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An Update on Systemic Conditions to Look Out for in OSD Management

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- Associated Eye Care
- Stillwater, MN

Disclosures

- Speaker/Advisor for; Novartis, Sun Pharma, Allergan, Ocular Therapeutix, Orasis, AOS, and Horizon

WHICH Systemic Condition?

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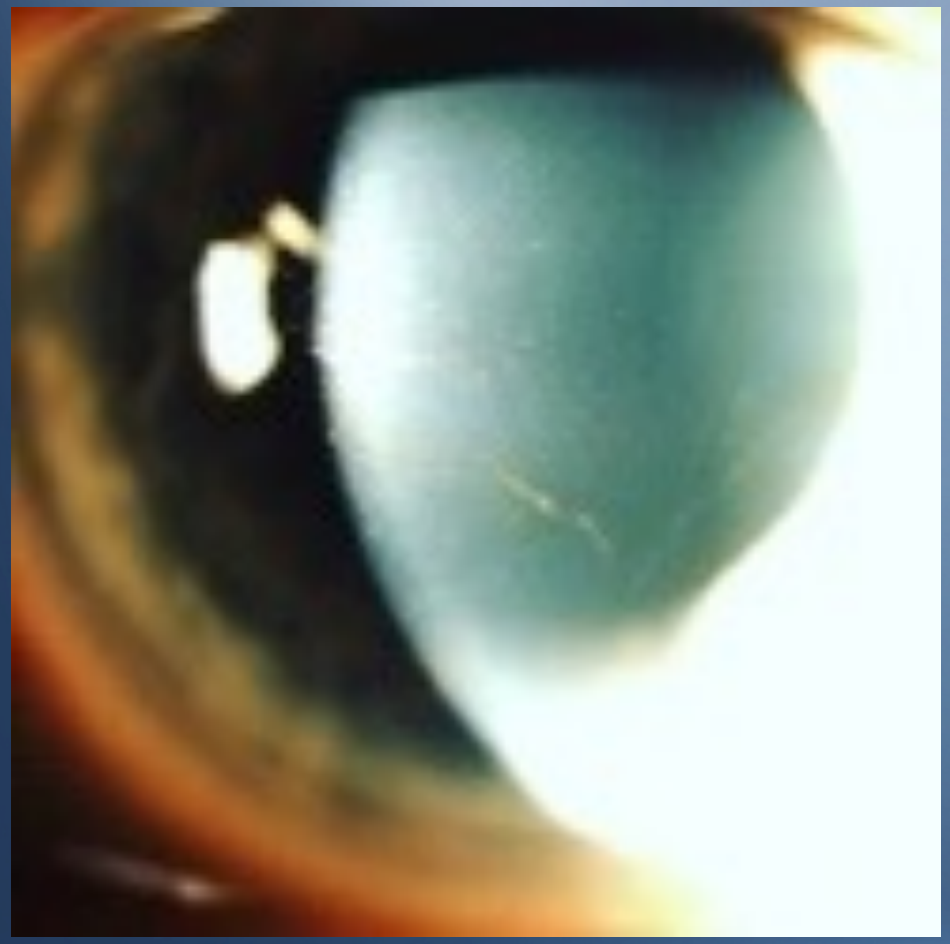

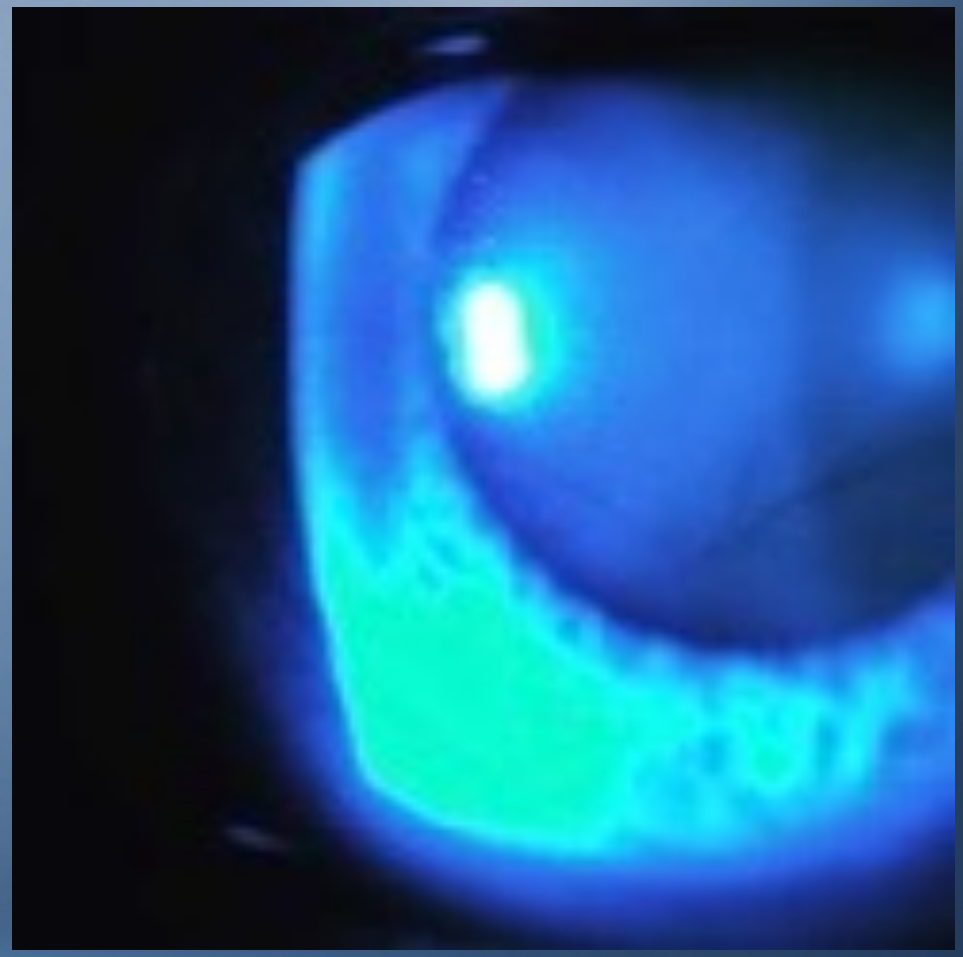

WHICH Systemic Condition?

