Does the Wolf Still Bite? Lupus 2022 Update

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Disclosures

Non-Declaration Statement: I have no relevant relationships with ineligible companies to disclose within the past 24 months. (Note: Ineligible companies are defined as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.)


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Renal • Cultural competence • Genetic and non-genetic factors • Health equity •
• Signs and symptoms of disease onset • Cardiovascular • Reproductive • Renal

Objectives

Upon completion of this session, participants will be able to:

- outline the diagnostic criteria and differential diagnosis for SLE.
- utilize basic approaches to management of SLE including steroids, DMARDs and biologics.
- perform routine monitoring for disease complications and comorbidities.

Patient EM

- EM, an 18-year-old African American female presents to the emergency department (ED) with acute onset of confusion and hallucinations
- Her parents report she has been complaining of “fatigue” for the past 6 months and has lost 5 pounds. An antinuclear antibody test (ANA) ordered by her primary physician last week was strongly positive
- Abnormal physical findings include a low-grade fever of 100 °F and several small oral ulcers
- Labs: strongly positive anti-dsDNA antibody, borderline anti-Sm and normal levels of C3 and C4
- EM develops disorganized thinking, lack of orientation, agitation, and delusions (consistent with acute confusional state). She is admitted to the hospital

Patient EM (cont.)

- Addressing EM's symptoms involves:
  - Exclusion of secondary causes of confusion (infectious, metabolic, drug-induced, vascular)
  - Imaging and lumbar puncture to help to determine cause
  - Measurement of antiphospholipid antibodies, which can, in some patients, alter the management plan
- Patient is treated with steroids and hydroxychloroquine
- Management with steroids/immunosuppression is complicated by an episode of *Escherichia coli* (*E. coli*) pyelonephritis in the hospital
- When an 18-year-old is seen at the ED, the physician usually addresses the acute problem and the teenager goes back to normal life; however, EM's journey is different[1]

1. Sacks JJ, Helmick CG, Langmaid G, Sniezek JE. *MMWR Morb Mortal Wkly Rep*. 2002;51(17):371-374.

“Lupus”

Latin-wolf

“Loup”
(mask)

French-wolf

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

Epidemiology

Prevalence: 2–140/100,000 worldwide but as high as 207/100,000

Incidence: 1–10/100,000 worldwide

Population at highest risk:

- Women in their reproductive years
- Female:male ratio is approximately 9:1 postpuberty and premenopausal

Variation in race/ethnicity: More common in African American (3−6x), Hispanic and Native American (2–3x), and Asian (2x) populations

Cost: There are direct costs associated with treatment (eg, $100 billion in healthcare cost associated with autoimmune diseases) and indirect cost related to lost productivity and wages

A wolf and a zebra

Mortality Rate in SLE Is 2–3 Times Higher Than General Population

- Death rates have decreased by 60% in the United States since the 1970s, especially for infections and renal disease
- Risks of death increased in females, African American, and younger-onset patients
- Most common causes of death in SLE patients in the United States
  - Heart disease and stroke (1.7 x general population)
  - Hematologic malignancies and lung cancer (2.1 x general population)
  - Infections (5 x general population; also a common cause of hospitalization)
  - Renal disease (7.9 x general population)

Bernatsky S, Boivin JF, Joseph L, et al. *Arthritis Rheum*. 2006;54(8):2550-2557.

Is it really lupus?

-Undifferentiated Connective Tissue Disease (UCTD)
    *Pt w/ some features of autoimmune dz, but not enough to meet criteria for dx

-Mixed Connective Tissue Disease (MCTD)
    *Manifestations similar to SLE, PSS, RA, myositis
    *Dx requires high titer (+) RNP
    *(-)anti SM/SS-A/SS-B/dsDNA

-Overlap Syndromes
    *Pt meets criteria for dx of more than one CTD (e.g. SLE+RA= “Rhupus”)

Which lupus is it?

-Systemic Lupus Erythematosus

-Cutaneous Lupus Erythematosus

-Drug-induced Lupus Erythematosus

-Neonatal Lupus

Drug Induced Lupus

Definite — Procainamide, hydralazine, minocycline, penicillamine, isoniazid, quinidine, anti-tumor necrosis factor alpha therapy, interferon-alfa, methyldopa, chlorpromazine, and practolol.

Probable — Anticonvulsants (phenytoin, mephenytoin, trimethadione, ethosuximide, carbamazepine), antithyroid drugs, antimicrobial agents (sulfonamides, rifampin, nitrofurantoin), beta blockers, lithium, paraaminosalicylate, captopril, interferon gamma, hydrochlorothiazide, glyburide, sulfasalazine, terbinafine, amiodarone, ticlopidine, and docetaxel.

Possible — Gold salts, penicillin, tetracycline, reserpine, valproate, statins (eg, lovastatin, simvastatin, and atorvastatin) griseofulvin, gemfibrozil, valproate, lamotrigine, ophthalmic timolol, and 5-aminosalicylate.

Merola JF, et al. Drug-induced lupus. UpToDate. Accessed 28 Feb 2022..

