SLE Through the Lifespan

Pediatric
Reproductive Issues
Postmenopausal

the upus initiative
Eliminating Health Disparities in Lupus

Eliminating health disparities • Cultura[illegible]ence • Genetic and non-genetic
• Genetic and non-genetic factors • [illegible]ty • Signs and symptoms of dise
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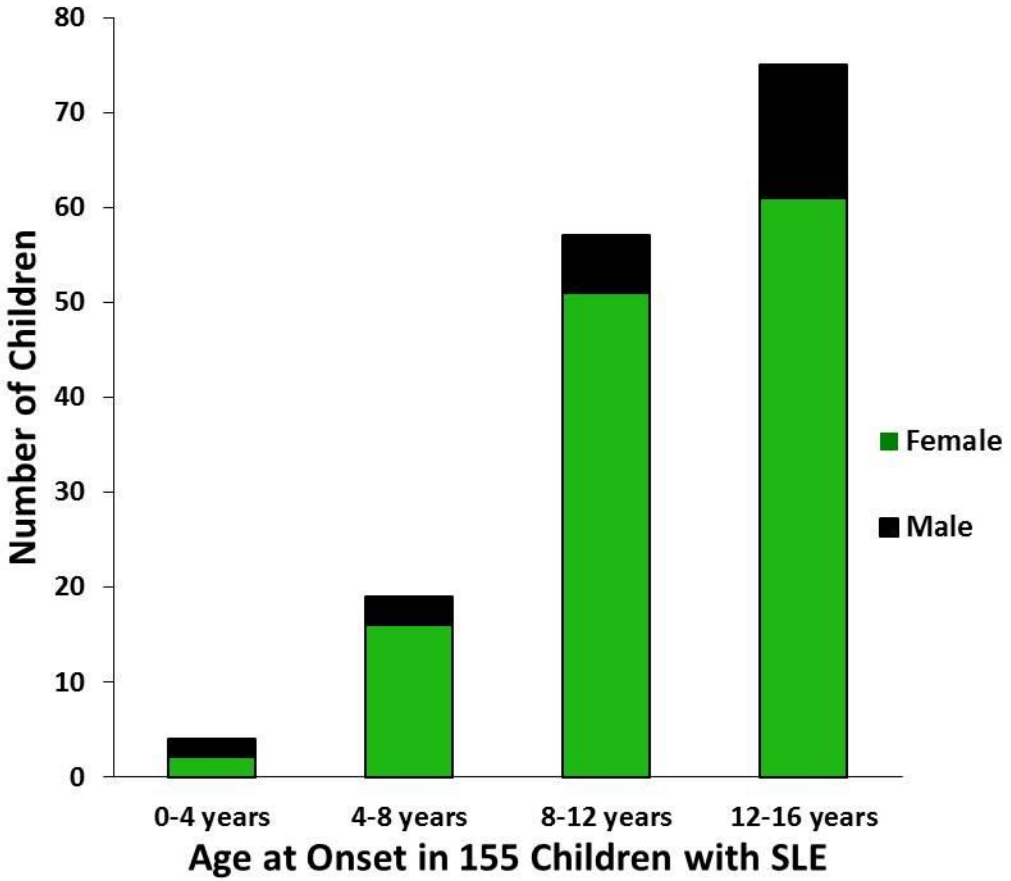
Renal • Cultural competence • Genetic and non-genetic factors • Health equity •
• Signs and symptoms of disease onset • Cardiovascular • Reproductive • Rena

Introduction—SLE Through the Lifespan

- Childhood systemic lupus erythematosus (SLE)
- Reproductive issues
- Pregnancy and SLE activity
- Implications for bone health
- Cancer risks
- Immunizations and SLE
- Cardiovascular disease
- Menopause and SLE
- Late-onset lupus

