Updates on Sjögren's Disease

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1

Disclosures

- Consultant: BMS, Novartis, Otsuka/Visterra, Horizon, Target RWE, Horizon, Kiniksa

2

Outline

- History
- Etiopathogenesis
- Diagnosis
- Management

3

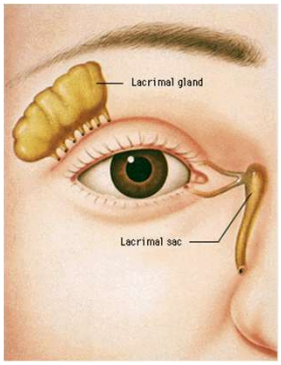
Objectives

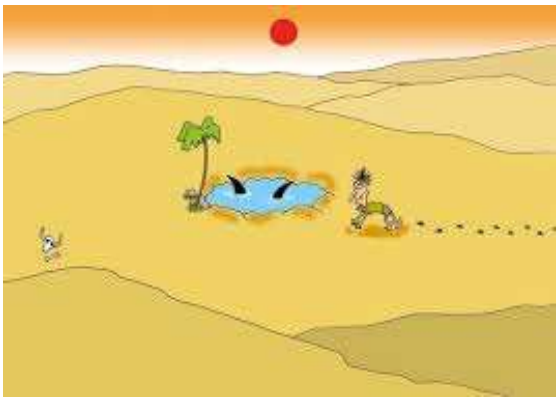
1) Detail how SjD endotypes provide insight to and management of SjD
2) Be familiar with how to diagnose SjD and how this might change in the future
3) Determine how disease activity metrics and trial criteria might affect future therapeutics selection

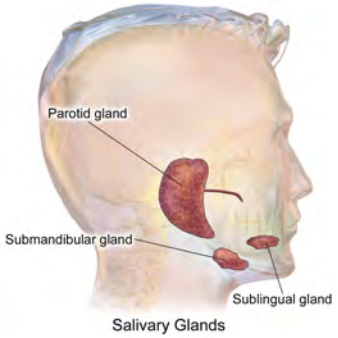
4

Sjögren's ~~Syndrome~~ Disease

Oral/ocular sicca due to chronic inflammation of exocrine glands







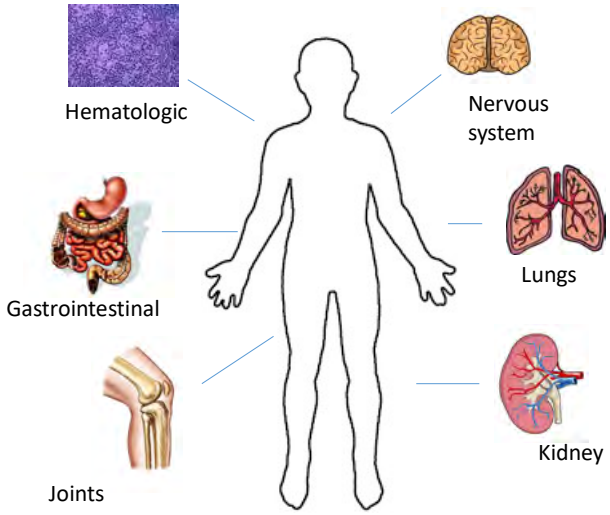
5

Primary vs. ~~Secondary~~ Overlap

- **Primary** Sjögren's
  - alone without another coexistent autoimmune disease
- **Overlap** Sjögren's
  - In presence of another autoimmune disease
  - Example: Rheumatoid arthritis, systemic lupus erythematosus
- Symptoms/diagnosis otherwise the same

6

Extraglandular Involvement



7

History

- 1888: Dr. W.B. Hadden
  - 65 year old female with severe dry mouth
    - Tongue red/ "…dry and cracked in all directions like crocodile skin"
    - Unable to swallow
    - No tears to cry
    - Treated with jaborandi (pilocarpine)
    - Coined "xerostomia"

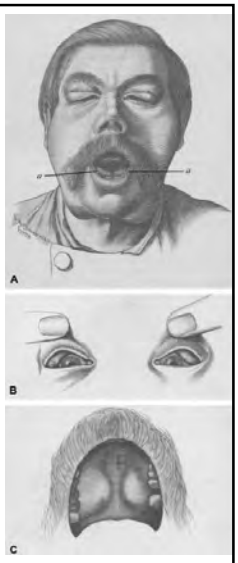
Jaborandi plant

Sarmiento-Monroy et al. 2013; Ihrler et al. 2005

8

History

- 1888: Dr. J Mukulicz
  - 42 year old farmer with painless symmetric swelling of lacrimal and salivary glands
    - Oral and ocular dryness
    - 1 year later died and autopsy showed swollen major salivary glands with inflammatory cell infiltrate
    - "Mukulicz syndrome"



Sarmiento-Monroy et al. 2013; Ihrler et al. 2005

9

History

- 1933 Henrik Sjögren
- 19 women with dryness-13 had RA
- Dr. Marie Sjögren, ophthalmologist, collaborator