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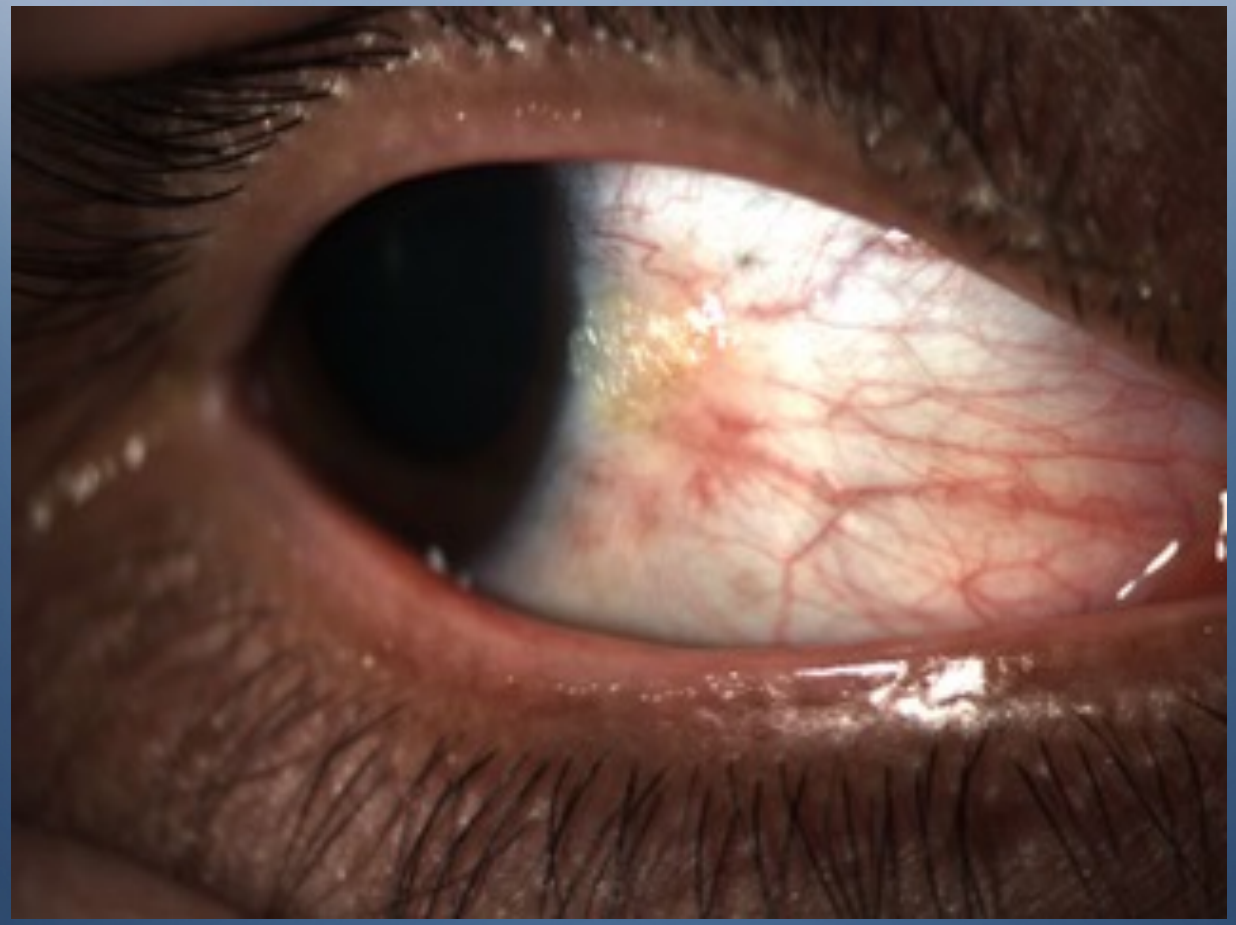

WHICH Systemic Condition?

