Systemic Lupus Erythematosus: Prevalence, Severity, and Identification in American Indian/Alaska Native Populations

Elizabeth D. Ferucci, MD, MPH

June 25, 2015

IHS Clinical Rounds

ALASKA NATIVE
TRIBAL HEALTH
CONSORTIUM

Disclosures

- I have no relationships with any entity producing, marketing, re-selling, or distributing health care goods or services.

- The standard of care for treatment of lupus is almost all off-label. I will discuss off-label medication use.

Objectives

1. Estimate the prevalence of systemic lupus erythematosus (SLE) in the US, and compare the prevalence in AI/AN populations to other racial/ethnic minorities.

2. Recognize possible clinical presentations of SLE and use these to guide the initial evaluation and assist with appropriate referrals.

3. Describe the range of severity that can be seen in SLE and understand that the disease is often worse in racial/ethnic minority populations.

"There is no more difficult disease to diagnose, understand, or treat than the disease called *systemic lupus erythematosus*."

Preface to Lupus Q&A, Robert Lahita and Robert Phillips

Systemic Lupus Erythematosus (SLE)

An inflammatory, multisystem, autoimmune disease of unknown etiology with protean clinical and laboratory manifestations and a variable course and prognosis. Lupus can be a mild disease, a severe and life-threatening illness, or anything in between.

Part 1

PREVALENCE AND INCIDENCE OF SLE

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 9, September 2014, pp 2494–2502
DOI 10.1002/art.38720

Prevalence and Incidence of Systemic Lupus Erythematosus in a Population-Based Registry of American Indian and Alaska Native People, 2007–2009

Elizabeth D. Ferucci,[1] Janet M. Johnston,[2] Jasmine R. Gaddy,[3] Lisa Sumner,[4] James O. Posever,[4] Tammy L. Choromanski,[1] Caroline Gordon,[5] S. Sam Lim,[6] and Charles G. Helmick[7]

Arthritis and Rheumatology, September 2014, Vol. 66, No. 9, pp. 2494-2502.

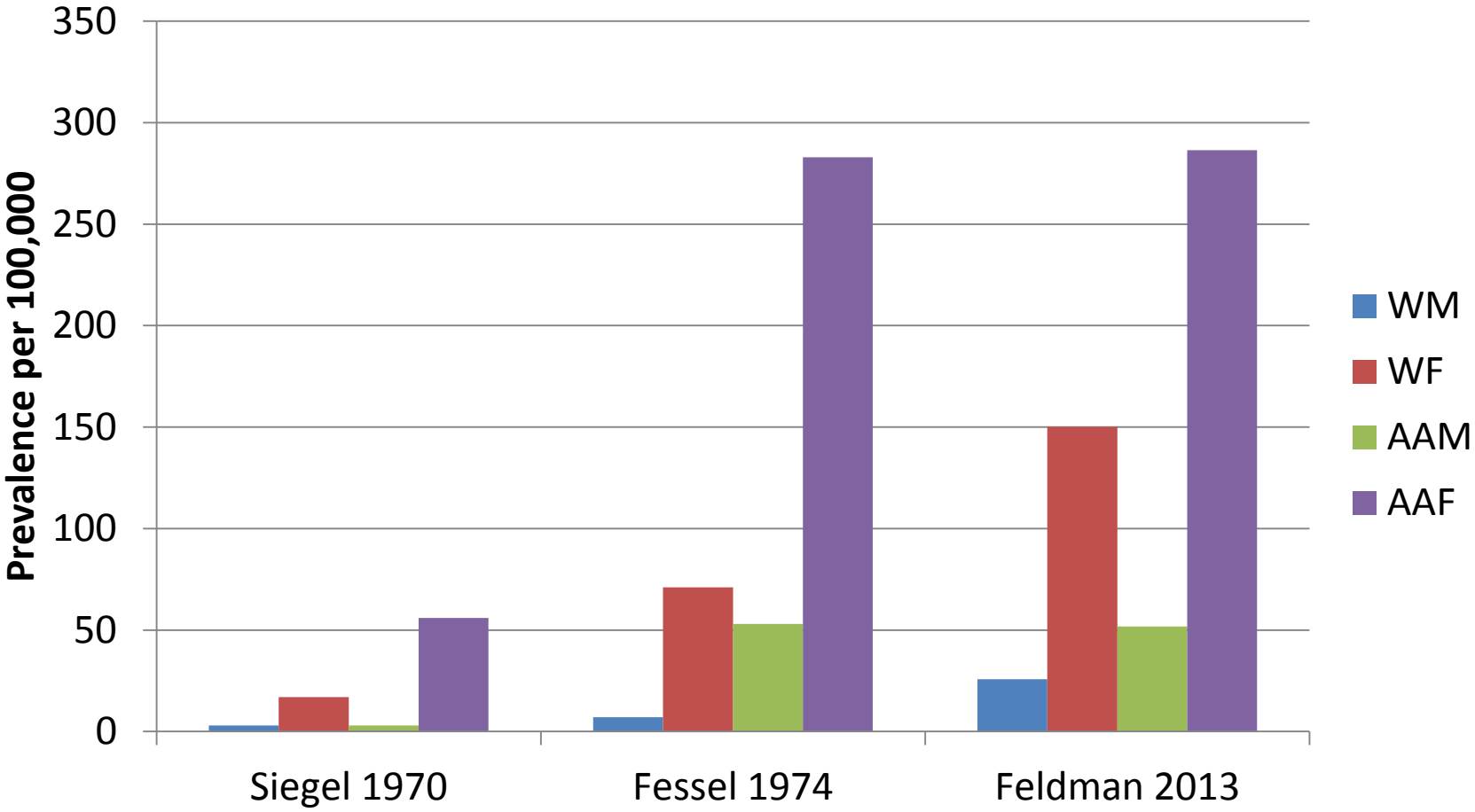
Background: SLE in Populations

- US population rates
  - **Prevalence: 15-144 per 100,000**
  - **Incidence: 1.8-23.2 per 100,000 per year**

- Highest rates in women and US blacks
  - 10:1 female:male ratio
  - Rates up to 5 times higher in blacks than whites
  - **Prevalence in black women: 58-286 per 100,000**

1. Lim SS, Drenkard C. Curr Rheumatol Rep 2008; 10:265
2. Feldman CH, et al. Arthritis Rheum 2013;65:753.

Disparities in Lupus Prevalence



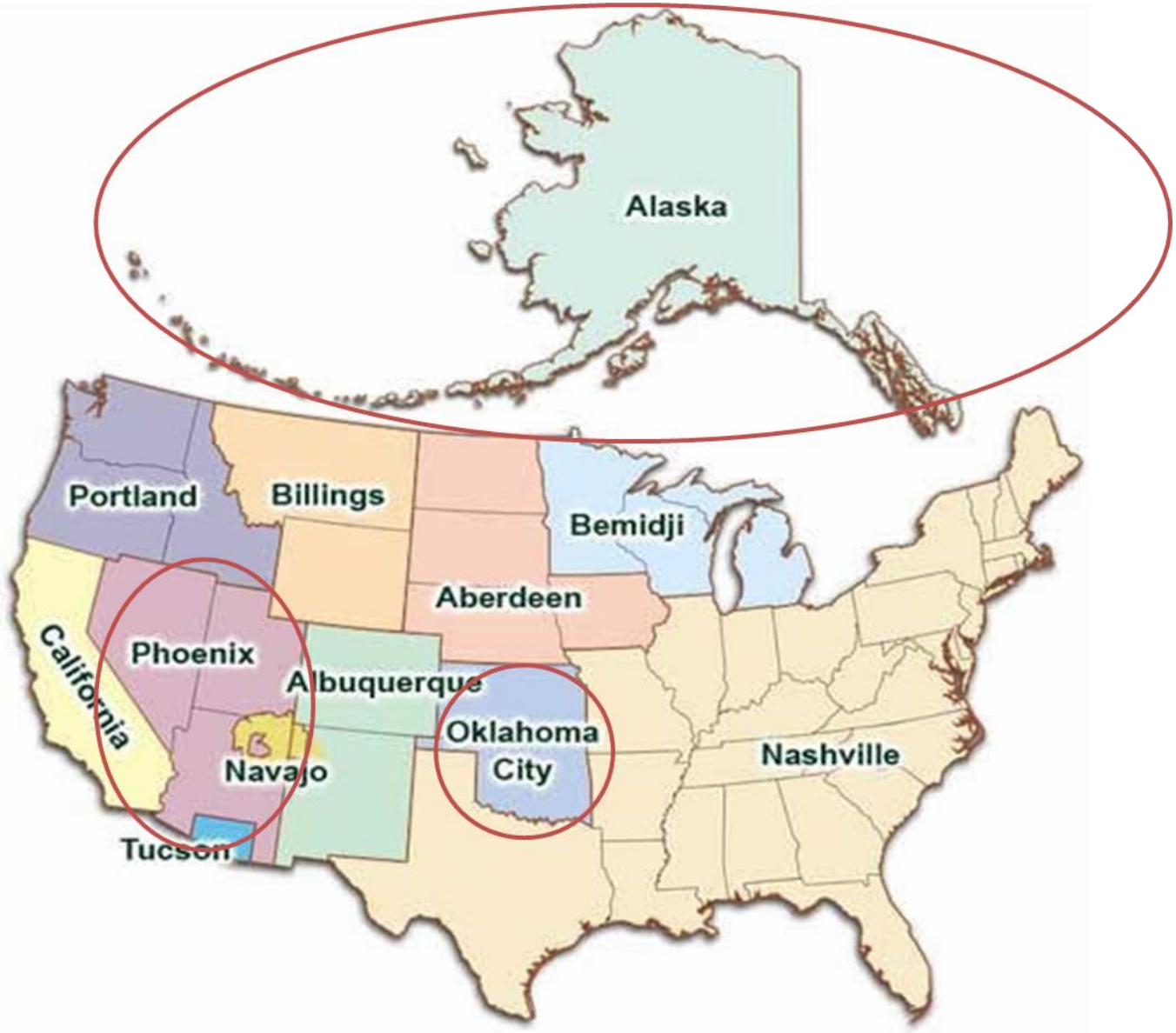
WM: white men; WF: white females; AAM: African-American men; AAF: African-American females