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Malar rash	Fixed erythema, flat or raised, sparing the nasolabial folds
Discoid rash	Raised patches, adherent keratotic scaling, follicular plugging; older lesions may cause scarring
Photosensitivity	Skin rash from sunlight
Oral or nasopharyngeal	Usually painless ulcers
Arthritis	Nonerosive, inflammatory in two or more peripheral joints
Serositis	Pleuritis or pericarditis

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

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Renal disorder	Persistent proteinuria or cellular casts
Neurologic disorder	Seizures or psychosis
Hematologic	Hemolytic anemia, leukopenia (<4,000/mm^3), lymphopenia (<1,500/mm^3), or thrombocytopenia (<100,00/mm^3)
Immunologic disorder	Antibodies to dsDNA or SM or positive antiphospholipid antibodies (IgG or IgM antibodies, lupus anticoagulant, or false-positive serologic test positive serologic test for syphilis)
Antinuclear antibody test	Positive

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

Systemic lupus erythematosus: 1997 classification criteria

Malar rash

Discoid rash

Photosensitivity

Oral ulcers

Arthritis

Serositis

Renal disorder

Neurologic disorder

Hematologic disorder

Immunologic disorder

Antinuclear antibody

American College of Rheumatology Slide Collection of Rheumatic Diseases, 3rd Edition, 2004.

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Hematologic disorder

Immunologic disorder

Antinuclear antibody

Jaccoud’s arthropathy

Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus

Petri, M, et al. Derivation and Validation of Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheum. 2012 August ; 64(8): 2677–2686.

Clinical criteria	Immunologic criteria
Acute cutaneous lupus	ANA
Chronic cutaneous lupus	Anti-dsDNA
Non scarring alopecia	Anti-Sm
Oral or nasal ulcers	Antiphospholipid
Joint disease	Low complement
Serositis	Direct Coombs' test
Renal	
Neurologic	
Hemolytic anemia	
Leukopenia or lymphopenia	
Thrombocytopenia	

Development of autoantibodies before the clinical onset of systemic lupus erythematosus.

N Engl J Med. 2003 Oct 16;349(16):1526-33

-Department of Defense Serum Repository

Serum of 130 persons before SLE dx (matched controls)

Results-115/130---at least one autoantibody before SLE dx (up to 9.4 yrs, mean 3.3 yrs)

-ANA-78% (dilution of ≥1:120)

-dsDNA-55%

-SS-A-47%

-SS-B-34%

-Antiphospholipid ab-18%

3.4 yrs before dx

-Sm-32%

-RNP-26%

1.2 yrs before dx

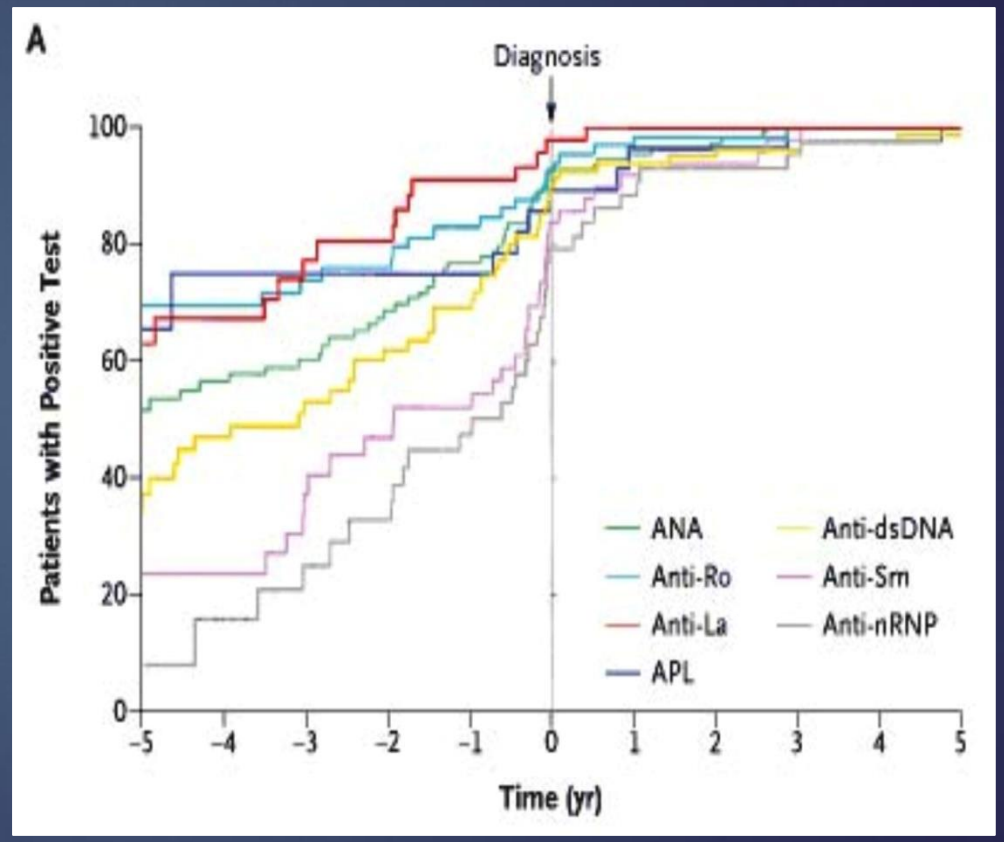
Control group---3.8% (+) for one or more autoantibody

See also---Heinlen, LD, McClain, MT, Merrill, J, et al. Clinical criteria for systemic lupus erythematosus precede diagnosis, and associated autoantibodies are present before clinical symptoms. Arthritis Rheum 2007; 56:2344.