Childhood SLE vs Adult SLE—Differences

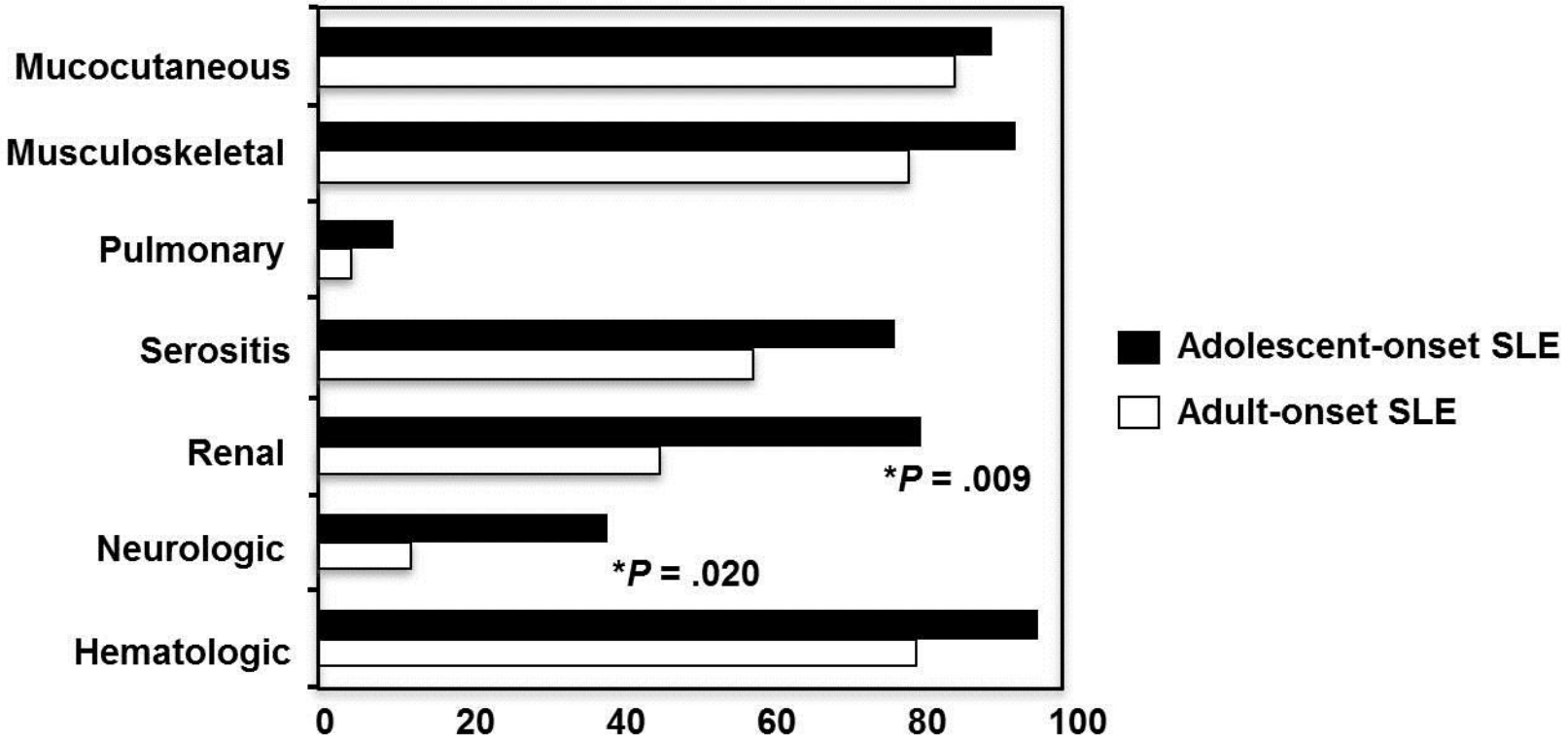
- 15%–20% of SLE presents in childhood
- Hormonal influence on presentation
  - Rare <5 years old
  - Uncommon before adolescence



Bader-Meunjer B, Armengaud JB, Haddad E, et al. *J Pediatr*. 2005;146:648-653.

Childhood SLE vs Adult SLE—Differences

- Disease activity, on average, is higher in childhood SLE than adult SLE at presentation



Tucker LB, Uribe AG, Fernández M, et al. *Lupus.* 2008;17:314-322. Mina R, Brunner H. *Rheum Dis Clin North Am.* 2010;36:53-80. doi:10.1016/j.rdc.2009.12.012. Font J, Cervera R, Espinosa G, et al. *Ann Rheum Dis.* 1998;57:456-459.