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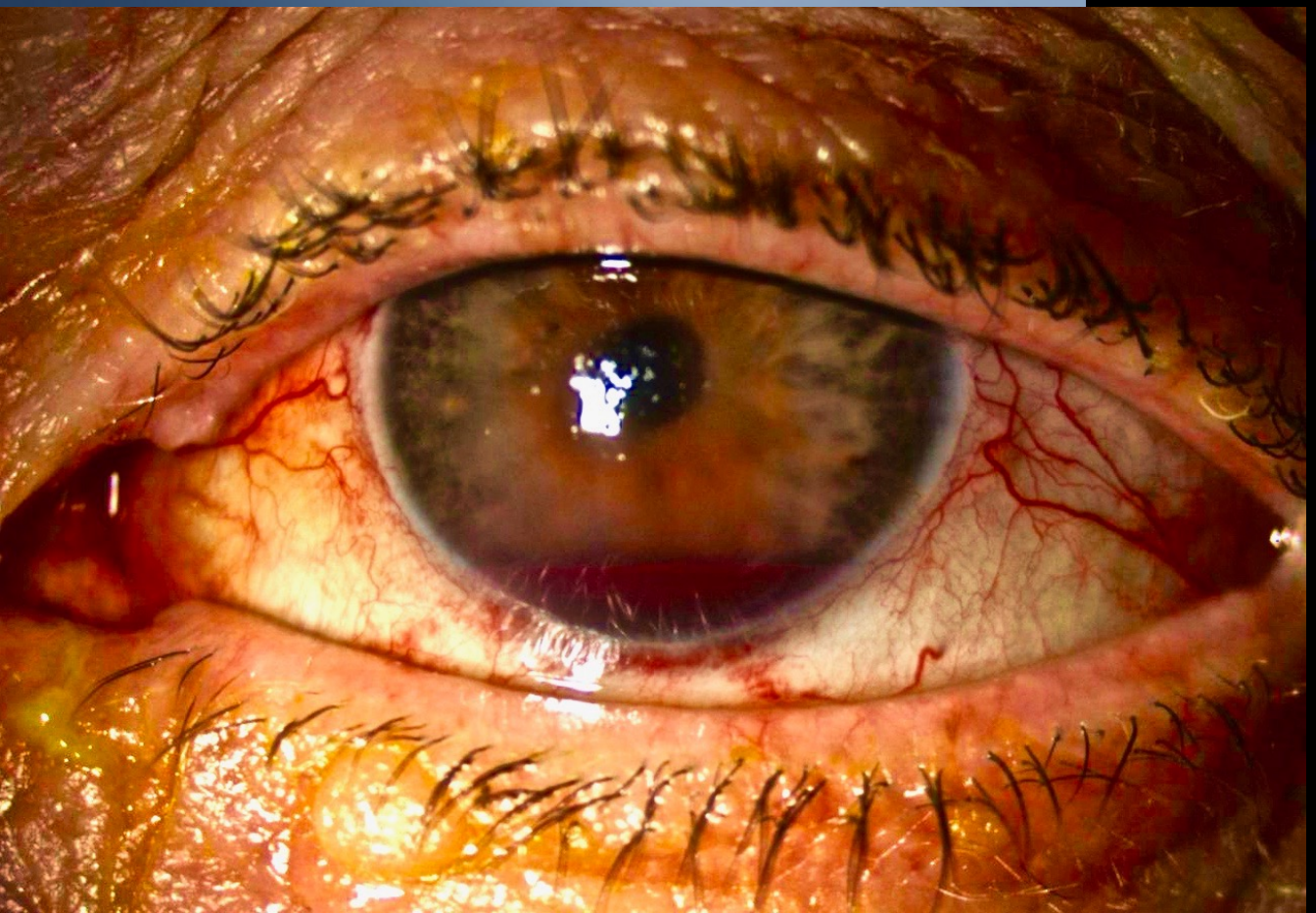

