

Classification Criteria for Herpes Simplex Virus Anterior Uveitis



THE STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP^{1,2,3,4,*}

- **PURPOSE:** The purpose of this study was to determine classification criteria for herpes simplex virus (HSV) anterior uveitis
- **DESIGN:** Machine learning of cases with HSV anterior uveitis and 8 other anterior uveitides.
- **METHODS:** Cases of anterior uveitides were collected in an informatics-designed preliminary database, and a final database was constructed of cases achieving supermajority agreement on the diagnosis, using formal consensus techniques. Cases were split into a training set and a

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¹ Members of the SUN Working Group are listed online at [AJO.com](https://ajocomm.sciencedirect.com).

² **Writing Committee:** Douglas A. Jabs, Nisha R. Acharya, Laure Caspers, Soon-Phaik Chee, Debra Goldstein, Peter McCluskey, Philip I. Murray, Neal Oden, Alan G. Palestine, James T. Rosenbaum, Jennifer E. Thorne, and Brett E. Trusko

³ **Writing Committee Affiliations:** From the Department of Epidemiology (D.A.J., J.E.T.), Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA; Department of Ophthalmology (D.A.J., J.E.T.), Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; Francis I. Proctor Foundation (N.R.A.), University of California San Francisco School of Medicine, San Francisco, California, USA; Department of Ophthalmology (L.C.), CHU St. Pierre, Université Libre de Bruxelles, Brussels, Belgium; Department of Ophthalmology (S.P.C.), Singapore National Eye Centre, Singapore Eye Research Institute, Yong Loo Lin School of Medicine, National University of Singapore, Duke-National University of Singapore Medical School, Singapore; Department of Ophthalmology (D.G.), Northwestern Feinberg School of Medicine, Chicago, Illinois, USA; Department of Ophthalmology (P.M.), Save Sight Institute, University of Sydney School of Medicine, Sydney, New South Wales, Australia; Academic Unit of Ophthalmology (P.I.M.), University of Birmingham, Birmingham, UK; Emmes Co, LLC (NO), Rockville, Maryland, USA; Department of Ophthalmology (A.G.P.), University of Colorado School of Medicine, Aurora, Colorado, USA; Departments of Medicine and Ophthalmology (J.T.R.), Oregon Health and Science University, Portland, Oregon, USA; Legacy Devers Eye Institute (J.T.R.), Portland, Oregon, USA; and the Department of Medicine (B.E.T.), Texas A&M University, College Station, Texas, USA.

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* Inquiries to Douglas A. Jabs, Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, 615 North Wolfe St, Baltimore, MD 21205, USA; E-mail: djabs@jhmi.edu.

validation set. Machine learning using multinomial logistic regression was used in the training set to determine a parsimonious set of criteria that minimized the misclassification rate among the anterior uveitides. The resulting criteria were evaluated in the validation set.

• **RESULTS:** A total of 1,083 cases of anterior uveitides, including 101 cases of HSV anterior uveitis, were evaluated by machine learning. The overall accuracy for anterior uveitides was 97.5% in the training set and 96.7% in the validation set (95% confidence interval: 92.4-98.6). Key criteria for HSV anterior uveitis included unilateral anterior uveitis with either 1) positive aqueous humor polymerase chain reaction assay for HSV; 2) sectoral iris atrophy in a patient ≤ 50 years old; or 3) HSV keratitis. The misclassification rates for HSV anterior uveitis were 8.3% in the training set and 17% in the validation set.

• **CONCLUSIONS:** The criteria for HSV anterior uveitis had a reasonably low misclassification rate and appeared to perform well enough for use in clinical and translational research. (*Am J Ophthalmol* 2021;228: 231-236. © 2021 Elsevier Inc. All rights reserved.)

