Childhood onset systemic lupus erythematosus

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disclaimer

- No financial disclosures or conflict of interest

Objective

- Understand childhood onset systemic lupus erythematosus cSLE and how it is different from a adult onset SLE (aSLE)
- Understand the clinical presentations/ signs and symptoms
- Discuss treatment options and transition of care for better outcomes

Systemic lupus erythematosus

- Complex autoimmune disease which can affect and cause inflammation of any organ systems (called the great mimicker)
- Our immune system protects us from foreign tissue like infections, cancers, etc by making antibodies
- In lupus patients the immune system gets confused and instead of making protective antibodies it makes antibodies against itself AKA “autoantibodies”

cSLE

- Onset before 18 years of age
- Rare in infancy: new neonatal lupus
- More common in females
- Highest in females in their reproductive years 14-45

cSLE: epidemiology
How common is lupus in children

- 15-20% of all SLE patients are children
- Incidence of cSLE in children 3-18 yr based on US Medicaid database from 47 states and Washington DC: **2.22 per 100,000 children/yr** (aSLE 23.17/100,000)
- Incidence of lupus nephritis: 0.71 **per 100,000 children/ yr** (aSLE 6.85/100,000)
- Prevalance of cSLE: **9.73/100,000 children** (aSLE 143/100,000 adults)
- Prevalence of lupus nephritis: **3.64/ 100,000 children** (aSLE 30.9/100,000)

cSLE: demographics
Who gets lupus

- Females > males
  - cSLE female: male 5:1
  - aSLE female: male 9:1
- Ethnicities most commonly affected:
  - Asians >
  - African Americans >
  - Hispanics >
  - Whites

Why does lupus occur

- Multi-hit theory
  - Genetics
    - Impaired clearing of debris/ dead cells
    - Immune cells become overactive
  - Environment
    - Viruses: EBV, CMV
    - sunlight
  - Drug exposure
    - Birth control pills
    - Certain anti-hypertensive

ACR 1997 classification criteria

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

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion 1. *OR* 2. Pericarditis--documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed 1. *OR* 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance 1. *OR* 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia--with reticulocytosis 1. *OR*

Criterion	Definition
	2. Leukopenia--< 4,000/mm³ on ≥ 2 occasions 1. *OR* 3. Lyphopenia--< 1,500/ mm³ on ≥ 2 occasions 1. *OR* 4. Thrombocytopenia--<100,000/ mm³ in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer 1. *OR* 2. Anti-Sm: presence of antibody to Sm nuclear antigen 1. *OR* 3. Positive finding of antiphospholipid antibodies on: 1. 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. 2. a positive test result for lupus anticoagulant using a standard method, or 3. 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Table 1. Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus

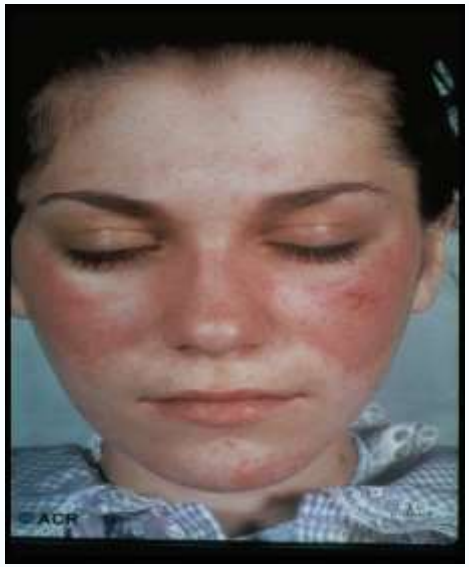
Clinical criteria	Immunological criteria
1. Acute cutaneous lupus: including lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash in the absence of dermatomyositis, or subacute cutaneous lupus	1. Antinuclear antibody above laboratory reference range
2. Chronic cutaneous lupus: including classical discoid rash, localized or generalized, hypertrophic lupus, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chillblain lupus, discoid lupus/lichen planus overlap	2. Anti-dsDNA antibody above laboratory reference range, except ELISA: twice above laboratory reference range
3. Oral ulcers: palate, buccal, tongue, or nasal ulcers, in the absence of other causes	3. Anti-Smith antibody
4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs) in the absence of other causes	4. Anti-phospholipid antibody: any of the following lupus anticoagulant, false-positive RPR, medium or high titer anticardiolipin (IgA, IgG or IgM), anti-β_2-glycoprotein I (IgA, IgG or IgM)
5. Synovitis involving two or more joints, characterized by swelling or effusion *or* tenderness in two or more joints and 30 minutes or more of morning stiffness	5. Low complement, low C3, low C4, low CH50
6. Serositis: typical pleurisy for more than 1 day, or pleural effusions, or pleural rub, typical pericardial pain for more than 1 day, or pericardial effusion or pericardial rub, or pericarditis by ECG, in the absence of other causes	6. Direct Coombs test in the absence of hemolytic anemia
7. Renal: urine protein/creatinine (or 24-hour urine protein) representing 500 mg protein/24 hours, red blood cell casts	SLICC criteria for SLE classification require:
8. Neurologic: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state, in the absence of other causes	1. Fulfillment of at least four criteria, with at least one clinical criterion *and* one immunologic criterion
9. Hemolytic anemia	*or*
10. Leukopenia (<4,000/mm^3 at least once) in the absence of other known causes or lymphopenia (<1,000/mm^3 at least once) in the absence of other known causes	2. Lupus nephritis as the sole clinical criterion in the presence of antinuclear antibody or anti-dsDNA antibodies
11. Thrombocytopenia (<100,000/mm^3) at least once in the absence of other known causes	

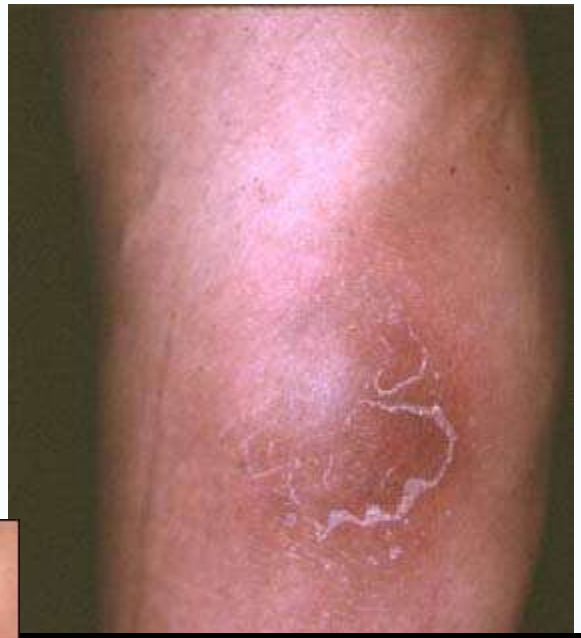
ECG, eletrocardiogram; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics. Adapted from [2].