Video of Dr. Emily Von Scheven

University of California, San Francisco
School of Medicine

Childhood SLE vs Adult SLE—Differences

Comparison of renal involvement between the SLE cohorts

	Childhood-Onset SLE n = 67	Adult-Onset SLE n = 131
Patients with *any* renal involvement	52/67 (78%)	68/131 (52%)*
Patients with at least 1 renal biopsy	43/67 (64%)	24/131 (18%)
WHO classification of the first renal biopsy		
Minimal mesangial	0	0
Mesangial proliferative	10/43 (23%)	5/22 (23%)
Focal proliferative	11/43 (26%)	4/22 (18%)
Diffuse proliferative	17/43 (40%)	7/22 (32%)
Membranous	5/43 (11%)	6/22 (27%)

******P* **= .0005**

Brunner HI, Gladman DD, Ibañez D, Urowitz MD, Silverman ED. *Arthritis Rheum*. 2008;58:556-562.

Bone Damage in Childhood SLE

- Bone mineral density is reduced and risk of osteoporotic fracture increases
  - Majority of bone is deposited by early 20s
- Height attainment is reduced due to corticosteroids
- Puberty is delayed
  - Treatment for SLE can cause early ovarian failure
- Risk for avascular necrosis is increased

Psychosocial Issues in Childhood SLE

- Family dynamics
- School
- Peer group
- Body image
  - Obesity
  - Striae
  - Hirsutism
  - Cushingoid facies
- Treatment adherence can be challenging

Adolescence and Beyond—Reproductive Issues in Lupus

- Lupus is not associated with decreased fertility
  - Reliable contraception is important
  - Many medications for SLE are teratogenic
- Exposure to cyclophosphamide is associated with a dose-related and age-dependent risk of infertility
  - Sperm cryopreservation
  - Egg “banking/harvesting”
  - Consider ovarian suppression

Reproductive Issues in Lupus—Pregnancies May Be High Risk

- Up to 1/3 require a cesarean section
- Up to 1/3 with preterm birth
- Increased pre-eclampsia
- Increased gestational diabetes
- Increased infection

Moland Y, Barkowski T, Monselise A, et al. *Lupus.* 2005;14:145-151. Julkunen H, Jouhikainen T, Kaaja R, et al. *Lupus.* 1993;2:125-131.

Reproductive Issues in Lupus—Pregnancies May Be High Risk

- An elevated creatinine at conception is a risk for pregnancy complications, including
  - Hypertension
  - Pre-eclampsia
  - Fetal loss
- Many lupus patients can have healthy pregnancies, but risks need to be managed
  - Pregnancy needs to be planned
  - Disease activity needs to be under control and well managed
  - Patient needs to be off risky medications

Moland Y, Barkowski T, Monselise A, et al. *Lupus.* 2005;14:145-151. Julkunen H, Jouhikainen T, Kaaja R, et al. *Lupus.* 1993;2:125-131.

Reproductive Issues in Lupus—Antiphospholipid Syndrome

- Antiphospholipid syndrome (APS): association of autoantibodies having an apparent specificity for negatively charged phospholipids with venous thrombosis, arterial thrombosis, and/or pregnancy loss
- Antiphospholipid antibodies (aPL)
  - Anticardiolipin antibodies
  - False-positive serologic tests for syphilis, eg, VDRL
  - Lupus anticoagulant
  - Anti-β_2-glycoprotein I antibodies
- APS and aPL in lupus
  - aPL present in approximately 1/3 of patients with SLE
  - Approximately 1/3 of those with aPL (10%−15% of SLE patients) have ≥1 clinical manifestations of APS

Antiphospholipid Syndrome—Pregnancy Morbidity and Mortality

- ≥1 unexplained deaths ≥10 weeks gestation
- ≥1 preterm births (<34 weeks gestation) due to severe pre-eclampsia, eclampsia, or placental insufficiency
- ≥3 unexplained consecutive miscarriages <10 weeks gestation

Adapted from Miyakis S, Lockshin MD, Atsumi T, et al. *J Thromb Haemost.* 2006;4:295-306.

Pregnancy and SLE Activity

"Will pregnancy make my lupus flare?"