HERPES SIMPLEX VIRUS (HSV) ANTERIOR UVEITIS is an infectious anterior uveitis presumed to be due to replicating virus in the eye, as shown by the detection of HSV viral DNA in the aqueous humor of eyes using polymerase chain reaction (PCR) analysis of aqueous humor obtained by paracentesis of the anterior chamber.¹⁻³ It nearly always is unilateral, may present with elevated intraocular pressure, may be chronic, in 30%-40% of cases may occur in the context of HSV keratitis (HSV keratouveitis) or may occur as a unilateral uveitis with sectoral iris atrophy without keratitis.⁴⁻⁶ In case series of patients with uveitis, it accounts for 3%-10% of all uveitis cases and 5%-10% of anterior uveitis cases.^{7,8} The correct diagnosis affects management as oral antiviral medications typically are used in the treatment of HSV anterior uveitis, with some patients requiring chronic suppressive antiviral medication.^{9,10}

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration, which has developed classification criteria for 25 of the most common uveitides using a formal approach to development and classification.¹¹⁻¹⁷ Among the anterior uveitides studied was HSV anterior uveitis.

METHODS

The SUN Developing Classification Criteria for the Uveitides project proceeded in four phases as previously described: 1) informatics, 2) case collection, 3) case selection, and 4) machine learning.^{12,13,15,16}

- **INFORMATICS:** As previously described, the consensus-based informatics phase permitted the development of a standardized vocabulary and the development of a standardized, menu-driven hierarchical case collection instrument.¹²

- **CASE COLLECTION AND CASE SELECTION:** De-identified information was entered into the SUN preliminary database by the 76 contributing investigators for each disease, as previously described.^{15,16} Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database, using formal consensus techniques described in the accompanying articles.^{15,16} Because the goal was to develop classification criteria, only cases with a supermajority agreement (>75%) that the case was the disease were retained in the final database (ie, were “selected”).

- **MACHINE LEARNING:** The final database then was randomly separated into a training set (~85% of cases) and a validation set (~15% of cases) for each disease, as described in the accompanying article.¹⁶ Machine learning was used in the training set to determine criteria that minimized misclassification. The criteria then were tested in the validation set; for both the training set and the validation set, the misclassification rate was calculated for each disease. The misclassification rate was the proportion of cases classified incorrectly by the machine learning algorithm compared to the consensus diagnosis. For HSV anterior uveitis, the diseases against which it was evaluated were: cytomegalovirus (CMV) anterior uveitis, varicella zoster virus (VZV) anterior uveitis, juvenile idiopathic arthritis (JIA)-associated anterior uveitis, spondylitis/HLA-B27-associated anterior uveitis, tubulointerstitial nephritis with uveitis (TINU), Fuchs uveitis syndrome, sarcoid anterior uveitis, and syphilitic anterior uveitis.

This study adhered to the principles of the Declaration of Helsinki. Institutional Review Boards (IRBs) at each participating center reviewed and approved the study; the study typically was considered either a minimal risk or exempt by individual IRBs.

RESULTS

A total of 250 cases of HSV anterior uveitis were collected, and 101 cases (40%) achieved supermajority agreement on

the diagnosis during the “selection” phase and were used in the machine learning phase. These cases of HSV anterior uveitis were compared to cases of other anterior uveitides, including 89 cases of CMV anterior uveitis; 123 cases of VZV anterior uveitis; 146 cases of Fuchs uveitis syndrome; 202 cases of JIA-associated anterior uveitis; 184 cases of spondylitis/HLA-B27-associated anterior uveitis; 94 cases of TINU; 112 cases of sarcoidosis-associated anterior uveitis; and 32 cases of syphilitic anterior uveitis. The characteristics at presentation to a SUN Working Group Investigator of the cases with HSV anterior uveitis are listed in [Table 1](#). The criteria developed after machine learning are listed in [Table 2](#). Key features included evidence of HSV infection, including: 1) positive PCR analysis for HSV in the aqueous; 2) sectoral iris atrophy ([Figure 1](#)) in a patient ≤50 years old; or 3) HSV keratitis, either epithelial or stromal.

