keratitis (without epithelial ulceration)

Oral Antiviral	Creatinine Clearance (ml/min)	Dose	Frequency
Acyclovir	Normal Dosage	400 mg	2 times daily
	> 10	400 mg	Every 12 hours
	0–10	200 mg	Every 12 hours
Famciclovir	Normal Dosage	125 mg	2 times daily
	≥ 40	125 mg	Every 12 hours
	20–39	125 mg	Every 12 hours
	< 20	125 mg	Every 24 hours
	HD	125 mg	Following each dialysis
Valacyclovir	Normal Dosage	500 mg	Once daily
	30–49	500 mg	Every 24 hours
	10–29	500 mg	Every 48 hours
	< 10	500 mg	Every 48 hours

Renal Dosing: HSV Stromal Keratitis (with epithelial ulceration)

Oral Antiviral	Creatinine Clearance (ml/min)	Dose	Frequency
Acyclovir	Normal Dosage	800 mg	3–5 times daily
	> 25	800 mg	3–5 times daily
	10–25	800 mg	Every 8 hours
	0–10	800 mg	Every 12 hours
Famciclovir	Normal Dosage	500 mg	2 times daily
	≥ 40	500 mg	Every 12 hours
	20–39	500 mg	Every 24 hours
	< 20	250 mg	Every 24 hours
	HD	250 mg	Following each dialysis
Valacyclovir	Normal Dosage	1 g	3 times daily
	30–49	1 g	Every 12 hours
	10–29	1 g	Every 24 hours
	< 10	500 mg	Every 24 hours

Renal Dosing: HSV Endothelial Keratitis

Oral Antiviral	Creatinine Clearance (ml/min)	Dose	Frequency
Acyclovir	Normal Dosage	400 mg	3–5 times daily
	> 25	400 mg	3–5 times daily
	10–25	400 mg	Every 8 hours
	0–10	400 mg	Every 12 hours
Famciclovir	Normal Dosage	250 mg	2–3 times daily
	≥ 40	250 mg	Every 12 hours
	20–39	125 mg	Every 12 hours
	< 20	125 mg	Every 24 hours
	HD	125 mg	Following each dialysis
Valacyclovir	Normal Dosage	500 mg	2 times daily
	30–49	500 mg	Every 12 hours
	10–29	500 mg	Every 24 hours
	< 10	500 mg	Every 24 hours

Renal Dosing: HSV Keratitis Prophylaxis

Oral Antiviral	Creatinine Clearance (ml/min)	Dose	Frequency
Acyclovir	Normal Dosage	400 mg	2 times daily
	> 10	400 mg	Every 12 hours
	0–10	200 mg	Every 12 hours
Famciclovir	Normal Dosage	250 mg	2 times daily
	≥ 40	250 mg	Every 12 hours
	20–39	125 mg	Every 12 hours
	< 20	125 mg	Every 24 hours
	HD	125 mg	Following each dialysis
Valacyclovir	Normal Dosage	500 mg	Once daily
	30–49	500 mg	Every 24 hours
	10–29	500 mg	Every 48 hours
	< 10	500 mg	Every 48 hours

Appendix B - Paediatric keratitis recommendations

1. **Australian Medical Handbook (Children's dosing companion)** [95]

a) Aciclovir

Less serious infections

3 months – 18 years, oral 10 mg/kg (maximum 400 mg) 5 times daily for 5–7 days or until there are no new lesions. Use 20 mg/kg (maximum 400 mg) 5 times daily for 7–14 days in the immunocompromised.

Keratitis

3 months – 18 years, put a small amount of eye ointment into the lower conjunctival sac 5 times daily for 14 days, or for at least 3 days after healing, whichever is shorter.

b) Valaciclovir:

Off-label use

Product information does not include doses for children <12 years, or for children with HSV or VZV infections.

2. **British National Formulary for Children** [96]

a) Valaciclovir (Child 12-17 years)

Herpes simplex, treatment of first infective episode

500 mg twice daily for 5 days (longer if new lesions appear during treatment or healing is incomplete).

Herpes simplex infections treatment of first episode in immunocompromised or HIV-positive patients

1 g twice daily for 10 days.

Herpes simplex, treatment of recurrent infections

500 mg twice daily for 3–5 days.

Treatment of recurrent herpes simplex infections in immunocompromised or HIV-positive patients

1 g twice daily for 5–10 days.

Herpes simplex, suppression of infections

500 mg daily in 1–2 divided doses, therapy to be interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences.

Herpes simplex, suppression of infections in immunocompromised or HIV-positive patients

500 mg twice daily, therapy to be interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences.

3. Side-effects

Very rare

Acute renal failure, anaemia, ataxia, confusion, convulsions, dizziness, drowsiness, dysarthria, dyspnea, hallucinations, hepatitis, jaundice, leucopenia, neurological reactions, thrombocytopenia

Frequency not known

Abdominal pain, diarrhoea, fatigue, headache, nausea, photosensitivity, rash, urticaria, vomiting

Renal impairment

For *treatment of herpes simplex,* 500 mg (1 g in immunocompromised or HIV-positive children) every 24 hours if estimated glomerular filtration rate less than 30 mL/minute/1.73 m^2.

For *suppression of herpes simplex,* 250 mg (500 mg in immunocompromised or HIV-positive children) every 24 hours if estimated glomerular filtration rate less than 30 mL/minute/1.73 m^2.

Appendix C - Data fields collected for retrospective case series

The following data fields were collected from medical records:

- Demographics
    - Date of birth
    - Gender: female, male
    - Country of birth
    - Post code:
        1. Murrumbidgee
        2. Sydney North West
        3. Sydney Hills
        4. Sydney West Central
        5. Sydney South West
        6. Sydney North Coast
        7. Sydney North
        8. Sydney city
        9. Wollongong
        10. Sydney South
        11. Central Coast
        12. Sydney Inner West
        13. Central West
        14. Hunter
        15. Newcastle
        16. South East
        17. North West
        18. Northern
        19. Richmond Tweed
        20. Mid North Coast
        21. Murray
        22. South Coast
        23. Overseas

24. Victoria

- Past medical history
    - Known immunosuppression
        1. Diabetes mellitus
        2. HIV/AIDS
        3. Solid organ transplant
        4. Steroid-sparing immunosuppressive use
        5. Oral steroid use for medical reason
        6. None
    - Medical reason for oral steroid use:
        1. Ocular
        2. Respiratory
        3. Solid organ transplant
        4. Autoimmune disease
        5. Other
- Ocular history
    - Current contact lens wear: Yes/No
    - Pre-existing eye conditions limiting visual acuity
        1. Amblyopia
        2. Cataract
        3. Glaucoma
        4. Macular degeneration
        5. Corneal pathology
        6. Retinal pathology
        7. Uveitis
        8. None
        9. Other
    - History of previous herpes simplex diagnosis
        1. Epithelial
        2. Stromal/Interstitial
        3. Endothelial/ Disciform

4. Keratouveitis
5. Unclear
6. Unknown

- Previous corneal graft
    1. PK
    2. LK
    3. DALK
    4. DSEK
    5. DMEK
    6. Unknown
- Significant ocular trauma
    1. Non-penetrating
    2. Penetrating
    3. Unknown
- Type of non-penetrating trauma
    1. Abrasion
    2. Blunt
    3. Thermal
    4. Chemical
    5. Other
- Current oral antiviral use
    1. Aciclovir
    2. Valaciclovir
    3. Famciclovir
- Current topical antiviral
    1. Aciclovir
    2. Ganciclovir
    3. Trifluorothyridine
- Current topical steroid
    1. FML/Flucon
    2. Flarex

3. Prednisolone Minims
4. Pred forte
5. Maxidex
6. Dexamethasone Minims
7. Hycor ointment

- Clinical features of presentation
  - Date of enrolment visit
  - Visual acuity (VA) right eye
  - Visual acuity (VA) left eye
  - Measurement means at inclusion
    1. Unaided
    2. Glasses
    3. Contact lenses
  - Study eye
    1. Right
    2. Left
  - Indication for antiviral
    1. Prophylaxis
    2. Therapeutic
  - Therapeutic indication
    1. Epithelial
    2. Stromal/Interstitial
    3. Endothelial/ Disciform
    4. Keratouveitis
    5. Corneal graft
    6. Unclear
  - Prophylaxis indication
    1. Epithelial
    2. Stromal/Interstitial
    3. Endothelial/ Disciform
    4. Keratouveitis

5. Corneal graft
6. Unclear

- Oral antiviral prescribed: Yes/No
- Name oral antiviral
    1. Aciclovir
    2. Valaciclovir
    3. Famciclovir
- Dose oral antiviral
    1. 200 mg
    2. 250 mg
    3. 400 mg
    4. 500 mg
    5. 800 mg
    6. 1000 mg
- Frequency of oral antiviral
    1. od
    2. bd
    3. tds
    4. QID
    5. 5 times a day
- Topical antiviral prescribed: Yes/No
- Name topical antiviral
    1. Aciclovir
    2. Ganciclovir
    3. Trifluorothyridine
- Frequency of topical antiviral
    1. od
    2. bd
    3. tds
    4. QID
    5. 5 times a day

6. q 2 hours
7. PRN

- Topical steroid prescribed: Yes/No
- Name of topical steroid
    1. FML/Flucon
    2. Flarex
    3. Prednisolone Minims
    4. Pred forte
    5. Maxidex
    6. Dexamethasone Minims
    7. Hycor ointment
- Frequency of topical steroid
    1. od
    2. bd
    3. tds
    4. QID
    5. 5 times a day
    6. 6 times a day
    7. q 1 hour
    8. every other day od
    9. q 2 hour
    10. Nocte
- Prescriber doctor
    1. Consultant
    2. Fellow
    3. Registrar
    4. Resident
    5. Other

- Subsequent investigations
    - Diagnostic test performed ever: Yes/No
    - Diagnostic test performed at enrolment visit: Yes/No

- Type of diagnostic test
    1. PCR
    2. Culture
    3. Serology
- Result of diagnostic test
    1. Positive type 1
    2. Positive type 2
    3. Negative

- Outcome
    - Date oral antiviral was stopped or changed
    - Duration initial oral therapy with antiviral
    - Date topical antiviral was stopped or changed
    - Duration initial topical therapy with antiviral
    - Date topical steroid was changed or stopped
    - Date topical steroid 2 was changed or stopped
    - Duration initial therapy with topical steroid
    - Duration initial therapy with topical steroid 2
    - Visual acuity (VA)of affected eye when oral antiviral was ceased/changed
    - Measurement means when oral antiviral was ceased/changed
        1. Unaided
        2. Glasses
        3. Contact lenses
    - Visual acuity (VA) of affected eye when topical antiviral was ceased/changed
    - Measurement means when topical antiviral was ceased/changed
        1. Unaided
        2. Glasses
        3. Contact lenses
    - Treatment outcome when oral antiviral cases/changed
        1. Success