Autoantibodies—Preclinical Detection

-Autoantibodies precede diagnosis by many years

-We are currently not able to predict which subjects with positive autoantibody titers will develop disease



*Anti-Ro = Anti-SSA
**Anti-La = Anti-SSB

Arbuckle MR, McClain MT, Rubertone MV, et al. *N Engl J Med*. 2003;349:1526-1533.

Development of autoantibodies before the clinical onset of systemic lupus erythematosus.

N Engl J Med. 2003 Oct 16;349(16):1526-33

CONCLUSION- "Autoantibodies are typically present many years before the diagnosis of SLE…"

See also---Heinlen, LD, McClain, MT, Merrill, J, et al. Clinical criteria for systemic lupus erythematosus precede diagnosis, and associated autoantibodies are present before clinical symptoms. Arthritis Rheum 2007; 56:2344.

Patient EM:
Systemic Lupus Erythematosus

- Neurologic symptoms: confusion, hallucinations, disorganized thinking, lack of orientation, agitation, and delusions
- Constitutional symptoms: fatigue, weight loss, low grade fever
- (+) ANA (strong), dsDNA, low level Smith
- WNL-C3, C4
- Oral Ulcers

Current Therapy for SLE
(FDA approved dates in parenthesis)

-Aspirin (1948)
-Azathioprine
-Belimumab (2011)
-Corticosteroids (1955)
-Cyclophosphamide
-Hydroxychloroquine (1955)
-Methotrexate
-Mycophenolate mofetil
-Rituximab
-Voclosporin (2021)
-Anifrolumab (2021)

http://www.fda.gov/newsevents/newsroom/pressAnnouncements/ucm246489.htm (accessed 22 Apr 2014)

Hydroxychloroquine

-≤5 mg/kg/day (200mg q day to bid)

-Low toxicity

*N/V, Myopathy, caution with Psoriasis

-Retinal toxicity---ophthalmologic exam q 6-12 months (Spectral-domain optical coherence tomography)

*Literature suggest ocular risk increases over time

*Increased risk with renal insufficiency, tamoxifen use

-Reduced mortality

-Decrease incidence of diabetes

-Antithrombotic effects

-Favorable lipid effects

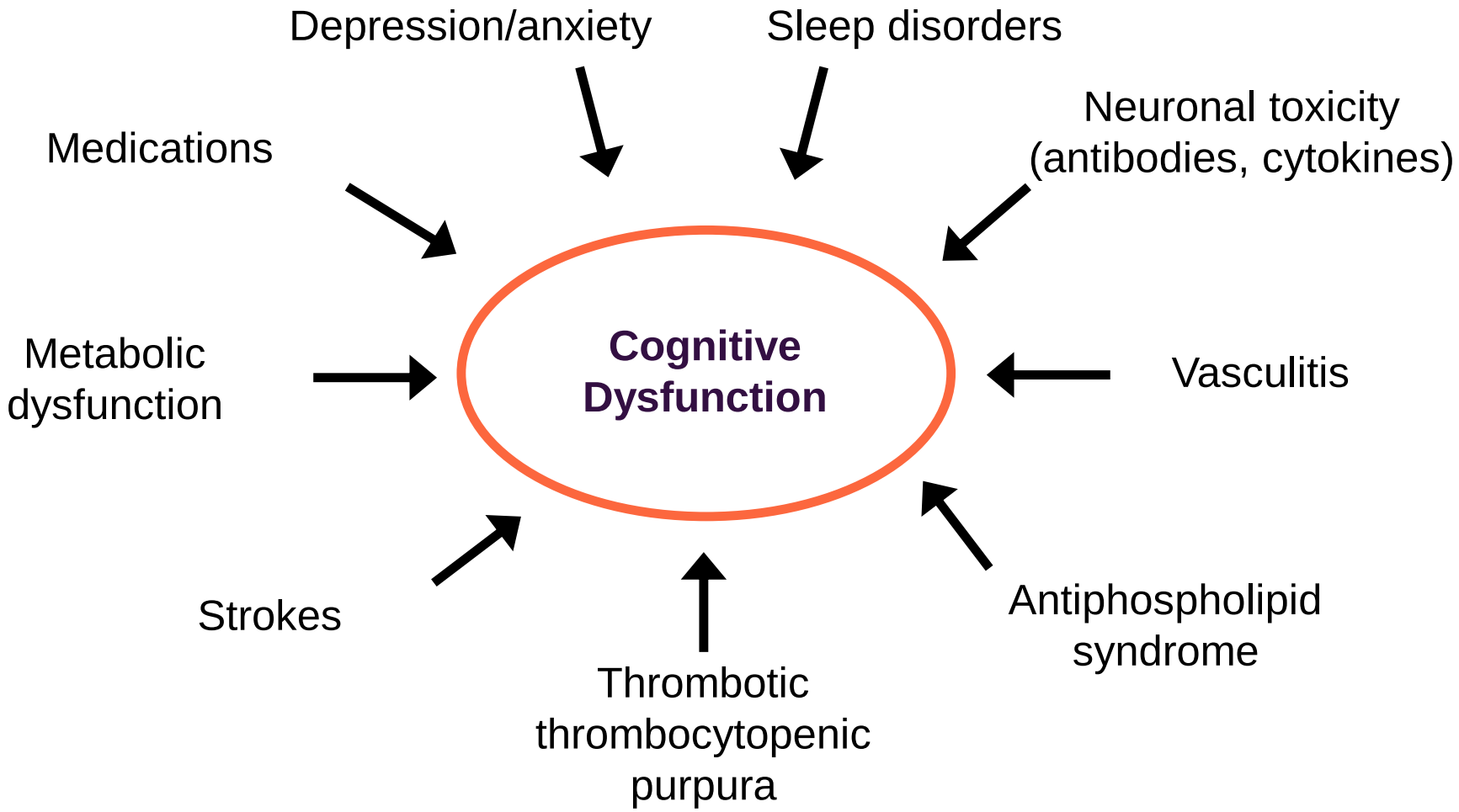
Neuropsychiatric Lupus (NPSLE)