10

1. Etiopathogenesis

11

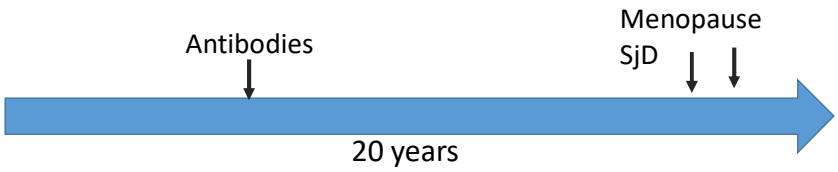
Epidemiology

- Women greater than men: 9:1 -20:1
- Average onset: 56
- Variable estimates of how prevalent: ~1%
- Prevalence in older patients (>55): ~5%

Alamanos et al. Rheumatology. 2006; Qin B et al. Ann Rheum Dis 2015; Patel R et al. Clin Epidemiol 2014

12

Epidemiology



Theander et al. Arthritis Rheumatol. 2015

13

Hormone exposure → increased risk vs. healthy controls

Risk Ratio of Sjögren's Associated with Endogenous and Exogenous Sex-Hormone Exposure			
			Multivariable*
Variable	SjD (n=546)	Control (n=1637)	RR (95% CI)
Endogenous Hormone Exposures			
Endometriosis	220 (40)	541 (33)	1.26 (1.05-1.52)
Hysterectomy, no bilat oophorectomy	**52 (10)**	**85 (5)**	**1.51 (1.13-2.03)**
Fibroids	285 (52)	673 (41)	1.44 (1.19-1.73)
Menstrual Irregularity	112 (21)	229 (14)	1.34 (1.07-1.67)
Menorrhagia	113 (21)	234 (14)	1.36 (1.09-1.68)
PCOS/hirsutism/cysts	**77 (14)**	**127 (8)**	**1.65 (1.28-2.12)**
Post-menopausal	360 (66)	898 (55)	1.46 (1.20-1.77)
Exogenous Hormone Exposures			
Combined HRT ever	48 (9)	98 (6)	1.36 (1.00-1.86)
ERT (any)	**208 (38)**	**386 (24)**	**1.78 (1.47-2.14)**
OCP ever	114 (21)	242 (15)	1.40 (1.09-1.79)
OCP dose (mcg)	11.9 (16)	8.5 (12)	1.01 (1.00-1.02)

McCoy S et al. J Clin Rheum. 2022.

14

BMI→decreased risk vs. healthy controls

Risk Ratio of Sjögren's Associated with Endogenous and Exogenous Sex-Hormone Exposure			
			Multivariable*
Variable	SjD (n=546)	Control (n=1637)	RR (95% CI)
BMI (continuous)	28.8 (10)	30.3 (8)	0.98 (0.97-0.99)

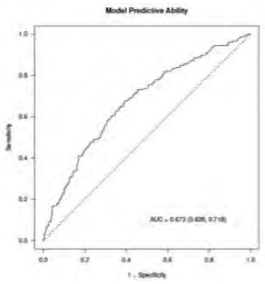


Table 6. Optimized Multivariable Model Association with Sjögren's

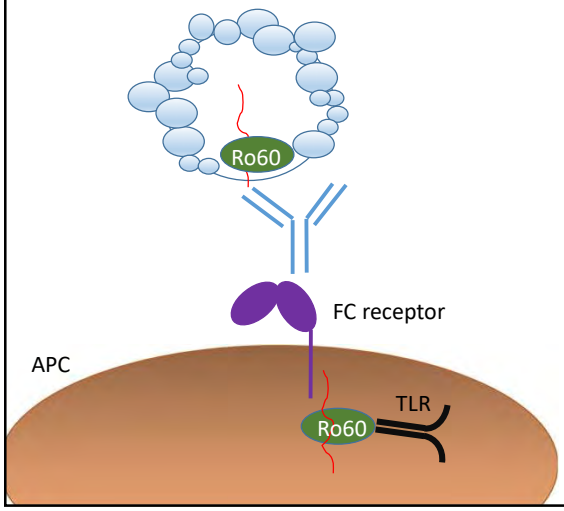
	Coefficient	OR (95% CI)	p-value
Intercept	-0.783		
Fibromyalgia	0.917	2.50 (1.93 – 3.25)	< 0.001
Diabetes	-1.303	0.27 (0.13 – 0.50)	< 0.001
Osteoporosis	0.612	1.84 (1.27 – 2.66)	0.001
BMI	-0.027	0.97 (0.95 – 0.99)	0.005
HRT Ever	0.0475	1.61 (1.22 – 2.12)	0.001

BMI=body mass index; HRT=estrogen-only hormone replacement therapy; n=96 subjects excluded for missing data.

McCoy S et al. J Clin Rheum. 2022.