2. Failure
3. Partial resolution
4. Not herpes simplex
5. Unknown
6. Lost follow up

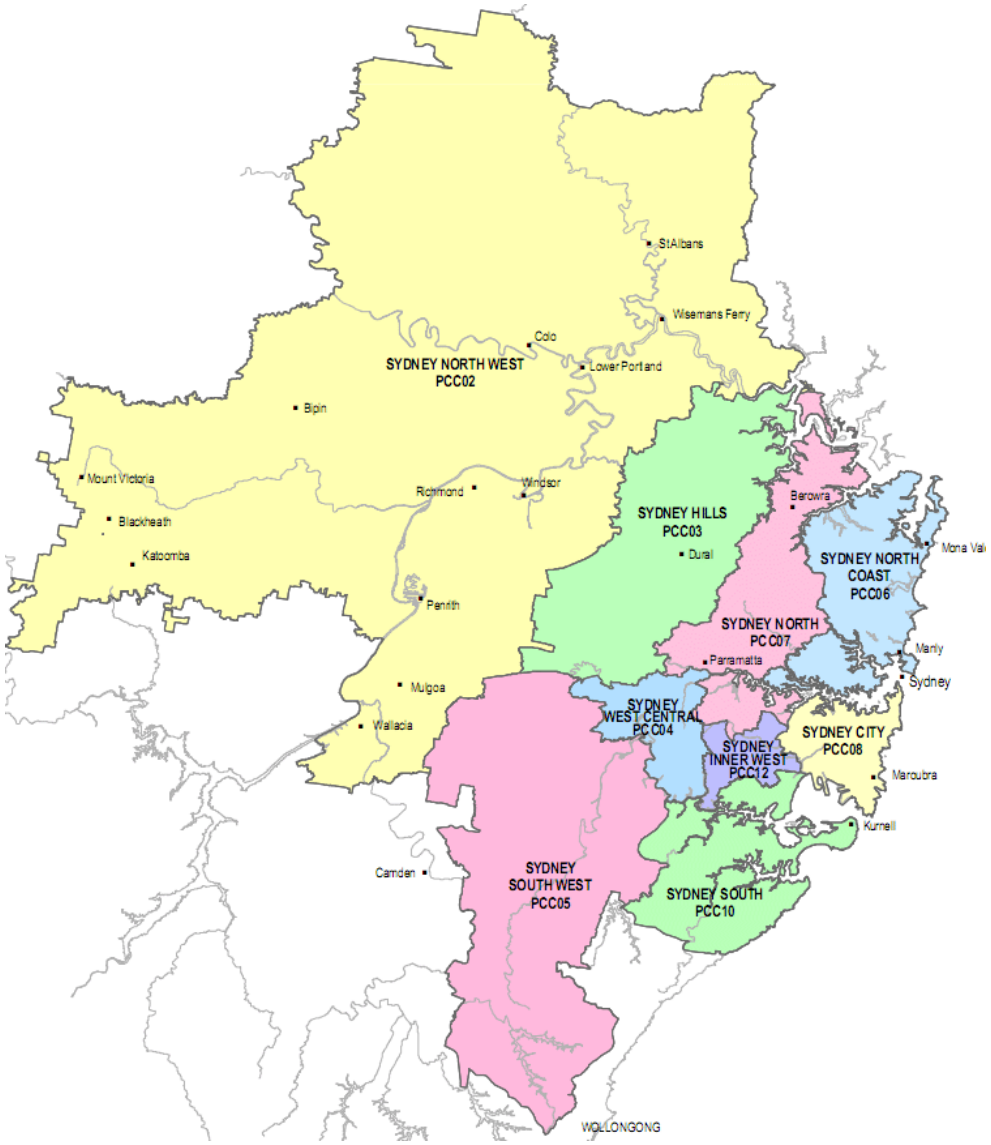
- Treatment outcome when topical antiviral cases/changed
    1. Success
    2. Failure
    3. Partial resolution
    4. Not herpes simplex
    5. Unknown
    6. Lost follow up
- Oral antiviral treatment completion
    1. Yes
    2. No
    3. Ongoing
    4. Unknown
- Topical antiviral treatment completion
    1. Yes
    2. No
    3. Ongoing
    4. Unknown
- Topical steroid treatment completion
    1. Yes
    2. No
    3. Ongoing
    4. Unknown
- Topical steroid 2 treatment completion
    1. Yes
    2. No
    3. Ongoing

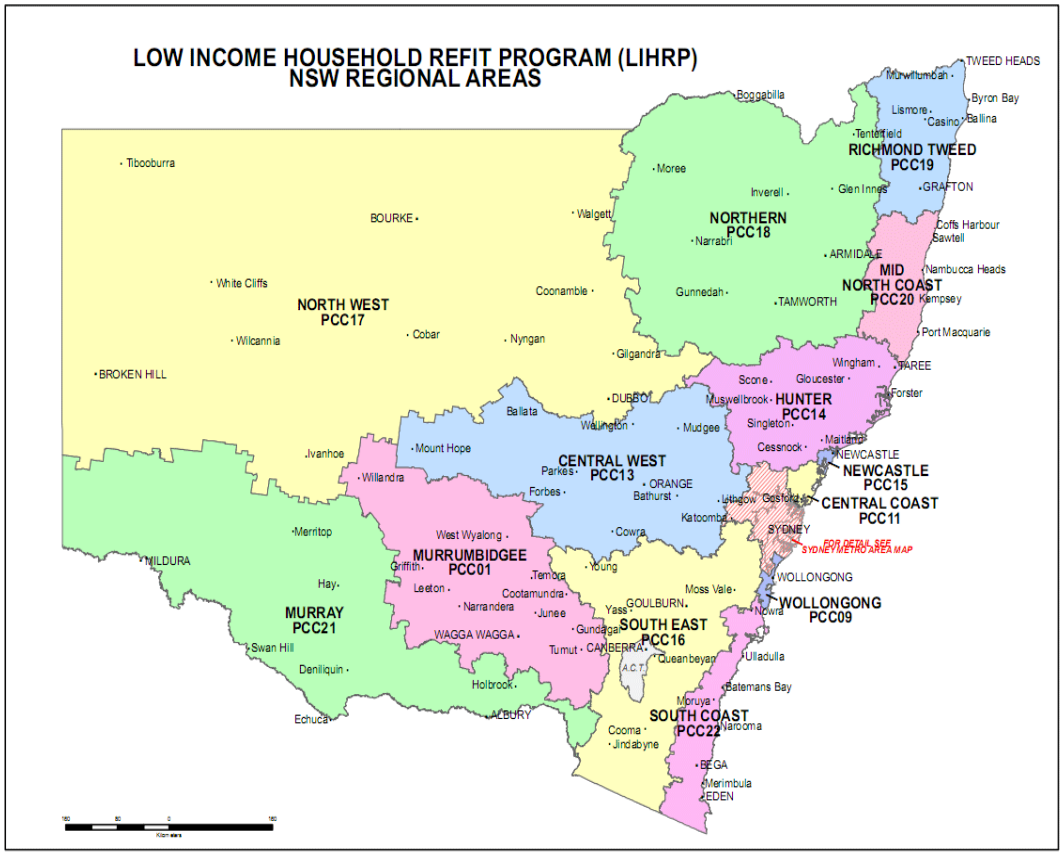
4. Unknown

- Reason for treatment not completed
- Admission date Sydney Eye Hospital
- Discharge date Sydney Eye Hospital
- Number of visits until keratitis episode was resolved or if ongoing
- Number of visits on prophylaxis without recurrence
- Number of visits until prophylaxis or treatment was stopped or failed
- Date final resolution
- Time final resolution
- Date failure therapeutic treatment
- Time to failure therapeutic treatment
- Date failure prophylaxis or was stopped
- Type adverse events
    1. Side effect to antiviral
    2. Allergy to antiviral
    3. Ocular toxicity
    4. Non-healing ulcer
    5. Secondary bacterial keratitis requiring intensive topical antibiotics
    6. Fungal keratitis
    7. Descemetocele
    8. Corneal perforation
    9. Corneal perforation requiring glue
    10. Corneal perforation corneal transplantation
    11. Other
- Last visit date

- Comments

Appendix D - Postcode clusters for New South Wales




LOW INCOME HOUSEHOLD REFIT PROGRAM (LIHRP)
NSW REGIONAL AREAS
TWEED HEADS
Murwillumbah
Byron Bay
Lismore
Casino
Ballina
Tenterfield
RICHMOND TWEED
PCC19
Boggabilla
Moree
Inverell
Glen Innes
GRAFTON
Tibooburra
BOURKE
Walgett
NORTHERN
PCC18
Narrabri
Coffs Harbour
Sawtell
ARMIDALE
MID
NORTH COAST
PCC20
Nambucca Heads
Kempsey
White Cliffs
NORTH WEST
PCC17
Coonamble
Gunnedah
TAMWORTH
Wilcannia
Cobar
Nyngan
Gilgandra
Port Macquarie
Wingham
TAREE
BROKEN HILL
Scone
Gloucester
Forster
DUBBO
Muswellbrook
HUNTER
PCC14
Singleton
Ballata
Wellington
Mudgee
Maitland
Cessnock
NEWCASTLE
Ivanhoe
Mount Hope
CENTRAL WEST
PCC13
Parkes
Willandra
Forbes
ORANGE
Bathurst
NEWCASTLE
PCC15
Lithgow
Gosford
CENTRAL COAST
PCC11
Katoomba
SYDNEY
FOR DETAIL SEE
SYDNEY METRO AREA MAP
Merritop
West Wyalong
Cowra
MURRUMBIDGEE
PCC01
Griffith
Young
MILDURA
Temora
WOLLONGONG
Hay
Leeton
Cootamundra
Moss Vale
GOULBURN
Narrandera
Junee
Yass
Nowra
WOLLONGONG
PCC09
MURRAY
PCC21
Gundagai
SOUTH EAST
PCC16
WAGGA WAGGA
Swan Hill
Tumut
CANBERRA
A.C.T.
Queanbeyan
Ulladulla
Deniliquin
Batemans Bay
Holbrook
Moruya
Narooma
ALBURY
SOUTH COAST
PCC22
Echuca
Cooma
Jindabyne
BEGA
Merimbula
EDEN

PCC	Location of PCC*	CMPA	Post Codes in Postcode Cluster
PCC01	Murrumbidgee	6,147	2590, 2649, 2650, 2651, 2652, 2653, 2655, 2656, 2661, 2663, 2665, 2666, 2668, 2669, 2671, 2672, 2675, 2680, 2681, 2700, 2701, 2702, 2703, 2705, 2706, 2707, 2720, 2721, 2722, 2725, 2726, 2727, 2729, 2730
PCC02	Sydney North West	11,081	2745, 2747, 2748, 2749, 2750, 2752, 2753, 2754, 2755, 2756, 2757, 2758, 2759, 2760, 2765, 2770, 2773, 2774, 2775, 2776, 2777, 2778, 2779, 2780, 2782, 2783, 2784, 2785, 2786
PCC03	Sydney Hills	10,136	2125, 2126, 2145, 2146, 2147, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2761, 2762, 2763, 2766, 2767, 2768
PCC04	Sydney West Central	12,518	2142, 2143, 2144, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2197, 2198, 2199, 2200, 2211, 2212, 2213, 2214
PCC05	Sydney South West	10,825	2167, 2168, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2555, 2556, 2557, 2558, 2559, 2560, 2563, 2564, 2565, 2566, 2567
PCC06	Sydney North Coast	9,951	2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2092, 2093, 2094, 2095, 2096, 2097, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2110, 2111
PCC07	Sydney North	13,747	2045, 2046, 2047, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2079, 2080, 2081, 2082, 2083, 2109, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2127, 2128, 2134, 2135, 2136, 2137, 2138, 2140, 2141, 2150, 2151, 2152
PCC08	Sydney City	15,712	2000, 2006, 2007, 2008, 2009, 2010, 2011, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2048, 2049, 2050, 2203, 2204
PCC09	Wollongong	9,799	2500, 2502, 2505, 2506, 2508, 2515, 2516, 2517, 2518, 2519, 2525, 2526, 2527, 2528, 2529, 2530, 2533, 2534
PCC10	Sydney South	9,680	2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234
PCC11	Central Coast	12,924	2250, 2251, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265
PCC12	Sydney Inner West	9,638	2130, 2131, 2132, 2133, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2205, 2206, 2207, 2208, 2209, 2210
PCC13	Central West	8,009	2787, 2790, 2791, 2792, 2793, 2794, 2795, 2797, 2798, 2799, 2800, 2803, 2804, 2805, 2806, 2807, 2808, 2809, 2810, 2820, 2845, 2846, 2847, 2848, 2849, 2850, 2852, 2864, 2865, 2866, 2867, 2868, 2869, 2870, 2871, 2873, 2874, 2875, 2876, 2877
PCC14	Hunter	12,996	2311, 2312, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2333, 2334, 2335, 2336, 2337, 2338, 2415, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430
PCC15	Newcastle	12,040	2267, 2278, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2302, 2303, 2304, 2305, 2306, 2307
PCC16	South East	7,496	2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585,