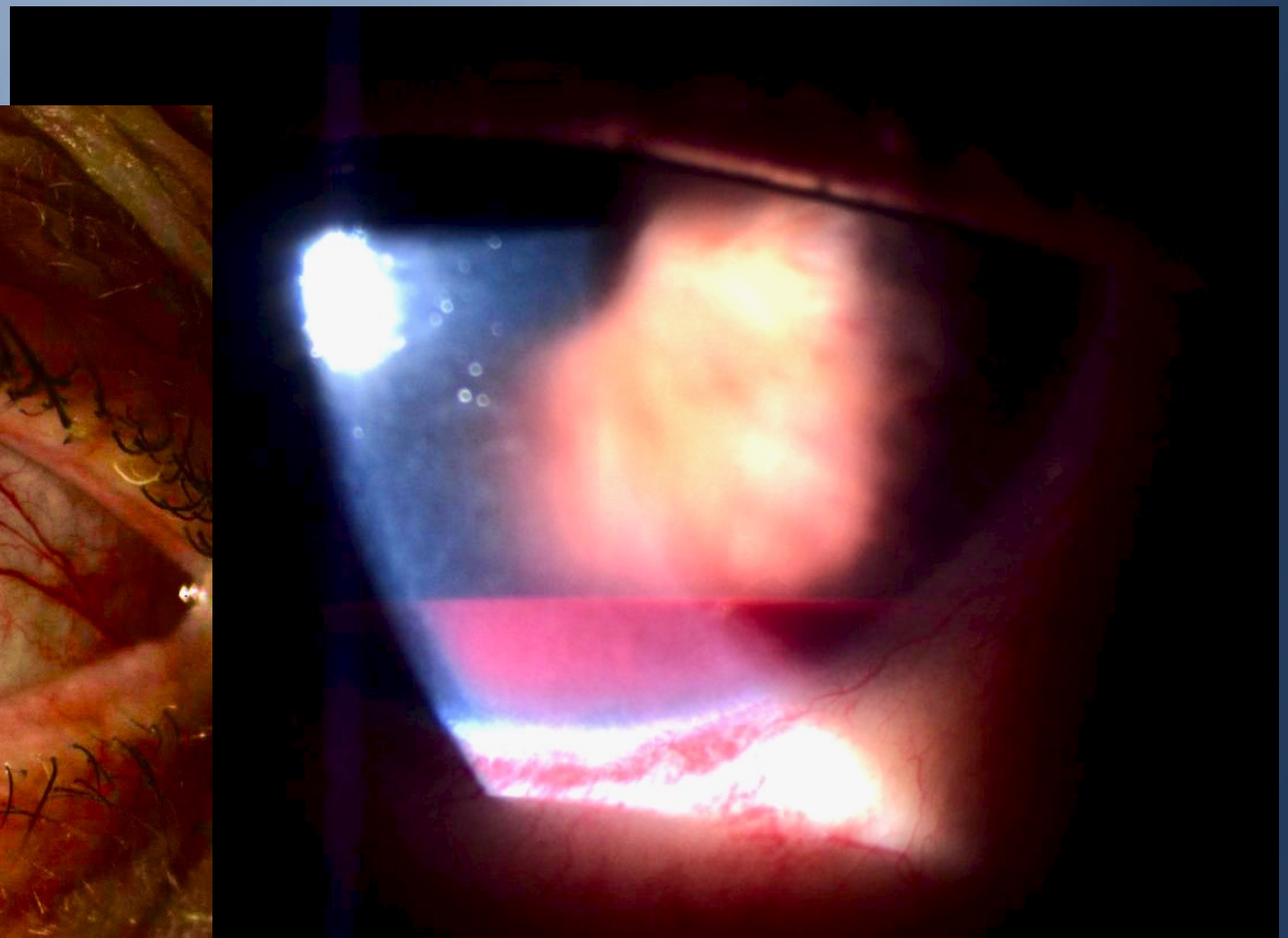

WHICH Systemic Conditions Cause OSD?

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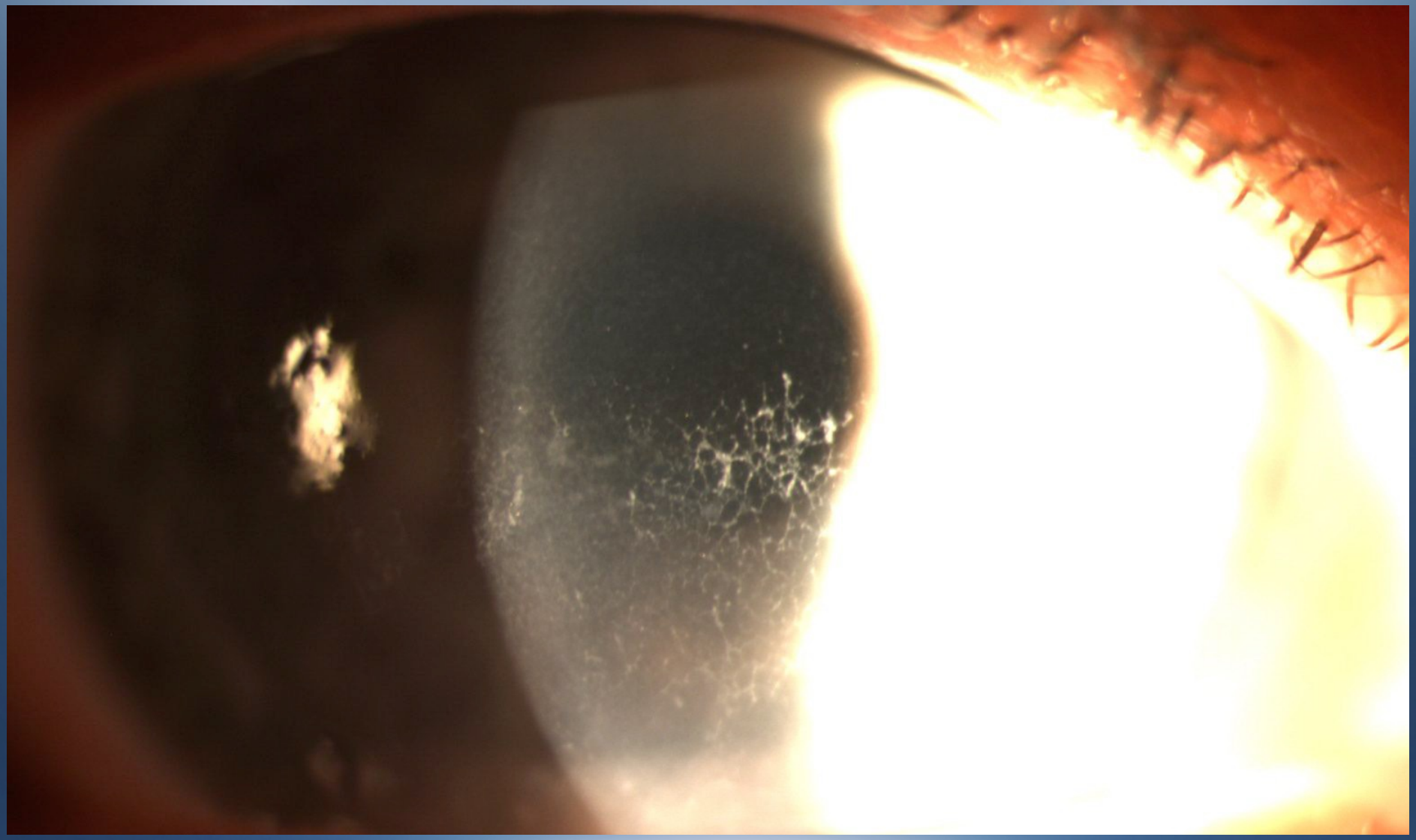

WHY do Systemic Conditions Cause OSD?

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WHY do Systemic Conditions Cause OSD?

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Definition from DEWS II

"Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."

WHY do Systemic Conditions Cause OSD?

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- Inflammation
- Loss of Homeostasis
- Neurosensory Abnormalities

WHY do Systemic Conditions Cause OSD?

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- Are you an Ocular Rheumatologist?

Dry Eye as a Mucosal Autoimmune Disease

Michael E. Stern,[1] Chris S. Schaumburg,[1] and Stephen C. Pflugfelder[2]

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[2]Ocular Surface Center, Cullen Eye Institute, Baylor College of Medicine, Houston, TX, USA

Autoimmune Disease Incidence

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- **Population Prevalence 7.6-9.4%**

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J Autoimmun. 2009 ; 33(3-4): 197–207. doi:10.1016/j.jaut.2009.09.008.

