Imaging System for Ocular Surface: Objective Assessment of Conjunctival Hyperemia (#41)

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Background & Purpose

Conjunctival hyperemia is a key sign of allergic conjunctivitis and is an important endpoint in clinical efficacy and safety trials. Most methods for assessing hyperemia are highly subjective and are inconsistent from site to site. The purpose of this study was to develop a software suite that could objectively and automatically quantify conjunctival hyperemia.

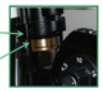
Methods: Participants and Conditions

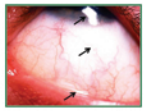
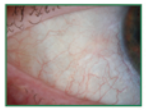
- Images were obtained from 13 participants with a history of allergic conjunctivitis upon exposure to ragweed.
- Images from baseline, postexposure, and posttreatment (various therapies) were captured from each participant at multiple prespecified time points over 7 visits.
- Allergen exposure conditions included:
  - Conjunctival Allergen Provocation Testing (CAPT)
  - Environmental Exposure Chamber (EEC)

Methods: Slit Lamp Photography

Images were captured from nasal and temporal aspects with a Haag-Streit BX-900 slit lamp equipped with a Canon digital camera, with the following settings and modifications:

- Slit: wide open, setting 8
- Camera: perpendicular to the ocular surface
- Aperture: 4 (depth of field)
- Lamp: tilted 40º to the camera/viewing angle
- Light filters and diffusers:
  - Illumination polarizing filter, set at 90º to an image path polarizing filter
  - Illumination holographic diffuser



Without Polarized Filters	With Polarized Filters
	
Specular Reflections (Arrows)	Matte Illumination

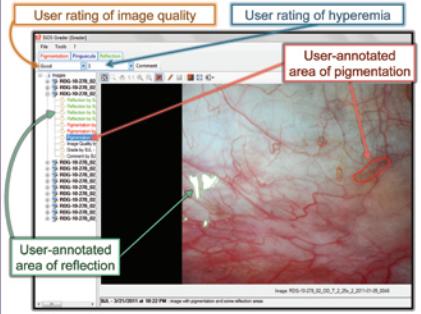
Methods: Manual Grading

- Ocular redness in the nasal and temporal conjunctivae were assessed separately in both eyes
- Hyperemia was graded in 25x images by 1 expert grader
- Scale was 0 (none/normal) to 4 (extremely severe hyperemia) in 0.5-unit increments
- Grades were assigned by evaluating the following parameters:
  - Vessel surface area
  - Average vessel diameter
  - Reduction of white surface areas due to emergence of episcleral vasculature and dilation of conjunctival vessels
  - Injection close to the limbus

Methods: Software Development

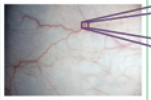
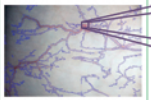
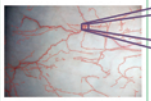
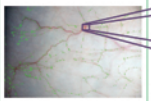
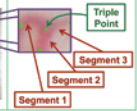
Imaging System for Ocular Surface (ISOS; Alcon) consists of a suite of software components:

- **An image acquisition interface**
- **A data synchronizer**, which allows users to upload images to a secure server
- **A manual image grading interface**, where users can annotate images and grade hyperemia:



- **An automatic image processor** that detects vessels and computes shape and densitometry measurements
- **An image reviewing interface** that allows users to easily compare manual and automatic measurements

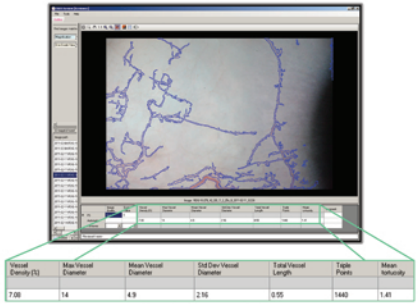
Results: Automatic Image Processing

Processing Step	Example Images	Image Detail
Software applies minor filtering to remove noise		
Software optimizes the detection of vessels		
Software applies a skeletonization transformation to allow measurement of vessel parameters		
Software detects "triple points" (intersections) to quantify vessel ramification (arborization)		

Results: Manual Grading of Images

- More than 2000 images from 25x magnification were manually graded to aid with software development.
- Exhaustive validation of software-generated results versus clinically graded images is ongoing.
- This interim report shows a case study of 1 study participant who exhibited clinical grades representing all severities of hyperemia (in whole-grade units; at different times, in different eyes, and in different regions of the eyes, throughout the study).

Results: Grade 0 (Normal) Example



Vessel Density [%]	Max Vessel Diameter	Mean Vessel Diameter	Std Dev Vessel Diameter	Total Vessel Length	Triple Points	Mean Tortuosity
7.08	14	4.9	2.16	0.55	1440	1.41

Vessel density = 7.08%
Vessel diameter = 4.9 ± 2.2 units
Total vessel length = 0.55 units
Triple points = 1440 points
Mean tortuosity = 1.41 (dimensionless, a ratio)

Results: Grade 1 (Mild) Example

- Vessel density: 13.63%
- Vessel diameter: 5.3 ± 2.6 units
- Total length: 1.08 units
- Triple points: 3286 points

Vessels Detected	Vessels Skeletonized
	

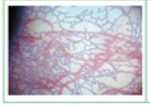
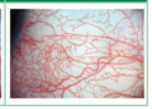
Results: Grade 2 (Moderate) Example

- Vessel density: 26.23%
- Vessel diameter: 5.7 ± 2.5
- Total length: 2.07 units
- Triple points: 6164 points

Vessels Detected	Vessels Skeletonized
	

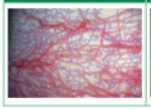
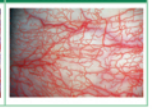
Results: Grade 3 (Severe) Example

- Vessel density: 31.33%
- Vessel diameter: 7.7 ± 3.0 units
- Total length: 1.87 units
- Triple points: 2824 points

Vessels Detected	Vessels Skeletonized
	

Results: Grade 4 (Extremely Severe)

- Vessel density: 39.74%
- Vessel diameter: 8.2 ± 3.1 units
- Total length: 2.18 units
- Triple points: 3432 points

Vessels Detected	Vessels Skeletonized
	

Results: Case Study Summary, Sample Parameters by Grade

Vessel Parameter	Hyperemia Grade 0	1	2	3	4
Density	7.08%	13.63%	26.23%	31.33%	39.74%
Diameter					
Software units	4.9 ± 2.2	5.3 ± 2.6	5.7 ± 2.5	7.7 ± 3.0	8.2 ± 3.1
Micrometers*	22 ± 10	24 ± 12	26 ±11	34 ± 13	37 ± 14

*Values converted via calibration

Discussion & Conclusions

- **Discussion:**
  - Preliminary results from this pilot study and case example indicated that the ISOS suite can objectively measure changes in conjunctival hyperemia.
  - Only a few automated techniques for the assessment of hyperemia have been reported;[1,2] neither method yielded any information about vessel morphology.
- **Conclusions:** These tools for the grading of conjunctival hyperemia were fast, were not prone to human bias, and were able to yield information about vessels that was not available with other automated methods.

References, Disclosures, & Acknowledgements

1. Wolffsohn JS. *British Journal of Ophthalmology* 2004;88:1434-14388.
2. Sorbara L, et al. *Contact Lens & Anterior Eye* 2007:30:53-59.

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- Authors MJT, RO, and GWW are employees of Alcon.
- Authors RO and GWW are named as inventors in the patent application.

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