PCC	Location of PCC*	CMPA	Post Codes in Postcode Cluster
			2586, 2587, 2588, 2594, 2611, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, (Notes: 2540 crosses NSW/OT, 2618 crosses ACT/NSW, 2620 crosses ACT/NSW)
PCC17	North West	4,223	2821, 2823, 2824, 2825, 2827, 2828, 2829, 2830, 2831, 2832, 2833, 2834, 2835, 2836, 2839, 2840, 2842, 2843, 2844, 2878, 2879, 2880, 4493
PCC18	Northern	7,809	2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2350, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2365, 2369, 2370, 2371, 2372, 2379, 2380, 2381, 2382, 2386, 2387, 2388, 2390, 2395, 2396, 2397, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2408, 2409, 2410, 2411, (Notes: 2406 crosses NSW/QLD)
PCC19	Richmond Tweed	13,090	2460, 2462, 2463, 2464, 2465, 2466, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490
PCC20	Mid North Coast	9,778	2431, 2439, 2440, 2441, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2452, 2453, 2454, 2455, 2456
PCC21	Murray	4,661	2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2658, 2659, 2660, 2710, 2711, 2712, 2713, 2714, 2715, 2716, 2717, 2731, 2732, 2733, 2734, 2735, 2736, 2737, 2738, 2739, 3644, 3707
PCC22	South Coast	7,742	2535, 2536, 2537, 2538, 2539, 2540, 2541, 2545, 2546, 2548, 2549, 2550, 2551

Appendix E - Ethics committee approval

Health
South Eastern Sydney
Local Health District
HUMAN RESEARCH ETHICS COMMITTEE
Room G71 East Wing
Edmund Blacket Building
Prince of Wales Hospital
RANDWICK NSW 2031
Tel: 02 9382 3587 Fax: 02 9382 2813
http://www.seslhd.health.nsw.gov.au/POWH/researchsupport/default.asp

11 December 2013

Dr Maria Cabrera Aguas
c/o Clinical Professor Stephanie Watson
Ophthalmology - Save Sight Institute
Sydney Hospital
8 Macquarie St
SYDNEY NSW 2000

Dear Dr Cabrera Aguas

HREC ref no: 13/296 (LNR/13/POWH/596)
Project title: Clinical translation of recommendations from randomized trials for management of herpes simplex keratitis.

Thank you for submitting the above Low/Negligible Risk Application for review by the Human Research Ethics Committee (HREC). Based on the information you have provided and in accordance with the NHMRC guidelines [National Statement 2007 – Section 5 Institutional Responsibilities and "*When does quality assurance in health care require independent ethical review?*" (2003)], this project has been assessed as low risk and is therefore exempt from full HREC review.

The project was considered by the HREC Executive Committee on 5 November 2013. The Committee asked for clarification of certain matters/modifications and delegated authority to grant final approval to the Executive Officer.

I am pleased to advise that with your correspondence dated 26 November 2013 the requested information and revised documents were received incorporating the recommendations of the Executive. Ethical approval has been granted for the above project to be conducted at:

- Sydney Eye Hospital

The following documentation has been approved:

- Low/negligible risk application, submission code AU/6/1984110, dated 17 September 2013
- Response Letter to the Executive, dated 26 November 2013
- Data Collection Sheet, version 2, dated 26 November 2013
- Participant ID-MRN-Name Sheet, not dated

Prince of Wales Hospital
Community Health Services
Barker Street
Randwick NSW 2031

51777 290711

Conditions of approval

1. This approval is valid for 5 years from the date of this letter.
2. Annual reports must be provided on the anniversary of approval.
3. A final report must be provided at the completion of the project.
4. Proposed changes to the research protocol, conduct of the research, or length of approval will be provided to the Committee.
5. The Principal Investigator will immediately report matters which might warrant review of ethical approval, including unforeseen events which might affect the ethical acceptability of the project and any complaints made by study participants.

For NSW Public Health sites only: You are reminded that this letter constitutes ethical approval only. You must not commence this research project until you have submitted your Site Specific Assessment (SSA) to the Research Governance Officer of the appropriate institution and have received a letter of authorisation from them.

Should you have any queries, please contact the Research Support Office on (02) 9382 3587. The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Research Support Office website:
http://www.seslhd.health.nsw.gov.au/POWH/researchsupport/default.asp.

Please quote **HREC ref no: 13/296** in all correspondence. We wish you every success in your research.

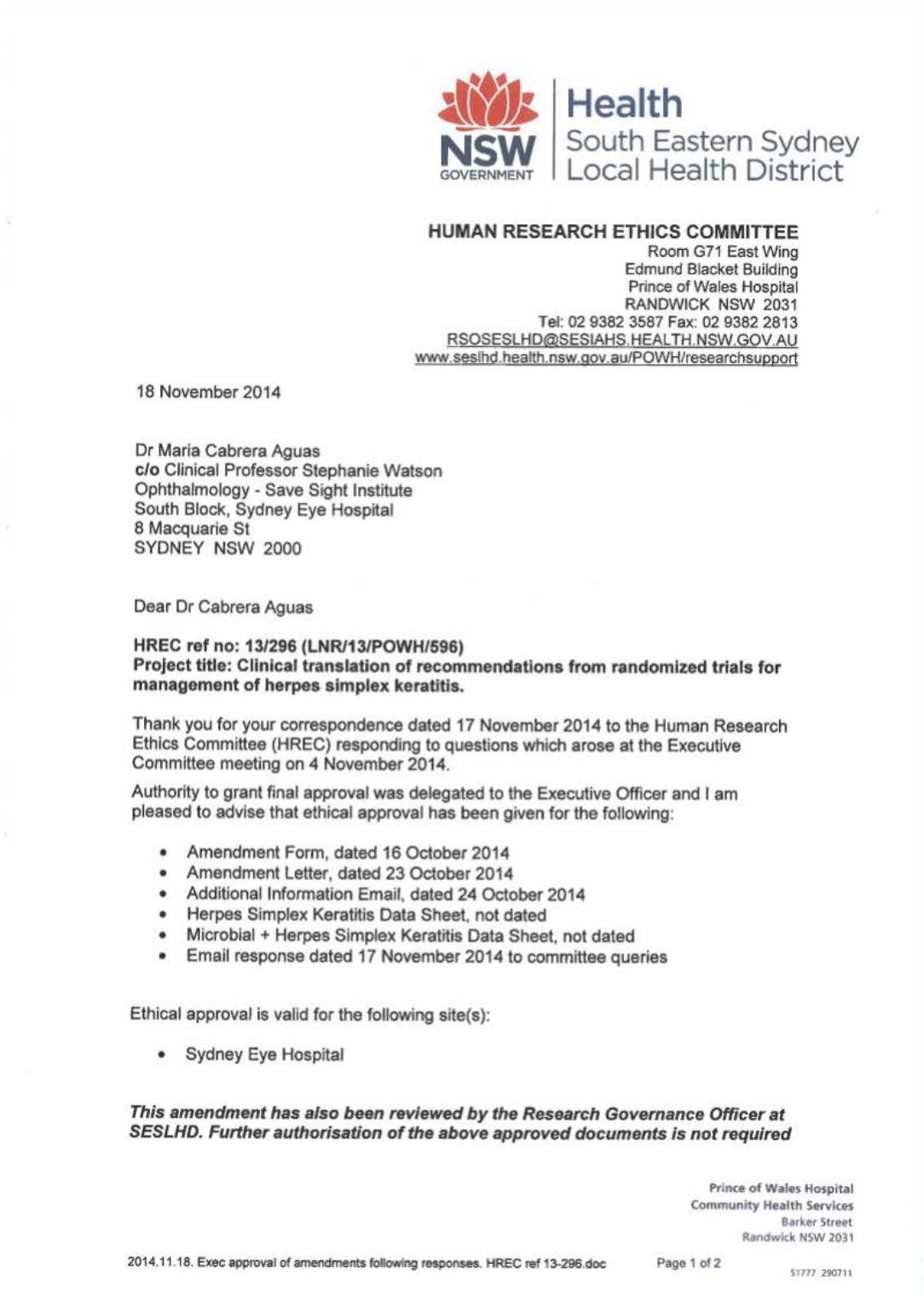
Yours sincerely

Amanda Idan
Acting Executive Officer, Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*, NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

CC. Clinical Professor Stephanie Watson

Appendix F - Ethics committee approval to first amendment



NSW GOVERNMENT Health
South Eastern Sydney Local Health District

HUMAN RESEARCH ETHICS COMMITTEE
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www.seslhd.health.nsw.gov.au/POWH/researchsupport

18 November 2014

Dr Maria Cabrera Aguas
c/o Clinical Professor Stephanie Watson
Ophthalmology - Save Sight Institute
South Block, Sydney Eye Hospital
8 Macquarie St
SYDNEY NSW 2000

Dear Dr Cabrera Aguas

HREC ref no: 13/296 (LNR/13/POWH/596)
Project title: Clinical translation of recommendations from randomized trials for management of herpes simplex keratitis.

Thank you for your correspondence dated 17 November 2014 to the Human Research Ethics Committee (HREC) responding to questions which arose at the Executive Committee meeting on 4 November 2014.

Authority to grant final approval was delegated to the Executive Officer and I am pleased to advise that ethical approval has been given for the following:

- Amendment Form, dated 16 October 2014
- Amendment Letter, dated 23 October 2014
- Additional Information Email, dated 24 October 2014
- Herpes Simplex Keratitis Data Sheet, not dated
- Microbial + Herpes Simplex Keratitis Data Sheet, not dated
- Email response dated 17 November 2014 to committee queries

Ethical approval is valid for the following site(s):

- Sydney Eye Hospital

This amendment has also been reviewed by the Research Governance Officer at SESLHD. Further authorisation of the above approved documents is not required

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Community Health Services
Barker Street
Randwick NSW 2031

for any site that has the Research Governance conducted by the SESLHD Research Support Office. Implementation of this amendment can now proceed.

For multi-site projects reviewed by the HREC after 1 January 2011 a copy of this letter must be forwarded to all Principal Investigators at every site approved by the SESLHD HREC for submission to the relevant Research Governance Officer along with a copy of the approved documents.

Should you have any queries, please contact the Research Support Office on (02) 9382 3587. The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Research Support Office website: http://www.seslhd.health.nsw.gov.au/POWH/researchsupport/default.asp

Please quote **HREC ref no 13/296** in all correspondence.

We wish you every success in your research.

Yours sincerely

[redacted]

Executive Officer, Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*, NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

Appendix G – Ethics committee approval to second amendment

Health
South Eastern Sydney
Local Health District

HUMAN RESEARCH ETHICS COMMITTEE
Room G71 East Wing
Edmund Blacket Building
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http://www.seslhd.health.nsw.gov.au/POWH/researchsupport/default.asp

02 July 2015

Dr Maria Cabrera Aguas
c/o Clinical Professor Stephanie Watson
Ophthalmology - Save Sight Institute
South Block, Sydney Eye Hospital
8 Macquarie St
SYDNEY NSW 2000

Dear Dr Cabrera Aguas

HREC ref no: 13/296 (LNR/13/POWH/596)
Project title: Clinical translation of recommendations from randomized trials for management of herpes simplex keratitis.

Thank you for your amendment request dated 06 May 2015 to the Human Research Ethics Committee (HREC). The Executive Committee reviewed your submission 07 April 2015.