Objectives of IHS Lupus Registry

- This population-based registry was created with the objective to determine the **prevalence (2007)** and **incidence (2007-2009)** of **SLE** in the **Indian Health Service** (IHS) active clinical population in 3 regions of the US.

- Using comparable methods to 4 other CDC-funded registries in order to compare rates by race/ethnicity.
  - Georgia, Michigan—1st round
  - New York City, California, IHS—2nd round

Indian Health Service Area Map



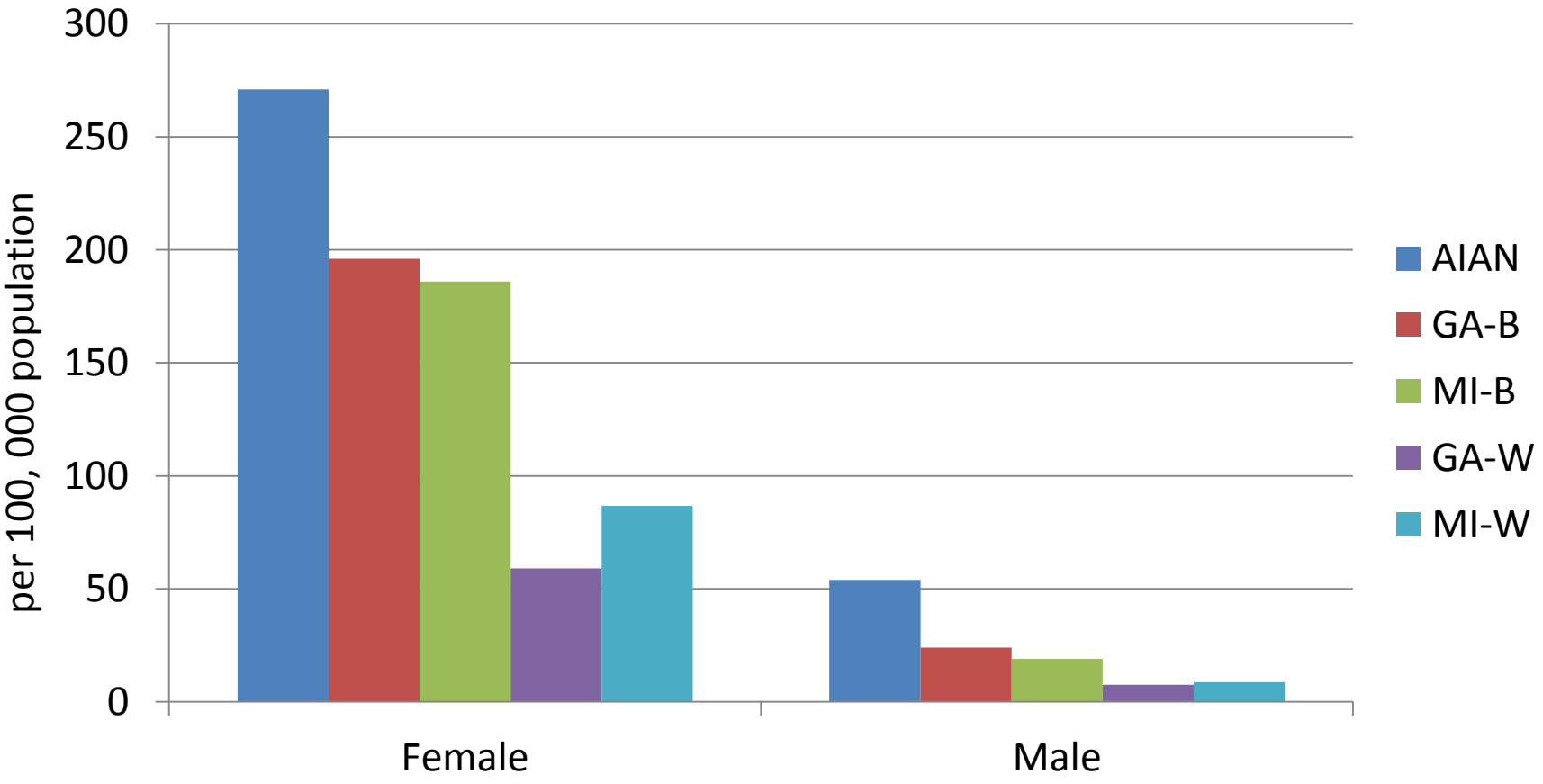
Methods

- Potential case ascertainment
  - Identified from the IHS National Data Warehouse
  - Using ICD-9 codes associated with SLE and related connective tissue disorders
  - Database populated with demographic information
- Field medical record abstraction
  - For all potential cases in the database
  - Data elements necessary for verification of SLE classification criteria
  - Trained abstractors with QC protocol

Primary Case Definition

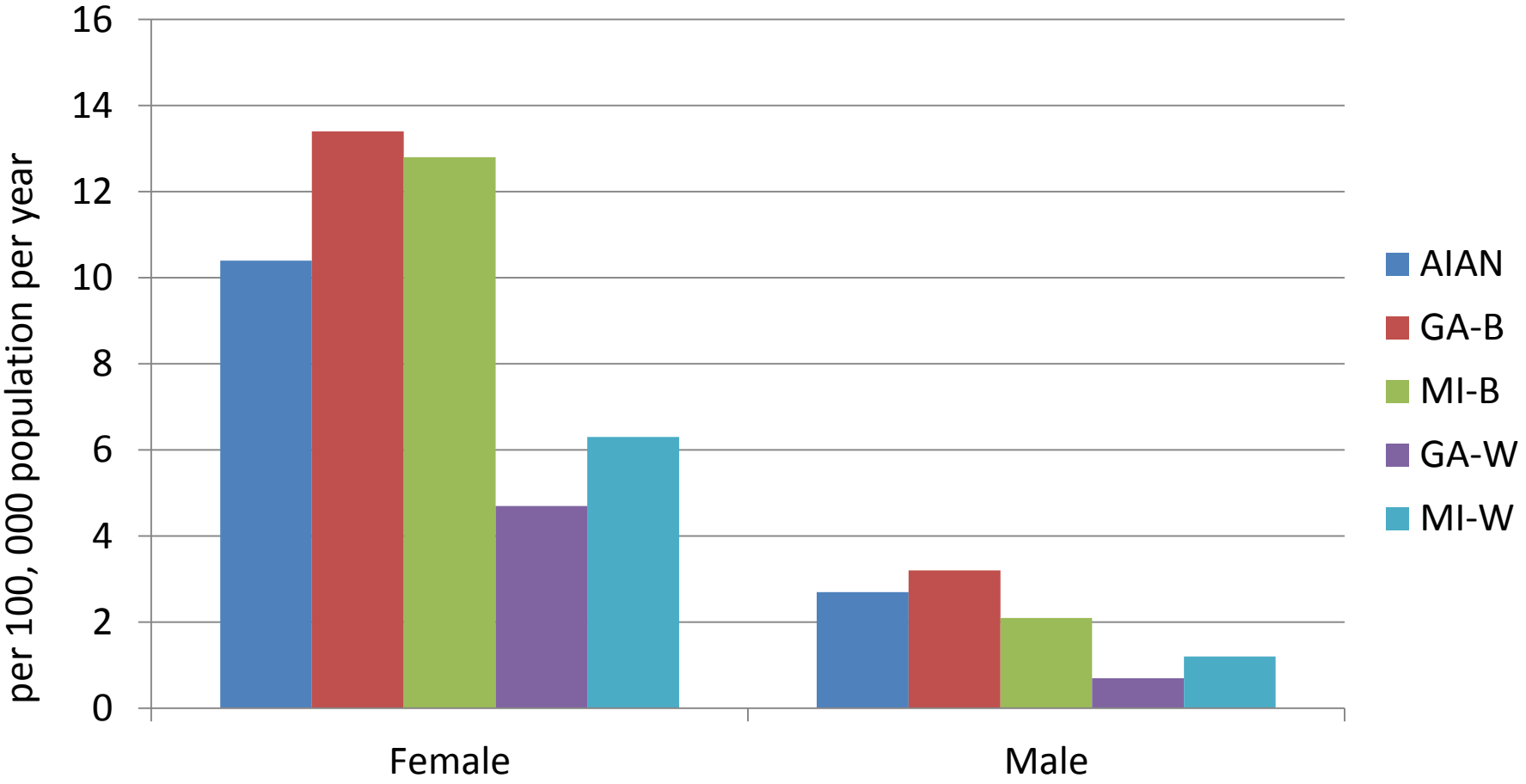
- 4 or more of the 11 American College of Rheumatology (ACR) classification criteria for SLE documented in the medical record

