American College of Rheumatology
Empowering Rheumatology Professionals

SYSTEMIC LUPUS (SLE) THROUGH THE LIFESPAN

the lupus initiative
Eliminating Health Disparities in Lupus

WELCOME

Before we get started…

ABOUT THIS PROJECT

- The presentation is designed to be easily incorporated into medical school lectures on a variety of topics; they are tailor-made for the classroom setting, and easy to digest
- The PowerPoint presentation is designed for medical students M3 and M4

DRUGS AND DOSES

When prescribing medications, the physician is advised to check the product information sheet accompanying each drug to verify conditions of use and to identify any changes in drug dosage schedule of contra-indications.

USE OF PROFESSIONAL JUDGMENT

This activity, including all educational links, is intended to be used as a tool to assess the base knowledge of the learner.
The information presented relates to basic principles of diagnosis and therapy, and is meant in no way to substitute for an individual patient assessment based upon the healthcare provider's examination of the patient and consideration of laboratory data and other factors unique to the patient.

ACR DISCLOSURE STATEMENT

The American College of Rheumatology is an independent, professional organization that does not endorse specific procedures or products of any pharmaceutical/biotech concern.

SUPPORT

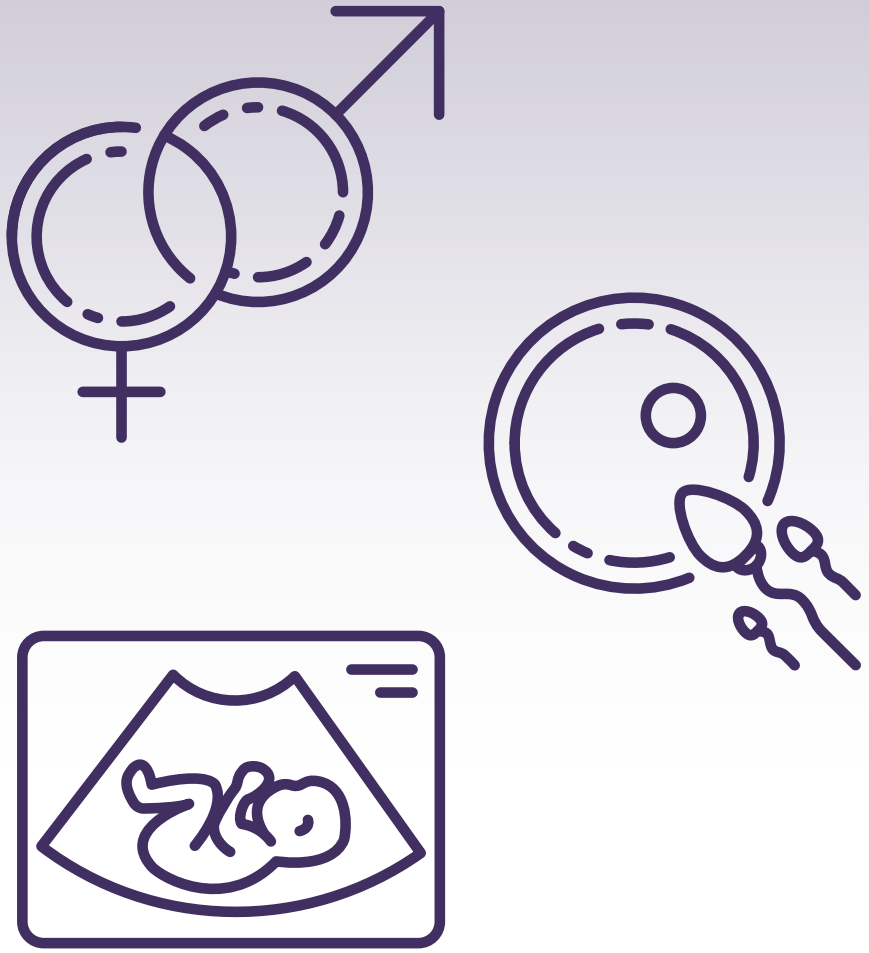
The project described is, in part, supported by the Centers for Disease Control and Prevention under Cooperative Agreement Number NU58 DP006138. Its contents are solely the responsibility of its developers/authors. Points of view or opinions do not, therefore, necessarily represent official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

FACULTY REPORTED DISCLOSURES

[To be filled in]