I am pleased to advise that the following documentation has been approved:

- Amendment Form, dated 6 March 2015
- Letter to send to Specialists, not dated
- Response Letter to Executive Officer dated 15 June 2015

Ethical approval is valid for the following site(s):

- Sydney Eye Hospital

This amendment has also been reviewed by the Research Governance Officer at SESLHD. Further authorisation of the above approved documents is not required for any site that has the Research Governance conducted by the SESLHD Research Support Office. Implementation of this amendment can now proceed.

For multi-site projects reviewed by the HREC after 1 January 2011 a copy of this letter must be forwarded to all Principal Investigators at every site approved by the SESLHD HREC for submission to the relevant Research Governance Officer along with a copy of the approved documents.

Prince of Wales Hospital
Community Health Services
Barker Street
Randwick NSW 2031

Should you have any queries, please contact the Research Support Office on (02) 9382 3587. The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Research Support Office website: http://www.seslhd.health.nsw.gov.au/POWH/researchsupport/default.asp.

Please quote **HREC ref no 13/296** in all correspondence.

We wish you every success in your research.

Yours sincerely

[redacted]

Andrew Bohlken
Acting Executive Officer, Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*, NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

Appendix H – Letter sent to specialists requesting missing information

THE UNIVERSITY OF SYDNEY

Clinical Professor Stephanie L Watson Bsc(Med), MMBS, FRANZCO, PhD

Name
Address line
Address line
Date

Study reference number: *HREC ref no:*

Dear [insert name],

We are currently evaluating the treatment trends for herpes simplex keratitis at the Sydney Eye Hospital. (See attached HREC approval).

We are writing to you to request some information about patients that were admitted to the Sydney Eye hospital and have visited you for a follow-up after the admission. You and your patients will not be identified.

You can find on the next page a list with the name(s) of the patient(s), the date of birth and an ID number for each patient. On the following page, you will find the ID number as the patient identifier on item 1 and the questionnaire.

We would appreciate if you can fax or mail the information requested on page 3. Do not send back the list of patients (page 2)

If you have any questions, please call Dr Maria Cabrera-Aguas on 0431 737 428.

Thank you for your time. Your help with this study is greatly appreciated.

Yours sincerely,

Clinical Professor Stephanie Watson

SAVE SIGHT INSTITUTE THE UNIVERSITY OF SYDNEY

Save Sight Institute
Discipline of Ophthalmology
Sydney Medical School
Ground Floor South Block
Sydney Hospital Campus
8 Macquarie Street
Sydney NSW 2000

T +61 2 9382 7300
F +61 2 9382 7372
ESTEPHANIE.WATSON@SYDNEY.EDU.AU

THE UNIVERSITY OF SYDNEY
Clinical Professor Stephanie L Watson Bsc(Med), MMBS, FRANZCO, PhD

Patient list

ID	Name	Date of birth

SAVE SIGHT INSTITUTE THE UNIVERSITY OF SYDNEY

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Sydney Medical School
Ground Floor South Block
Sydney Hospital Campus
8 Macquarie Street
Sydney NSW 2000

T +61 2 9382 7300
F +61 2 9382 7372
ESTEPHANIE.WATSON@SYDNEY.EDU.AU

THE UNIVERSITY OF SYDNEY
Clinical Professor Stephanie L Watson Bsc(Med), MMBS, FRANZCO, PhD

1. ID number: [Insert ID number of patient]

2. Medical history details: [Insert patient relevant information: date of admission at Sydney Eye Hospital/ date of appointment of interest at private rooms]

3. What is the date when [insert name of antiviral medication] was changed or stopped?

4. What was the visual acuity on the date [insert name of antiviral medication] was changed or stopped?

Right eye:	a) Unaided	b)Glasses	c)Contact lenses
Left eye:	a) Unaided	b)Glasses	c)Contact lenses

5. What is the date when [insert name topical steroid] was changed or stopped?

6. What was the outcome of the keratitis when [insert name of antiviral medication] was changed or stopped?

   a. Success (infection resolved)
   b. Failure (Infection deteriorated)
   c. Partial resolution of the infection
   d. Keratitis not caused by herpes simplex virus
   e. Other

7. Was [insert name of antiviral medication] treatment completed?

   a. Yes
   b. No
   c. Still ongoing treatment
   d. Unknown

8. What was the date when the keratitis was resolved?

9. What was the date when the keratitis treatment failed?

10. Any adverse events?

    1, Side effect to antiviral
    2, Allergy to antiviral
    3, Ocular toxicity
    4, Non-healing ulcer
    5, Secondary bacterial keratitis requiring intensive topical antibiotics
    6, Fungal keratitis
    7, Descematocele
    8, Corneal perforation
    9, Corneal perforation requiring glue
    10, Corneal perforation corneal transplantation
    11, Other

SAVE SIGHT INSTITUTE THE UNIVERSITY OF SYDNEY

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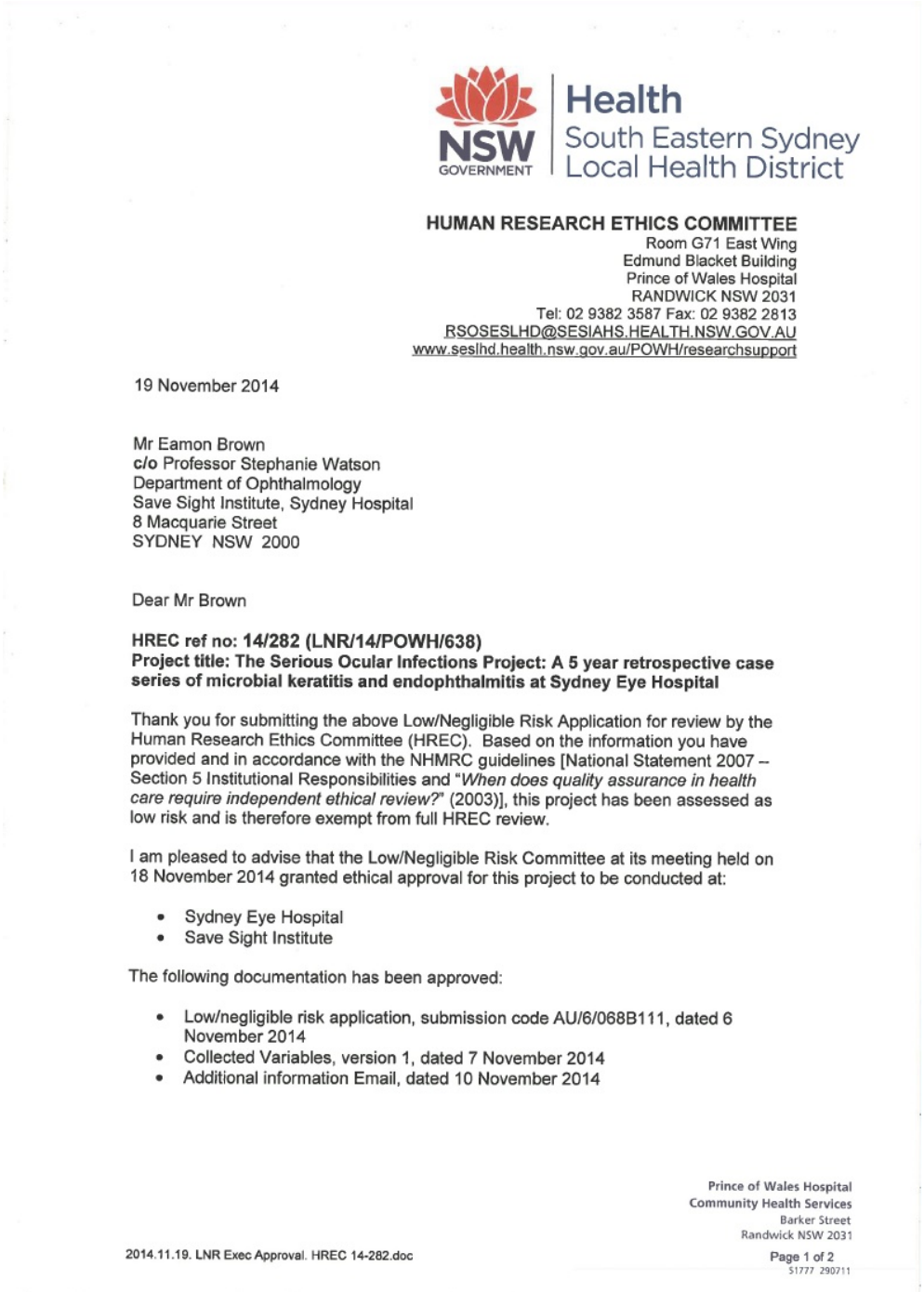
ESTEPHANIE.WATSON@SYDNEY.EDU.AU

Appendix I - Ethics committee approval for concomitant microbial keratitis and herpes simplex keratitis retrospective study and addition of main investigator to the study



NSW GOVERNMENT Health
South Eastern Sydney Local Health District

HUMAN RESEARCH ETHICS COMMITTEE
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www.seslhd.health.nsw.gov.au/POWH/researchsupport

19 November 2014

Mr Eamon Brown
c/o Professor Stephanie Watson
Department of Ophthalmology
Save Sight Institute, Sydney Hospital
8 Macquarie Street
SYDNEY NSW 2000

Dear Mr Brown

HREC ref no: 14/282 (LNR/14/POWH/638)
Project title: The Serious Ocular Infections Project: A 5 year retrospective case series of microbial keratitis and endophthalmitis at Sydney Eye Hospital

Thank you for submitting the above Low/Negligible Risk Application for review by the Human Research Ethics Committee (HREC). Based on the information you have provided and in accordance with the NHMRC guidelines [National Statement 2007 – Section 5 Institutional Responsibilities and "*When does quality assurance in health care require independent ethical review?*" (2003)], this project has been assessed as low risk and is therefore exempt from full HREC review.

I am pleased to advise that the Low/Negligible Risk Committee at its meeting held on 18 November 2014 granted ethical approval for this project to be conducted at:

- Sydney Eye Hospital
- Save Sight Institute

The following documentation has been approved:

- Low/negligible risk application, submission code AU/6/068B111, dated 6 November 2014
- Collected Variables, version 1, dated 7 November 2014
- Additional information Email, dated 10 November 2014

Prince of Wales Hospital
Community Health Services
Barker Street
Randwick NSW 2031

2014.11.19. LNR Exec Approval. HREC 14-282.doc

Page 1 of 2
51777 290711

Conditions of approval

1. This approval is valid for 5 years from the date of this letter.
2. Annual reports must be provided on the anniversary of approval.
3. A final report must be provided at the completion of the project.
4. Proposed changes to the research protocol, conduct of the research, or length of approval will be provided to the Committee.
5. The Principal Investigator will immediately report matters which might warrant review of ethical approval, including unforeseen events which might affect the ethical acceptability of the project and any complaints made by study participants.

Optional It is the responsibility of the sponsor or the principal (or co-ordinating) investigator of the project to register this study on a publicly available online registry (eg Australian New Zealand Clinical Trials Registry www.anzctr.org.au).

For NSW Public Health sites only: You are reminded that this letter constitutes ethical approval only. You must not commence this research project until you have submitted your Site Specific Assessment (SSA) to the Research Governance Officer of the appropriate institution and have received a letter of authorisation from them.

Should you have any queries, please contact the Research Support Office on (02) 9382 3587. The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Research Support Office website:
http://www.seslhd.health.nsw.gov.au/POWH/researchsupport/default.asp.

Please quote **HREC ref no: 14/282** in all correspondence.

We wish you every success in your research.