Recent Insights in the Epidemiology of Autoimmune Diseases: Improved Prevalence Estimates and Understanding of Clustering of Diseases

Glinda S. Cooper[a,*], **Milele L.K. Bynum**[b], and **Emily C. Somers**[c]

[a]National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC 20460, USA

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[c]Division of Rheumatology, University of Michigan Health System, Ann Arbor, MI, 48109, USA

Autoimmune Disease Incidence

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- Population Prevalence of Autoimmune Disease 7.6-9.4%
- **The global prevalence of glaucoma for population aged 40–80 years is 3.54%**
- **Of individuals with significant aqueous deficient dry eye, 10% are likely to have Sjogren's syndrome . DEWS II**
- **26% of patients with either aqueous tear deficiency or evaporative dry eye have an underlying rheumatic condition, including Sjogren's syndrome. DEWS II**
- **Of 1208 participants in an international Sjogren's syndrome registry, 85% reported symptoms of dry eye. DEWS II**

Sjogren('s) Syndrome

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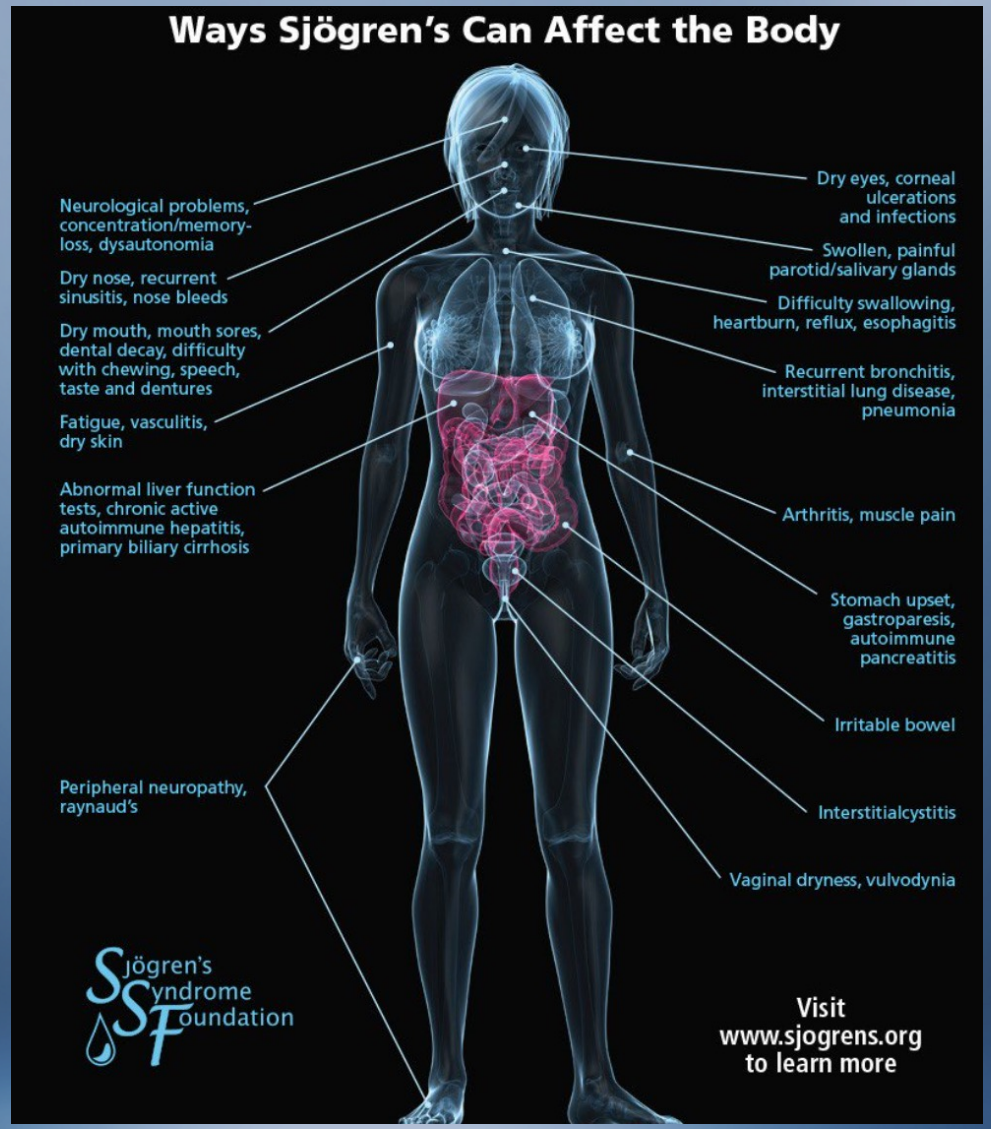
- Does a Diagnosis Matter?