- 19 case definitions of neuropsychiatric manifestations
- Most commonly:
  - Cognitive dysfunction
  - Headache
  - Psychiatric disorders (anxiety, psychosis,* depression)
  - Seizures*
  - Stroke (may be associated with antiphospholipid antibodies)
  - Peripheral neuropathies

*Part of the classification criteria for SLE.

Bertsias GK, Boumpas DT. *Nat Rev Rheumatol*. 2010;6:358-367.

Many Causes of Cognitive Dysfunction in Lupus



Patient EM

- Resolution of symptoms and decrease in anti-dsDNA antibodies over 6–8 weeks is followed by steroid taper over the next 6 months. She was maintained on hydroxychloroquine and followed every 3 months but is lost to follow-up after 2 years
- 3 years later, at age 23, she presents with fever and joint pains after returning from a trip to Jamaica. In the last 3 days, she has noticed mild swelling of both ankles
- Anti-dsDNA antibodies have significantly increased since her last visit. Both C3 and C4 are decreased below normal
- Urinalysis reveals 300 mg/dL proteinuria and 5 WBC/hpf. Her serum creatinine is normal

Epidemiology of Lupus Nephritis

- Prevalence: 30%–65% in adults and 80% in children
- 10% annual incidence in 1 large cohort
- More frequent and severe in children, African Americans, Hispanics, and males
- Strong predictor of morbidity and mortality

Bastian HM, Roseman JM, McGwin G Jr, et al; LUMINA Study Group. *Lupus*. 2002;11(3):152-160. Danchenko N, Satia JA, Anthony MS. *Lupus.* 2006; 15:308-318. Fernández M, Alarcón GS, Calvo-Alén J, et al; LUMINA Study Group. *Arthritis Rheum*. 2007;57(4):576-584. Hiraki LT, Feldman CH, Liu J, et al. *Arthritis Rheum.* 2012;64(8):2669-2676. Patel M, Clarke AM, Bruce IN, et al. *Arthritis Rheum*. 2006;54(9):2963-2969. Petri M. *Lupus.* 2005;14(12):970-973.

Patient EM:
Systemic Lupus Erythematosus

- Neurologic symptoms: confusion, hallucinations, disorganized thinking, lack of orientation, agitation, and delusions
- Constitutional symptoms: fatigue, weight loss, low grade fever
- (+) ANA (strong), dsDNA, low level Smith,
- WNL-C3, C4; then reduced
- Oral Ulcers
- Polyarthralgia/-itis
- Proteinuria

Clinical Diagnosis of SLE Nephritis

- Increase in proteinuria is most common
  - Measured by spot protein:creatinine ratio >0.5 or 24-hour collection >500 mg/24 hours
  - The absolute increase in proteinuria that defines a nephritis flare is arbitrary
- Microscopic abnormalities on urinalysis
  - White cells or red blood cells >5 cells/hpf in the absence of infection or other causes
  - Cellular casts (white cell or red cell)
  - White cells and red blood cells are seen more frequently than casts

Hahn BH, McMahon MA, Wilkinson A, et al. *Arthritis Care Res (Hoboken).* 2012;64(6):797-808.

Lupus Renal Pathology

- Renal biopsy is used routinely to evaluate disease type and severity and to direct management
- All patients with clinical evidence of active lupus nephritis, and previously untreated, should have a kidney biopsy (unless strongly contraindicated)
- Treatment is based on biopsy results
  - Proliferative disease is treated more aggressively than mesangial and membranous disease because it progresses more rapidly and is more likely to cause chronic damage

Classes of Lupus Nephritis

Class of Lupus Nephritis*	Typical Laboratory/Clinical Findings	Prognosis
I Minimal mesangial		Good, no treatment
II Mesangial proliferative		Good, no treatment
III Focal proliferative	Hypertension, proteinuria, active urine sediment, +dsDNA, low C3/C4, rising Cr	Severe, aggressively treat
IV Diffuse proliferative		
V Membranous	Heavy proteinuria, bland sediment	Intermediate, treat
VI Advanced sclerosing		End-stage renal disease

*Patients can have mixed classes; for example, proliferative and membranous lupus nephritis.