- Approximately 50% of women will have measurable SLE activity during pregnancy
- Pregnancy probably increases lupus activity. Increased disease activity may occur at any time during pregnancy and postpartum
- Risk of flare is significantly reduced if planned pregnancy is preceded by 3 months of inactive disease

Lê Huong D, Wechsler B, Vauthier-Brouzes D, et al. *Br J Rheumatol*. 1997;36:772-777.

Lupus Pregnancies Require Coordinated Care by High-Risk Obstetrics and Rheumatology

- Management of medications
- Many medications used in treatment of lupus are teratogenic
  - Discontinue ACE inhibitors, angiotensin receptor blockers, warfarin, methotrexate, mycophenolate mofetil, mycophenolate acid, cyclophosphamide
  - Make appropriate pregnancy-safe substitutions
- Continue hydroxychloroquine, azathioprine, and corticosteroids when appropriate, although there are associated risks that should be managed

Pregnancy vs Lupus Flare

Pregnancy	Lupus Flare
Facial blush, alopecia	Photosensitive rash
Arthralgias	Synovitis
Proteinuria (pre-eclampsia)	Proteinuria with casts
Leukocytosis (very slight)	Leukopenia
No autoantibodies	+anti-dsDNA antibodies
C3 and C4 high	C3 and C4 low

Reproductive Issues in Lupus—Fetal Outcome

The presence of anti-SSA and/or anti-SSB antibodies confers a small but significant risk of a clinical syndrome that has very little resemblance to pediatric or adult SLE**: *neonatal lupus***

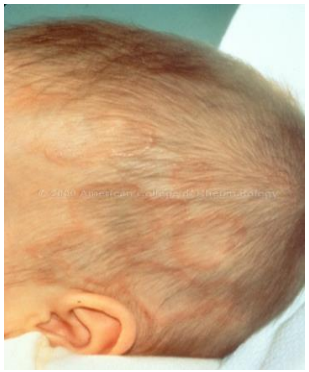


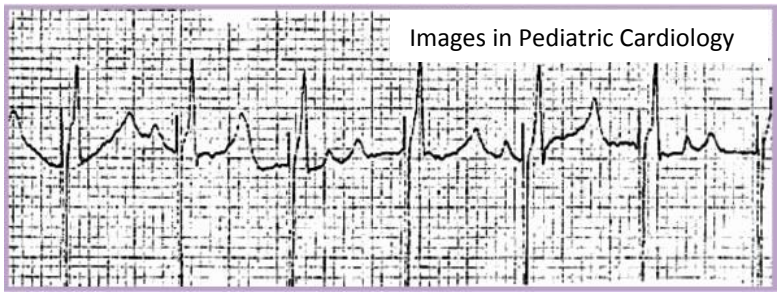
Image courtesy of the Rheumatology Image Bank

Cutaneous features

- Annular, erythematous rash
- Often photosensitive
- Transient

Cardiac disease

- 1st-, 2nd-, or 3rd-degree block
- May be permanent and require pacing



Buyon JP. *Bull NYU Hosp Jt Dis.* 2009;67:271. Friedman D, Duncanson LJ, Glickstein J, Buyon JP. *Pediatr Cardiol.* 2003;5:36-48.

Reproductive Issues—
Fetal Outcome: Neonatal Lupus

Auto-antibody induces clinical syndrome

Maternal circulation
anti-SSA/SSB antibodies

↓

Cross placenta

↓

Fetal circulation
anti-SSA/SSB antibodies

Buyon JP. *Bull NYU Hosp Jt Dis.* 2009;67:271.

Reproductive Issues in Lupus—Family Planning

- Teratogenic drug use is common in lupus
  - Barrier methods are not recommended by the WHO for women using teratogens (Farr, et al), but should be used in conjunction with 1 of the methods outlined below
- Contraceptive choices should be individualized after considering each patient's risk profile
  - Low-dose estrogens are relatively safe if lupus is stable, there is no history of thromboembolism and negative antiphospholipid (aPL) antibodies
  - IUDs are a safe and effective option for most patients and do not increase vascular risk
  - Progestin-only methods can also be considered in those with contraindications to estrogen

Petri M, Kim MY, Kalunian KC, et al. *N Engl J Med*. 2005;353:2550-2558. Sanchez-Guerrero J, Uribe AG, Jiménez-Santana L, et al. *N Engl J Med*. 2005;353:2539-2549. Farr S, Folger SG, Paulen M, et al. *MMWR Recomm Rep.* 2010;59(RR-4):1-86.