15

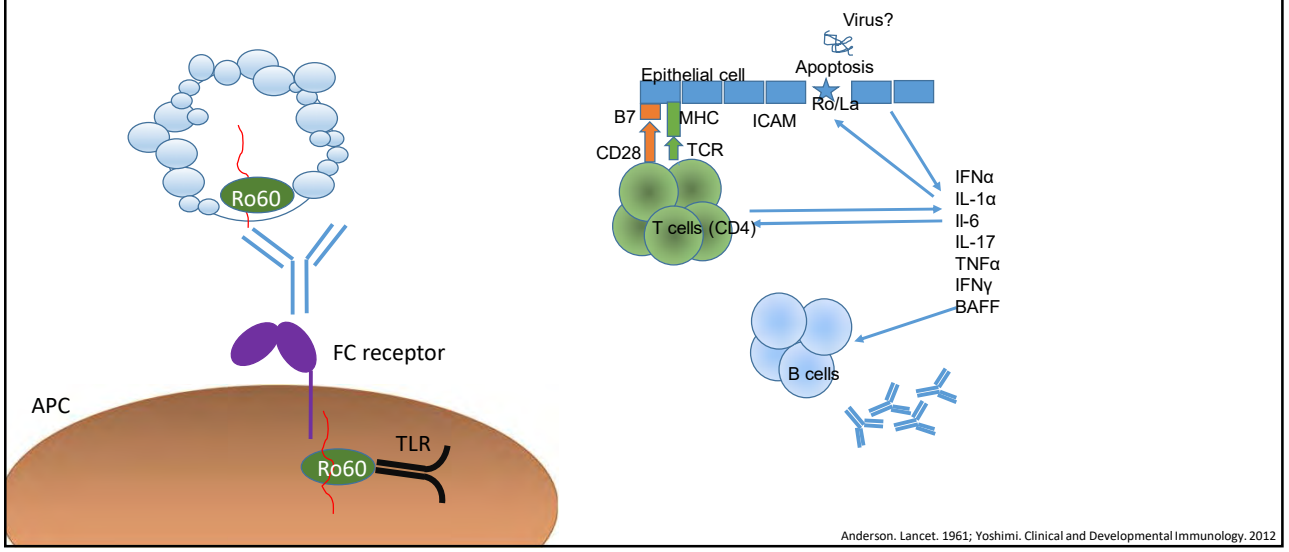
Pathogenesis



Anderson. Lancet. 1961; Yoshimi. Clinical and Developmental Immunology. 2012

16

Pathogenesis



Anderson. Lancet. 1961; Yoshimi. Clinical and Developmental Immunology. 2012

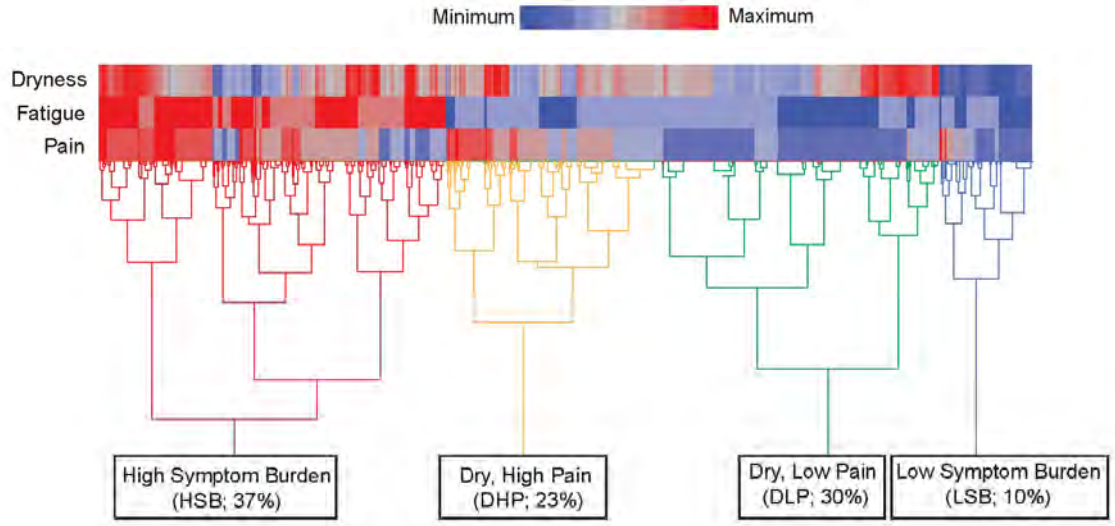
17

Stratification for Pathogenic Insights

- Heterogeneity
- Stratification→
  - Increased pathogenic insight into subgroups
  - Promotes therapy tailored to subgroup
  - Improves patient-provider relationships