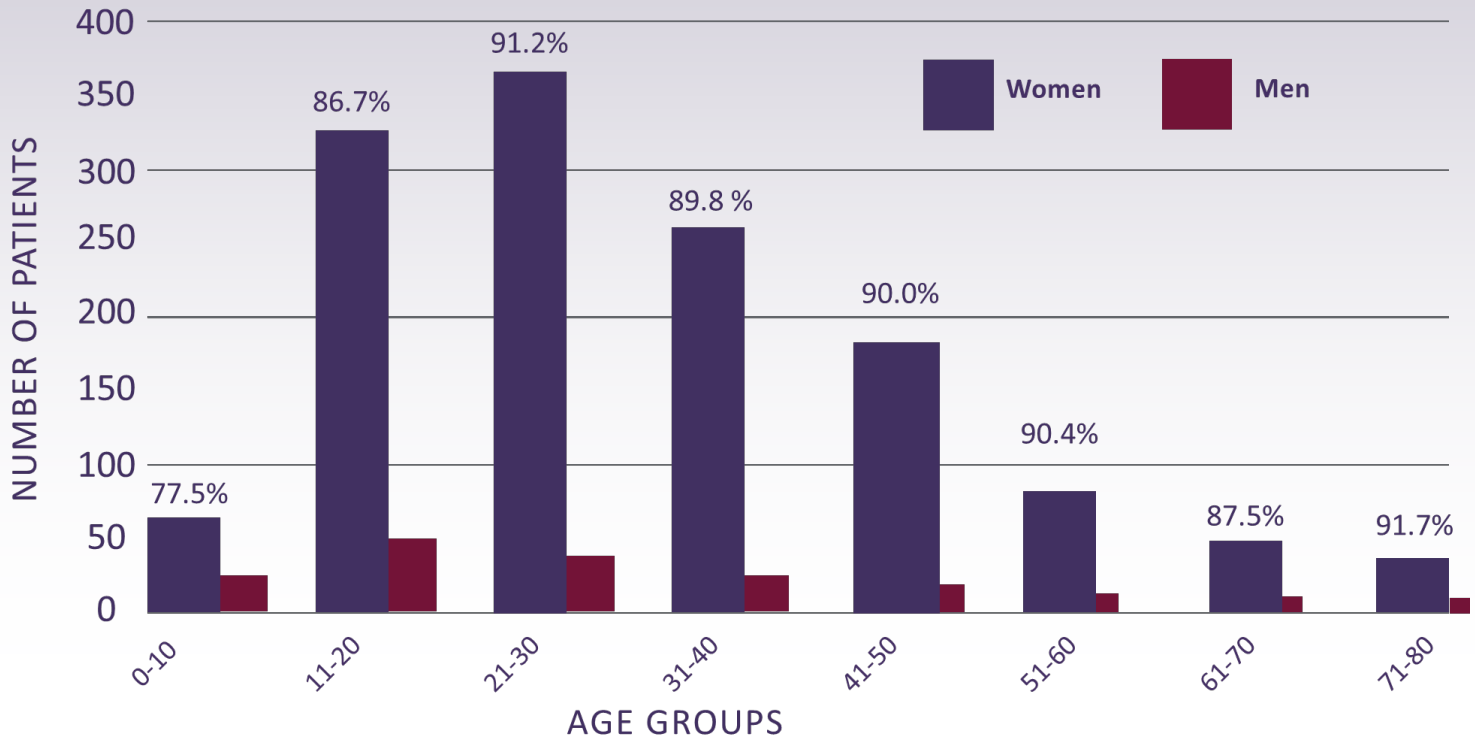
Learning Objectives

- Recognize the presentation of SLE at different ages and across genders
- Understand the psychosocial issues and comorbidity impact of SLE through the lifespan
- Identify the reproductive health needs for people with SLE
- Discuss pregnancy morbidity and mortality for SLE mothers and their fetus



Lupus can occur across the spectrum of ages

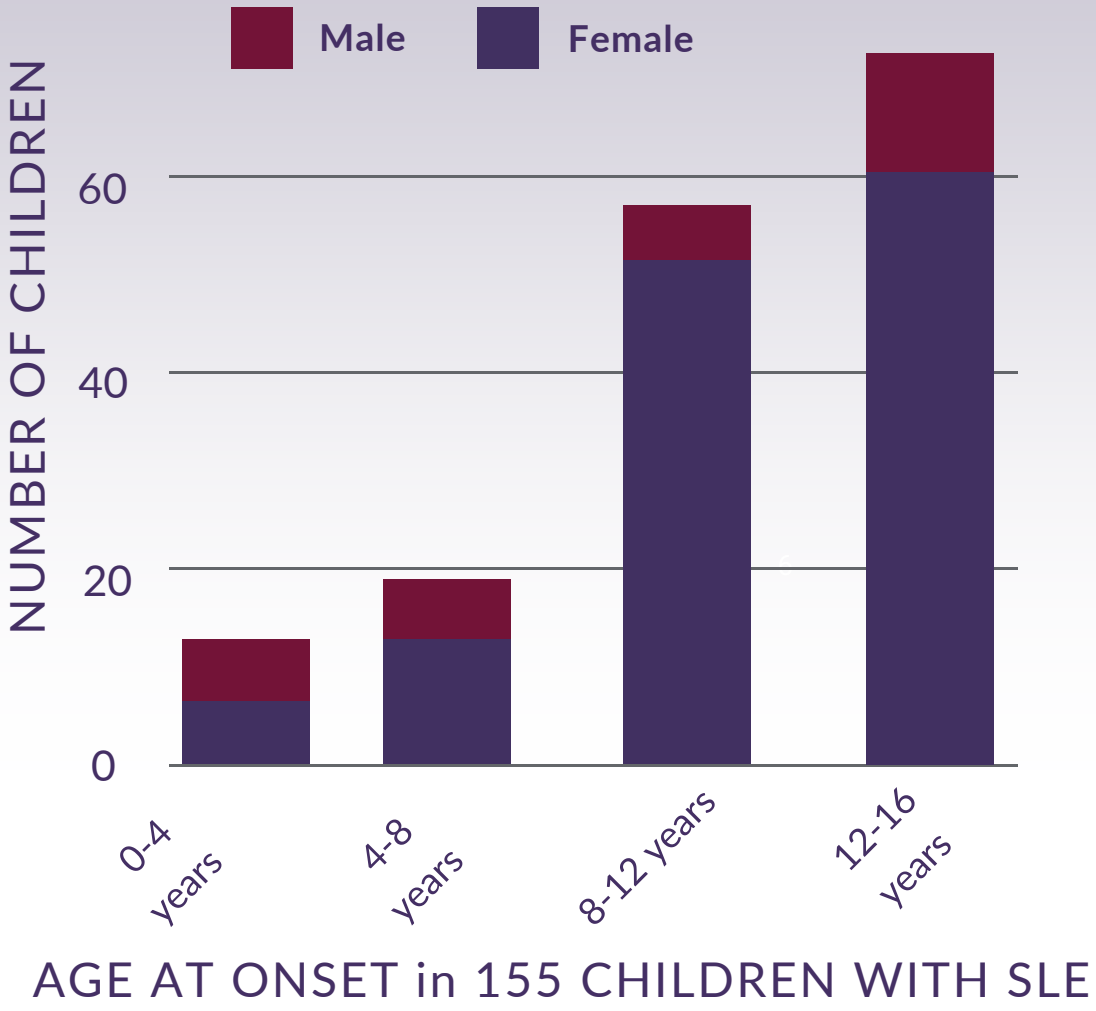
- Majority of SLE is diagnosed in those of child-bearing age, 15-44
- While biologic males don't bear children, age 15-44 is also when diagnosis is most common
- Across ages, significant female predominance
- Patients with childhood SLE are more often non-Caucasian
- Rare for the elderly to have a new diagnosis of SLE