Prevalence of SLE in CDC registries



AIAN: American Indian/Alaska Native from IHS registry; GA-B: Georgia Registry—Black; MI-B: Michigan Registry—Black; GA- W: Georgia Registry—White; MI-W: Michigan Registry—White

Incidence of SLE in CDC registries



AIAN: American Indian/Alaska Native from IHS registry; GA-B: Georgia Registry—Black; MI-B: Michigan Registry—Black; GA- W: Georgia Registry—White; MI-W: Michigan Registry—White

Possible explanations for high rates in AI/AN populations

- Genetic factors
  - HLA, multiple other loci associated with SLE in large genomewide association studies
  - Frequency/role of individual genes/SNPs unknown in AI/AN populations

- Environmental facotrs
  - Tobacco, UV light exposure, infections all found to play a role in SLE development
  - Role of these unknown in AI/AN populations

SLE in US Hispanics and Asians

- California Lupus Surveillance program found highest prevalence in Black women, with Hispanic and Asian women's prevalence intermediate between Black and White

- Hawaiian study from 1970s found rates in Asian and Native Hawaiian population were higher than Whites in Hawaii

1. Arthritis Research and Therapy 2014, Volume 16 Suppl 1;
2. Arthritis Rheum. 1979;22(4):328.

Part 2

CLINICAL PRESENTATION AND INITIAL EVALUATION

Case 1

- 39 year old woman has had swollen and stiff hand joints for one year (MCP and PIPs), with morning stiffness, referred to rheumatology for suspected rheumatoid arthritis
- ROS: photosensitivity
- Exam: patchy alopecia, inflammatory arthritis
- Labs: WBC 3.0, ALC 0.8, SCr 0.6, UA normal, ANA+ 1:320 titer, RF-, CCP-, Sm+, dsDNA-, SSA/SSB-, RNP-
- What is the diagnosis, and **why?**

Case 2

- 33 year old woman presents with:
- Inflammatory arthritis, +ANA for 4 years
- 1 year ago: pericardial and pleural effusions, resolved with prednisone
- Now: fever, cough. Labs: SCr 3.8, WBC 3.4, C3 61↓, C4 9↓, 3.1 g proteinuria, UA lrg bld
- Autoantibodies: ANA/dsDNA/SSA/SSB/RNP+
- Other sx's: photosensitivity, Raynaud's, pruritic rash, oral ulcers
- What is the diagnosis, and **why?**

Systemic lupus erythematosus

- Systemic autoimmune disease
- Not organ-specific
  - Diverse presentations, evolve over time
- Hallmark is autoantibodies
- Characterized by remissions and exacerbations (“flares”)
- Prognosis (and therapy) varies by organ involvement and severity

ACR Classification Criteria (4 of 11 required for classification as SLE)

1. **Malar rash**
2. **Discoid rash**
3. **Photosensitivity**
4. **Oral ulcers**
5. **Arthritis**
6. **Serositis**
7. **Renal disorder**: proteinuria, cellular casts
8. **Neurologic disorder:** Seizures and/or psychosis
9. **Hematologic disorder:** Immune-mediated hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia
10. **Antinuclear antibodies (ANA)**
11. **Immunologic disorder:** anti-DNA antibody, anti-Sm antibody, or antiphospholipid antibodies

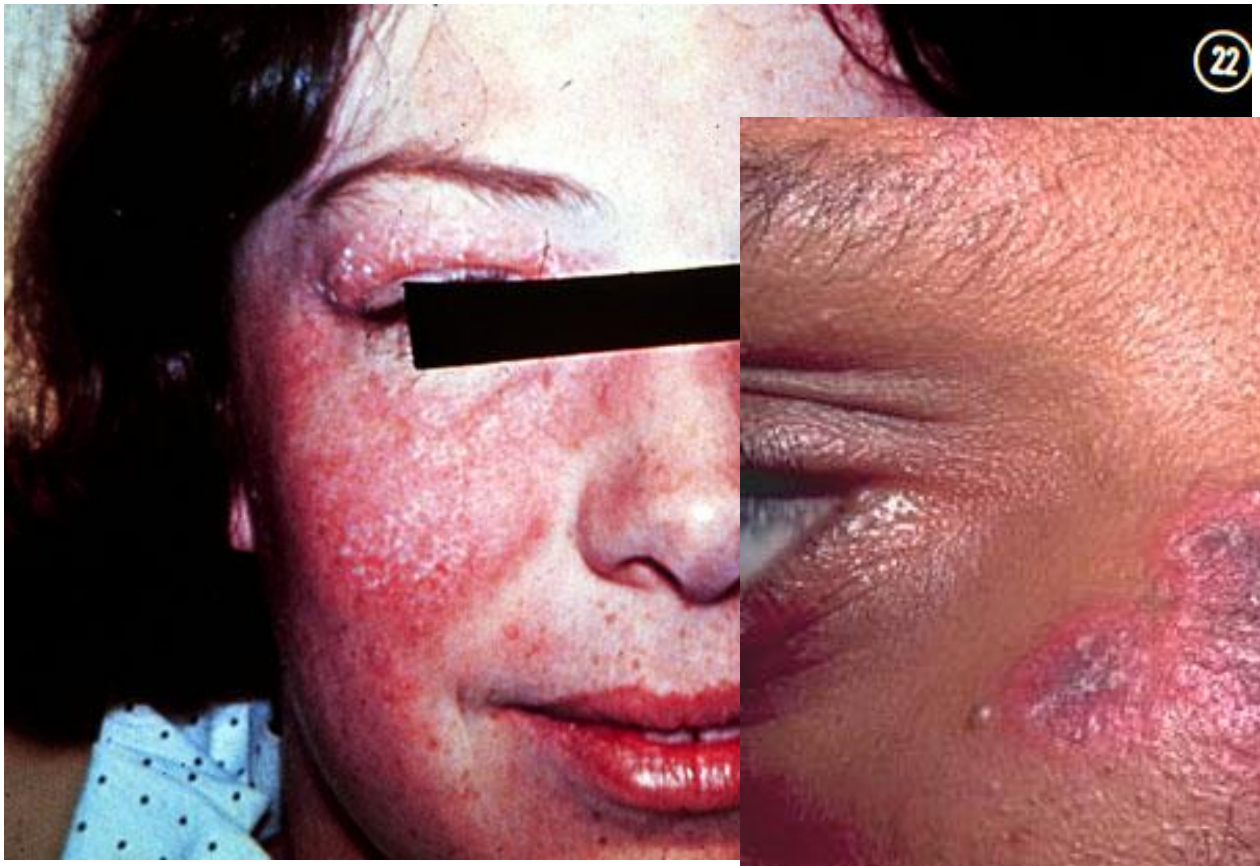
Tan EM, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.