As a check on the clinical criteria for patients without PCR being performed, the 14 cases of patients ≥51 years of age with positive aqueous humor PCR results were evaluated for HSV for clinical features. Of the 4 cases 51-60 years old, 3 of the 4 cases had HSV keratitis in addition to the uveitis (and HSV uveitis would have been diagnosed on clinical grounds), and 1 case had no distinguishing features on clinical grounds (and hence needed PCR analysis of the aqueous humor to complete the diagnosis). Of the 10 cases >60 years old, 5 cases had HSV keratitis in addition to the uveitis (and HSV uveitis would have been diagnosed on clinical grounds); 3 cases had atypical iris atrophy (not sectoral and hence needed PCR analysis of the aqueous for the diagnosis); and 1 case had no distinguishing clinical features (and hence needed PCR analysis off the aqueous to complete the diagnosis). Therefore, none of these cases would have been diagnosed as a different infectious uveitis (eg, VZV anterior uveitis) by the clinical criteria, supporting the utility of the HSV criteria.

The overall accuracy for anterior uveitides was 97.5% in the training set and 96.7% in the validation set (95% confidence interval: 92.4-98.6).¹⁶ The misclassification rate for HSV anterior uveitis in the training set was 8.3% and 17% in the validation set. The disease with which it most often was confused was VZV anterior uveitis.

DISCUSSION

The classification criteria outlined in [Table 2](#) appear to perform reasonably well with reasonably low misclassification rates. Because of the sample size of the validation set, it is estimate is more subject to one or two cases having a disproportionate effect, and the misclassification rate in the training set was 8.3%.

Herpes simplex anterior uveitis has an appearance often distinct from noninfectious anterior uveitides but has ocular features that may overlap with other anterior uveitides caused by an active viral infection, particularly VZV ante-

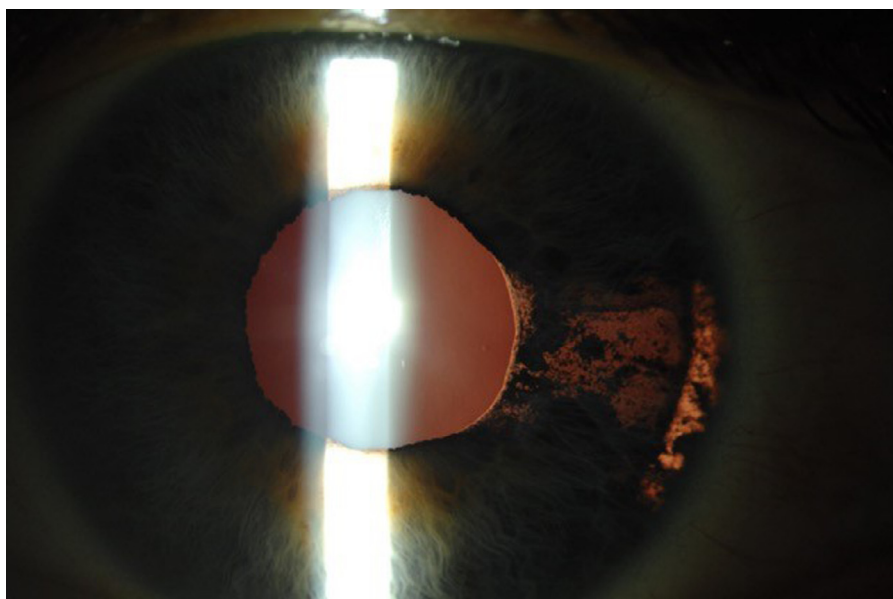


FIGURE 1. Sectoral iris atrophy in a patient with herpes simplex virus anterior uveitis.

rior uveitis.^{1,3,5,6,18,19} Herpes simplex anterior uveitis occurs in a younger age group than VZV anterior uveitis, but the age distributions overlap.^{3,5,18} Concomitant or recent dermatomal zoster is present in most patients with VZV anterior uveitis and is useful in its diagnosis.¹⁶ Keratitis is seen in 30%-40% of eyes with HSV anterior uveitis but <3% of eyes with VZV anterior uveitis.⁵ Endotheliitis can be seen with CMV anterior uveitis, but the coin-shaped nodular keratic precipitates seen in CMV anterior uveitis are not present in HSV uveitis, and the iris atrophy, when present in eyes with CMV anterior uveitis, tends to be patchy rather than sectoral as in HSV and VZV anterior uveitis.²⁰