Lalani S, Pope J, de Leon F, Peschken C; Members of CaNIOS/1000 Faces of Lupus. Clinical features and prognosis of late-onset systemic lupus erythematosus: results from the 1000 faces of lupus study. J Rheumatol. 2010 Jan;37(1):38-44.

SLE occurs in children and teens

- 1 case per 100,000 children annually
- Since SLE is a chronic illness, it continues into adulthood
- Pediatric-onset SLE makes up 20% of the total SLE population
- What might a pediatric patient with lupus look like?
- What should be covered in their initial evaluation?

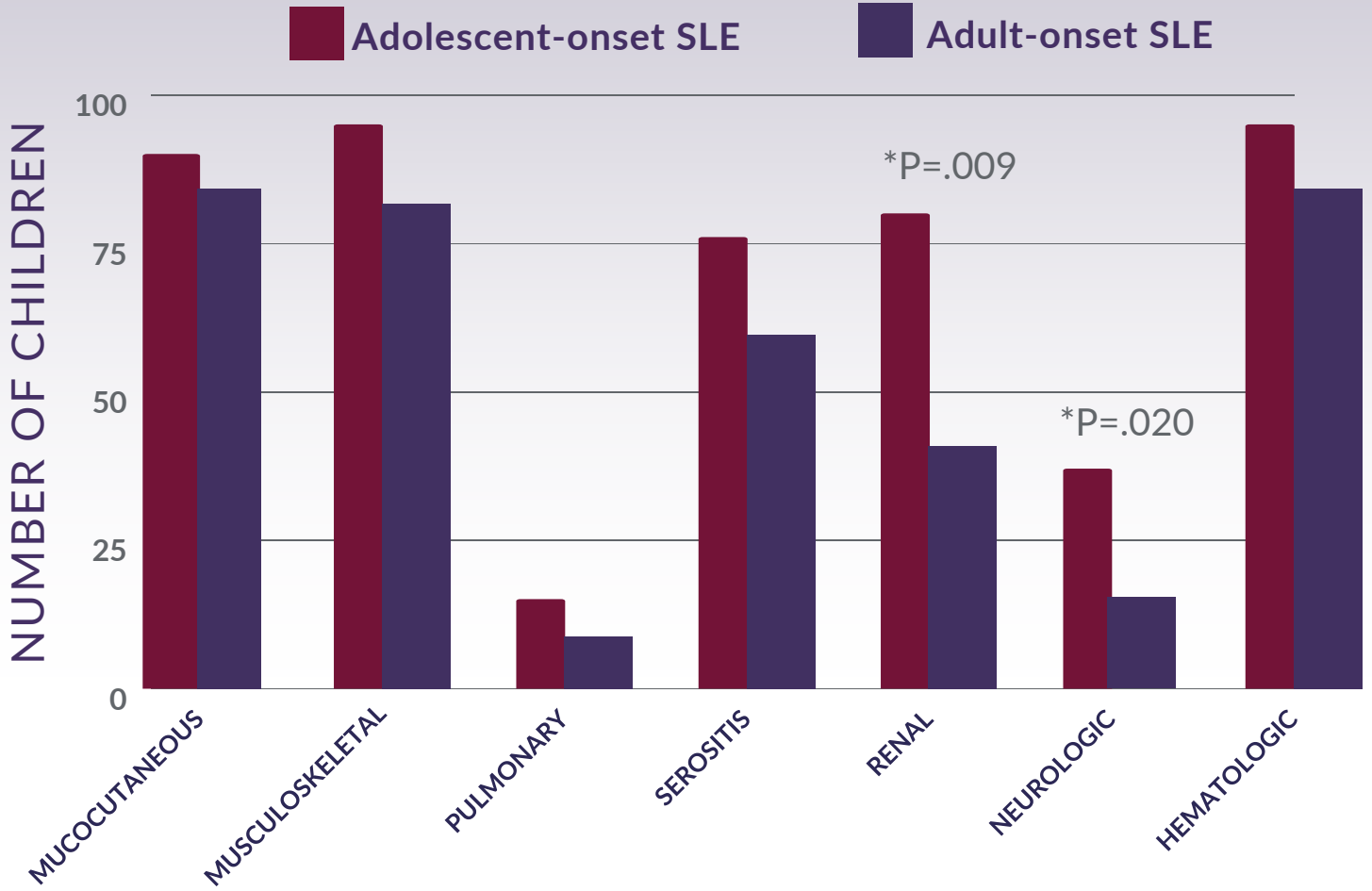


AGE AT ONSET in 155 CHILDREN WITH SLE

Bader-Meunjer B, Armengaud JB, Haddad E, et al. Initial presentation of childhood-onset systemic lupus erythematosus: a French multicenter study. J Pediatr. 2005;146:648-653.