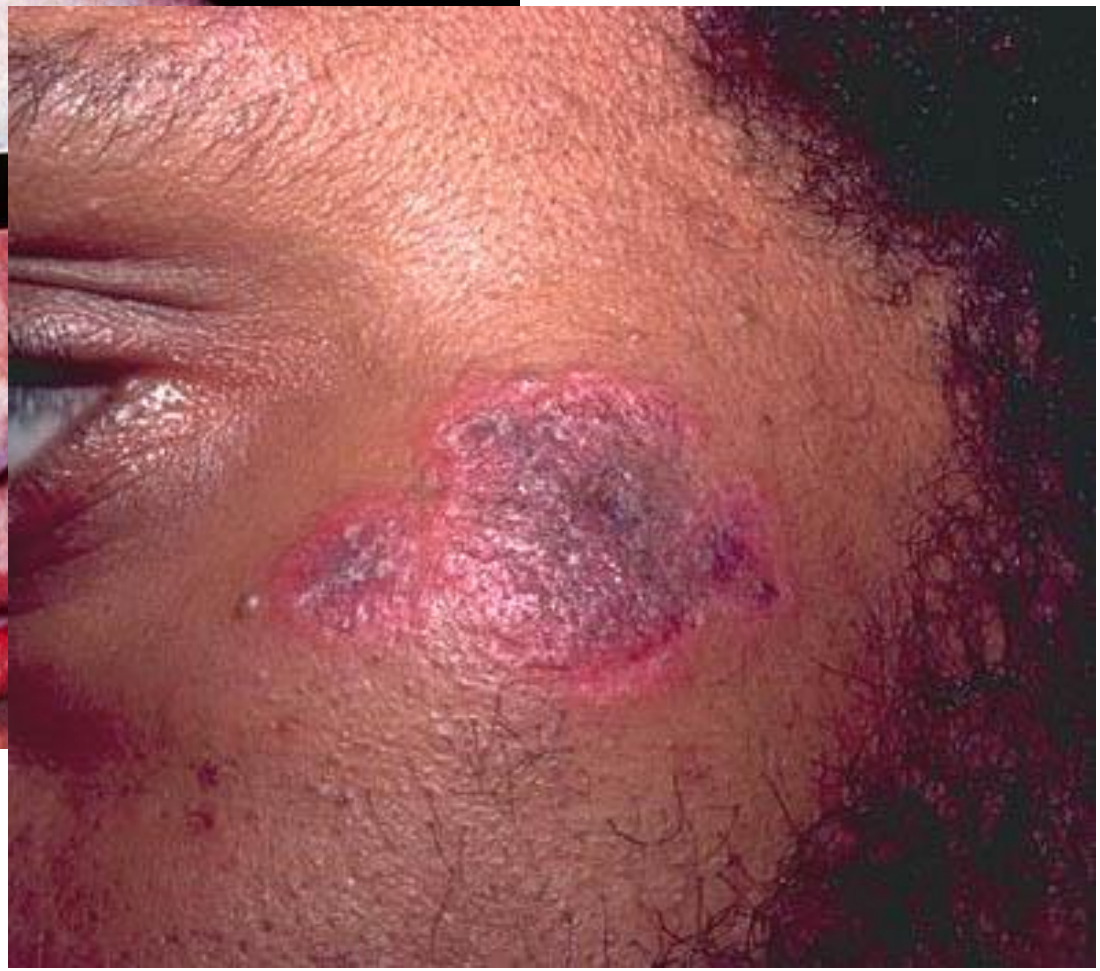
Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum* 1997;40:1725.

Diagnostic Criteria for SLE

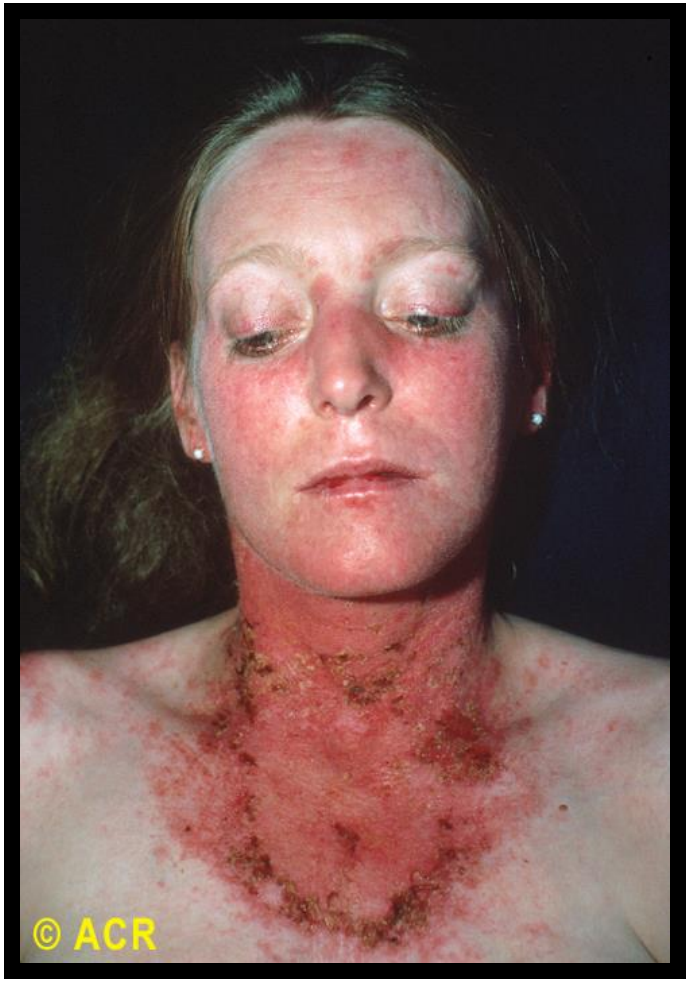
- Clinical (history and physical)
  - Rashes (malar, discoid, photosensitivity)
  - Oral ulcers
  - Arthritis
  - Pleuritis or pericarditis
  - Seizures, psychosis
- Lab
  - Renal (proteinuria, cellular casts)
  - Hematologic (leukopenia, lymphopenia, hemolytic anemia, thrombocytopenia)
  - Autoantibodies (ANA, dsDNA, Sm, antiphospholipid antibodies)

SLE Rashes



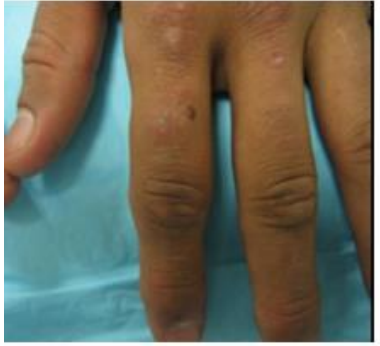


Systemic lupus erythematosus: photosensitivity, face and neck

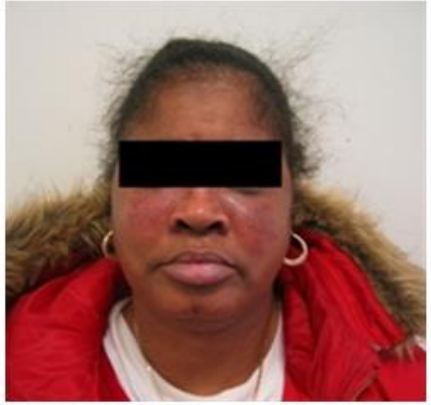


Other manifestations of SLE

- Acute or chronic cutaneous LE, not malar or discoid
- Neurologic disorders, other than seizures or psychosis
- Alopecia
- Low complements (C3, C4)
- Pneumonitis
- Myocarditis, Libman-Sacks endocarditis
- Autoimmune hepatitis