Yours sincerely

[redacted]

Deborah Adrian
Executive Officer, Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*, NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

Supervisor section was signed electronically by Dr Dana Robaei on 05/11/2014 17:32

Job Title/Post: Clinical Senior Lecturer
Organisation: University of Sydney
Email: dana.robaei@sydney.edu.au
Decision/Comments:

Name	Designation	Signature	Date
Eamon Brown	Student		05/11/2014
Prof. Stephanie Watson	Principal Investigator		05/11/2014
Dr. Dana Robaei	Investigator		05/11/2014

Appendix J - Data fields collected for the concomitant microbial and herpes simplex keratitis retrospective study

Demographic Information

Record ID	_____
Study Code	_____ (MRN)
Event No.	_____
Date of Birth (DOB)	_____
Gender	◯ Male ◯ Female ◯ Unknown
Region (Geographical Location)	◯ Murrumbidgee ◯ Sydney North West ◯ Sydney Hills ◯ Sydney West Central ◯ Sydney South West ◯ Sydney North Coast ◯ Sydney North ◯ Sydney City ◯ Wollongong ◯ Sydney South ◯ Central Coast ◯ Sydney Inner West ◯ Central West ◯ Hunter ◯ Newcastle ◯ South East ◯ North West ◯ Northern ◯ Richmond Tweed ◯ Mid North Coast ◯ Murray ◯ South Coast ◯ Victoria ◯ Queensland ◯ ACT ◯ South Australia ◯ Western Australia ◯ Northern Territory ◯ Overseas/Traveller
Occupation	_____
Which Eye (Left/Right/Bilateral)	◯ Right ◯ Left ◯ Bilateral

Which Eye (this record for bilateral cases)	◯ Right ◯ Left (This field is to indicate which eye is recorded for this record in bilateral cases)
Entered By:	◯ Eamon Brown ◯ Dominic McCall ◯ Nicole Carnt ◯ Stephanie Watson ◯ Dana Robaei ◯ Susan Chin ◯ Maria Cabrera ◯ Shereen Lobb ◯ Pauline Khoo

Patient History

Was the approximate date symptoms started recorded?	◯ Yes ◯ No
When (approximately) did symptoms start?	_____
Did the patient present elsewhere first?	◯ Yes ◯ No
Where did the patient present before this Hospital?	☐ GP ☐ Pharmacy ☐ Other Ophthalmologist ☐ Optometrist
What date (approximately) did the patient first present elsewhere?	_____
Recent Ocular Surgery in affected eye?	◯ Yes ◯ No
Type of Ocular Surgery	☐ Cataract ☐ Corneal Graft ☐ Glaucoma Surgery ☐ Retinal Surgery ☐ Intravitreal injections ☐ Refractive Corneal Surgery (LASIK, LASEK, PRK, RK, PTK) ☐ Pterygium/pinguecular remova ☐ Not recorded ☐ Leave for later ☐ Other
Type of Ocular Surgery-Other	_____
Relevant Systemic Diagnosis	☐ Diabetes ☐ Rheumatoid arthritis ☐ Sjogrens syndrome ☐ HIV/AIDS ☐ Asthma/COPD ☐ Organ Transplant ☐ Thyrotoxicosis ☐ Malnutrition ☐ NONE ☐ Leave for later

Relevant Systemic Medication	☐ Prednisone ☐ Methotrexate ☐ Mycophenolate ☐ Ciclosporin ☐ Hydroxychloroquine (Plaquenil) ☐ Leflunomaide (Arava) ☐ NONE ☐ Not specified ☐ Leave for later
Recent overseas travel within the last 14 days	◯ Yes ◯ No
If yes, what country?	_____
Prior Topical Antimicrobials used in the last 14 days:	☐ G. Chloramphenicol (Chlorsig) ☐ G. Tobramycin ☐ G. Gentamicin ☐ G. Ciprofloxacin ☐ G. Ofloxacin ☐ G. Cephazolin ☐ G. Cephalothin ☐ G. Vancomycin ☐ G. Cefuroxime ☐ G. Penicillin ☐ Oc.Chloramphenicol ☐ Oc.Tobrex ☐ NONE ☐ Not specified ☐ Leave for later ☐ Other
Name of other topical antimicrobial	_____
Still using Topical antimicrobials at presentation	◯ Yes ◯ No ◯ Not recorded

Prior other ocular medication used within the last 14 days:	☐ Oc. Acyclovir (Zorvirax) ☐ Oc. Ganciclovir ☐ G. Trifluorothimidine ☐ PO. Valacyclovir (Valtrex) ☐ PO. Famciclovir ☐ G. Dexamethasone (Maxidex) ☐ G. Dexamethasone Minims ☐ G. Prednisolone acetate (Pred forte) ☐ G. Prednisolone sodium phosphate Minims (Predsol) ☐ G. Fluorometholone (FML Liquifilm/ Flucon) ☐ G. Fluorometholone acetate (Flarex) ☐ G. Hydrocortisone (Hycor Ointment) ☐ G. Ciclosporin ☐ G. Ketorolac trimetamol (Acular) ☐ G. Diclofenac sodium (Voltaren Ophtha) ☐ G. Flurbiprofen sodium (Ocufen) ☐ NONE ☐ Not specified ☐ Leave for later ☐ Other
Name other ocular medication	_____
Still using ocular medication at presentation	◯ Yes ◯ No ◯ Not recorded
Current glaucoma medication:	☐ G. Latanoprost (Xalatan) ☐ G. Bimatoprost (Lumigan) ☐ G. Travaprost (Travatan) ☐ G. Tafluprost (Saflutan) ☐ G. Brinzolamide (Azopt) ☐ G. Dorzolamide (Trusopt) ☐ G. Brimonidine (Alphagan, Alphagan P, Enidin) ☐ G. Apraclonidine (Iopidine) ☐ G. Timolol (Tenopt, Nyogel) ☐ G. Betaxolol (Betoptic) ☐ G. Latanoprost + G. Timolol (Xalacom) ☐ G. Travaprost + G. Timolol (Duotrav) ☐ G. Bimatoprost + G. Timolol (Ganfort) ☐ G. Brinzolamide + G. Timolol (Azarga) ☐ G. Dorzolamide + G. Timolol (Cosopt) ☐ G. Brimonidine + G. Timolol (Combigan) ☐ G. Pilocarpine ☐ NONE ☐ Not specified ☐ Leave for later

Diagnosis work-up

Previous Keratitis (outside 5 year study period) (Do not include Marginal Keratitis - as it is sterile)	◯ No ◯ Yes (NB: Add as separate event if in study time period)
Type of Previous Keratitis	☐ Bacterial ☐ Herpetic (HSV or VZV) ☐ Fungal ☐ Acanthamoeba ☐ Not specified ☐ Leave for later
Foreign Body	◯ Yes ◯ No
Type of Foreign Body	☐ Metallic ☐ Organic (e.g. soil, vegetative matter) ☐ Suture ☐ Other (e.g. Glass) ☐ Not specified
Description type foreign body	_____
Corneal Trauma	◯ No ◯ Yes
Type of Corneal Trauma	☐ Blunt or penetrating ☐ Weapon ☐ Chemical (acid, alkali) ☐ Thermal ☐ Animal ☐ Not recorded ☐ Leave for later
Penetrating/ Non- Penetrating	◯ Penetrating ◯ Non- Penetrating ◯ Unknown
Description corneal trauma	_____
Existing Corneal Disease	◯ No ◯ Yes
Type of Corneal Disease	☐ Dystrophy (e.g. Cogan's, Lattice, Granular) ☐ Transplantation (e.g. DALK, PK, DESK) ☐ Degenerative (e.g. Keratopathy, Salzmann nodules, Keratoconus) ☐ Limbal stem cell failure ☐ Pterygium ☐ Other ☐ Leave for later

Type of Corneal Disease_other	_____
External Eye Disease	◯ No ◯ Yes
Type of External Eye Disease	☐ Blepharitis ☐ Trichiasis ☐ Ocular Rosacea ☐ Toxic (eye drop-related) ☐ MMP ☐ GVHD ☐ Sjogren's Syndrome ☐ Neurotropic cornea (pre-existing HSV, VZV, 5th CN palsy) ☐ Atopic/vernal keratoconjunctivitis ☐ MGD ☐ Dry Eye ☐ Ptosis ☐ Other ☐ Leave for later
Type of External Disease_other	_____

At Presentation (Ocular Medical Only)

Presentation Date	_____
Was patient admitted?	◯ Yes ◯ No
Admission Date	_____
Was Presentation BCVA Recorded?	◯ Yes ◯ No
BCVA Numerator (Affected Eye)	_____
BCVA Denominator (Affected Eye)	_____
BCVA partial (Affected Eye)	_____
BCVA Numerator (Non-affected Eye)	_____
BCVA Denominator (Non -affected Eye)	_____
BCVA Partial (Non- affected Eye)	_____
BCVA aided?	◯ Yes ◯ No ◯ Not recorded ◯ Leave for later
Mode of correction	◯ Glasses ◯ Contact Lenses ◯ Not recorded ◯ Leave for later
Satellite lesions	◯ Yes ◯ No ◯ Leave for later
Hypopyon	◯ Yes ◯ No ◯ Leave for later
Epithelial Defect (ED) Present	◯ Yes ◯ No ◯ Leave for later

ED measured	◯ Yes ◯ No
Ulcer (ED) Major Axis (mm)	_____
Ulcer (ED) Minor Axis (mm)	_____
Corneal Infiltrate Present	◯ Yes ◯ No ◯ Leave for later
Corneal Infiltrate measured	◯ Yes ◯ No ◯ Leave for laler
Largest Corneal Infiltrate Major Axis (mm)	_____
Largest Corneal Infiltrate Minor Axis (mm)	_____
Ring Infiltrate/immune response	◯ Yes ◯ No
Corneal Thining Noted?	◯ Yes_no perforation ◯ Perforated_Seidel +ve ◯ Perforated Seidel negative ◯ No ◯ Leave for later

Contact Lens Wear

Did the patient wear contact lenses in the past month prior to presentation?	◯ Yes ◯ No ◯ Not Recorded
Contact lens Risk Factors noted:	☐ Overnight wear ☐ Water ☐ Poor compliance ☐ No recorded CL related risk factors ☐ Not applicable ☐ Not recorded ☐ Leave for later
Details of CL Risk factors:	_____
What type of CLs were worn in the month leading up to the infection?	☐ Daily Disposable ☐ Weekly - Monthly Disposable ☐ Conventional Soft (disposal> 1 Month) ☐ RGPs ☐ OrthoK ☐ Not applicable ☐ Not recorded ☐ Leave for later
Any other featured notes on CL:	_____

Pathology

Corneal Scrape Performed?	◯ Yes ◯ No ◯ Not applicable ◯ Leave for later
Corneal Scrape Date	_____
Gram Stain Result	☐ Gram Positive ☐ Gram Negative ☐ Pus Cells ☐ Fungi ☐ Negative ☐ Not taken ☐ Results unavailable ☐ Insufficient material on slides
Cultured organism	◯ Yes ◯ No ◯ Results unavailable
Organism Type 1:	_____
Broth culture (organism1)	◯ Yes ◯ No ◯ Not recorded
Sensitivities organism type1	☐ Amoxycillin ☐ Cephalothin/cephazolin ☐ Chloramphenicol ☐ Ciprofloxacin ☐ Clindamycin/Lincomycin ☐ Flucloxacillin/Dicloxacillin ☐ Gentamicin ☐ Penicillin ☐ Ceftazidime ☐ Augmentin ☐ Moxifloxicin ☐ Cefepime ☐ Ticarcillin/clavulanate ☐ Meropenem ☐ Methicillin ☐ Vancomycin ☐ Tazocin ☐ Tobramycin ☐ No information available ☐ Tetracycline ☐ Other
	_____