18

Four symptom based clusters



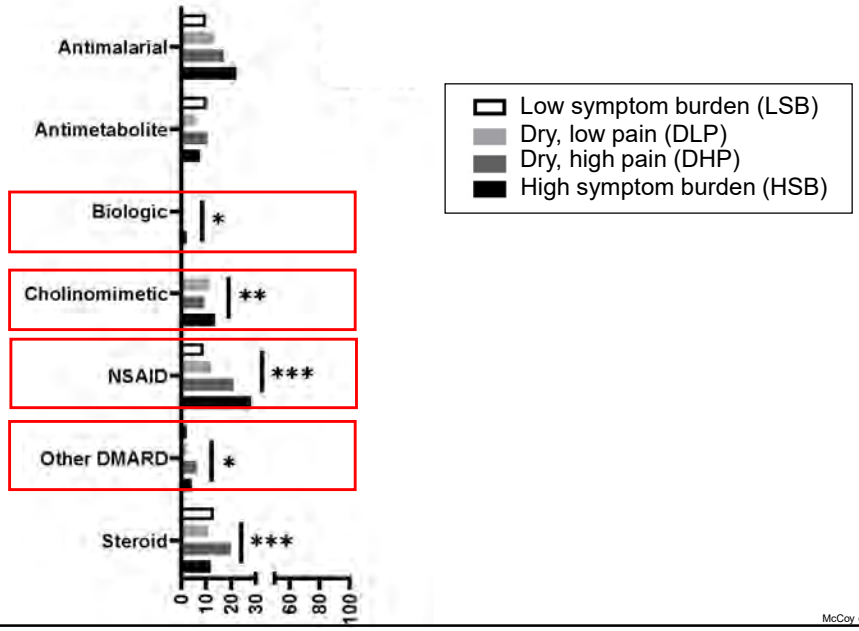
Total: 1,454

N=540 N=336 N=432 N=146

McCoy et al. A&R 2022

19

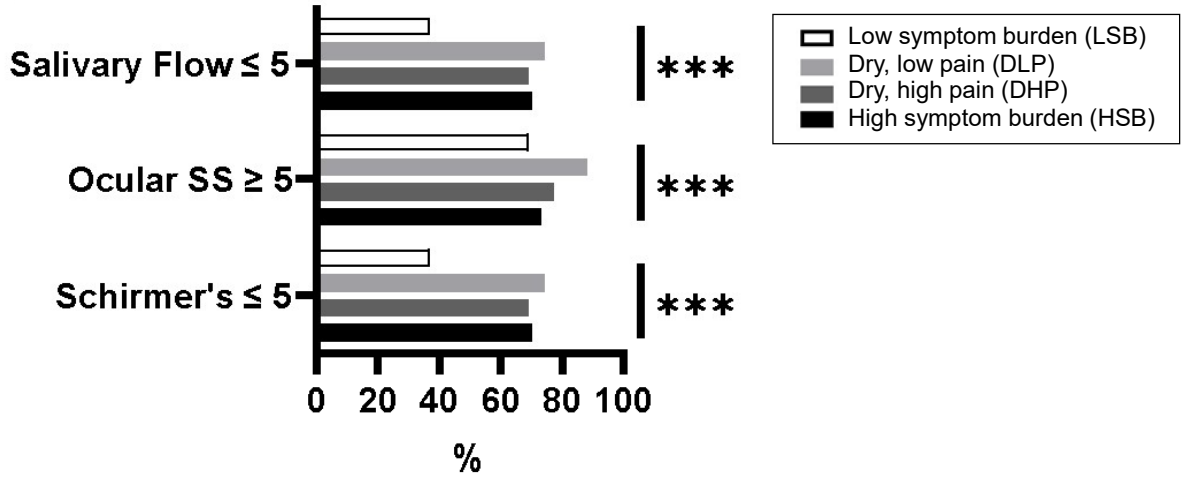
High symptom burden cluster uses cholinomimetics, NSAIDs, DMARDs & biologics frequently



McCoy et al. A&R 2022

20

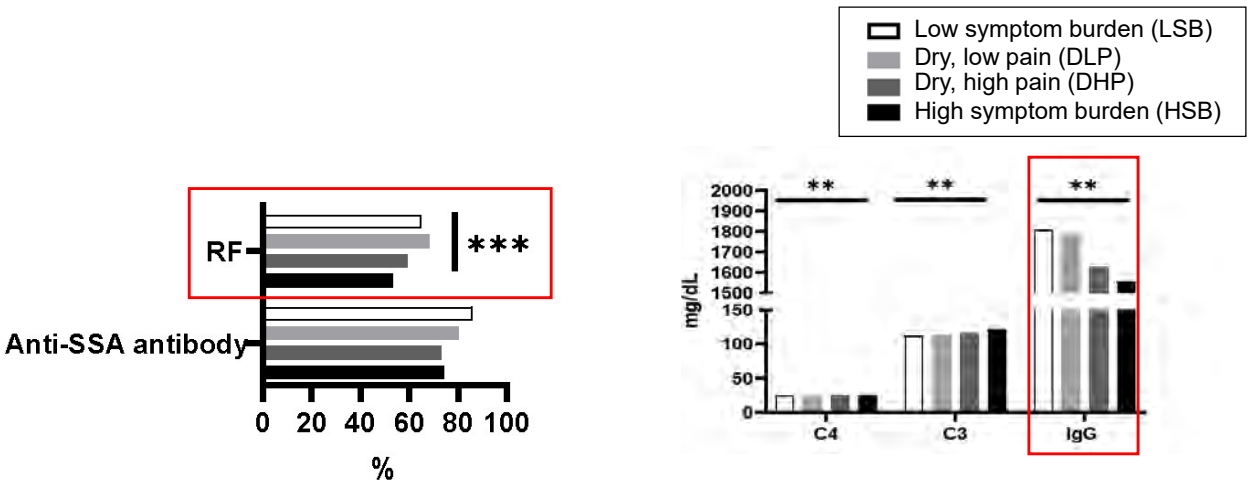
Dry, high pain cluster has the highest sicca frequency