Hahn BH, McMahon MA, Wilkinson A, et al. *Arthritis Care Res.* 2012;64(6):797-808. Markowitz GS, D'Agati VD. *Kidney Int.* 2007;71:491-495. Weening JJ, D'Agati VD, Schwartz MM, et al. *Kidney Int.* 2004;65:521-530.

Progression to End-Stage Renal Disease

- 10%–30% progress within 15 years
- Rate of end-stage renal disease (ESRD) in the United States due to SLE appears to be increasing (especially in younger age groups, African Americans, and the Southeast)
- Mortality rates from ESRD are stable
- 5-year mortality of children with ESRD is 22%
- Many disparities exist in access to treatment and transplantation

Costenbader KH, Desai A, Alarcón GS, et al. *Arthritis Rheum.* 2011;63(6):1681-1688; Hiraki LT, Feldman CH, Liu J, et al. *Arthritis Rheum*. 2012;64(8):2669-2676. Hiraki LT, Lu B, Alexander SR, et al. *Arthritis Rheum*. 2011;63(7):1988-1997.

Arthritis Care & Research
Vol. 64, No. 6, June 2012, pp 797–808
DOI 10.1002/acr.21664

SPECIAL ARTICLE

American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis

BEVRA H. HAHN,[1] MAUREEN A. McMAHON,[1] ALAN WILKINSON,[†] W. DEAN WALLACE,[1] DAVID I. DAIKH,[2] JOHN D. FITZGERALD,[1] GEORGE A. KARPOUZAS,[1] JOAN T. MERRILL,[3] DANIEL J. WALLACE,[4] JINOOS YAZDANY,[2] ROSALIND RAMSEY-GOLDMAN,[5] KARANDEEP SINGH,[1] MAZDAK KHALIGHI,[1] SOO-IN CHOI,[1] MANEESH GOGIA,[1] SUZANNE KAFAJA,[1] MOHAMMAD KAMGAR,[1] CHRISTINE LAU,[1] WILLIAM J. MARTIN,[1] SEFALI PARIKH,[1] JUSTIN PENG,[1] ANJAY RASTOGI,[1] WEILING CHEN,[1] AND JENNIFER M. GROSSMAN[1]

Treatment of Proliferative Lupus Nephritis Classes III/IV

- **Induction** – intensive immunosuppression to reduce inflammation by controlling immunologic causes of injury
- Immunosuppression with either cyclophosphamide or high-dose mycophenolate mofetil and steroids is superior to steroids alone
- Mycophenolate mofetil is preferred in patients who desire to preserve fertility
- The ACR guidelines recommend mycophenolate mofetil in African Americans over cyclophosphamide as the drug of first choice
- The ACR guidelines recommend a 3-day IV pulse of steroid as part of induction of therapy
- Induction therapy is recommended for 6 months

Hahn BH, McMahon MA, Wilkinson A, et al. *Arthritis Care Res (Hoboken)*. 2012;64(6):797-808.

Treatment of Proliferative Lupus Nephritis Classes III/IV (cont.)

- **Maintenance** – longer period of less-intensive therapy to prevent flare
  - Mycophenolate mofetil is the current standard of care; azathioprine can be used as an alternative
  - Length of time needed is not well defined (>3 years)
- **Adjunct therapy**
  - Hydroxychloroquine
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Control blood pressure to goal of ≤130/80 mm

Hahn BH, McMahon MA, Wilkinson A, et al. *Arthritis Care Res (Hoboken).* 2012;64(6):797-808.

Limitations of Current Therapies

- **Toxicity**
  - Infections (especially in leukopenic patients)
  - Infertility (cyclophosphamide)
  - Malignancy – bladder (cyclophosphamide), cervical dysplasia
  - Multiple toxicities of long-term or high-dose steroid use
- **Efficacy**
  - Remission rates ~50%
  - Relapse rates 30%–50% by 2–3 years
  - Rates of ESRD due to SLE are increasing in the United States, especially in Blacks

Costenbader KH, Desai A, Alarcón GS, et al. *Arthritis Rheum.* 2011;63(6):1681-1688.

Risks for Developing End-Stage Renal Disease

- Demographics
  - Younger age or male gender
  - Poverty
- Clinical features
  - Hypertension
  - Autoantibodies and low complement
  - Abnormal renal function at presentation
- Delay in treatment
- Failure to respond to treatment, or flare after remission

Franco C, Yoo W, Franco D, Xu Z. *Bull NYU Hosp Jt Dis*. 2010;68(4):251-256.