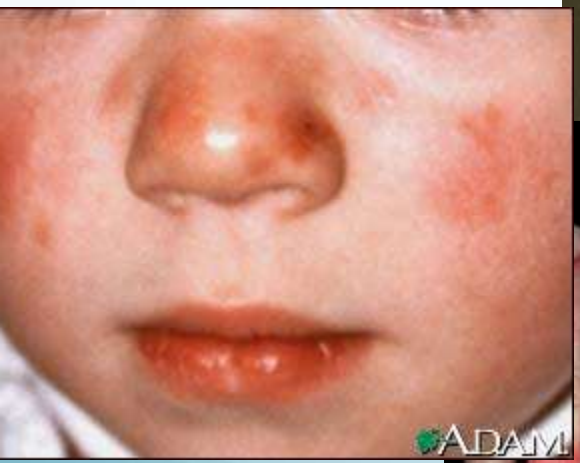
What are the symptoms of cSLE

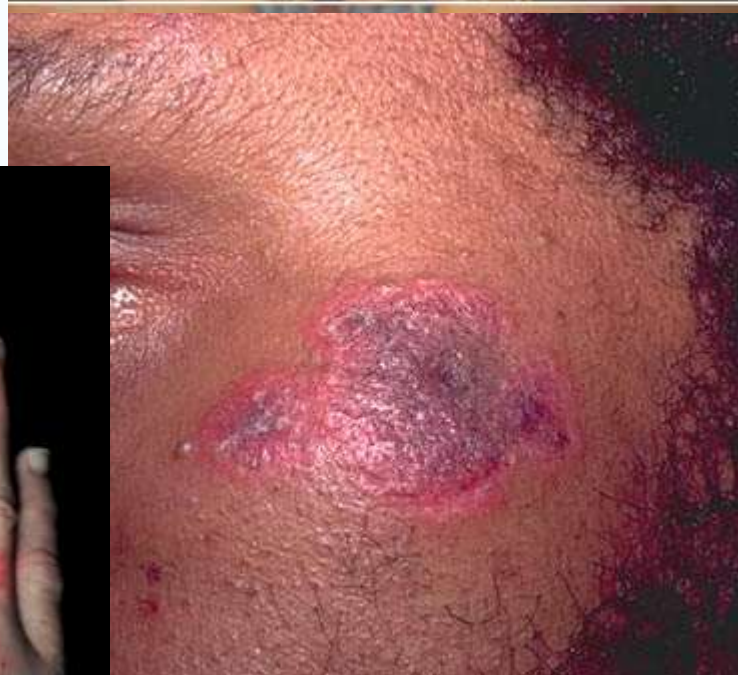
- Fatigue/ malaise
- Fevers
- Weight loss/ weight gain
- Joint pain/ swelling
- Rash
- Seizures (other CNS issues)
- Blood in the urine/ other renal issues
- Chest pain/ fluid around the heart or lung
- Muscle pain/ weakness