McCoy et al. A&R 2022

21

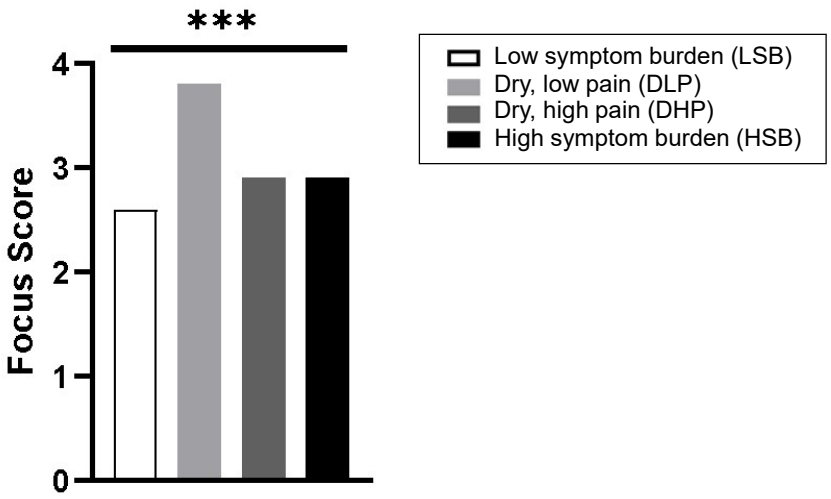
High symptom burden cluster has lowest RF & IgG



McCoy et al. A&R 2022

22

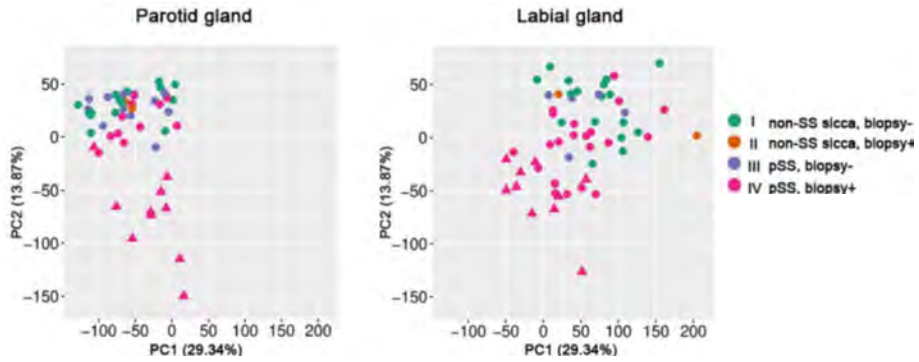
Dry, low pain cluster has highest focus score



McCoy et al. A&R 2022

23

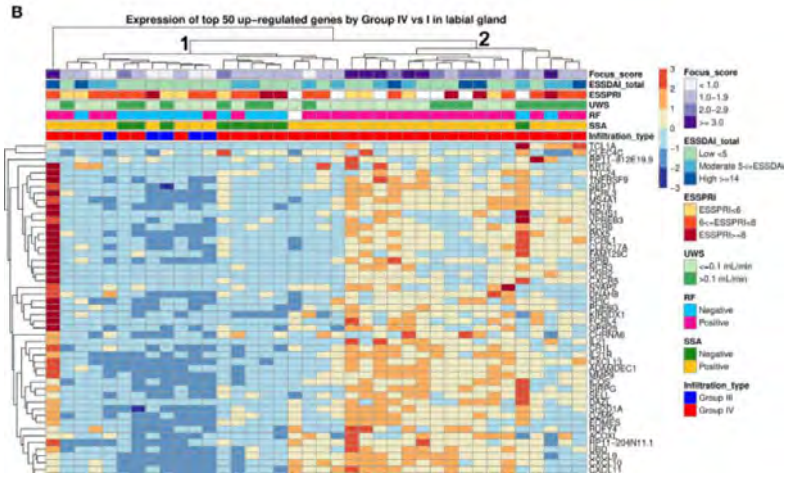
Subtypes: gland transcriptome



Verstappen et al. Frontiers in Immunology. 2021.

24

Subtypes: gland transcriptome



Verstappen et al. Frontiers in Immunology. 2021.

25

Etiopathogenesis summary

- Evolving role for sex hormones in SjD
- Increased understanding of SjD endotypes

Future directions

- scRNAseq
- Tissue-based methods

26

2. Diagnosis

27

Symptoms of Dry Eye

- "Do you have a recurrent sensation of sand or gravel in the eyes?"
- "Have you had daily, persistent, troublesome dry eyes for more than three months?"
- "Do you use tear substitutes more than three times a day?"

Vitali c et al. A&R 1993

28

Symptoms of Dry Mouth

- Have you had a daily feeling of dry mouth for more than 3 months
- Do you frequently drink liquids to aid in swallowing dry food (crackers)?
- "Have you had recurrently or persistently swollen salivary glands as an adult?"
  - Specificity 98%

Vitali c et al. A&R 1993

29

Evaluation: SjD specific

- Physical Exam
  - Ocular and Oral
  - Gland
  - Neuro

30

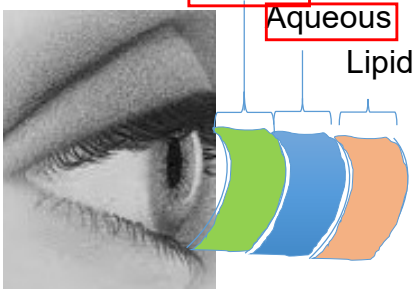
Oral Exam

- Rule out other causes
- Salivary pooling
- Glandular exam
- Unstimulated Salivary Flow
  - Weigh collection receptacle
  - Position/prepare patient
  - Collect in receptacle x 5 minutes
  - Weigh collection receptacle
  - Classification criteria: ≤0.1 ml/minute
    - 1 g = 1mL