Patient EM

- EM responds to high-dose mycophenolate mofetil and prednisone. She is maintained on low-dose mycophenolate mofetil and 5 mg prednisone daily for 2 years, and is then switched to azathioprine as she wants to get pregnant
- She gains 50 pounds over this time, which she is unable to lose
- 2 subsequent arthritic flares are treated with moderate-dose prednisone. She is maintained on hydroxychloroquine and prednisone 7.5 mg/day
- She requires an ACE inhibitor for mild hypertension and at age 36 develops type 2 diabetes. Her HbA1C is always above normal
- At age 43 she presents to the ED with central chest pain on exertion and is found to have an inferior myocardial infarction

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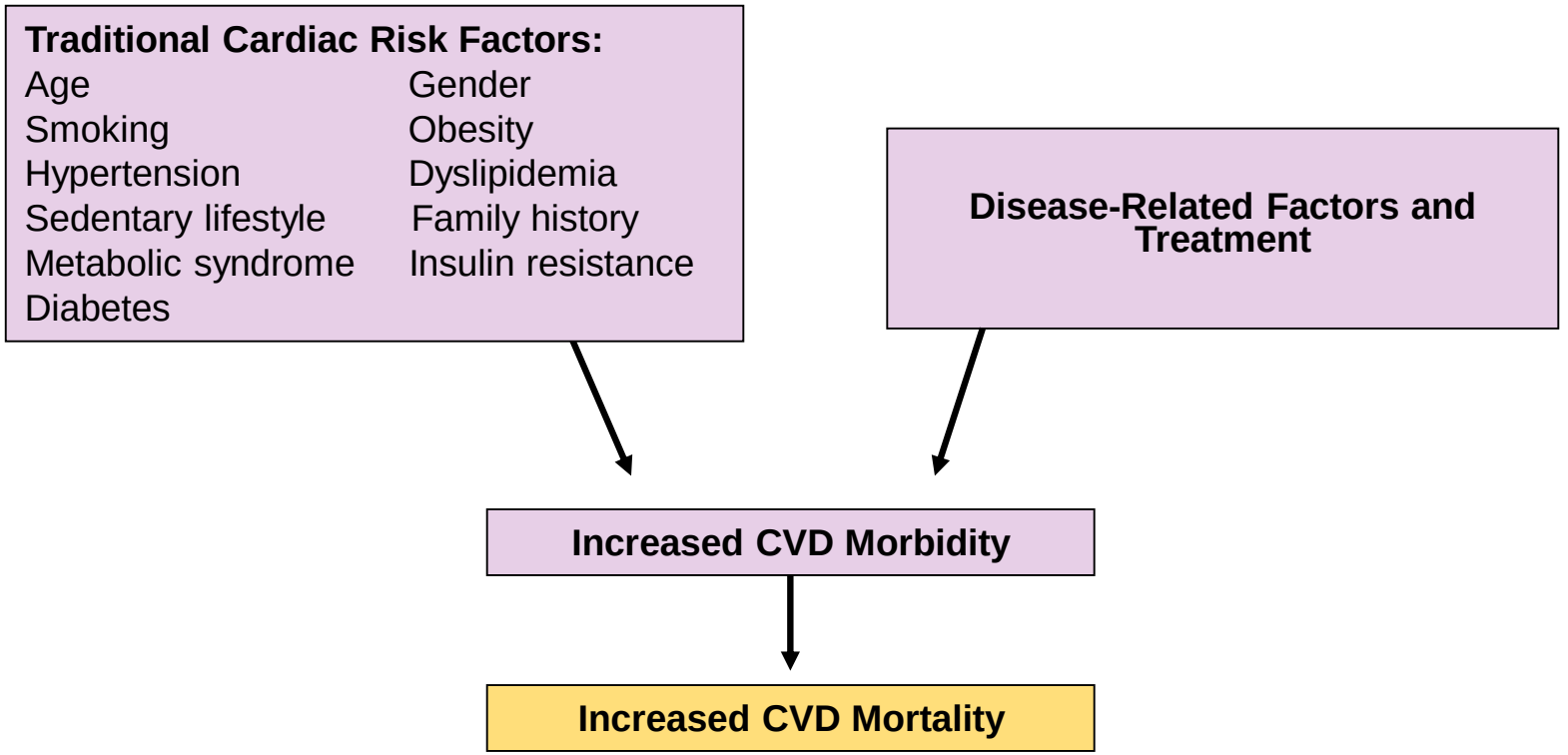
- Neurologic symptoms: confusion, hallucinations, disorganized thinking, lack of orientation, agitation, and delusions
- Constitutional symptoms: fatigue, weight loss, low grade fever
- (+) ANA (strong), dsDNA, low level Smith,
- WNL-C3, C4; then reduced
- Oral Ulcers
- Arthralgia
- Nephropathy: Proteinuria, S/P mycophenolate-then azathioprine, ACE-I requiring HTN
- Inferior MI (age 43)

Premature Atherosclerosis and SLE

- A leading cause of mortality in lupus patients
- 5-fold increased risk of coronary artery disease, especially in younger patients
  - Overall, 10-year risk for a coronary event or stroke is 7.5- to 17-fold increased
  - Rate of myocardial infarction is 50-fold higher in 35- to 44-year-old age group
  - 1st cardiac event occurs at ≤55 years old in more than 2/3 patients
- Pathology and clinical presentation is similar to that of general population but outcomes are worse
- Women in general can present atypically

Elliott JR, Manzi S. *Best Pract Res Clin Rheumatol.* 2009;23(4):481-494. McMahon M, Hahn BH. *Curr Opin Immunol.* 2007;19(60):633-639.