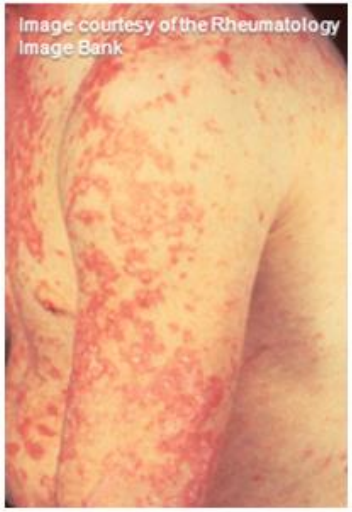


synovitis

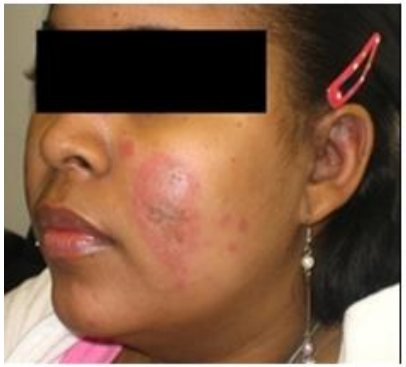


malar rash

oral ulcer

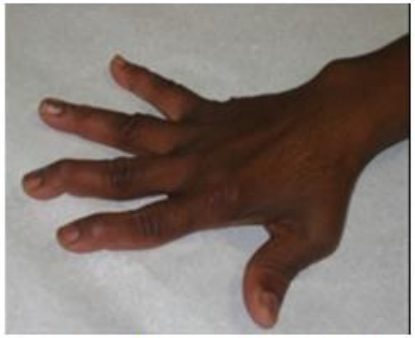


subacute cutaneous lupus erythematosus

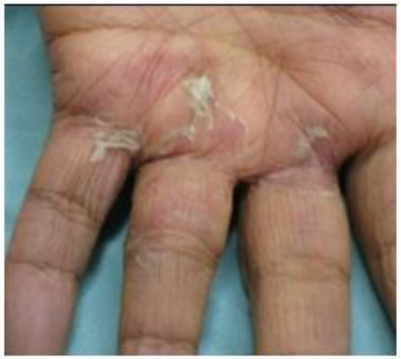


discoid rash

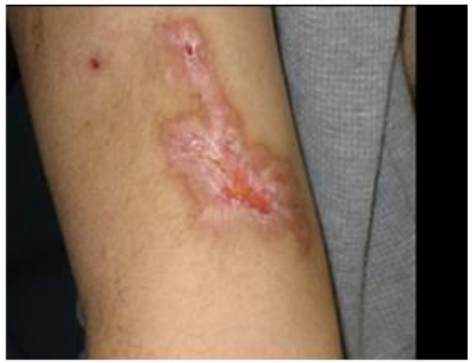
Lupus
on the Outside



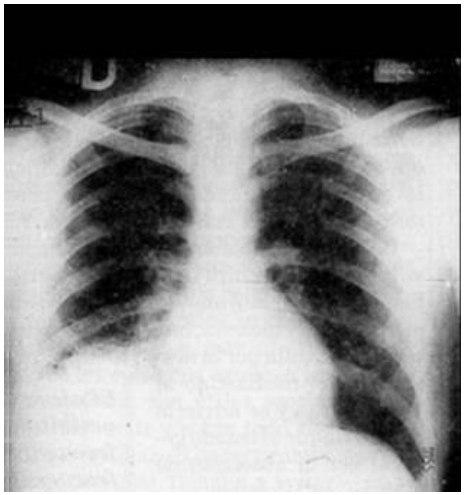
Jaccoud's arthropathy



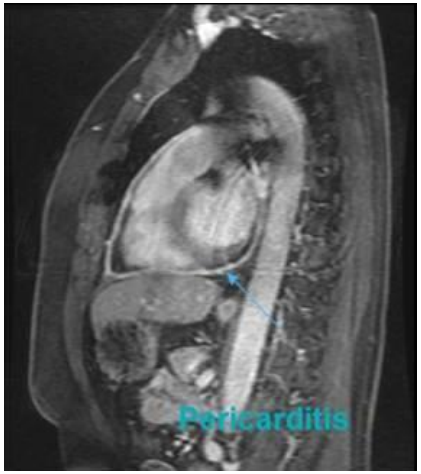
vasculitis



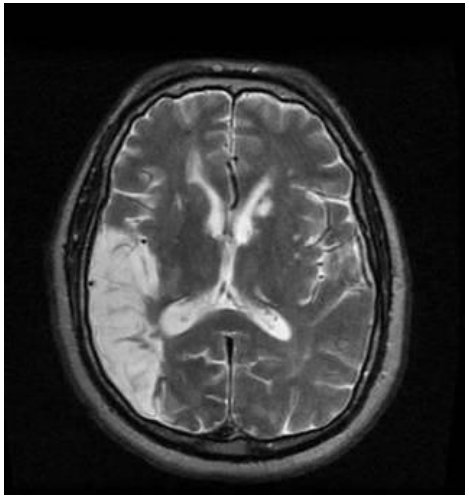
lupus profundus



serositis

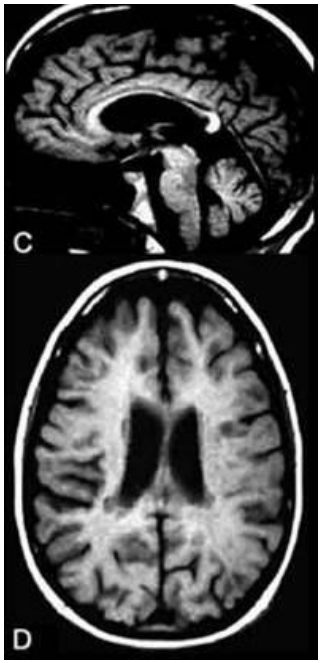


pericardial effusion

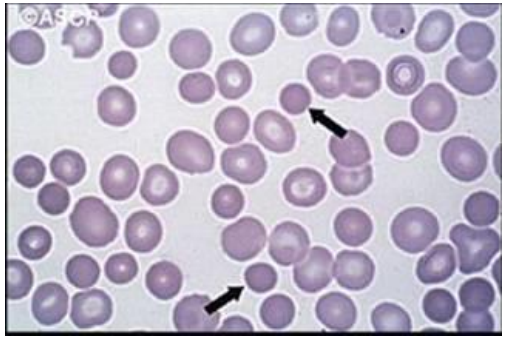


cerebral infarct

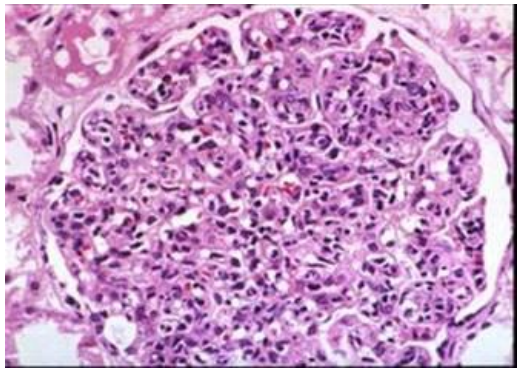
Lupus on the Inside



brain atrophy



spherocytes



glomerulonephritis

Fatigue

Lupus

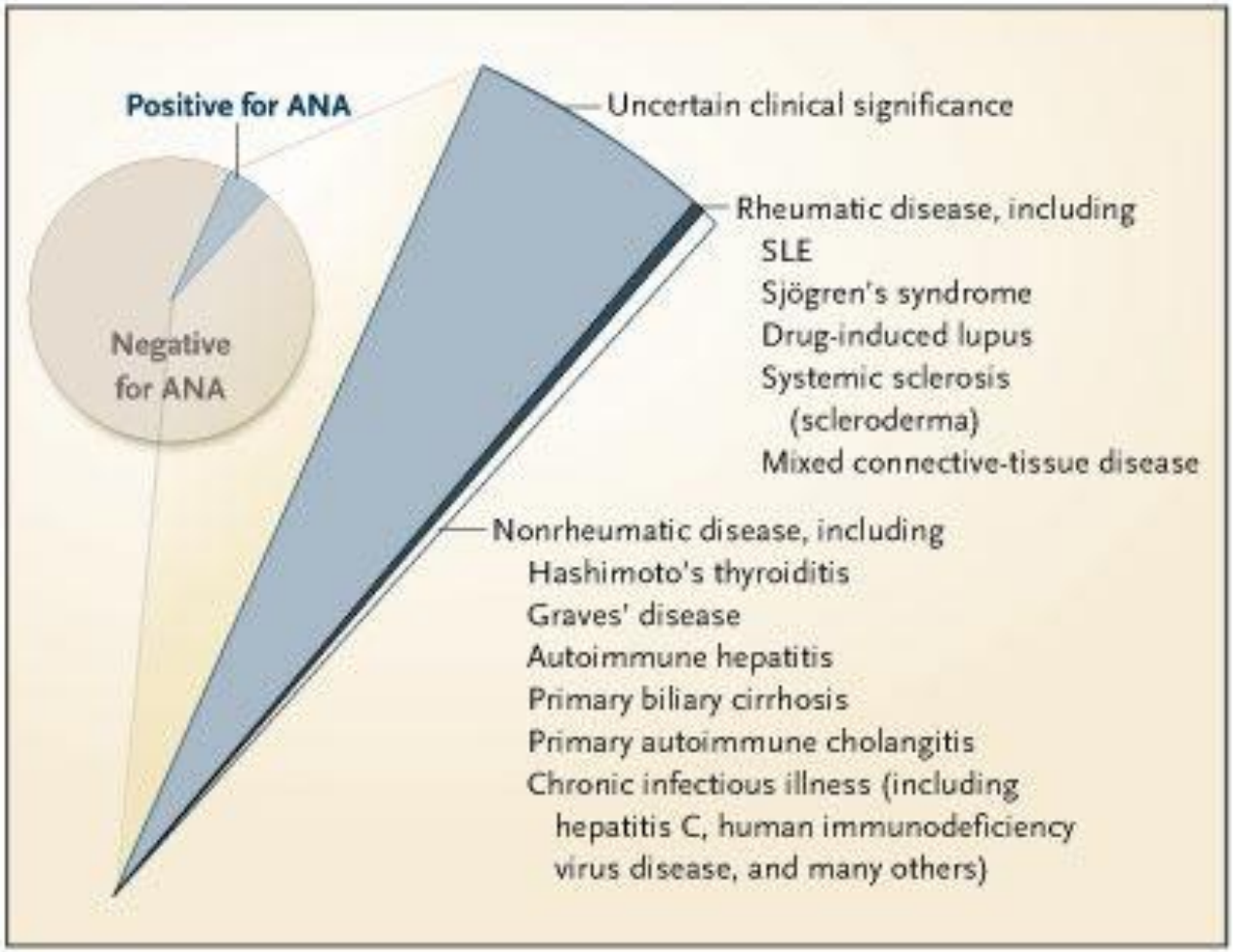
intangibles

Memory thief

Depression

Tests to order if SLE is suspected

- Need CBC with diff, UA, renal function
  - Urine protein/creatinine ratio if any proteinuria on UA
- Antinuclear antibody
  - Positive in vast majority of patients
  - Titer and pattern may be helpful at diagnosis
  - If ANA is positive, order additional autoantibodies
    - dsDNA, Sm most specific
    - SSA (Ro), SSB (La), and RNP can be found in SLE)



Case 1

- 39 year old woman has had swollen and stiff hand joints for one year (MCP and PIPs), with morning stiffness, referred for suspected RA
- ROS: photosensitivity
- Exam: patchy alopecia, inflammatory arthritis
- Labs: WBC 3.0, ALC 0.8, SCr 0.6, UA normal, ANA+ 1:320 titer, RF-, CCP-, Sm+, dsDNA-, SSA/SSB-, RNP-
- What is the diagnosis, and **why?**

SLE (criteria met: +ANA, hematologic, arthritis, immunologic, and photosensitivity)

Case 2

- 33 year old woman presents with:
- Inflammatory arthritis, +ANA for 4 years
- 1 year ago: pericardial and pleural effusions, resolved with prednisone
- Now: fever, cough. Labs: SCr 3.8, WBC 3.4, C3 61↓, C4 9↓, 3.1 g proteinuria, UA lrg bld
- Autoantibodies: ANA/dsDNA/SSA/SSB/RNP+
- Other sxs: photosensitivity, Raynaud's, pruritic rash, oral ulcers
- What is the diagnosis, and **why?**

SLE (criteria met: +ANA, hematologic, arthritis, immunologic, photosensitivity, mucosal ulcers, renal disorder, serositis)