Sjogren('s) Syndrome

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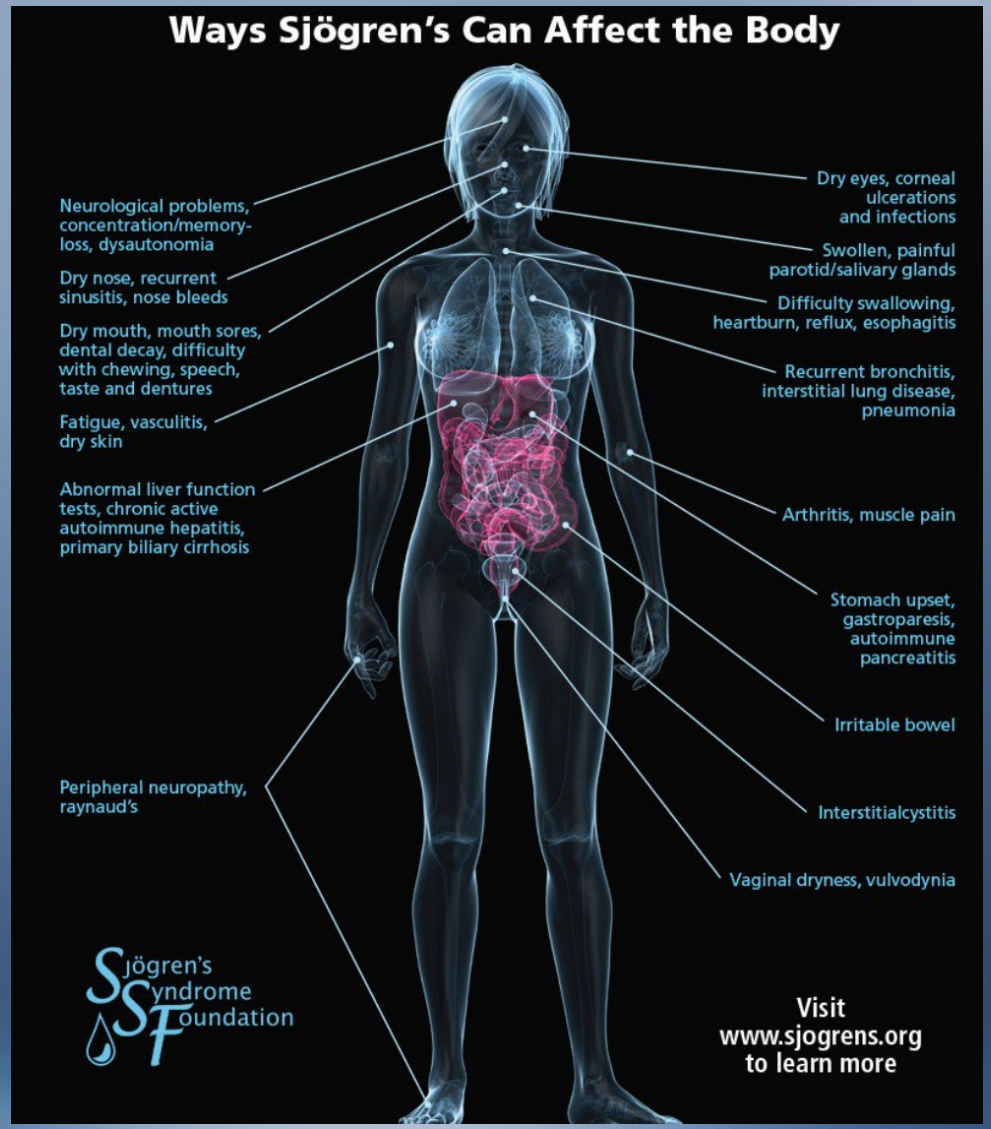
- Does a Diagnosis Matter?
  - Lymphoma
  - Kidney Disease
  - Liver Disease
  - Lung Disease
  - Neurocognitive Effects
  - GI Disease
  - Gluten Sensitivity
  - Raynaud's

People with Sjogrens have **five to nine times** the risk of developing non-Hodgkin's lymphoma (NHL) than people in the general population.



Diagnostic Criteria---Sjogren's Syndrome

- 2 Main Classification Criteria
- The Revised American-European Consensus Group (AECG) Classification Criteria 2002
- The American College of Rheumatology (ACR) Classification Criteria 2012

The Revised American-European Consensus Group (AECG) Classification Criteria 2002

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- Ocular symptoms: a positive response to at least one of the following questions:
  1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
  2. Do you have a recurrent sensation of sand or gravel in the eyes?
  3. Do you use tear substitutes more than 3 times a day?

- Oral symptoms: a positive response to at least one of the following questions:
  1. Have you had a daily feeling of dry mouth for more than 3 months?
  2. Have you had recurrently or persistently swollen salivary glands as an adult?
  3. Do you frequently drink liquids to aid in swallowing dry food?

- Objective ocular signs - a positive result for at least one of the following two tests:
  1. Schirmer's I test, performed without anesthesia (≤5 mm in 5 minutes)
  2. Rose Bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system)

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The Revised American-European Consensus Group (AECG) Classification Criteria 2002

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- **Histopathology**: in minor salivary glands (obtained through normal appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥ 1, defined as number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue

- Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
  1. Unstimulated whole salivary flow (≤1.5 ml in 15 min)
  2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in major ducts
  3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

- Presence in the serum of the following autoantibodies: Antibodies to Ro (SSA) and/or La (SSB) antigens

The Revised American-European Consensus Group (AECG) Classification Criteria 2002

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Sjogren's may be diagnosed when:

The presence of any 4 of the 6 items is indicative of primary SS, as long as either (Histopathology) **or** (Serology) is positive

The American College of Rheumatology (ACR) Classification Criteria

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- Keratoconjunctivitis sicca with ocular staining score ≥3
- Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm2

- Autoantibodies: presence in the serum of the following autoantibodies:
  - Antibodies to Ro (SSA) and/or La (SSB) antigens,
  - **OR** Positive rheumatoid factor **and** ANA titer ≥1:320

- Sjogren's may be diagnosed when:
  Patients' have at least 2 of the 3 objective features previously described

2016 ACR, EULAR Criteria

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PDF

2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome

Caroline H Shiboski[1], Stephen C Shiboski[1], Raphaèle Seror[2], Lindsey A Criswell[1], Marc Labetoulle[2], Thomas M Lietman[1], Astrid Rasmussen[3], Hal Scofield[4], Claudio Vitali[5, 6], Simon J Bowman[7], Xavier Mariette[2], the International Sjögren's Syndrome Criteria Working Group

Author affiliations +

A consensus and data-driven methodology involving three international patient cohorts

2016 ACR, EULAR CONCENSUS Criteria

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- The new classification criteria are based on the weighted sum of five items, which reflect the higher importance of the immunologic abnormalities granted by the majority of clinician experts

- Anti-SSA(Ro) antibody positivity (3 Points) (No credit for SSB)
- Focal lymphocytic sialadenitis with a focus score of ≥1 foci/mm^2 (3 Points)
- An abnormal ocular staining score of ≥5 (or a van Bijsterveld score ≥4) in at least one eye (1 Point)
- A Schirmer test of ≤5 mm/5 minutes in at least one eye (1 Point)
- An unstimulated salivary flow rate of ≤0.1 mL/minute (1 Point)

Individuals who meet eligibility criteria and who have a total score of ≥4 for the items above meet the criteria for SS.