Causes of Cardiovascular Mortality in Lupus



Adapted from: Symmons DP, Gabriel SE. *Nat Rev Rheumatol*. 2011;7(7):399-408.

Other Morbidities to Consider

- Bone-related
- Malignancy
- Infections
- Hematologic

Bone Health in Women With Lupus

- Osteonecrosis, a rare condition in healthy individuals, is a major cause of morbidity in some lupus patients. Patients with this condition often require surgical intervention
- Women with lupus are nearly 5 times more likely to experience a fracture from osteoporosis than those without lupus
- Likely contributors to this increased risk include:
  - Glucocorticoid use
  - Sun avoidance (contributing to vitamin D deficiency)
  - Disease-related mechanisms

Gladman DD, Chaudhry-Ahluwalia V, Ibanez D, et al. *J Rheumatol.* 2001;28(10):2226-2229; Grossman JM, Gordon R, Ranganath VK, et al. *Arthritis Care Res*. 2010;62(11):1515-1526; Ramsey-Goldman R, Dunn JE, Huang CF, et al. *Arthritis Rheum*. 1999;42(5):882-890.

Bone Health in Women With Lupus (cont.)

- Prevention and management of bone loss is critical to prevent fractures
  - Ensure adequate calcium and vitamin D intake
  - Encourage regular exercise, particularly weight-bearing
  - Advise avoidance of smoking or heavy drinking, which can worsen bone loss
  - Assess risk with bone densitometry (DXA) and/or fracture risk assessment tools (FRAX) according to National Osteoporosis Foundation guidelines
  - Treat with medications, such as bisphosphonates, when indicated and appropriate

Ramsey-Goldman R, Dunne JE, Huang CF, et al. *Arthritis Rheum*. 1999;42(5):882-890. Grossman J, Gordon R, Ranganath VK, et al. *Arthritis Care Res*. 2010;62(11):1515-1526.

Increased Malignancy Risk With SLE

Cancers observed and expected, with standardized incidence ratio (SIR) and 95% confidence intervals (95% CI)*

Malignancy	Observed	Expected	SIR	95% CI†
Total cancers	**431**	**373.3**	**1.15**	**1.05–1.27**
Hematologic cancers				
All‡	67	24.4	2.75	2.13–3.49
Non-Hodgkin's lymphoma	42	11.5	3.64	2.63–4.93
Hodgkin's lymphoma	5	2.1	2.36	0.75–5.51
Leukemia	7	3.7	1.89	0.76–3.88
Reproductive cancers				
Breast	73	96.1	0.76	0.60–0.95
Ovary	9	14.5	0.62	0.28–1.18
Cervix §	14	11.1	1.26	0.69–2.11
Vagina	2	0.4	4.91	0.49–17.69
Vulva	2	1.3	1.60	0.16–5.76
Uterus	6	16.9	0.36	0.13–0.78
Other cancers				
Lung	62	45.3	1.37	1.05–1.76
Hepatobiliary	10	3.8	2.60	1.25–4.78
Colorectal	40	39.5	1.01	0.72–1.38
Pancreas, gastric, colorectal, thyroid, bladder, prostate, melanoma—low #, nonsignificant				

*Data shown are for 23 participating sites in North America, Europe, Iceland, and Asia. The total number of patients was 9547 (76,948 patient-years). The calendar period was 1958–2000. In addition to the categories presented, the total included the following cancers: 21 nonmelanoma skin, 18 primary unknown, 15 head and neck, 12 kidney, 7 central nervous system, 5 esophagus, 5 connective tissue, 3 larynx or mediastinum, 2 small intestine, 2 other female genitourinary, 1 adrenal gland. †Determined using the Poisson distribution. ‡Includes 7 multiple myeloma and 6 lymphoid malignancies not otherwise specified. §Includes invasive cancers; the only cancer registry data that include both invasive and in situ cervical neoplasms are data from the Saskatchewan Cancer Centre.

Bernatsky S, Boivin JF, Joseph L, et al. *Arthritis Rheum*, 2005;52(5):1481-1490.

Infections and SLE

- Infections are a significant cause of hospitalizations and death
- Risk for infection is increased by:
  - Active disease
  - Immunosuppressive therapies
  - Leukopenia/lymphopenia
  - Low complement

Bernatsky S, Boivin JF, Joseph L, et al. *Arthritis Rheum.* 2006;54(8):2550-2557; Ginzler E, Dvorkina O. In: Wallace DJ, Hahn B. *Dubois' Lupus Erythematosus (7th Ed)*. Philadelphia, PA: Walters Kluwer Health: Lippincott Williams & Wilkins; 2007:901-910; Sacks JJ, Helmick CG, Langmaid G, Sniezek JE. *MMWR Morb Mortal Wkly Rep.* 2002;51(17):371-374; Staples PJ, Gerding DN, Decker JL, Gordon RS. *Arthritis Rheum.* 1974;17(1):1-10.