The HEDS (Herpetic Eye Disease Study) used the following criteria for diagnosis of HSV anterior uveitis: anterior uveitis plus either 1) confirmed prior HSV ocular disease; 2) HSV stromal keratitis; or 3) positive serum antibodies to HSV in the absence of other identifiable uveitides.⁹ However, the HEDS enrolled patients prior to the use of PCR of the aqueous for diagnosis of viral uveitis, and positive serum antibodies to HSV have a poor positive predictive value due to their widespread presence in the general population. Studies using PCR analysis in eyes with anterior uveitis and sectoral iris atrophy have demonstrated the presence of either HSV or VZV in more

TABLE 2. Classification Criteria for Herpes Simplex Anterior Uveitis.

Criteria
1. Evidence of anterior uveitis
a. Anterior chamber cells
b. If anterior vitreous cells are present, severity is less than anterior chamber inflammation
c. No evidence of retinitis
AND
2. Unilateral uveitis (unless there is a positive aqueous PCR result for herpes simplex virus)
AND
3. Evidence of herpes simplex infection in the eye
a. Aqueous humor PCR positive for herpes simplex virus OR
b. Sectoral iris atrophy in a patient ≤ 50 years of age OR
c. Herpes simplex keratitis
Exclusions
1. Concomitant dermatomal/cutaneous varicella zoster virus (unless aqueous specimen PCR positive for herpes simplex virus)
2. Positive serology for syphilis using a treponemal test
3. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating noncaseating granulomata)
4. Aqueous specimen PCR positive for cytomegalovirus or varicella zoster virus

PCR = polymerase chain reaction.

TABLE 1. Characteristics of Cases with Herpes Simplex Anterior Uveitis.

Characteristic	Result
Number of cases	101
<i>Demographics</i>	
Median IQR (25th, 75th) age	44 (2, 87)
Age category, years %	
≤16	2
17–50	71
51–60	12
>60	14
Men, %	42
Women, %	58
Race/ethnicity, %	
White, non-Hispanic	65
Black, non-Hispanic	3
Hispanic	3
Asian, Pacific Islander	6
Other	7
Missing	16
<i>Uveitis History</i>	
Uveitis course, %	
Acute, monophasic	13
Acute, recurrent	31
Chronic	40
Indeterminate	16
Laterality, %	
Unilateral	99
Unilateral, alternating	0
Bilateral	1
<i>Ophthalmic examination</i>	
Cornea	
No keratitis	77
Keratitis	23
Keratic precipitates, %	
None	26
Fine	24
Round	18
Stellate	5
Mutton Fat	26
Other	2
Anterior chamber cells, %	
Grade ½+	22
1+	31
2+	25
3+	14
4+	2
Hypopyon, %	0
Anterior chamber flare, %	
Grade 0	38
1+	47
2+	15
3+	0
4+	1

(continued on next column)

TABLE 1. (continued)

Characteristic	Result
Iris, %	
Normal	36
Posterior synechiae	18
Sectoral iris atrophy	46
Patch iris atrophy	9
Diffuse iris atrophy	9
Heterochromia	1
IOP involved eyes	
Median IQR (25th, 75th), mm Hg	16 (12, 21)
Proportion patients with IOP >24 mm Hg in either eye, %	34
Vitreous cells, %	
Grade 0	78
1+	12
2+	6
3+	4
4+	0
<i>Laboratory</i>	
Aqueous PCR positive for HSV (% all cases)	41
Aqueous PCR positive for HSV (% cases tested)	100

Forty-one patients were tested, and 41 (100%) were positive.
HSV = herpes simplex virus; IOP = intraocular pressure;
IQR = interquartile range; PCR = polymerase chain reaction.

than 95% of eyes.^{3,6} Patients younger than 50 years old typically had HSV, whereas patients older than 60 years of age had VZV infection.^{3,6} Nevertheless, the overlapping age distributions make it impossible to diagnose which virus is causative in patients 50-60 years old without a positive PCR result or HSV keratitis (for HSV) or concurrent dermatomal herpes zoster (for VZV). As sectoral iris atrophy is a later manifestation of HSV anterior uveitis,¹⁸ HSV anterior uveitis can be diagnosed in its absence with either HSV keratitis or a PCR analysis of the aqueous positive for HSV.