31

Ocular Exam

- Rule out other causes



32

Ocular Exam

- Dry Eyes
  - Schirmer's Test
    - ≤5 mm/5 minutes
  - Ocular Staining Score
    - ≥ 5 in at least one eye

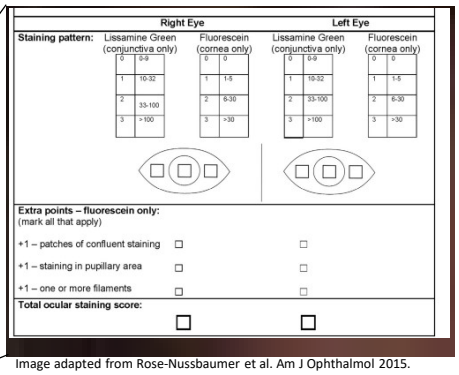
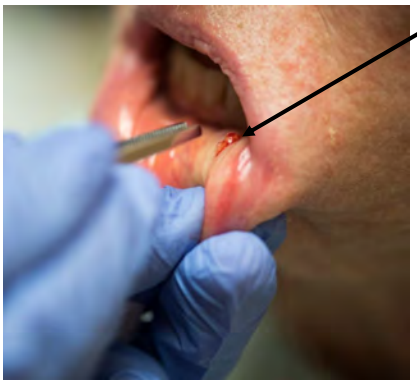


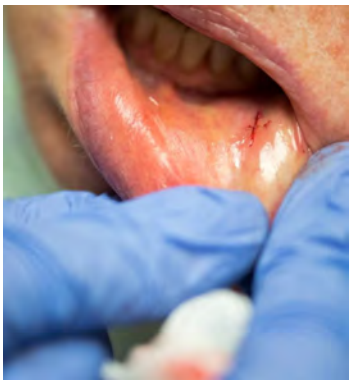
Image adapted from Rose-Nussbaumer et al. Am J Ophthalmol 2015.

33

Further testing-Minor salivary gland (lip) biopsy

Minor Salivary Gland

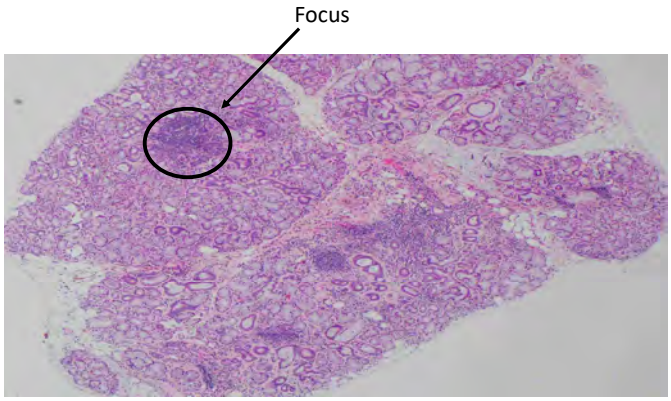


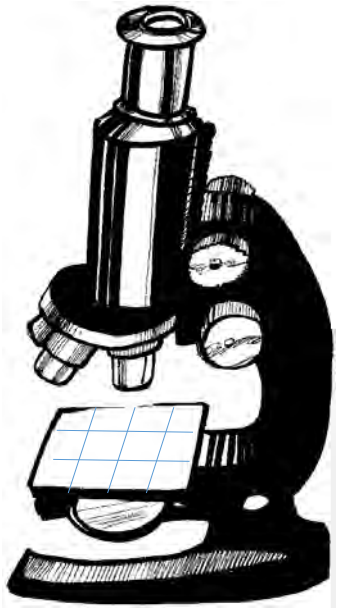


34

Focus Score

- Number of foci (50 lymphocytes) per 4 mm^2





Focus score ≥ 1 foci/4mm^2 supports diagnosis

35

Autoantibodies

Lab	Prevalence
Anti-SSA Ab	60-80%
ANA	60-85%
Rheumatoid Factor	50%

Others: Complement , hypergammaglobulinemia, inflammatory marks (ESR and CRP)

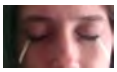
Mariette X et al. NEJM. 2018; Patel R et al. Clin Epidemiol. 2014

36

Diagnosis: ACR/EULAR Classification Criteria

- Total score ≥ 4

Category	Score
Schirmer's ≤5 mm/5 minutes	1
Ocular Staining Score ≥ 5 in at least one eye	1
Unstimulated Whole Salivary Flow ≤0.1 ml/minute	1
Focus score ≥ 1	3
Ant-SSA (Ro) antibody (Or RF + ANA?)	3



Criteria does not = diagnosis

Shiboski C et al. Arthritis Rheumatol. 2017

37

SjD other testing

- CBC with dif→cytopenias
- CMP→acidosis, renal disease, autoimmune hepatitis, PBC
- Complement, Cryoglobulins, Immunoglobulins→Disease Activity
- LDH, SPEP, UPEP→Malignancy/monoclonal IgGs (10-20%)
- UA/UPC→Renal disease

38

What about the new antibodies?