Infections and SLE (cont.)

- Organisms
  - Bacterial (respiratory, urinary tract, and skin)
  - Viruses (herpes zoster, human papillomavirus)
  - Opportunistic (pneumocystis pneumonia, fungi)
- Opportunities for prevention
  - Vaccinations (inactivated influenza, pneumococcal, no live vaccines)
  - Screening for tuberculosis, hepatitis
  - Pneumocystis pneumonia prophylaxis for patients on more intensive immunosuppressive therapies

Hematologic Manifestations in Lupus—Peripheral Blood Cytopenias

- Any or all of the major lineages can be affected
  - Anemia
  - Leukopenia
    - Neutropenia
    - Lymphopenia
  - Thrombocytopenia
- Treatment depends upon identifying cause and assessing severity

Hematologic Manifestations in Lupus—Anemia

- Anemia is very common in lupus and often multifactorial
  - 25% mild (hematocrit 30%–35%)
  - 8% moderate (hematocrit 25%–29%)
  - 4% severe (hematocrit <25%)

    (cause not attributed)
- Most common causes
  - Anemia of chronic inflammatory disease
  - Anemia associated with renal disease (low erythropoietin)
  - Iron deficiency

Bertoli AM, Vila LM, Apte M, et al. *Rheumatology.* 2007;46:1471-1476. Kao AH, Manzi S, Ramsey-Goldman R. *Lupus.* 2004;13(11):865-868.

Hematologic Manifestations in Lupus—Anemia (cont.)

- Hemolytic anemia (an ACR classification criteria)
  - Relatively rare, ranging from 5%–13%
  - Requires evidence of hemolysis (low haptoglobin and increased reticulocytes)
  - Coombs positivity (antibodies to red blood cells) alone much more common, as high as 40%

Bertoli AM, Vila LM, Apte M, et al. *Rheumatology.* 2007;46:1471-1476. Kao AH, Manzi S, Ramsey-Goldman R. *Lupus.* 2004;13(11):865-868.

Hematologic Manifestations in Lupus—Leukopenia and Lymphopenia

- Leukopenia
  - Defined as <4000 cells/µL
  - Usually an element of neutropenia
  - Prevalence of up to 50% sometime during course
- Lymphopenia
  - Defined as <1500 cells/µL
  - May be present in absence of leukopenia
  - Prevalence of up to 60%–70% sometime during course

Kao AH, Manzi S, Ramsey-Goldman R. *Lupus.* 2004;13(11):865-868.

Hematologic Manifestations in Lupus—Thrombocytopenia

- Defined as <100,000 platelets/µL
- Seen in 10%–25% of patients but severe (<50,000) less than 10%
- Causes
  - From lupus
    - Antiplatelet antibodies
    - Antiphospholipid antibodies
    - Thrombotic thrombocytopenic purpura/microangiopathic hemolytic anemia
  - From complications
    - Drug-induced bone marrow suppression
    - Infection

Levine AB, Erkan D. *Curr Rheumatol Rep.* 2011;13:291-299.

Patient EM:
Systemic Lupus Erythematosus

- Neurologic symptoms: confusion, hallucinations, disorganized thinking, lack of orientation, agitation, and delusions
- Constitutional symptoms: fatigue, weight loss, low grade fever
- (+) ANA (strong), dsDNA, low level Smith,
- WNL-C3, C4; then reduced
- Oral Ulcers
- Arthralgia
- Nephropathy: Proteinuria, mycophenolate-then azathioprine, ACE-I requiring HTN
- Inferior MI (age 43)

EM—What Could We Have Done Better?

- Education and attention to psychosocial factors
  - Advise sun protection: year-round use of SPF-45 or higher, clothing that is UV impenetrable and avoidance of UV exposure when possible
  - Encourage weight loss and exercise
  - Encourage compliance with clinic visits and medications
- Keep vaccinations up to date
- Monitor for early detection of flares
- Minimize steroid use
- Treat cardiac risk factors aggressively
- Monitor bone health

Disease Activity

- SLE is characterized by periods of flare (increased disease activity) and remission or low-level disease activity
- Varying flare rates
- Predictors of flare (in some but not all cases)
  - New evidence of complement consumption
  - Rising anti-dsDNA titers
  - Increased ESR
  - New lymphopenia

Objectives

- Upon completion of this session, participants will be able to:
  - outline the diagnostic criteria and differential diagnosis for SLE.
  - utilize basic approaches to management of SLE including steroids, DMARDs and biologics.
  - perform routine monitoring for disease complications and comorbidities.

Lupus—In Summary

- Clinical disease is characterized by
  - Symptom diversity
  - Periods of flare and remission
- Pathogenesis is related to
  - Genetic susceptibility combined with environmental and/or behavioral triggers
  - Immune dysregulation characterized by autoantibody production
- Treatment is targeted to
  - Clinical manifestations
  - Severity of organ system involvement

Evidence-Based Medicine

- Aringer, M, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheum. 2019; 71(9): 1400–1412 .
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- Marmor MF, et al, American Academy of O. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). *Ophthalmology*. 2016.
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- Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter*]. Arthritis Rheum.* 1997;40:1725.
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