capriCORN - Comprehensive Analysis of Pathogens, Resistomes, and Inflammatory-markers in the Cornea

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In this proposal, we will collect samples from both US and international corneal ulcers, identify etiology, AMR, and local host immune response, and correlate with presentation and outcome.Specific Aim 1. Worldwide surveillance of organisms...

Ethical review	Approved WMO
Status	Pending
Health condition type	Ocular infections, irritations and inflammations
Study type	Observational non invasive

Summary

ID

NL-OMON57312

Source
ToetsingOnline

Brief title
Improving Corneal Ulcer Outcomes with Pathogen and AMR Detection

Condition

- Ocular infections, irritations and inflammations

Synonym
infectious keratitis; corneal ulcer

Research involving
Human

Sponsors and support

Primary sponsor: Francis I. Proctor Foundation/University of California San Francisco (UCSF)
Source(s) of monetary or material Support: University of California

Intervention

Keyword: Antimicrobial resistance, Corneal infection, Metagenomic deep sequencing

Outcome measures

Primary outcome

1. Worldwide surveillance of organisms responsible for infectious keratitis.

- To identify pathogens causing infectious keratitis in an unbiased manner with MDS.

- To determine the optimal diagnostic technique (stains, cultures, MDS) for corneal ulcers.

- To determine the effect of seasonality on pathogen profile and visual outcomes.

Secondary outcome

2. Worldwide surveillance of antimicrobial resistance (AMR) in corneal ulcer pathogens.

- To determine the frequency and richness of AMR in pathogens causing keratitis.

- To determine AMR genotype and phenotype correlation with clinical outcomes.

3. To define host immune response transcriptional profiles in keratitis.

- To determine the host transcriptional signatures for pathogen types.

- To determine the host transcriptional signatures for clinical outcomes.

Study description

Background summary

Undiagnosed corneal infection leads to blindness. Worldwide, vision loss from corneal ulcers is a major public health problem. Identification of causative organisms is key in the treatment of any infectious disease, yet many corneal infections go undiagnosed. Empirical treatment of infectious keratitis for a presumed organism is the rule not the exception. Only a minority of corneal infections are actually cultured. More accurate identification of the cause of infectious ulcers can help lower the burden of vision loss from corneal ulcers.

Global surveillance of corneal infections is needed. The cause of corneal ulcers varies widely by location. Climatic, geographic, season, cultural, and economic differences all contribute to this variability. Awareness of the most common organisms in a region can guide initial therapy while lab tests are pending, or where labs are not available. As the prior information, knowledge of the likely spectrum of organisms in a region can even improve the interpretation of indeterminate lab results.

Metagenomic deep sequencing (MDS) is transforming infectious disease diagnostics. Traditional corneal ulcer smear and culture have limited sensitivity and cannot identify a number of etiologies. Targeted nucleic acid amplification tests can be sensitive but requires clinical suspicion of a specific etiology. MDS allows for the identification of pathogen, whether anticipated or not. In fact, the sequence can add to our knowledge about the pathogen. For example, microsporidia was previously classified as an intracellular parasite but now is identified as a fungus. MDS also allows for identification of pathogens at the subspecies level. Subspecies variability has been associated with clinical outcome in many diseases, including Fusarium keratitis.

Antimicrobial resistance (AMR) is increasing in keratitis. Decreased susceptibility to an antimicrobial predicts worse visual outcomes in both bacterial and fungal keratitis. The same MDS analysis that reveals the organism also provides known AMR determinants for the identified organism. Cataloging AMR in infectious keratitis over different regions can facilitate appropriate initial treatment. Global surveillance of AMR patterns may prevent vision loss.

Characterization of host response transcription signatures may aid in pathogen identification and clarify disease outcome. If surface samples of the cornea fail to reveal a deeper stromal infection, deep sequencing the host immune response transcriptome may reveal a fingerprint characteristic of bacterial, fungal, parasitic, or viral infection. The transcriptional profile may also predict which cases are more likely to perforate.

Study objective

In this proposal, we will collect samples from both US and international corneal ulcers, identify etiology, AMR, and local host immune response, and correlate with presentation and outcome.

Specific Aim 1. Worldwide surveillance of organisms responsible for infectious keratitis.
SA 1A: To identify pathogens causing infectious keratitis in an unbiased manner with MDS.
SA 1B: To determine the optimal diagnostic technique (stains, cultures, MDS) for corneal ulcers.
SA 1C: To determine the effect of seasonality on pathogen profile and visual outcomes.

We hypothesize the spectrum of etiology will vary significantly by geographic location, and novel organisms not typically associated with infectious keratitis will be identified with MDS. In the absence of a diagnostic gold standard, we hypothesize the use of latent class analysis (LCA) will predict MDS affords the highest sensitivity compared to other tests. Furthermore, we hypothesize that geographic location and seasonality will affect pathogen profile and disease outcomes.

Specific Aim 2. Worldwide surveillance of antimicrobial resistance (AMR) in corneal ulcer pathogens.
SA 2A: To determine the frequency and richness of AMR in pathogens causing keratitis.
SA 2B: To determine AMR genotype and phenotype correlation with clinical outcomes.

We hypothesize that AMR will differ by geographic location and that genotypic AMR profiles will predict clinical outcomes.

Specific Aim 3. To define host immune response transcriptional profiles in keratitis.
SA 3A: To determine the host transcriptional signatures for pathogen types.
SA 3B: To determine the host transcriptional signatures for clinical outcomes.

We hypothesize that host transcriptome signatures can differentiate between bacterial, fungal, viral, and parasitic infections and predict clinical outcomes.

Rapid and accurate identification of etiology can inform vision-saving therapy. The results of this proposed study will provide a new paradigm for diagnostics and treatment approaches to improve clinical outcomes.

Study design

This study is designed to apply new technologies to increase the diagnosis rate and track AMR for infectious corneal ulcers. Genotypic data including sequences of microbial RNA transcripts, antimicrobial resistance determinants, and human RNA transcripts derived from each patient*sdonated specimen. Phenotypic data includes, but is not limited to a patient*s age, diagnosis, sex, race, or

ethnicity.
We will obtain corneal ulcer and conjunctival samples from patients with signs and symptoms of infectious corneal ulcers from sites around the world. Samples will be shipped to UCSF for all molecular analysis. We will also collect clinical photography on eligible patients.

- We will ask the patient if we can collect 2 conjunctival swabs and a corneal swab to be analyzed using high throughput sequencing.
- We will also collect 2 clinical photos (of the eyes) using a mobile device.

Study burden and risks

There are minimal risks (<1:100) to the participant during corneal and conjunctiva swabbing, the risks are comparable to the risks when material is taken as part of standard diagnostics. Trained staff will collect the samples from the patient. Participants may experience some temporary discomfort, but the swabbing involves minimal risk.

Adverse effects that may occur as a minimum are:
- Enlargement of the epithelium of the infection, increasing the damage. However, this chance is also present if material is taken for standard diagnostics to discover which pathogen is causing the corneal infection.
- Irritation/discomfort of the cornea or conjunctiva

Clinical photography offers minimal risk as well. Participants may experience temporary discomfort from the flash of the camera.
For the study, it is necessary that the patient visits the hospital one more time after sample collection for a check-up visit. This appointment may be part of a scheduled visit as part of standard treatment or scheduled as a specific study visit. A visit takes about 10 minutes.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Presence of corneal ulcer: defined as a corneal epithelial defect with underlying corneal infilitrate and signs of acute inflammation

Exclusion criteria

Corneal perforation
Inability to give consent

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2025
Enrollment:	71
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	21-02-2025
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL83198.068.23