Part 3

SEVERITY OF SLE AND HEALTH DISPARITIES

Major organ vs. non-major organ
“Bad” vs. “Not so bad” SLE

Major organ:

- Glomerulonephritis
- CNS
- Pneumonitis
- Myocarditis
- Severe hematologic involvement

Non-major organ:

- Arthritis
- Rashes
- Oral ulcers

Disease Activity

- Important determinant of need for ongoing immunosuppressive therapy
- Defined by lupus manifestations present NOW
- In contrast to “Damage” or organ dysfunction that has accumulated over time due to previous SLE disease activity

Available Therapy for SLE

- Corticosteroids
- Anti-malarials
- Immunosuppressive agents
  - Azathioprine, mycophenolate mofetil (CellCept)
- Cytotoxics
  - Cyclophosphamide
- DMARDs
  - Methotrexate, leflunomide (Arava)
- Biologics
  - Belimumab, rituximab

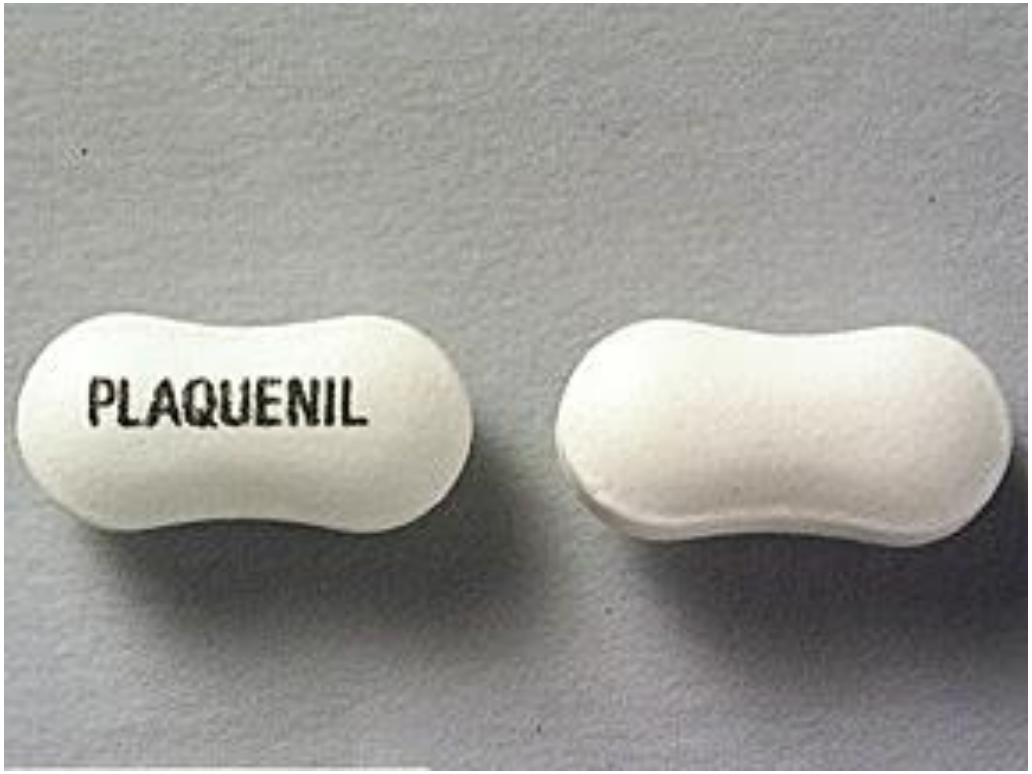
Corticosteroids

- IV pulse dosing often used early in severe disease
  - 1 gram IV methylprednisolone daily for 3 days
- 1 mg/kg/day oral prednisone in organ-threatening disease
- Rarely use more than 10-15 mg/day in non-organ-threatening disease
- Dose should be minimized in long term

Case 3

- 24 year old woman newly diagnosed with SLE
- Manifestations include:
  - Inflammatory arthritis
  - Lab abnormalities: +ANA, +dsDNA, lymphopenia
- She was given a prednisone taper by her PCP and her joint symptoms improved
- She is very concerned about internal organ involvement and how to avoid complications of SLE in the long-term.
- **What medication is best for her? What other advice can we give her?**

First-line therapy in SLE



Hydroxychloroquine is the most commonly prescribed anti-malarial medication.
Chloroquine is available but more toxic.
Quinacrine may be used in some cases, but availability is limited.

Benefits of hydroxychloroquine

- Controls skin and joint disease
- Long-term use prevents major renal or CNS damage
- Protective effect on survival in SLE
- Lower fasting glucose in women with SLE or RA taking hydroxychloroquine
- Pre-clinical use may delay onset of SLE

1. Fessler BJ et al Arthritis Rheum 2005;52:1473. 2. Penn SK et al. J Rheumatol. 2010 Jun;37(6):1136-42
3. Alarcon GS et al. Ann Rheum Dis 2007;66:1168. 4. James JA et al. Lupus. 2007;16(6):401-9.