Resistance organism type1	☐ Amoxycillin ☐ Cephalothin/cephazolin ☐ Chloramphenicol ☐ Ciprofloxacin ☐ Clindamycin/Lincomycin ☐ Flucloxacillin/Dicloxacillin ☐ Gentamicin ☐ Penicillin ☐ Ceftazidime ☐ Augmentin ☐ Moxifloxicin ☐ Cefepime ☐ Ticarcillin/clavulanate ☐ Meropenem ☐ Methicillin ☐ Vancomycin ☐ Tazocin ☐ Tobramycin ☐ No information available ☐ Tetracycline ☐ Other
	_____
Organism Type 2:	_____
Broth culture (organism2)	◯ Yes ◯ No ◯ Not recorded
Sensitivities organism type2	☐ Amoxycillin ☐ Cephalothin/cephazolin ☐ Chloramphenicol ☐ Ciprofloxacin ☐ Clindamycin/Lincomycin ☐ Flucloxacillin/Dicloxacillin ☐ Gentamicin ☐ Penicillin ☐ Ceftazidime ☐ Augmentin ☐ Moxifloxicin ☐ Cefepime ☐ Ticarcillin/clavulanate ☐ Meropenem ☐ Methicillin ☐ Vancomycin ☐ Tazocin ☐ Tobramycin ☐ No information available ☐ Tetracycline ☐ Other
	_____

Resistance organism type2	☐ Amoxycillin ☐ Cephalothin/cephazolin ☐ Chloramphenicol ☐ Ciprofloxacin ☐ Clindamycin/Lincomycin ☐ Flucloxacillin/Dicloxacillin ☐ Gentamicin ☐ Penicillin ☐ Ceftazidime ☐ Augmentin ☐ Moxifloxicin ☐ Cefepime ☐ Ticarcillin/clavulanate ☐ Meropenem ☐ Methicillin ☐ Vancomycin ☐ Tazocin ☐ Tobramycin ☐ No information available ☐ Tetracycline ☐ Other
	_____
Organism Type 3:	_____
Broth culture (organism3)	◯ Yes ◯ No ◯ Not recorded
Sensitivities organism type3	☐ Amoxycillin ☐ Cephalothin/cephazolin ☐ Chloramphenicol ☐ Ciprofloxacin ☐ Clindamycin/Lincomycin ☐ Flucloxacillin/Dicloxacillin ☐ Gentamicin ☐ Penicillin ☐ Ceftazidime ☐ Augmentin ☐ Moxifloxicin ☐ Cefepime ☐ Ticarcillin/clavulanate ☐ Meropenem ☐ Methicillin ☐ Vancomycin ☐ Tazocin ☐ Tobramycin ☐ No information available ☐ Tetracycline ☐ Other
	_____

Resistance organism type3	☐ Amoxycillin ☐ Cephalothin/cephazolin ☐ Chloramphenicol ☐ Ciprofloxacin ☐ Clindamycin/Lincomycin ☐ Flucloxacillin/Dicloxacillin ☐ Gentamicin ☐ Penicillin ☐ Ceftazidime ☐ Augmentin ☐ Moxifloxicin ☐ Cefepime ☐ Ticarcillin/clavulanate ☐ Meropenem ☐ Methicillin ☐ Vancomycin ☐ Tazocin ☐ Tobramycin ☐ No information available ☐ Tetracycline ☐ Other
	_____
Organism Type 4:	_____
Organism Type 5:	_____
Corneal Biopsy taken?	◯ Yes ◯ No
Corneal Biopsy Date	_____
Histology Result from Biopsy or Corneal Button (if taken):	_____
Corneal Biopsy repeated?	◯ Yes ◯ No
Second Corneal Biopsy Date	_____
Histology Result from second Biopsy or Corneal Button (if taken):	_____
PCR Date	_____
PCR Performed?	◯ Yes ◯ No ◯ Not applicable ◯ Not recorded ◯ Leave for later

PCR Result	☐ Negative ☐ Positive - Fungal ☐ Positive - Acanthamoeba ☐ Positive - HSV ☐ Not recorded
Confocal Microscopy performed?	◯ Yes ◯ No
Confocal Microscopy Date	_____
Confocal Result	☐ Hyphae - Probable ☐ Hyphae - Possible ☐ Hyphae - No ☐ Acanthamoeba - Probable ☐ Acanthamoeba - Possible ☐ Acanthamoeba - No
AC Tap taken?	◯ Yes ◯ No
AC Tap Date	_____
AC Tap Result	_____
Vitreous Biopsy Taken?	◯ Yes ◯ No
Vitreous Biopsy Date	_____
Vitreous Biopsy Result	_____
Was corneal scrape repeated?	◯ Yes ◯ No
Repeat corneal scrape date:	_____
Organism growth on repeat corneal scrape:	◯ Yes ◯ No ◯ Result unavailable ◯ Leave for later
Organism on 2nd corneal scrape:	_____
Broth culture (2nd scrape, organism 1)	◯ Yes ◯ No ◯ Not recorded

Sensitivities organism 2scrape	☐ Amoxycillin ☐ Cephalothin/cephazolin ☐ Chloramphenicol ☐ Ciprofloxacin ☐ Clindamycin/Lincomycin ☐ Flucloxacillin/Dicloxacillin ☐ Gentamicin ☐ Penicillin ☐ Ceftazidime ☐ Augmentin ☐ Moxifloxicin ☐ Cefepime ☐ Ticarcillin/clavulanate ☐ Meropenem ☐ Methicillin ☐ Vancomycin ☐ Tazocin ☐ Tobramycin ☐ No information available ☐ Tetracycline ☐ Other
	_____
Resistance organism 2scrape	☐ Amoxycillin ☐ Cephalothin/cephazolin ☐ Chloramphenicol ☐ Ciprofloxacin ☐ Clindamycin/Lincomycin ☐ Flucloxacillin/Dicloxacillin ☐ Gentamicin ☐ Penicillin ☐ Ceftazidime ☐ Augmentin ☐ Moxifloxicin ☐ Cefepime ☐ Ticarcillin/clavulanate ☐ Meropenem ☐ Methicillin ☐ Vancomycin ☐ Tazocin ☐ Tobramycin ☐ No information available ☐ Tetracycline ☐ Other
	_____
Organism2 on 2nd corneal scrape:	_____
Broth culture (2nd scrape, organism 2)	◯ Yes ◯ No ◯ Not recorded

Sensitivities organism2_ 2scrape	☐ Amoxycillin ☐ Cephalothin/cephazolin ☐ Chloramphenicol ☐ Ciprofloxacin ☐ Clindamycin/Lincomycin ☐ Flucloxacillin/Dicloxacillin ☐ Gentamicin ☐ Penicillin ☐ Ceftazidime ☐ Augmentin ☐ Moxifloxicin ☐ Cefepime ☐ Ticarcillin/clavulanate ☐ Meropenem ☐ Methicillin ☐ Vancomycin ☐ Tazocin ☐ Tobramycin ☐ No information available ☐ Tetracycline ☐ Other
	_____
Resistance organism2_ 2scrape	☐ Amoxycillin ☐ Cephalothin/cephazolin ☐ Chloramphenicol ☐ Ciprofloxacin ☐ Clindamycin/Lincomycin ☐ Flucloxacillin/Dicloxacillin ☐ Gentamicin ☐ Penicillin ☐ Ceftazidime ☐ Augmentin ☐ Moxifloxicin ☐ Cefepime ☐ Ticarcillin/clavulanate ☐ Meropenem ☐ Methicillin ☐ Vancomycin ☐ Tazocin ☐ Tobramycin ☐ No information available ☐ Tetracycline ☐ Other
	_____

Initial Anti--Infective Treatment

Anti-microbial Start Date	_____
Topical/Oral Antimicrobials	☐ None ☐ G. Chloramphenicol ☐ G. Tobramycin ☐ G. Gentamicin ☐ G. Ciprofloxacin ☐ G. Ofloxacin ☐ G. CephaZOLIN ☐ G. CephaLOTHIN ☐ G. Vancomycin ☐ G. Cefuroxime ☐ G. Penicillin ☐ P.O. Ciprofloxacin ☐ Oc Tobramycin (Tobrex) ☐ Oc Chloramphenicol ☐ Other
Other topical/ral antimicrobial	_____
Ocular Specific Medication	☐ None ☐ Oc. Acyclovir (Zovirax) ☐ Oc. Ganciclovir ☐ G. Trifluorothymidine ☐ PO. Acyclovir ☐ PO. Valacyclovir (Valtrex) ☐ PO. Famciclovir ☐ PO. Doxycycline ☐ G. Homatropine ☐ G. Atropine ☐ G. Cyclopentolate ☐ G. Tropicamide ☐ IV Ceftriaxone ☐ PO Azithromycin ☐ Other
Other ocular antimicrobial	_____
Anti-inflammatories	☐ None ☐ G. Dexamethasone (Maxidex) ☐ G. Prednisolone acetate (Pred forte) ☐ G. Prednisolone sodium phosphate Minims (Predsol) ☐ G. Fluorometholone (FML Liquifilm/ Flucon) ☐ G. Fluorometholone acetate (Flarex) ☐ G. Dexamethasone Minims ☐ G. Hydrocortisone (Hycor Ointment) ☐ G. Ciclosporin ☐ G. Ketorolac trimetamol (Acular) ☐ G. Diclofenac sodium (Voltaren Ophtha) ☐ G. Flurbiprofen sodium (Ocufen) ☐ P.O. Prednisolone ☐ IV Methyl Prednisolone

Antifungals used:	☐ G. Natamycin ☐ G. Voriconazole ☐ G. Amphotericin ☐ PO. Voriconazole ☐ Interstromal Voriconazole ☐ IV. Amphotericin ☐ IV. Caspofungin ☐ None ☐ PO Fluconazole
Topical Antiamoebic Medication	☐ G. PHMB ☐ G. Chlorexidine ☐ G. Propamidine (Brolene) ☐ None

Adjunctive Anti_Inflammatory Treatment

Steroid used during treatment	◯ Yes ◯ No ◯ Leave for later
Date Topical steroid during treatment phase started?	_____
Date Topical steroid during treatment phase stopped?	_____
Topical Steroids first used	☐ G. Dexamethasone (Maxidex) ☐ G. Prednisolone acetate (Pred forte) ☐ G. Prednisolone sodium phosphate Minims (Predsol) ☐ G. Fluorometholone (FML Liquifilm/ Flucon) ☐ G. Fluorometholone acetate (Flarex) ☐ G. Dexamethasone Minims ☐ G. Hydrocortisone (Hycor Ointment)
Topical Steroid changes	☐ None ☐ G. Dexamethasone (Maxidex) ☐ G. Prednisolone acetate (Pred forte) ☐ G. Prednisolone sodium phosphate Minims (Predsol) ☐ G. Fluorometholone (FML Liquifilm/ Flucon) ☐ G. Fluorometholone acetate (Flarex) ☐ G. Dexamethasone Minims ☐ G. Hydrocortisone (Hycor Ointment)
Other Anti-inflammatories used	☐ None ☐ G. Ciclosporin ☐ G. Ketorolac trimetamol (Acular) ☐ G. Diclofenac sodium (Voltaren Ophtha) ☐ G. Flurbiprofen sodium (Ocufen) ☐ P.O. Prednisolone ☐ IV Methyl Prednisolone ☐ Mycophenolate ☐ Other
Name other anti-inflammatory	_____

Anti-Infective Changes?