Childhood vs Adult SLE—Differences

Disease activity at diagnosis is higher in children with SLE than adults



Tucker LB, Uribe AG, Fernández M, et al. Adolescent onset of lupus results in more aggressive disease and worse outcomes: results of a nested matched case—control study within LUMINA, a multiethnic US cohort (LUMINA LVII). Lupus. 2008;17:314-322.

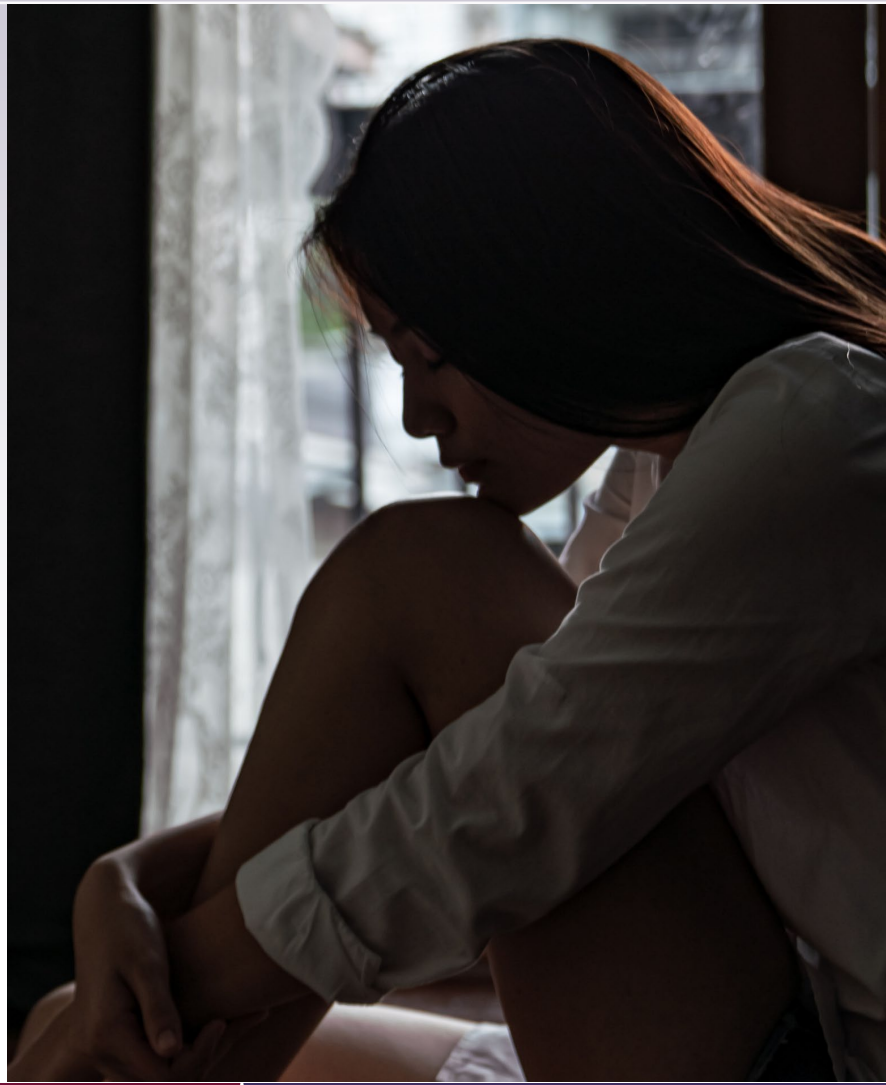
Mina R, Brunner H. Pediatric lupus – are there differences in presentation, genetics, response to therapy, damage accrual compared to adult lupus? Rheum Dis Clin North Am. 2010;36:53-80. doi:10.1016/j.rdc.2009.12.012.

Font J, Cervera R, Espinosa G, et al. Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. Ann Rheum Dis. 1998;57:456-459.

Bundhun PK, Kumari A, Huang F. Differences in clinical features observed between childhood-onset versus adult-onset systemic lupus erythematosus: A systematic review and meta-analysis. Medicine (Baltimore). 2017 Sep;96(37)

Psychosocial Issues in Childhood SLE

- Impact of having a life-long chronic medical illness
- Family dynamics and stressors
- School impact due to attendance and performance
- Bullying/Change in peer interactions/Revealing diagnosis to others
- Weight gain and Striae as side effect of medications and/or SLE
- Hirsutism and Acne
- Cushingoid facies aka “moon face”
- Hair loss
- Medication adherence
- Mental health, especially depression
- Fatigue



MANY ISSUES STEM FROM CORTICOSTEROID USE

https://www.healthline.com/health/moon-face#causes

Comorbidities associated with SLE

Lupus at any age is associated with increased:

- Cardiovascular disease
- Metabolic syndrome
- Malignancy
- Osteoporosis
- Depression/Anxiety
- Other autoimmune diseases

Due to longer disease duration and therefore longer steroid and other immunosuppressive exposure, these are increased in adults with childhood-onset SLE

Immunizations in Lupus Patients

- Live attenuated vaccines are not recommended for use in immunosuppressed patients
- 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

Elkayam O, Paran D, Caspi D, et al. Immunogenicity and safety of pneumococcal vaccination in patients with rheumatoid arthritis or systemic lupus erythematosus. Clin Infect Dis. 2002;34:147-153.

Abu-Shakra M, Press J, Varsano N, et al. Specific antibody response after influenza immunization in systemic lupus erythematosus. J Rheumatol. 2002;29:2555-2557.