Other advice for this young woman

- Avoid sun exposure
- Pregnancy is possible but should be planned when lupus is under control
  - SSA (Ro) antibody increases risk of neonatal lupus
- Stay up to date on immunizations
- Do not use tobacco
- Prognosis appears to be good at this time

Case 4

- 19 year old woman with new diagnosis of lupus with nephritis
- Presented with anasarca and elevated BP
- Other findings: leukopenia, lymphopenia, Coombs+ anemia, thrombocytopenia
- Nephrotic range proteinuria; hematuria
- +ANA, +dsDNA, low C3 and C4
- Diagnosed with class IV lupus nephritis (diffuse proliferative glomerulonephritis)

- **How should her treatment plan differ from Case 3? In what ways should it be similar?**

Lupus Nephritis

- Aggressive Rx in short term
  - Induce remission

- Long term goals:
  - Prevent damage
  - Reduce corticosteroid exposure

Recommendations in this case

- Same as Case 3 PLUS
- Appropriate nephritis therapy
  - Corticosteroids and immunosuppressive agent
  - Aim to taper off steroids
- Blood pressure control
- ACE or ARB if proteinuria

Disparities in Lupus Severity

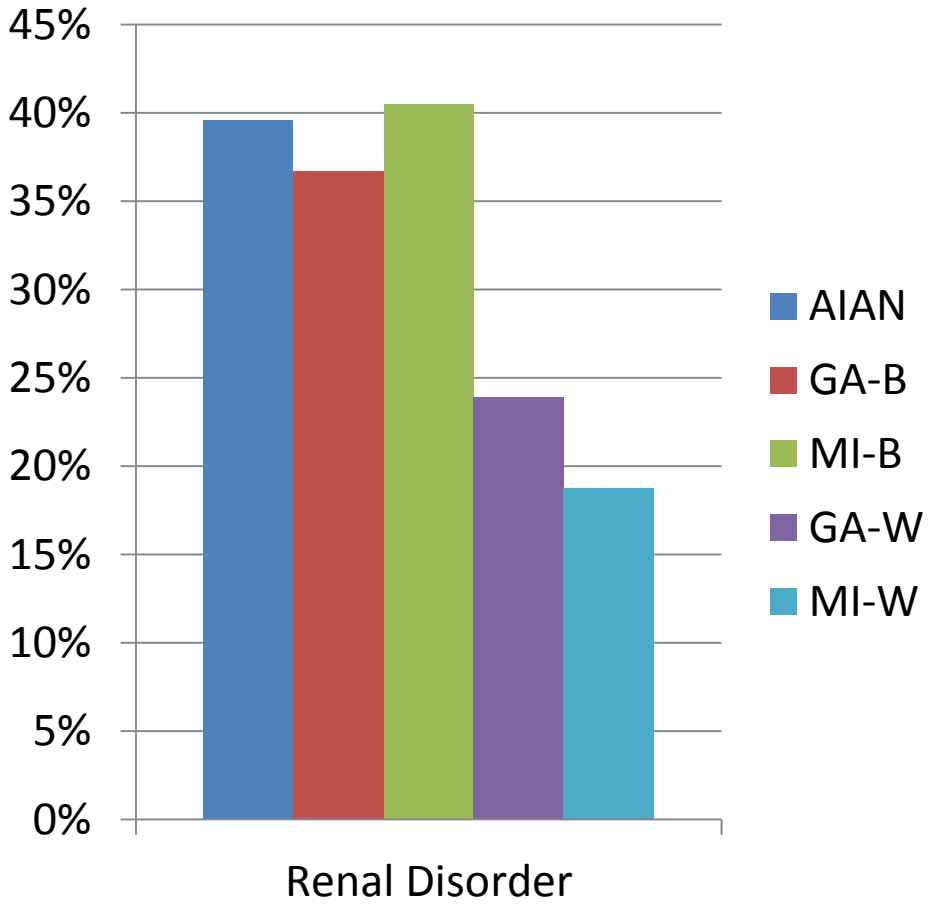
- Racial/ethnic minorities are more likely to develop lupus at a younger age and to have more severe symptoms at onset.

- Manitoba First Nations data:
  - Mean age of onset, 31 vs. 37 years
  - More severe disease at diagnosis (SLEDAI score)

McCarty DJ, *et al.* Arthritis Rheum 1995; 38:1260-1270.
Cooper GS, *et al*. Lupus 2002; 11:161-167.
Peschken, *et al*. J Rheumatol 2000;27:1884-91.

Renal disease

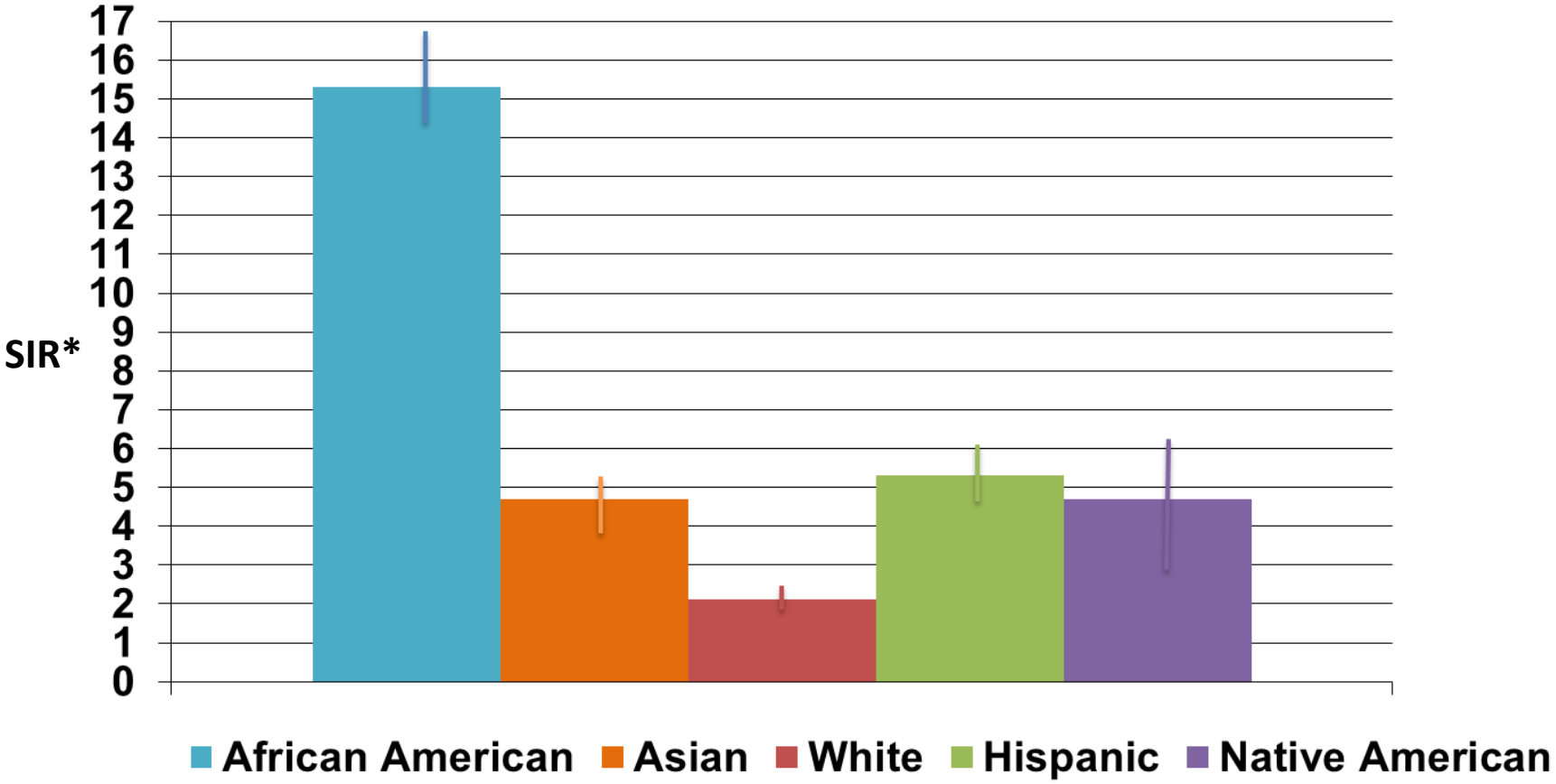
- Most important predictor of mortality in SLE
- Present more often in black and AI/AN people with SLE in CDC registries



AIAN: American Indian/Alaska Native from IHS registry; GA-B: Georgia Registry—Black; MI-B: Michigan Registry—Black; GA- W: Georgia Registry—White; MI-W: Michigan Registry—White

Disparities in End-Stage Renal Disease

Standardized Incidence Rates, End-stage Renal Disease due to Lupus Nephritis, U.S., 2001-2006



*** Standardized Incidence Rate: end-stage renal disease cases/million person-years**

Costenbader KH et al, Arthritis Rheum, 2011;63(6):1681-8.