2016 ACR, EULAR CONCENSUS Criteria

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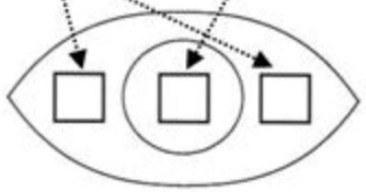
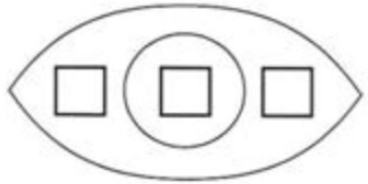
SICCA Ocular Staining Score

Staining pattern score:

	Right Eye		Left Eye	
	Lissamine Green (conjunctiva only)	Fluorescein (cornea only)	Lissamine Green (conjunctiva only)	Fluorescein (cornea only)
Grade	Dots	Dots	Dots	Dots
0	0-9	0	0-9	0
1	10-32	1-5	10-32	1-5
2	33-100	6-30	33-100	6-30
3	>100	>30	>100	>30





Extra points–fluorescein only:
(Mark all that apply and add to fluorescein score)

- ☐ +1 - patches of confluent staining
- ☐ +1 - staining in pupillary area
- ☐ +1 - one or more filaments

Total Ocular Staining score: ☐☐

Total ocular staining scores of 3 to 12 per eye assess the range of severity for keratoconjunctivitis sicca.

2016 ACR, EULAR Criteria

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- The new criteria do not include outdated, painful or expensive examinations, such as sialography and salivary scintigraphy, which were part of the AECG criteria.
- Preexisting lymphoma, which was included in the exclusion criteria list in the AECG criteria, has been deleted from that list, because diagnosis of SS is sometimes made after a prior lymphoma occurrence.
- Investigators from both the SICCA team and the EULAR Sjogren's Task Force formed the International Sjogren's Syndrome Criteria Working Group in 2012, with the primary purpose of developing classification criteria for primary SS that combined features of the ACR and AECG criteria. The 2016 document is the result of that work.

Modified Criteria

- Salivary Gland Ultrasound may improved diagnostic criteria

RESEARCH ARTICLE

Combined classification system based on ACR/EULAR and ultrasonographic scores for improving the diagnosis of Sjögren's syndrome

Yukinori Takagi[1], Hideki Nakamura[2], Misa Sumi[1], Toshimasa Shimizu[2], Yasuko Hirai[2], Yoshiro Horai[2,3], Ayuko Takatani[2], Atsushi Kawakami[2], Sato Eida[1], Miho Sasaki[1], Takashi Nakamura[1]*

1 Department of Radiology and Cancer Biology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, **2** Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, **3** Clinical Research Center, National Hospital Organization (NHO) Nagasaki Medical Center, Nagasaki, Japan

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Modified Criteria

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- Salivary Gland Ultrasound may improved diagnostic criteria

Table 6. Integrated score system based on the ACR/EULAR and US classifications.

classification item	score assigned
anti-SS-A/Ro antibody	3
labial gland biopsy	3
Schirmer's test	1
ocular staining	1
salivary flow test[a]	1
salivary gland US[b]	3
integrated score threshold for SS	≥5

Limitations of “Criteria”

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- What about the “Grey Area”
- Criteria designed for classifying individuals for enrollment in clinical trials

- Are there Sjogren’s “Suspects”?
- Do you ever treat “Glaucoma Suspects”?

Labs and Testing

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SSA and SSB

- Antibodies against SSA/Ro are found in approximately 50% of patients with the disease
  - 75% of patients with primary Sjögren syndrome
  - 15% of patients with secondary Sjögren syndrome
  - The absence of anti-SSA/Ro antibodies does not eliminate the diagnosis of primary or secondary Sjögren syndrome.

- Anti-Ro is a polyclonal antibody directed against nuclear and nucleolar RNA binding protein of 60KD or cytoplasmic protein of 52KD (E3 ubiquitin ligase)

- Anti-La SSB is an oligoclonal antibody that is predominantly directed against nuclear 47KD RNA binding protein.

- Antibodies against SSA/Ro are present in 50% of patients with SLE and are sometimes found in healthy individuals. Thus, the presence of antibody against SSA/Ro cannot by itself be used to establish a diagnosis of Sjogren's syndrome.

Labs and Testing

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SSA and SSB

- Antibodies against SSB/La are present in 40-50% of patients with primary Sjogren syndrome and in 15% of patients with SLE. Finding antibodies against SSB/La in patients without antibodies against SSA/Ro is unusual, but this combination has occurred in patients with primary biliary cirrhosis and autoimmune hepatitis.

- Titers of anti-SSA/Ro and anti-SSB/La antibodies do not reflect disease activity.

- Antibodies against SSA/Ro are also associated with the annular erythematous lesions of subacute cutaneous lupus. They are also found in the mothers of newborns with neonatal lupus syndromes and congenital heart block, and some of these mothers have or will develop Sjogren's syndrome.

Labs and Testing

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- Rheumatoid factor

  RF is present in 52% of patients with primary Sjogren's syndrome and in 98% of patients with the secondary disease, occurring even when rheumatoid arthritis is not present.