Bone Health in Women with Lupus

- 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

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

Bone Health in Women with Lupus

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 when appropriate. Many drugs used to treat osteoporosis are unsafe, or have an undetermined safety profile for women who intend to become pregnant

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

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 N 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 CNS, 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;52:1481-1490.

Malignancy Risk

Potential risk factors

- Disease activity (chronic lymphocyte stimulation)
- Associated confounding disease (Sjögren's Syndrome)
- Cytotoxic medication exposure
- Other less-defined mechanisms (eg, decreased clearance of the human papilloma virus)

Bernatsky S, Boivin JF, Joseph L, et al. *J Rheumatol.* 2002;29:2551-2554. Bernatsky S, Ramsey-Goldman R, Clarke AE. *Best Pract Res Clin Rheumatol.* 2009;23:534-547.

Immunizations in Lupus Patients

- Live attenuated vaccines are contraindicated in immunosuppressed patients and immediate family members
- Immunizations (with inactivated or component vaccines) are especially important for immunosuppressed patients
- No evidence that vaccination triggers disease flares
- Antibody response may not be as robust in immunosuppressed patients
- Recommended vaccines
  - Inactivated influenza
  - Pneumococcus
  - Meningococcus
  - HPV vaccine

Elkayam O, Paran D, Caspi D, et al. *Clin Infect Dis.* 2002;34:147-153. Abu-Shakra M, Press J, Varsano N, et al. *J Rheumatol.* 2002;29:2555-2557.

Accelerated Atherosclerosis in Lupus Patients

- Atherosclerotic events are among the leading causes of mortality in lupus patients
- Women sometimes present atypically
- Vasculitis is extremely rare
- Traditional risk factors are more prevalent in lupus patients but do not fully explain the increased risk

Therefore:

- A high degree of suspicion is essential to diagnose and treat, even at “young” ages
- Control modifiable risk factors (blood pressure, glucose, tobacco exposure, cholesterol, sedentary lifestyle), even at “young” ages

Elliott JR, Manzi S. *Best Pract Res Clin Rheumatol*. 2009;23:481-494. doi:10.1016/j.berh.2009.03.005.

Effects of Menopause

- Disease activity is greater in premenopausal than postmenopausal women with lupus
- Disease activity improves with disease duration
  - This improvement is not due to menopausal status, rather to time
- However, the postmenopausal era should not be viewed as a period of natural disease improvement due to comorbidities common in older patients

Urowitz MB, Ibañez D, Jerome D, Gladman DD. *J Rheumatol*. 2006;33:2192-2198.

Late-Onset Lupus—Epidemiology

- Defined as onset at age 50 or older
- Represents 5%−15% of all lupus patients in reported cohorts
- Still predominantly female, but higher percentage of Whites
- Drug-induced lupus must be ruled out, especially in elderly patients
- The incidence of false-positive ANA increases with age

Formiga F, Moga I, Pac M, Mitjavila F, Rivera A, Pujol R. *Lupus*. 1999;8:462-465.

Late-Onset Lupus

- Clinical characteristics
  - Reduced likelihood of proteinuria, cellular casts, and seizures
  - Reduced prevalence of anti-RNP, anti-Sm, and anti-dsDNA antibodies, and low complement levels
  - Lower levels of disease activity
- Unique feature of late-onset lupus
  - Increased photosensitivity
- Poorer outcome likely reflects aging and increased number of comorbidities present at diagnosis

Bertoli AM, Alarcón GS, Calvo-Alén J, et al. *Arthritis Rheum*. 2006;54:1580-1587. Lalani S, Pope J, de Leon F, et al. *J Rheumatol*. 2010;37:38-44.

Conclusions—Lupus Through the Lifespan

- Lupus presents unique challenges in pediatric, adult, and late-onset populations
- Lupus patients face significant difficulties during the childbearing years
- There are important comorbidities associated with lupus across the lifespan

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