- anti-salivary protein 1 (anti-SP-1)
- anti-carbonic anhydrase 6 (anti-CA 6)
- anti-parotid secretory protein (anti-PSP)
- Sjo panel

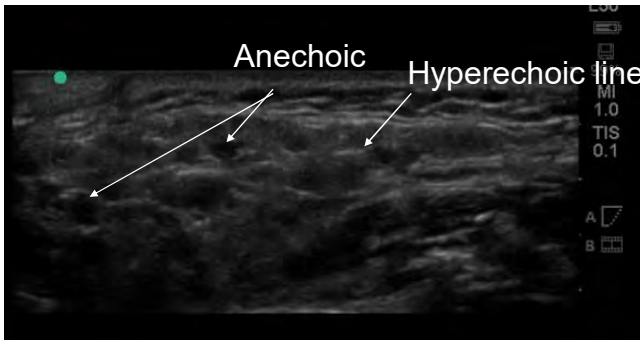
39

SjD Imaging

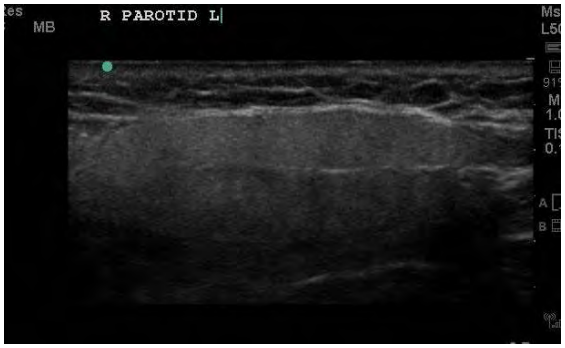
- Imaging
  - Salivary scintigraphy
  - X-ray sialography
  - MR sialography
  - PET
  - US

40

SjD imaging characteristics



Sjögren's parotid gland

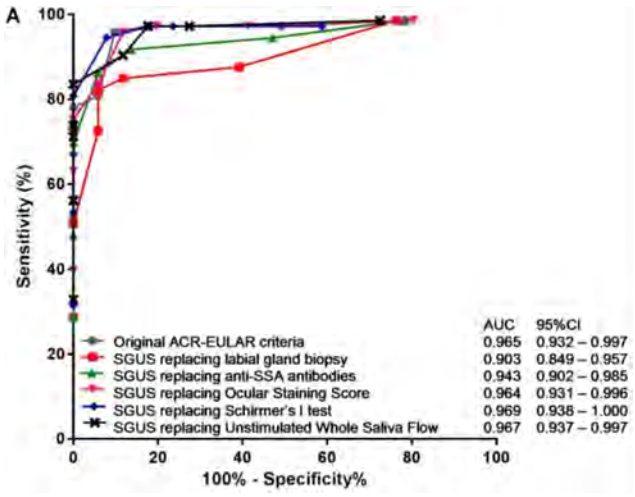


Normal parotid gland

Cornec D et al. Arthritis Rheum 2013; Takagi Y et al. Plos One 2018, Mossel E Ann Rheum Dis. 2017