Other Anti-Infective Medications used during treatment phase?	◯ Yes ◯ No
Changes in Topical Antimicrobial	☐ None ☐ G. Chloramphenicol ☐ G. Tobramycin ☐ G. Gentamicin ☐ G. Ciprofloxacin ☐ G. Ofloxacin ☐ G. Cephazolin ☐ G. Cephalothin ☐ G. Vancomycin ☐ G. Cefuroxime ☐ G. Penicillin ☐ P.O. Ciprofloxacin ☐ Oc. Tobramycin (Tobrex) ☐ Oc. Chloramphenicol ☐ Other
Other topical antimicrobial	_____
Changes in Ophthalmic Specific Medication	☐ None ☐ Oc. Acyclovir (Zovirax) ☐ Oc.Ganciclovir ☐ G. Trifluorothymidine ☐ PO. Valacyclovir (Valtrex) ☐ PO. Famciclovir ☐ PO. Doxycycline ☐ PO. Acyclovir ☐ G. Homatropine ☐ G. Atropine ☐ G. Cyclopentolate ☐ G. Tropicamide ☐ G. Amikacin ☐ G. Moxifloxacin ☐ PO. Claritromicin ☐ IV Ceftriaxone ☐ PO Azithromycin ☐ PO Metronidazole ☐ Other
Other ophthalmic medication	_____
Changes in Topical Antifungals	☐ G. Natamycin ☐ G. Voriconazole ☐ G. Amphotericin ☐ PO. Voriconazole ☐ Interstromal Voriconazole ☐ IV. Amphotericin ☐ IV. Caspofungin ☐ None ☐ PO Fluconazole

Changes in Topical Antiamoebic Medication	☐ G. PHMB ☐ G. Chlorexidine ☐ G. Propamidine (Brolene) ☐ None

Final Outcome

Surgery to preserve anatomy (tectonic)?	☐ No Surgery Required ☐ Penetrating Keratoplasty ☐ DALK ☐ LK ☐ Leave for later
Date of tectonic surgery	_____
Surgery to improve vision required?	☐ No Surgery Required ☐ Penetrating Keratoplasty ☐ DALK ☐ Refractive Corneal Surgery (LASIK, LASEK, PRK, RK, PTK) ☐ Leave for later ☐ DSEK
Date of vision improvement surgery	_____
Was Final BCVA Recorded?	◯ Yes ◯ No
(Fin) BCVA - Affected Eye (Num)	_____
(Fin) BCVA - Affected Eye (Den)	_____
(Fin) BCVA - Affected Eye (Par)	_____
(Fin) BCVA - Non- affected Eye (Num)	_____
(Fin) BCVA - Non- affected Eye (Den)	_____
(Fin) BCVA - Non - affected Eye (Par)	_____
BCVA aided?	◯ Yes ◯ No ◯ Not recorded ◯ Leave for later
Mode of correction	◯ Glasses ◯ Contact Lenses ◯ Not recorded ◯ Leave for later
Date BCVA recorded	_____

Complication type	☐ Corneal perforation requiring glue ☐ Corneal perforation requiring transplant or graft ☐ Non-healing epithelial defect needing botox ptosis ☐ Non-healing epithelial defect needing temporary tarsorrhaphy ☐ Non- healing epithelial defect needing amniotic membrane graft ☐ Endophthalmitis requiring eviseration ☐ Endophthalmitis needing intravitreal antimicrobials or antifungals ☐ Glaucoma needing drainage device or trabeculectomy or cycloablation ☐ Descemetocele formation ☐ IOP rise requiring topical management ☐ IOP rise requiring oral management ☐ Acute Cataract ☐ Scleritis ☐ Non resolving infection requiring transplantation ☐ Other ☐ NO COMPLICATIONS
Other Complications	_____
Did the epitheliel defect resolved?	◯ Yes ◯ No ◯ Unknown
Re-epithelialised date	_____
Was antimicrobial cease date recorded in an outpatient clinic or during discharge?	◯ Yes ◯ No
Date all Antimicrobials ceased:	_____
Total duration of antimicrobial use (days)	_____
Final Corneal Thinning	◯ Yes ◯ No ◯ Unknown
New Vascularisation Present	◯ Yes ◯ No ◯ Not recorded ◯ Leave for later ◯ Unknown
Vascularisation Type	☐ Not specified ☐ Superficial ☐ Deep
Vascularisation_Number of quadrants	_____

Scar	◯ Yes ◯ No ◯ Unknown
Was scar measured?	◯ Yes ◯ No
Scar Major Axis (mm)	_____
Scar Minor Axis (mm)	_____
Inpatient Discharge Date	_____
Did the patient have readmission due to the same event?	◯ Yes ◯ No
Date readmission 1	_____
Date discharge admission 1	_____
Date readmission 2	_____
Date discharge admission 2	_____
Number of Clinic visits at last Hospital visit (when infection was resolved)?	_____
Followed up in Rooms?	◯ Yes ◯ No
Lost to follow up (Did not attend last Hospital scheduled visit)?	◯ Yes ◯ No
Date of Last Hospital Visit (when infection was resolved)?	_____
Comments	_____

Appendix K - Herpes simplex keratitis treatment guidelines awareness survey

1. What is your role at the hospital?
    a. Consultant
    b. Fellow
    c. Registrar
    d. Resident

2. Have you treated patients with herpes simplex keratitis (HSK) in the last 6 months (1 June to November 30, 2017)?
    a. Yes
    b. No

3. How did you hear about the Sydney Eye Hospital's 'Herpes Simplex Keratitis treatment guidelines'?
    a. Have not heard
    b. Registrar talk at Claffy Theatre in June 2017
    c. Received lanyard card
    d. Word of mouth
    e. As a PDF attachment via email
    f. A4 posters in emergency and consultation rooms
    g. Sydney Eye Hospital Intranet
    h. A4-size laminated sheet, lanyard card and invitation letter.

4. How did you receive the Sydney Eye Hospital's 'Herpes simplex keratitis treatment guidelines' lanyard card?
    a. Have not received lanyard card
    b. Registrar talk at Claffy Theatre in June 2017
    c. Via post
    d. Via pharmacist
    e. Via registrar
    f. Via specialist
    g. Via fellow

5. Are you aware that the Sydney Eye Hospital's 'Herpes simplex keratitis treatment guidelines' are accessible on the following sources (chose all that apply)?
    a. Lanyard card
    b. A4-size poster in emergency consultation rooms

c. A4-size poster in consultation rooms at Bicentennial Clinic and Sydney Eye Hospital outpatient clinic
d. A4-size poster on examination room at wards
e. Sydney Eye Hospital intranet
f. Not aware

6. What sources do you use to review the Sydney Eye Hospital's 'Herpes simplex keratitis treatment guidelines'?
    a. Lanyard card
    b. A4-size poster in emergency consultation rooms
    c. A4-size poster in consultation rooms at Bicentennial Clinic and Sydney Eye Hospital outpatient clinic
    d. A4-size poster in examination room at wards
    e. PDF file
    f. Sydney Eye Hospital intranet
    g. Don not use the treatment guidelines

7. How often do you use the Sydney Eye Hospital's 'Herpes simplex keratitis treatment guidelines'?
    a. Never
    b. Rarely
    c. 1-2 times a month
    d. 1-2 times a fortnight
    e. 1-2 times a week
    f. Daily
8. What sections of the Sydney Eye Hospital's 'Herpes simplex keratitis treatment guidelines' have you consulted?
    a. Epithelial HSK
    b. Stromal HSK
    c. Endothelial HSK
    d. Keratouveitis
    e. HSK prophylaxis
    f. Renal dosing for oral antivirals
    g. Use in pregnancy
    h. Paediatric local treatment
    i. Paediatric systemic treatment

9. Any suggestions for implementing the guidelines: _____

Appendix L - Ethics committee approval to third amendment

NSW GOVERNMENT Health
South Eastern Sydney Local Health District

HUMAN RESEARCH ETHICS COMMITTEE
Room G71 East Wing
Edmund Blacket Building
Prince of Wales Hospital
RANDWICK NSW 2031
Tel: 02 9382 3587 Fax: 02 9382 2813
SESLHD-RSO@health.nsw.gov.au
www.seslhd.health.nsw.gov.au/POWH/researchsupport

13 December 2017

Dr Maria Cabrera Aguas
c/o Clinical Professor Stephanie Watson
Ophthalmology - Save Sight Institute
South Block, Sydney Eye Hospital
8 Macquarie St
SYDNEY NSW 2000

Dear Dr Cabrera Aguas

HREC ref no: 13/296 (LNR/13/POWH/596)
Project title: Clinical translation of recommendations from randomized trials for management of herpes simplex keratitis.

Thank you for correspondence dated 01 December 2017 to the Human Research Ethics Committee (HREC). Standard Operating Procedures allow the Executive Officer to review administrative and minor matters.

I am pleased to advise that the following documentation has been approved:

- Amendment form dated 01 December 2017

Ethics approval is valid for the following site(s):

- Sydney Eye Hospital

This amendment has also been reviewed by the Research Governance Officer at SESLHD. Further authorisation of the above approved documents is not required for any site that has the Research Governance conducted by the SESLHD Research Support Office. Implementation of this amendment can now proceed.

For multi-site projects reviewed by the HREC after 1 January 2011 a copy of this letter must be forwarded to all Principal Investigators at every site approved by the SESLHD HREC for submission to the relevant Research Governance Officer along with a copy of the approved documents.

Prince of Wales Hospital
Community Health Services
Barker Street
Randwick NSW 2031

Should you have any queries, please contact the Research Support Office on (02) 9382 3587. The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Research Support Office website: www.seslhd.health.nsw.gov.au/POWH/researchsupport/ .

Please quote **13/296** in all correspondence.

We wish you every success in your research.

[redacted]

Andrew Bohlken
Executive Officer, Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*, NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

Appendix M - Herpes simplex keratitis prescribing protocol for the hospital intranet (version 1)

Herpes Simplex Keratitis Prescribing Protocol

Title	Prescribing Protocol for the Treatment of Herpes Simplex Keratitis
Areas where Protocol/Guideline **applicable**	Ophthalmology
Areas where Protocol/Guideline **not applicable**	Non Ophthalmology
Authorised Prescribers:	Corneal Unit
Indication for use	Herpes Simplex keratitis and keratouveitis
Clinical condition Patient selection: Inclusion criteria (list investigations necessary and relevant results)	Diagnosis based on clinical findings Criteria: • Epithelial keratitis: dendritic ulcer • Stromal keratitis: Vascularisation, scarring, lipid keratopathy, ulceration • Endothelial keratitis: Stromal oedema and keratitic precipitates • Keratouveitis: Corneal epithelial and/or stromal edema, stromal keratitis, keratic precipitates, and anterior chamber cells. Investigations: Herpes simplex virus (HSV) PCR
Contra-indications	**Allergy** to aciclovir or valaciclovir
Precautions	**Renal** • Increased risk of neurological adverse effects in renal impairment • dose adjustment is required **Pregnancy** • Valaciclovir is metabolised rapidly to aciclovir; limited data do not suggest an increased risk of congenital malformations, **however, aciclovir is preferred as there is more clinical experience** valaciclovir may be used from 36 weeks of pregnancy **Breastfeeding** • Safe to use
Proposed Place in Therapy State whether drug to be used as first, second or third line. Where not first line describe therapies to be used first. (Consider using algorithm)	First line of therapy
If part of combination therapy then list other drugs	

Dosage (Include dosage adjustment for specific patient groups)	**ADULT DOSING** **Epithelial HSK** *Local treatment:* **Topical aciclovir 5 times a day for 14 days** *Systemic treatment:* • Immunocompromised patients • Non-compliance, inability to use or tolerate, or ocular toxicity from topical aciclovir **Valaciclovir 500 mg BD for 7 days** **Stromal HSK** *Without epithelial ulcer:* **Valaciclovir 500 mg ONCE a day** during topical steroid use PLUS **Prednefrin Forte eye drops 4-6 times a day** tapered over > 10 weeks *With epithelial ulcer:* Valaciclovir 1 g TDS for 7-10 days * PLUS Prednefrin Forte eye drops BD tapered slowly as disease comes under control **Endothelial HSK** **Valacicovir 1 g TDS for 7-10 days*** **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over > 10 weeks **Keratouveitis** **Valaciclovir 1 g TDS for 7-10 days*** **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over > 10 weeks Refer patient to cornea/uveitis clinic, respectively depending on degree of cornea or uveal involvement **Prophylaxis** Indications: • Multiple recurrences of any type of HSK, especially stromal HSK • Patients with a history of ocular HSV: ➢ following any ocular surgery, including penetrating keratoplasty ➢ during immunosuppressive treatment **Aciclovir 400 mg BD** **OR** **Valaciclovir 500 mg ONCE a day** * **Reduce Valaciclovir to prophylactic dose after 7-10 days and maintain for as long as frequent topical steroids are in use**

ADULT RENAL DOSING FOR ORAL ANTIVIRALS

Adult Renal Dosing for oral antivirals		
CrCl (mL/min)	**Dose**	**Frequency**
Normal dosage Valaciclovir 500 mg ONCE a day		
<30	500 mg	Every 48 hours
Normal dosage Valaciclovir 500 mg BD		
<30	500 mg	Every 24 hours
Normal dosage Valaciclovir 1 g TDS		
30-49	1 g	Every 12 hours
10-29	1 g	Every 24 hours
<10	500 mg	Every 24 hours
Normal dosage Aciclovir 400 mg BD		
0-10	200 mg	Every 12 hours

USE IN PREGNANCY

Aciclovir – Preferred due to more clinical experience. Category B3.