Survival in SLE in Manitoba

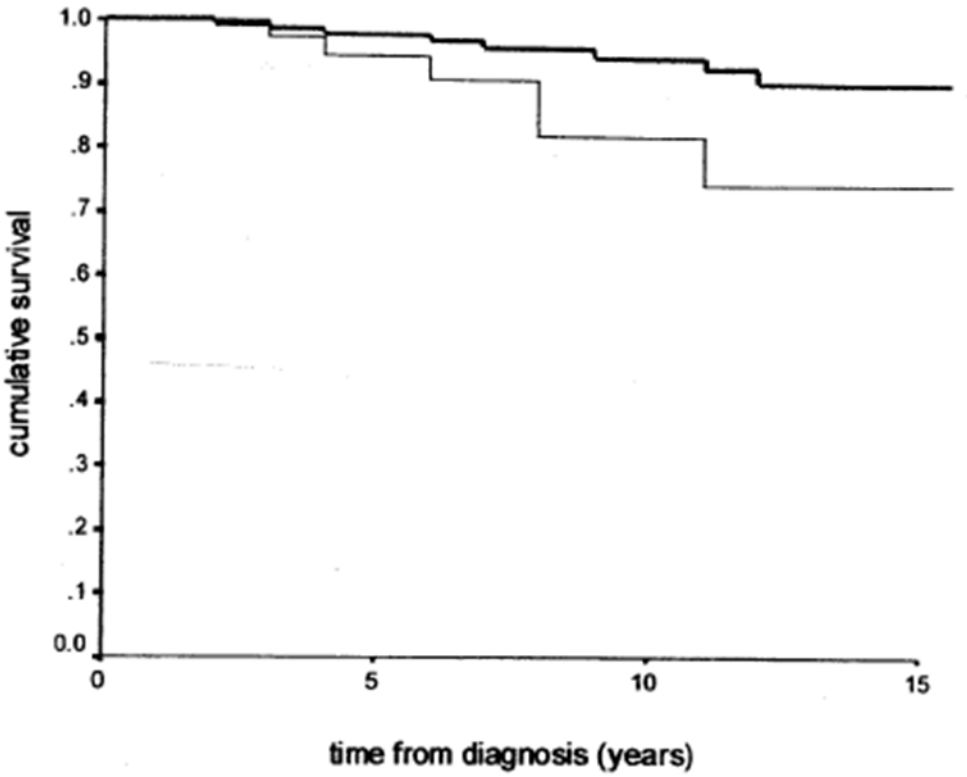


Figure 3. Cumulative survival of Caucasian (heavy line) and North American Indian (fine line) patients with SLE ($p = 0.04$).

← Caucasian

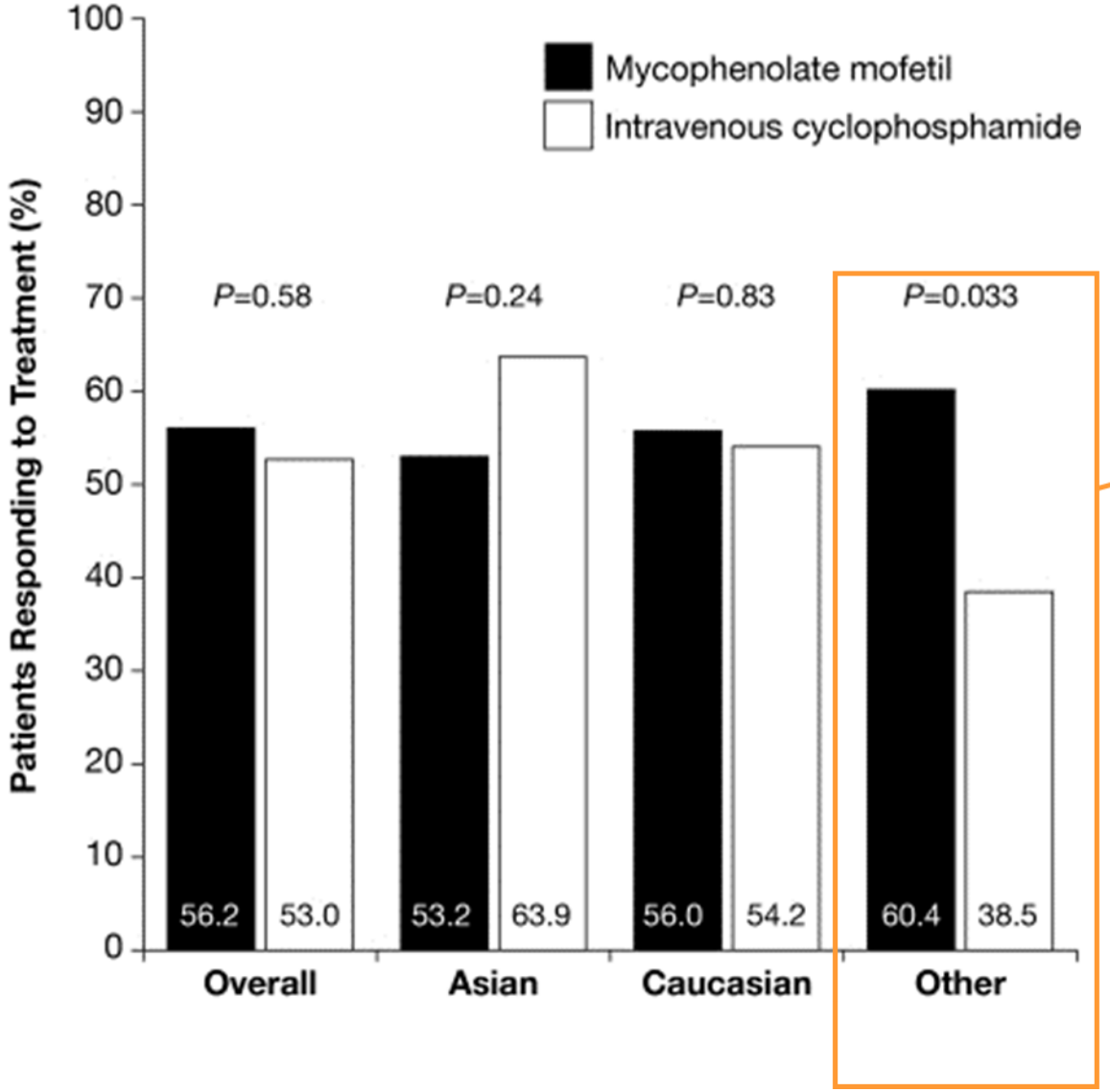
← First Nations

Infection Rates

- In nationwide Medicaid dataset, adjusted hazard ratio for serious hospitalized infections in SLE patients was high in these groups:
  - **Men 1.33 (95% CI 1.20-1.47)**
  - **Blacks 1.14 (95% CI 1.06-1.21)**
  - **AI/AN 1.37 (95% CI 1.12-1.67)**

Feldman CH et al. Arthritis Rheumatol 2015; doi: 10.1002/art.39070

Response to treatment: variation by race



"Other": total n=100

Self-reported race:

Black (46)

Mixed race (37)

Etc.

ALMS MMF vs. IVC for LN induction: Appel GB et al. JASN 2009;20:1103

Risk Factors for Health Disparities in SLE

- Non-modifiable:
  - Genetics, sex
  - Intrinsic severity of disease
- Potentially modifiable:
  - Environmental factors
  - Health system factors
  - Knowledge of SLE

The Lupus Initiative

- The Lupus Initiative® is a national education program designed to reduce health disparities in lupus.

- ANTHC has an educational series called LupusConnect that was developed in partnership with The Lupus Initiative® as an interactive educational series for providers working in Indian Health Service or tribal facilities.

CME/CE

ABOUT ACR EDUCATION

The American College of Rheumatology is an organization of and for physicians, health professionals, and scientists that advances rheumatology through programs of education, research, advocacy and practice support that foster excellence in the care of people with arthritis and rheumatic and musculoskeletal diseases. Toward that goal, The Lupus Initiative® offers FREE CME/CE for physicians and other health professionals to improve the quality of care in those with, or at risk for, lupus.

FOR PHYSICIANS

The ACR/ARHP is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to award credit towards the American Medical Association Physician's Recognition Award. Physicians must claim their credit hours after participating in each ACR/AHRP sponsored CME activity in order for their credit totals to be accurately recorded and to download documentation of their participation. One hour of learning is the equivalent of 1 credit.

FOR HEALTH PROFESSIONALS

The ACR's CME purpose is to provide comprehensive education to improve the competence and performance of physicians, scientists and other health professionals. The educational activities are designed to improve the quality of care and patient outcomes in those with, or at risk for, arthritis and rheumatic and musculoskeletal diseases.

http://thelupusinitiative.org/

CME LECTURES:

Systemic Lupus Erythematosus

- Health Disparities in Systemic Lupus Erythematosus
  (0.5 credit hour)
- Pregnancy & Systemic Lupus Erythematosus
  (1 credit hour)
- Dermatology in Systemic Lupus Erythematosus
  (0.5 credit hour)