41

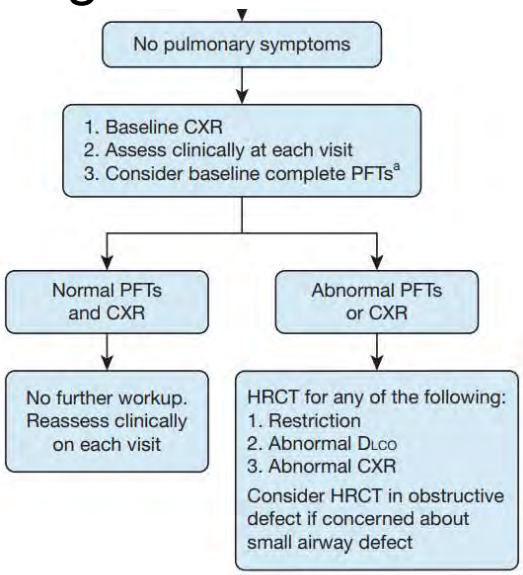
SGUS in ACR/EULAR criteria



Nimwegen et al. Arthritis care Res. 2020

42

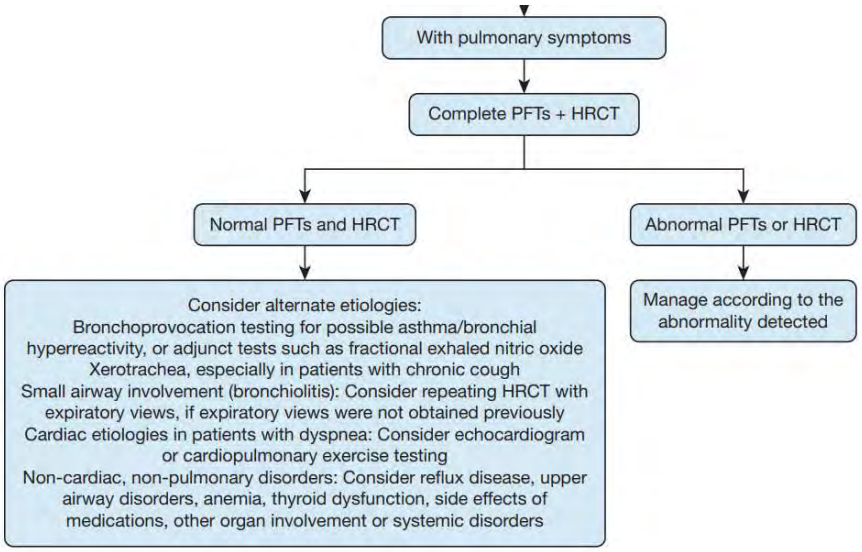
Pulm Screening Guidelines



Lee et al. Chest. 2021

43

Pulm Screening Guidelines



Lee et al. Chest. 2021

44

3. Management

45

Treatment-Dry Eye

- Evaluate for other causes
  - ie blepharitis, retinoids
- Over the counter wetting drops/gels
  - Preservative free
- Protection/humidification
  - Moisture chamber eyewear
- Punctal Plugs
- Prescriptions
  Cyclosporine
  Lifitigrast
- Scleral Lens
- Serum Tears

46

Treatment-Dry mouth

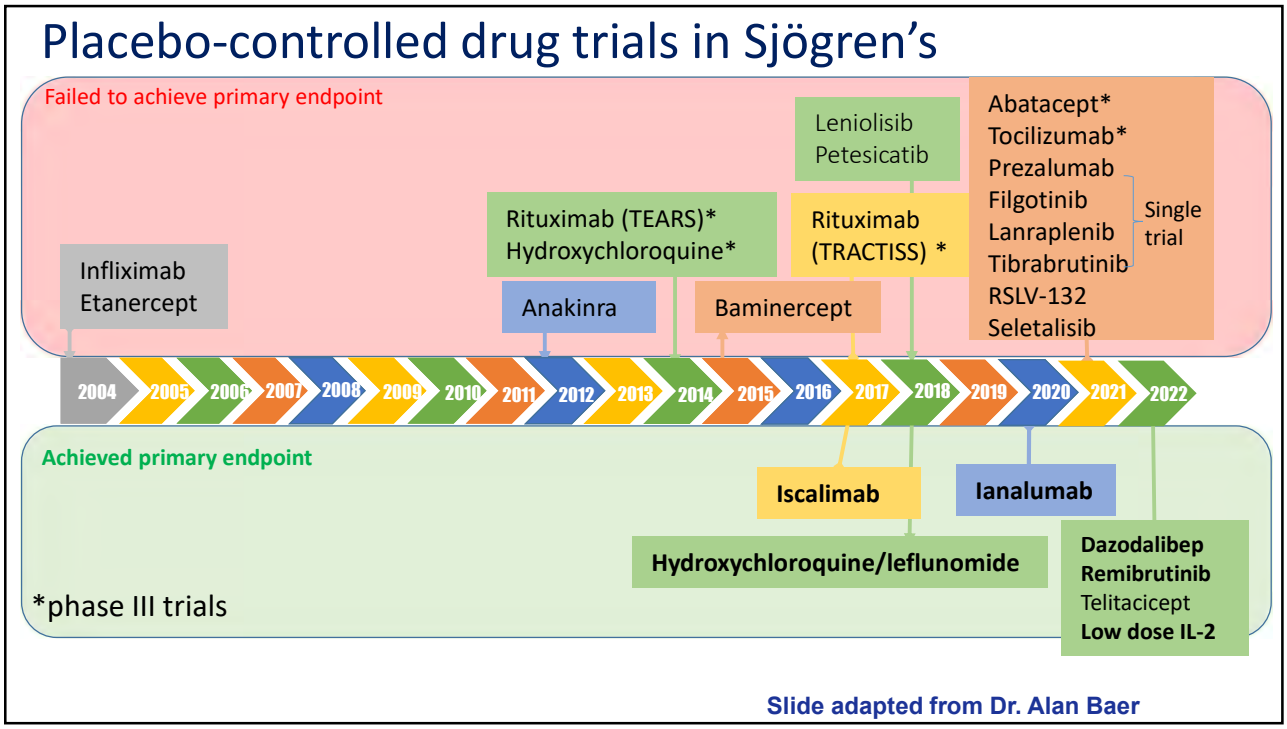
- Avoid mouthwash or rinse containing astringents (e.g., alcohol)
- Use sugar-free gum, candies, or lozenges (Xylitol preferred)
- Wetting sprays for short term relief
- Moisturizing gels and oils (coconut oil, sesame oil, olive oil)
- Treat concomitant candida infections
- Sialagogues

47

Treatment-Caries Prevention

- Nightly use of prescription-strength toothpaste
- Fluoride varnish applied by a dentist every 3 months
- Promote saliva production
- Avoid tooth abrasives
- If acids are consumed, rinse the mouth with 1 tsp baking soda mixed in 8 oz of water

48



49

Wrap up

1) Increasing pathogenic insights into SjD endotypes will hopefully yield improved care for SjD patients
2) Correct diagnosis is of utmost importance and might have significant future treatment consequences.
3) Promising new drugs-but not might be applicable to all

50

Acknowledgements

Mentors/Collaborators

- Jacques Galipeau
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- Franklin Zhao

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Sjögren's Foundation (PI McCoy)

CTSA through NCATS, 1KL2TR002374 (PI McCoy)

NIDCR R03 (PI McCoy)

51

Questions?

"Medicine is a science of uncertainty and an art of probability"

-William Osler

52