Anterior uveitis due to HSV is nearly always unilateral, 99% in the present series, but bilateral cases do occur, often in the context of immune compromise.^{19,20} Therefore, for a patient with bilateral anterior uveitis to be diagnosed as HSV anterior uveitis, a positive PCR result should be obtained. Because aqueous paracentesis for PCR for viruses is not always performed in patients with unilateral anterior uveitis,^{21,22} the criteria need to provide methods for diagnosis in its absence. Hence the criteria outlined in Table 2 were developed, and they have an acceptable misclassification rate.

The presence of any of the exclusions in Table 2 suggests an alternate diagnosis, and the HSV anterior uveitis should not be diagnosed in their presence. In prospective studies many of these tests will be performed routinely, and the

alternative diagnoses excluded. However, in retrospective studies based on clinical care, not all of these tests may have been performed. Hence the presence of an exclusionary criterion excludes HSV anterior uveitis, but the absence of such testing does not exclude the diagnosis of HSV anterior uveitis if the criteria for the diagnosis are met.

Classification criteria are used to diagnose individual diseases for research purposes.¹⁷ Classification criteria differ from clinical diagnostic criteria in that, although both seek to minimize misclassification, when a tradeoff is needed, diagnostic criteria typically emphasize sensitivity, whereas classification criteria emphasize specificity,¹⁷ in order to define a homogeneous group of patients for inclusion in research studies and to limit the inclusion of patients without the disease in question that might confound the data. The machine learning process used did not explicitly use sensitivity and specificity; instead it minimized the misclassification rate. Because classification criteria were being developed and because the typical agreement between 2 uveitis experts on diagnosis is moderate at best,¹⁵ the selection of cases for the final database (“case selection”) included only cases which achieved supermajority agreement on the diagnosis. It is likely that there will be some cases which clinicians believe have HSV anterior uveitis which will not meet the criteria outlined in Table 2. In sum, the criteria outlined in Table 2 appear to perform reasonably well enough to be used as classification criteria for research.¹⁶

CREDIT ROLES

Douglas A. Jabs, MD, MBA: Conceptualization, Method-

ology, Validation, Investigation, Data curation, Writing–Review and editing, Visualization, Supervision, Project administration, Funding acquisition. **Nisha R. Acharya, MD:** Investigation, Writing–Review and editing. **Laure Caspers, MD:** Investigation, Writing–Original draft, Writing–Review and editing. **Soon-Phaik Chee, FR-COphth, FRCS (G), FRCS (Ed), MMed (Singapore):** Investigation, Writing–Review and editing. **Debra Goldstein, MD:** Investigation, Writing–Review and editing. **Peter McCluskey, MD:** Investigation, Data curation, Writing–Review and editing. **Philip I. Murray, PhD, FRCP, FRCS, FRCOphth:** Investigation, Writing–Review and editing. **Neal Oden, PhD:** Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing–Review and editing. **Alan G. Palestine, MD:** Investigation, Writing–Review and editing. **James T. Rosenbaum, MD:** Investigation, Writing–Review and editing. **Jennifer E. Thorne, MD, PhD:** Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing–Review and editing. **Brett E. Trusko, PhD, MBA:** Methodology, Software, Resources, Data curation, Investigation, Writing–Review and editing.

TOC

A formalized approach was adopted to develop classification criteria, including informatics-based case collection, consensus-technique-based case selection, and machine learning, classification criteria for herpes simplex virus (HSV) anterior uveitis were developed. Key criteria included unilateral anterior uveitis with either 1) positive aqueous humor polymerase chain reaction assay for HSV; 2) sectoral iris atrophy in a patient ≤ 50 years old; or 3) HSV keratitis. The resulting criteria had an acceptable misclassification rate.

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