- Antinuclear antibodies

  ANAs are typically present in patients with Sjogren's syndrome

- Serum protein electrophoresis

  Patients with Sjogren's syndrome often have a `. Loss of a previously detected polyclonal gammopathy can be observed in some patients with Sjogren's syndrome who develop lymphoma. Development of a monoclonal gammopathy can also signal the development of a lymphoma.

- Sedimentation rate

  The ESR is elevated in 80% of patients with Sjogren's syndrome, but the finding is nonspecific

Labs and Testing

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CBC

- In patients with Sjogren's syndrome, the complete blood count (CBC) is most often within the reference range, but anemia of chronic disease may be present. Pernicious anemia may be associated with the atrophic gastritis.

- An abnormal white blood cell (WBC) count, especially with an abnormal differential count, should prompt concerns for a lymphoreticular malignancy. In addition, although a low platelet or WBC count can occur in persons with primary Sjogren's syndrome, the finding should also prompt consideration for coexisting SLE.

Labs and Testing

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Biopsy

- Minor salivary gland biopsy is currently is the **best single test** to establish a diagnosis of Sjogren's syndrome. Obtaining the biopsy sample from below normal-appearing mucosa is important in order to avoid false-positive results. At least 4 salivary gland lobules should be obtained for analysis.

- Salivary gland biopsy can also help to detect pseudolymphoma or lymphoma, as well as the noncaseating granulomas of sarcoidosis.

Labs and Testing---Sjo by B&L

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Biomarker	Type	Diagnostic Characteristics
SS-A (Ro)	Traditional	Expressed in approximately 70% of patients and typically appears later in the course of the disease than novel biomarkers[1,7]
SS-B (La)	Traditional	Expressed less frequently than Ro and typically appears later in course of disease than novel biomarkers[1,7]
Antinuclear Antibody (ANA) by HEp-2	Traditional	Expressed in about 70% of Sjögren's Syndrome patients[1]
Rheumatoid Factor (RF) Levels (IgA, IgG, IgM)	Traditional	Found in many rheumatic conditions but is not unique to Sjögren's Syndrome[1]
Salivary Protein-1 (SP-1, IgA, IgG, IgM)	**Novel, proprietary**	**Provides high specificity and sensitivity for early Sjögren's Syndrome[7]**
Carbonic Anhydrase-6 (CA-6, IgA, IgG, IgM)	**Novel, proprietary**	**Offers additional sensitivity for an early diagnosis[7]**
Parotid Secretory Protein (PSP, IgA, IgG, IgM)	**Novel, proprietary**	**Expressed early in disease course[7]**

Neuropathic Pain- A Systemic Condition?

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The triad of **hyperalgesia**, **allodynia**, and **spontaneous pain** have been used to describe neuropathic pain.

- **Allodynia** is defined pain due to innocuous stimuli and **photoallodynia** is inappropriate sensitivity to light.
- **Hyperalgesia** is an enhanced or heightened pain perception[8]. Essentially, this is when a low stimulus from normal activity initiates a painful sensation. For example, airflow from walking would be perceived as excruciating corneal pain.
- **Spontaneous Pain** is perception of pain in the absence of stimuli

Depression & Mental Illness

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Published in final edited form as:
Am J Ophthalmol. 2015 March ; 159(3): 470–474. doi:10.1016/j.ajo.2014.11.028.

The Association Between Dry Eye Disease and Depression and Anxiety in a Large Population-Based Study

Robert van der Vaart, M.D.,
The University of North Carolina at Chapel Hill, Department of Ophthalmology,
rvanderv@unch.unc.edu

"Perhaps there is a role for the eye care provider to initiate screening measures in dry eye patients for these comorbidities. To our knowledge, ours is the first study to discuss this as a possible role for the eye care provider."

"Perhaps the treatment of dry eye disease, then, would also benefit from treatment of depression and/or anxiety. "

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CURRENT OPINION

The role of the intestinal microbiome in ocular inflammatory disease

Phoebe Lin

Curr Opin Ophthalmol 2018, 29:261–266

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CURRENT OPINION

The role of the intestinal microbiome in ocular inflammatory disease

Phoebe Lin

"The intestinal commensal microbiota are important in shaping immune cell repertoire and are influenced by host genetics. Because of this intricate interaction, an intestinal dysbiosis has been associated with multiple immune-mediated polygenic diseases. This review summarizes the literature on how alterations in the intestinal microbiota contribute to immune-mediated ocular disease, and how to potentially target the gut microbiome for therapeutic benefit."

Treating the Intestinal Microbiome?

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- Targeting specific causative bacteria. This could be employed by intelligent, highly specific techniques such as designing immunoglobulins that target specific bacteria or bacterial components/ metabolites that are proven to be contributors to the inflammatory condition, without affecting beneficial bacteria.

- Targeting the intestinal microbiome through the administration of oral live bacterial strains that are known to promote immune homeostasis by enhancing regulatory T cell differentiation. Although these probiotics would need to be designed to maximize colonization in the human gut, in preclinical studies, there appears to be great potential.

Treating the Intestinal Microbiome?

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- Utilizing chemical drugs. For instance, using antibiotics that are not broad-spectrum but instead are chemicals designed to target the metabolic pathways of only a specific community of bacteria.

- Dietary modifications, for example exposing individuals to a **diet high in non-digestible fibers** to enhance the production of endogenous short chain fatty acids by the intestinal microbiota.

- Supplanting an entire community of intestinal bacteria with a normal community using a fecal microbial transplant. This approach has been proven to be curative in antibiotic-resistant *Clostridium difficile* colitis in large clinical trials.

Get Along

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Thank You

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