CDC.Gov website for vaccination recommendations (updated)

Immunizations in Lupus Patients

Lupus at any age is associated with increased:

- Age-appropriate recommended vaccinations during childhood
- Inactivated influenza (not the nasal spray)
- Pneumococcus per recommendations for immunocompromised patients
- Meningococcus
- HPV
- Covid
- Inactivated shingles
- Tdap

Neonatal Lupus is not Childhood SLE

Transplacental crossing of Anti-Ro (SSA) and Anti-La (SSB) antibodies

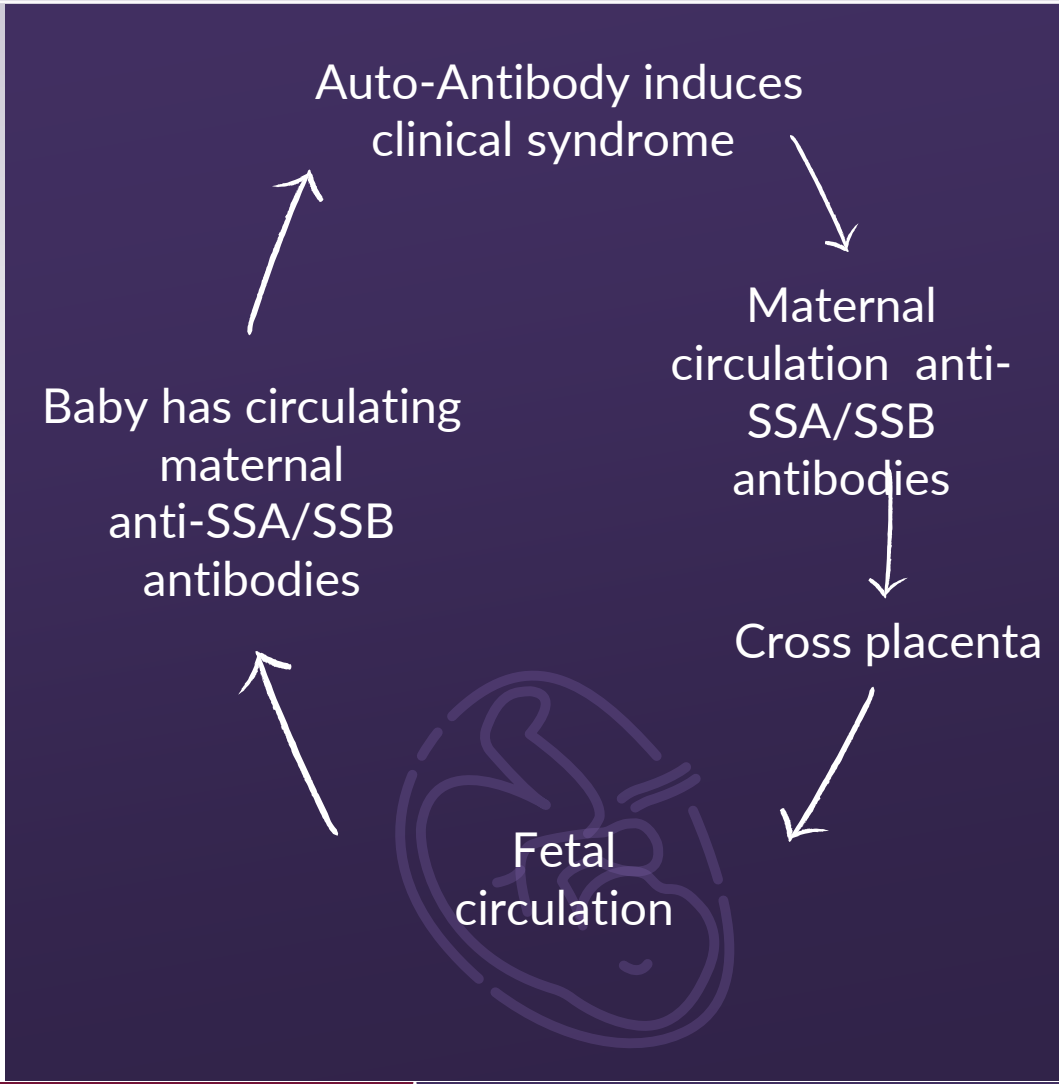
Neonate manifestations:

- Transient, photosensitive rash
- Transaminitis
- Thrombocytopenia
- Anemia
- Neutropenia
- Heart block

Image courtesy of the Rheumatology Image Bank

Neonatal lupus

- Unless heart block is present, no treatment needed for infant
- At birth, antibodies found in the infant's serum will be the mother's
- Does infant need to be evaluated for SLE?→ No
- Does child have increased risk of SLE in lifetime?→ No greater than those born to anyone with SLE
- If antibodies are known prenatally, pregnant patient should be started on or continue hydroxychloroquine and have routine fetal cardiac monitoring
- If mother has no autoimmune history, should be evaluated by rheumatologist
- Increased risk for neonatal lupus in subsequent pregnancies



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

Late-Onset “Elderly” Lupus—Epidemiology

- Defined as onset at age 50 or older
- Represents ~10 % of all SLE patients
- Still predominantly female, but higher percentage Caucasian
- Drug-induced lupus must be ruled out
- Many cancers can mimic SLE and can have a positive ANA
- The incidence of clinically insignificant ANA increases with age, upwards of 70% of elderly can have a low level +ANA

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

Men K, Chen Y, Zhang J, Wei D. The evaluation of cellular immune function in elderly patients with systemic lupus erythematosus. Korean J Intern Med. 2019;34(4):932-937. doi:10.3904/kjim.2017.224

Late-Onset Lupus

Clinical characteristics

- Reduced likelihood of renal and neurologic symptoms
- Reduced prevalence of dsDNA and Smith antibodies and low complement levels
- Lower levels of disease activity

Unique feature of late-onset lupus

- Increased prevalence of photosensitivity
- Poorer outcomes 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.