Valaciclovir – Limited data do not suggest an increased risk of congenital malformations. May be used from 36 weeks of pregnancy. Category B3.

PAEDIATRIC DOSING

- Aciclovir is the drug of choice
- Valaciclovir must only be used in children >12 years old

Local Treatment

3 months to 18 years

Epithelial HSK:

Topical aciclovir 5 times a day for 14 days[1,2] or for at least **3 days** after healing, whichever is shorter

Systemic Treatment

Indications:

- Stromal HSK
- Skin involvement
- Coexistent systemic disease
- Non-compliance, inability to use or tolerate, or ocular toxicity from topical aciclovir
- Immunocompromised patients – seek advice from a Paediatric Infection Diseases Physician

Birth (at term) to 3 months

Seek advice from a Paediatric Infection Diseases Physician

3 months to 12 years

Oral aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days[1] or until there are no new lesions

PLUS

Prednefrin Forte eye drops BD-QID a day. (For severe inflammation, consider hourly dosing for 1-2 days [1])

	12 years to 18 years **Oral aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days**[1] or until there are no new lesions **OR** **Valaciclovir 500 mg BD for 5 days**[2] if first episode (longer if new lesions appear during treatment or healing is incomplete) **Valaciclovir 500 mg BD for 3-5 days**[2] if recurrent episode **PLUS** **Prednefrin Forte eye drops BD-QID a day**. (For severe inflammation, consider hourly dosing for 1-2 days[1]) [1] Dosages taken from Australian Medical Handbook Children's Dosing Companion [2] Dosages taken from British National Formulary for children
Duration of therapy	See **Dosage** above
Important Drug Interactions	**Mycophenolate** • Mycophenolate may increase aciclovir/valaciclovir concentration; renal excretion of both drugs may be reduced in renal impairment, may increase risk of adverse effects, e.g. neutropenia; dosage adjustment not usually necessary **Theophylline** • Aciclovir/valaciclovir may increase theophylline concentration and risk of adverse effects; monitor theophylline concentration and for adverse effects; decrease theophylline dose as needed
Administration instructions	• With systemic treatment, ensure adequate hydration (especially if receiving high doses) to minimise renal adverse effects • Patient to be advised to take tablets with a full glass of water • Need to ensure patients have the correct technique for administration for eye drops / ointment

Monitoring requirements	Patient needs to be reviewed by ophthalmologist once the therapy has started according to the guidelines.
Safety	***Blood and lymphatic system disorders:*** Very rare: anaemia, leukopenia, thrombocytopenia. ***Immune system disorders:*** Rare: anaphylaxis. ***Psychiatric and nervous system disorders:*** Common: headache, dizziness, confusion, hallucinations, somnolence, convulsions. Very rare: agitation, tremor, ataxia, dysarthria, psychotic symptoms, encephalopathy, coma. The above events are reversible and usually reported in patients with renal impairment in whom the dosage was in excess of that recommended, or with other predisposing factors. ***Respiratory, thoracic and mediastinal disorders:*** Rare:dyspnoea. ***Gastrointestinal disorders:*** Common: nausea, vomiting, diarrhoea, abdominal pains. ***Hepatobiliary disorders:*** Rare: reversible rises in bilirubin and liver related enzymes. Very rare: hepatitis, jaundice. ***Skin and subcutaneous tissue disorders:*** Common: pruritus, rashes (including photosensitivity). Uncommon: urticaria, accelerated diffuse hair loss. Rare: angioedema. ***Renal and urinary disorders:*** Rare: increases in blood urea and creatinine. Very rare: acute renal failure, renal pain. Renal pain may be associated with renal failure. ***General disorders:*** Common: fatigue, fever.
Effectiveness (state objective criteria)	Improvement of vision acuity and of clinical signs including: • Resolution of epithelial defect or punctate corneal staining • Reduction in inflammation of cornea stromal or anterior chamber • Resolution stromal infiltrates
Management of complications	• Changes in renal function during systemic treatment usually responds to rehydration, dosage reduction or stopping the drug

Basis of Protocol/Guideline: (including sources of evidence, references)	1. Herpes Simplex Virus keratitis: a treatment guideline. Michelle Lee White and James Chodosh. Department of Ophthalmology, Harvard Medical School. June 2014 2. Guess S, Stone DU, Chodosh J. Evidence-Based Treatment of Herpes Simplex Virus Keratitis: A Systematic Review. The Ocular Surface. 2007; 5(3):240-50. 3. Barron BA, Gee L, Hauck WW, Kurinij N, Dawson CR, Jones DB, et al. Herpetic Eye Disease Study. A controlled trial of oral acyclovir for herpes simplex stromal keratitis. Ophthalmology. 1994;101(12):1871-82. 4. A controlled trial of oral acyclovir for the prevention of stromal keratitis or iritis in patients with herpes simplex virus epithelial keratitis. The Epithelial Keratitis Trial. The Herpetic Eye Disease Study Group. Arch Ophthalmol. 1997;115(6):703-12. 5. Acyclovir for the prevention of recurrent herpes simplex virus eye disease. Herpetic Eye Disease Study Group. N Engl J Med. 1998;339(5):300-6. 6. Australian Medical Handbook Children's Dosing Companion 7. British National Formulary for children
Groups consulted in development of this guideline	Cornea and uveitis teams Sydney/Sydney Eye Hospital Pharmacy Sydney/Sydney Eye Hospital

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GOVERNANCE	
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Chairperson, Drug and Therapeutics Committee	Signature _____ Name Dr P. Rumma Date 19.12.16
Approved Protocol/Guideline distributed#	Signature _____ Name Dr P Rumma Date 04.07.17 (designated authority)
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Protocol/Guideline Number (issued by DTC)	SSEH Protocol: 002
Version Number (issued by DTC)	Version 0

Note: All formulary submissions should be accompanied by a prescribing protocol or guideline. This form may be used to record the prescribing protocol. It should be completed and submitted with the formulary submission form to the Director of Pharmacy.

Appendix N - Herpes simplex keratitis prescribing protocol for the hospital intranet (version 2)

Herpes Simplex Keratitis Prescribing Protocol

Title	Prescribing Protocol for the Treatment of Herpes Simplex Keratitis
Areas where Protocol/Guideline **applicable**	Ophthalmology
Areas where Protocol/Guideline **not applicable**	Non Ophthalmology
Authorised Prescribers:	Corneal Unit
Indication for use	Herpes Simplex keratitis and keratouveitis
Clinical condition Patient selection: Inclusion criteria (list investigations necessary and relevant results)	Diagnosis based on clinical findings Criteria: • Epithelial keratitis: dendritic ulcer • Stromal keratitis: Vascularisation, scarring, lipid keratopathy, ulceration • Endothelial keratitis: Stromal oedema and keratitic precipitates • Keratouveitis: Corneal epithelial and/or stromal edema, stromal keratitis, keratic precipitates, and anterior chamber cells. Investigations: Herpes simplex virus (HSV) PCR
Contra-indications	**Allergy** to aciclovir or valaciclovir
Precautions	**Renal** • Increased risk of neurological adverse effects in renal impairment • dose adjustment is required **Pregnancy** • Valaciclovir is metabolised rapidly to aciclovir; limited data do not suggest an increased risk of congenital malformations, **however, aciclovir is preferred as there is more clinical experience** valaciclovir may be used from 36 weeks of pregnancy **Breastfeeding** • Safe to use
Proposed Place in Therapy State whether drug to be used as first, second or third line. Where not first line describe therapies to be used first. (Consider using algorithm)	First line of therapy
If part of combination therapy then list other drugs	

Dosage (Include dosage adjustment for specific patient groups)	**ADULT DOSING** **Epithelial HSK** *Local treatment:* **Topical aciclovir 5 times a day for 7-10 days** *Systemic treatment:* • Immunocompromised patients • Non-compliance, inability to use or tolerate, or ocular toxicity from topical aciclovir **Oral Valaciclovir 500 mg BD for 7 days** **Stromal HSK** *Without epithelial ulcer:* **Oral Valaciclovir 500 mg ONCE a day** during topical steroid use PLUS **Prednefrin Forte eye drops 4-6 times a day** tapered over > 10 weeks *With epithelial ulcer:* Oral Valaciclovir 1 g TDS for 7-10 days * PLUS Prednefrin Forte eye drops BD tapered slowly as disease comes under control **Endothelial HSK** **Oral Valacicovir 500mg daily to 1 g TDS for 7-10 days†** **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over > 10 weeks **Keratouveitis** **Oral Valaciclovir 1 g TDS for 7-10 days*** **PLUS** **Prednefrin Forte eye drops 4-6 times a day** tapered over > 10 weeks Refer patient to cornea/uveitis clinic, respectively depending on degree of cornea or uveal involvement **Prophylaxis** Indications: • Multiple recurrences of any type of HSK, especially stromal HSK • Patients with a history of ocular HSV: ➢ following any ocular surgery, including penetrating keratoplasty ➢ during immunosuppressive treatment **Oral Aciclovir 400 mg BD** **OR** **Oral Valaciclovir 500 mg ONCE a day** *** Reduce Valaciclovir to prophylactic dose after 7-10 days and maintain for as long as frequent topical steroids are in use** **†There is a lack of clinical evidence to guide dosage in this situation**

ADULT RENAL DOSING FOR ORAL ANTIVIRALS

Adult Renal Dosing for oral antivirals		
CrCl (mL/min)	**Dose**	**Frequency**
Normal dosage Valaciclovir 500 mg ONCE a day		
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3 months to 18 years

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Indications:

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Birth (at term) to 3 months

Seek advice from a Paediatric Infection Diseases Physician

3 months to 12 years

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PLUS

Prednefrin Forte eye drops BD-QID a day. (For severe inflammation, consider hourly dosing for 1-2 days [1])

	12 years to 18 years **Oral aciclovir 10 mg/kg (max 400 mg) 5 times a day for 5-7 days**[1] or until there are no new lesions **OR** **Oral Valaciclovir 500 mg BD for 5 days**[2] if first episode (longer if new lesions appear during treatment or healing is incomplete) **Oral Valaciclovir 500 mg BD for 3-5 days**[2] if recurrent episode **PLUS** **Prednefrin Forte eye drops BD-QID a day**. (For severe inflammation, consider hourly dosing for 1-2 days[1]) [1] Dosages taken from Australian Medical Handbook Children's Dosing Companion [2] Dosages taken from British National Formulary for children
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Groups consulted in development of this guideline	Cornea and uveitis teams Sydney/Sydney Eye Hospital Pharmacy Sydney/Sydney Eye Hospital

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GOVERNANCE	
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Chairperson, Drug and Therapeutics Committee	Signature _____ Name Dr P. Rumma Date _____
Approved Protocol/Guideline distributed#	Signature _____ (designated authority) Name Dr P Rumma Date _____
#Note Protocol/Guideline must be distributed in a format which prevents modification eg. PDF file	
Location	SSEH policy page
Protocol/Guideline Number (issued by DTC)	SSEH Protocol: 002
Version Number (issued by DTC)	Version 1

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