Reproductive Health Concerns for the Systemic Lupus Patient

Reproductive health

Reproductive health has many facets that are applicable to SLE patients including:

- Puberty
- Menses
- Contraception
- HPV and Gynecologic Cancers
- Infertility
- Pregnancy
- Breastfeeding
- Menopause

Puberty

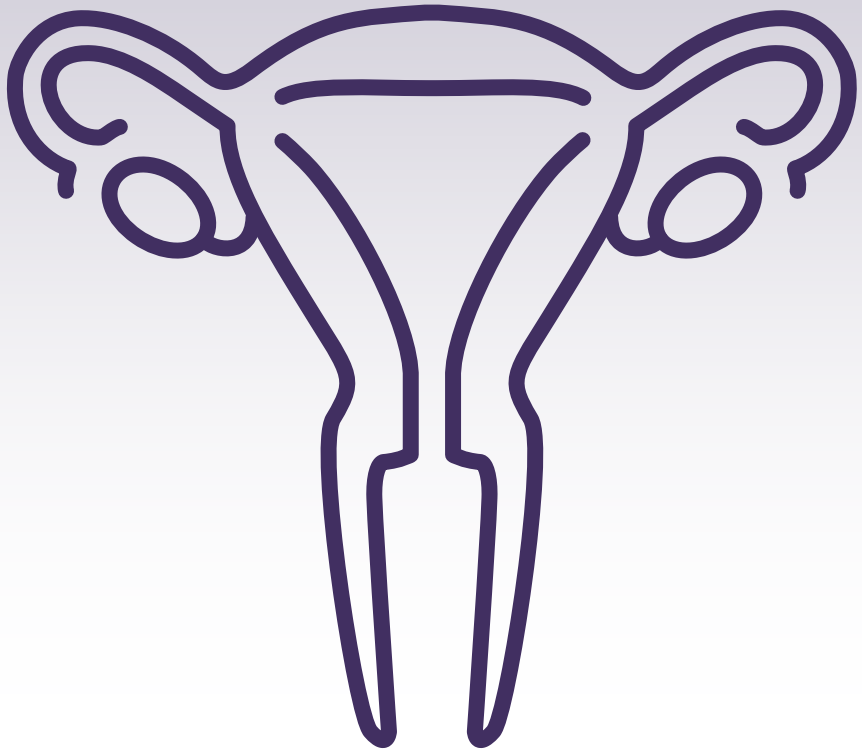
- The onset of puberty has been found to be delayed in patients with childhood SLE
  - Disease activity and corticosteroid use plays a role in its delay
  - Found in across genders
- Due to this delay, compounded by medication side effects and other disease characteristics, bone growth can also be affected resulting in short stature

Medeiros PB, Febronio MV, Bonfa E, Borba EF, Takiuti AD, Silva CA. Menstrual and hormonal alterations in juvenile systemic lupus erythematosus. Lupus. 2009;18(1):38-43.

Silva CA, Leal MM, Leone C, et al. Gonadal function in adolescents and young women with juvenile systemic lupus erythematosus. Lupus. 2002;11(7):419-425

Menses

- The onset of one's first menstrual cycle has also been found delayed in those with childhood SLE
  - Disease activity and corticosteroid use also plays a role in its delay
- If diagnosed after menarche, active SLE can lead to oligomenorrhea or secondary amenorrhea
- Cyclic hormonal changes have also been associated with increased disease activity



Medeiros PB, Febronio MV, Bonfa E, Borba EF, Takiuti AD, Silva CA. Menstrual and hormonal alterations in juvenile systemic lupus erythematosus. Lupus. 2009;18(1):38-43.

Pasoto SG, Mendonca BB, Bonfa E. Menstrual disturbances in patients with systemic lupus erythematosus without alkylating therapy: clinical, hormonal and therapeutic associations. Lupus. 2002;11(3):175-180.

Contraception is essential to the care of SLE patients

- Allows for optimal pregnancy timing: right time for patient, their lupus, and when on pregnancy-compatible medications
- Recommended use when being treated with teratogenic medications
- Some SLE patients have contraindications to pregnancy like severe lung, heart or kidney disease, recent stroke, or have already had pregnancy complications like severe pre-eclampsia or HELLP

Birru Talabi M, Clowse MEB, Blalock SJ, Moreland L, Siripong N, Borrero S. Contraception Use Among Reproductive-Age Women With Rheumatic Diseases. Arthritis Care Res (Hoboken). 2019;71(8):1132-1140

Contraception is essential to the care of SLE patients

- Non-contraceptive benefits include
  - improving bone health and anemia due to lighter menses
  - less mood swings
  - treating acne
  - premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD)
  - dysmenorrhea
  - metrorrhagia
  - menorrhagia
  - hirsutism
  - PCOS
  - endometriosis
  - menstrual headaches
- Ease of participation in sports, work, travel, and pursue higher education
- Shown to decrease lupus flares

Birru Talabi M, Clowse MEB, Blalock SJ, Moreland L, Siripong N, Borrero S. Contraception Use Among Reproductive-Age Women With Rheumatic Diseases. Arthritis Care Res (Hoboken). 2019;71(8):1132-1140

Contraception is essential to the care of SLE patients

There are safe options for contraception for everyone with SLE

Best method is determined by:

- Lupus activity
- Proteinuria
- Antiphospholipid antibody (aPL) positivity
- Thrombus history or risk
- Effectiveness and Compliance

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SLE & Reproductive Health

Pre-conception Checklist

Providers: Review this checklist when planning to discuss your patient's reproductive health plans, if they indicate a desire to become pregnant.

Lupus disease activity

- ☐ Establish care with a rheumatologist to assess disease activity
- ☐ Low lupus disease activity
- ☐ No flares within previous 6 months
- ☐ Consider evaluation by high-risk obstetrics/maternal fetal medicine
- ☐ Establish care with appropriate organ-specific specialist if needed

Pregnancy risk assessment

- ☐ Blood pressure evaluation
- ☐ Complete blood count
- ☐ Serum Creatinine
- ☐ Urine protein to creatinine ratio
- ☐ Liver Function Test
- ☐ Antiphospholipid Antibody testing
- ☐ SSA/Anti-Ro and SSB/Anti-La testing

Pregnancy medication safety

The below medications are compatible with pregnancy.

- ☐ Azathioprine
- ☐ Chloroquine
- ☐ Colchicine
- ☐ Cyclosporine
- ☐ Hydroxychloroquine
- ☐ NSAIDs (until 20 weeks)
- ☐ Prednisone, Methylprednisolone
- ☐ Rituximab up until conception
- ☐ Tacrolimus

If on other medications, need to discuss stopping or switching to medications that are compatible with pregnancy.

These educational materials were supported by a medical education grant from GlaxoSmithKline to address Systemic Lupus Erythematosus (SLE) and Reproductive Health education to support patients, educators, and clinical teams. Its contents are solely the responsibility of the authors and do not necessarily reflect the official views of GlaxoSmithKline.

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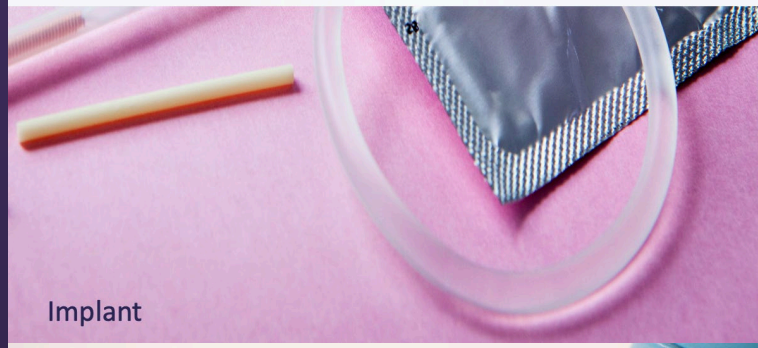
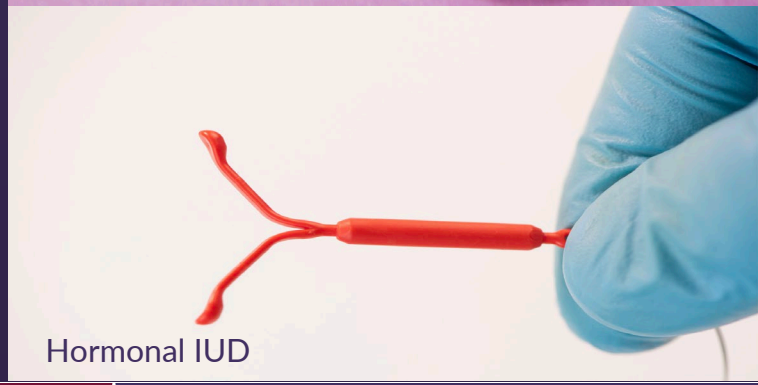
Preferred Contraception

- Long-acting reversible contraceptives (LARCs) are recommended by the American College of Rheumatology:
  - Highly effective
  - High compliance
  - Safe in those with thrombus or those with positive aPLs
- Estrogen is not recommended for high-risk patients including those with significant proteinuria from lupus nephritis, thrombus history, or positive aPLs


Copper IUD


Implant


Hormonal IUD

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Emergency Contraception

Emergency contraception includes:

- Oral Pills (levonorgestrel and ulipristal)
- IUDs
- Both methods are safe for those with SLE as they do not contain estrogen
- No age restrictions to use
- Some available without a prescription or online
- IUDs may remain in place for long-term use

American College of Obstetricians and Gynecologists. Access to emergency contraception. Committee Opinion No. 542. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120:1250–3

HPV vaccination in SLE

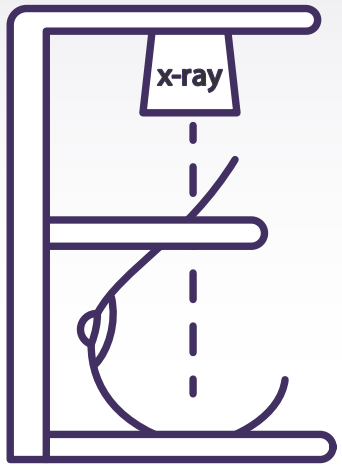
- SLE patients have decreased clearance of HPV→ Therefore have increased risk of HPV-related cancers, including cervical cancer
- All SLE patients should be recommended to receive the HPV vaccinations
  - Vaccination has not been associated with disease flare
- SLE patients should receive the 3 dose HPV series at the same age recommended for non-SLE patients

Kim SC, Feldman S, Moscicki AB. Risk of human papillomavirus infection in women with rheumatic disease: cervical cancer screening and prevention. Rheumatology (Oxford). 2018;57(suppl_5):v26-v33

Soybilgic A, Onel KB, Utset T, Alexander K, Wagner-Weiner L. Safety and immunogenicity of the quadrivalent HPV vaccine in female Systemic Lupus Erythematosus patients aged 12 to 26 years. Pediatr Rheumatol Online J. 2013;11:29.

Gynecologic Cancers

- Due to decreased clearance of HPV, patients with SLE are recommended to undergo cervical cancer screening at the same intervals as HIV patients, which is earlier and more frequent than the general public
- Breast cancer screening is lacking in women with SLE and should be encouraged starting at age 40



Moscicki AB, Flowers L, Huchko MJ, et al. Guidelines for Cervical Cancer Screening in Immunosuppressed Women Without HIV Infection. J Low Genit Tract Dis. 2019;23(2):87-101.

Infertility in Lupus Patients

SLE is associated with decreased fertility

- Sequalae of chronic inflammation resulting in gonadal dysfunction
- Medication related, specifically cyclophosphamide and corticosteroids
- Increased premature ovarian insufficiency and antibodies against oocyte and sperm identified

Hickman RA, Gordon C. Causes and management of infertility in systemic lupus erythematosus. Rheumatology (Oxford). 2011 Sep;50(9):1551-8.

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Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocr Rev. 2002;23(3):327-364

Infertility in Lupus Patients

Exposure to cyclophosphamide is associated with a dose-related and age-dependent risk of infertility

- For males:
  Consider cryopreservation “sperm banking”
- For females:
  Ovarian suppression or oocyte harvesting

Hickman RA, Gordon C. Causes and management of infertility in systemic lupus erythematosus. Rheumatology (Oxford). 2011 Sep;50(9):1551-8.

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Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocr Rev. 2002;23(3):327-364

SLE patients can have healthy pregnancies, but risks need to be managed

- Pregnancy optimally should be planned
- Disease activity optimally should be under control for 6 months prior to conception
- Patient should discontinue teratogenic medications prior to pregnancy
  - Cyclophosphomide
  - Methotrexate
  - Mycophenolate
  - Leflunomide
  - ACE inhibitors/ARBs
- Continue hydroxychloroquine, azathioprine, and corticosteroids

SLE patients should see High Risk Obstetric/ Maternal Fetal Medicine physicians and their rheumatologist throughout their pregnancy for coordinated care

Moland Y, Borkowski T, Monselise A, et al. Maternal and fetal outcome of lupus pregnancy: a prospective study of 29 pregnancies. Lupus. 2005;14:145-151.
Julkunen H, Jouhikainen T, Kaaja R, et al. Fetal outcome in lupus pregnancy: a retrospective case-control study of 242 pregnancies in 112 patients. Lupus. 1993;2:125-131.
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Another risk: Antiphospholipid Syndrome (APS)

APS is diagnosed based on:

- Presence of Antiphospholipid Antibodies (aPL)
  - Anticardiolipin antibodies
  - Positive Lupus anticoagulant/DRVVT
  - Anti-□2-glycloprotein antibodies
- Clinical manifestations of venous thrombosis and/or arterial thrombosis

OR

- Pregnancy morbidity/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

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

Antiphospholipid Syndrome in Pregnancy

A history of APS increases risk of:

- Miscarriage
- Stillbirth
- Pre-Eclampsia
- Pre-term delivery
- Maternal death

Aspirin and Heparin/Low Molecular Weight Heparin is recommended in SLE pregnancies with a history of APS, pre-eclampsia, HELLP, or thrombus

Aspirin is also recommended in all SLE pregnancies to decreased development of pre-eclampsia

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Pregnancy and SLE Activity

"Will pregnancy make my lupus flare?"

- Approximately 50% of women will have measurable SLE activity during pregnancy
- Flares increase risk of poor pregnancy outcomes
- Risk of flare is significantly reduced if planned pregnancy is preceded by 6 months of inactive disease and pregnancy-compatible medications are continued
- Up to 30% of SLE patients flare post-partum
  - Can have new disease manifestations including lupus nephritis

Lê Huong D, Wechsler B, Vauthier-Brouzes D, et al. Br J Rheumatol. 1997;36:772-777.
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Concerns for Pregnant Lupus Patients

- Increased risk of miscarriage and stillbirth
- Significantly increased risk of pre-eclampsia
- Increased risk of gestational diabetes
- Up to 1/3 require a cesarean section
- Up to 1/3 with preterm birth
- 20x increased risk of maternal death

Planned pregnancies with controlled lupus improves pregnancy outcomes

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.
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Lupus and lactation

- It is recommended that lupus patients consider breastfeeding as guided by the infant's pediatrician and other providers
- Medications need to be managed to ensure safety during lactation for mom and baby

Medications ok to use in breastfeeding:

- Hydroxychloroquine
- Azathioprine
- Corticosteroids
- Sulfasalazine
- NSAIDs
- Belimumab
- Tacrolimus

Bone Health

- In addition to risk factors of general population, patients with SLE have decreased bone density due to:
  - Chronic inflammatory state
  - Low vitamin D from sun avoidance
  - Decreased physical activity
  - Corticosteroid use
  - Delayed puberty

- Focus on osteoporosis prevention through alternate medication use, vitamin D supplementation, encouragement of physical activity, bisphosphonates to prevent osteoclastic activity, particularly if on corticosteroids, avoidance of alcohol/tobacco
- No guidelines exist for bone density screening in SLE patients

Edens C, Robinson AB. Systemic lupus erythematosus, bone health, and osteoporosis. Curr Opin Endocrinol Diabetes Obes. 2015 Dec;22(6):422-31

Effects of Menopause on SLE

- Disease activity is greater in premenopausal than postmenopausal women with SLE
- 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.

Lupus and Hormone Replacement Therapy

Patients who do not have APS, have negative aPLs, and have quiet lupus activity can consider HRT treatment to help with severe vasomotor symptoms

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Conclusions—Lupus Through the Lifespan

- Lupus presents unique challenges in pediatric, adult, and late-onset populations
- With careful planning, many people with lupus can achieve their family planning goals
- By addressing contraception, pregnancy, lactation, immunization, and bone health, the outcomes and quality of life of lupus patients can be improved
- There are important comorbidities associated with lupus across the lifespan

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Visit: https://thelupusinitiative.org/

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