Rashes of SLE

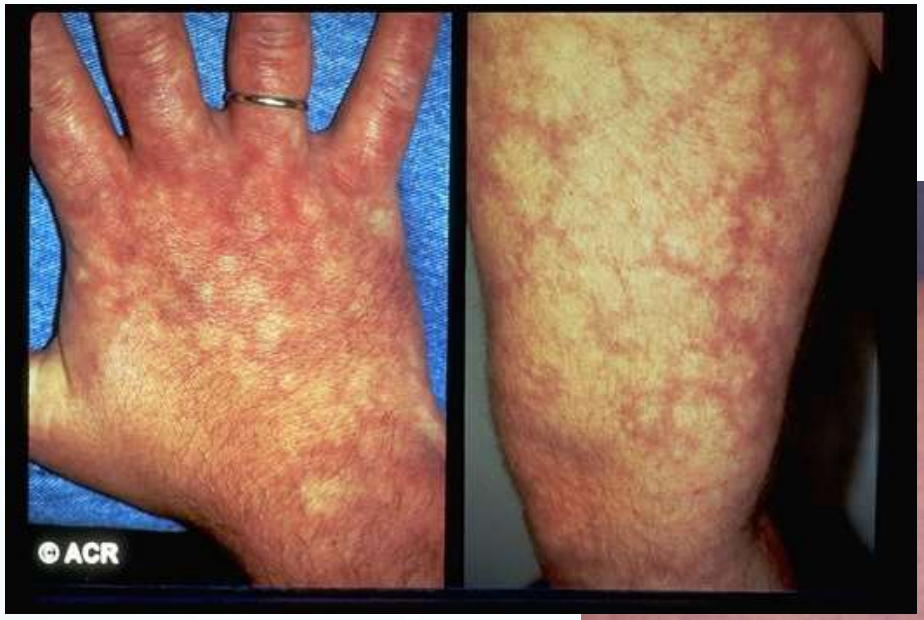


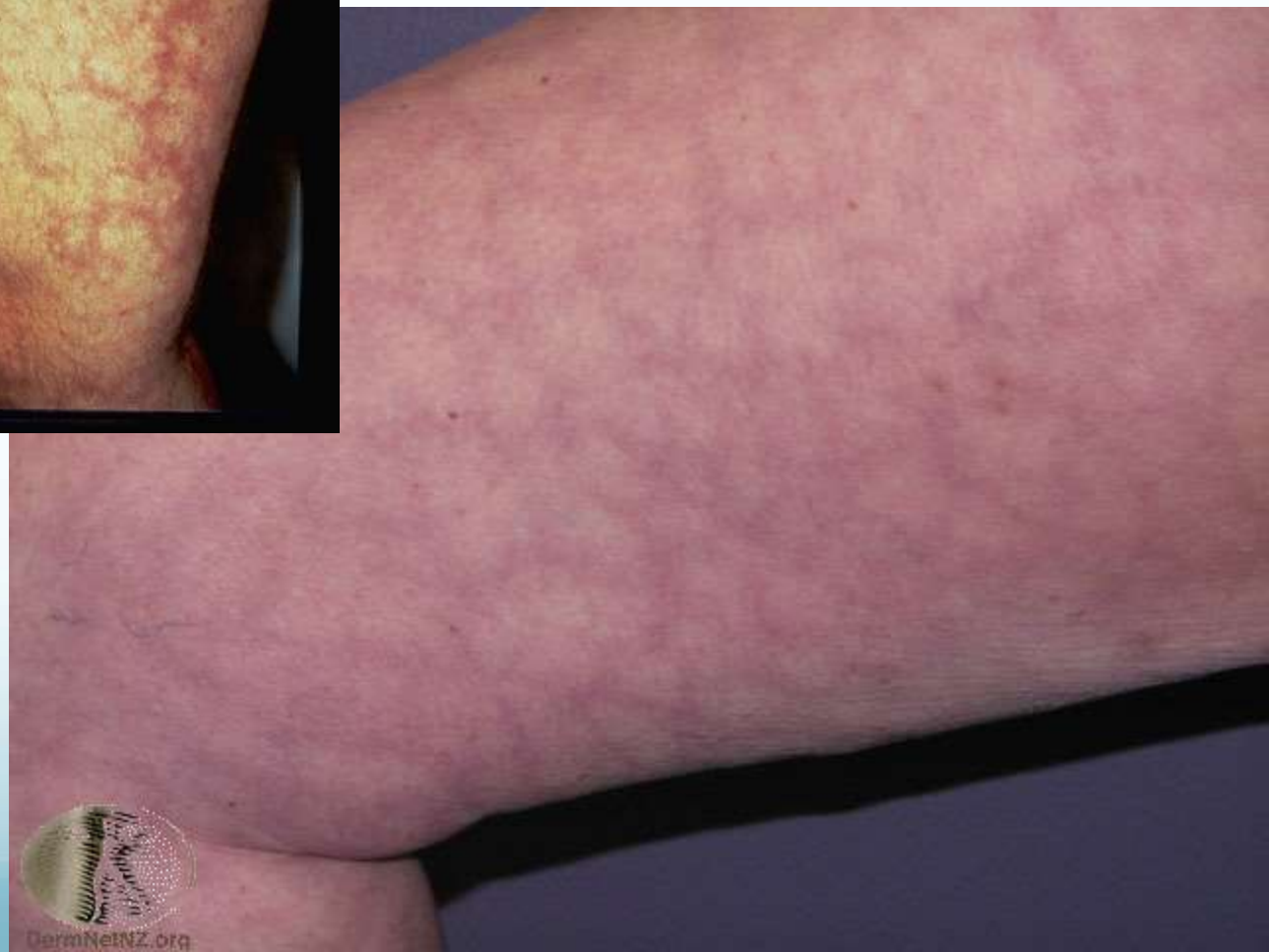




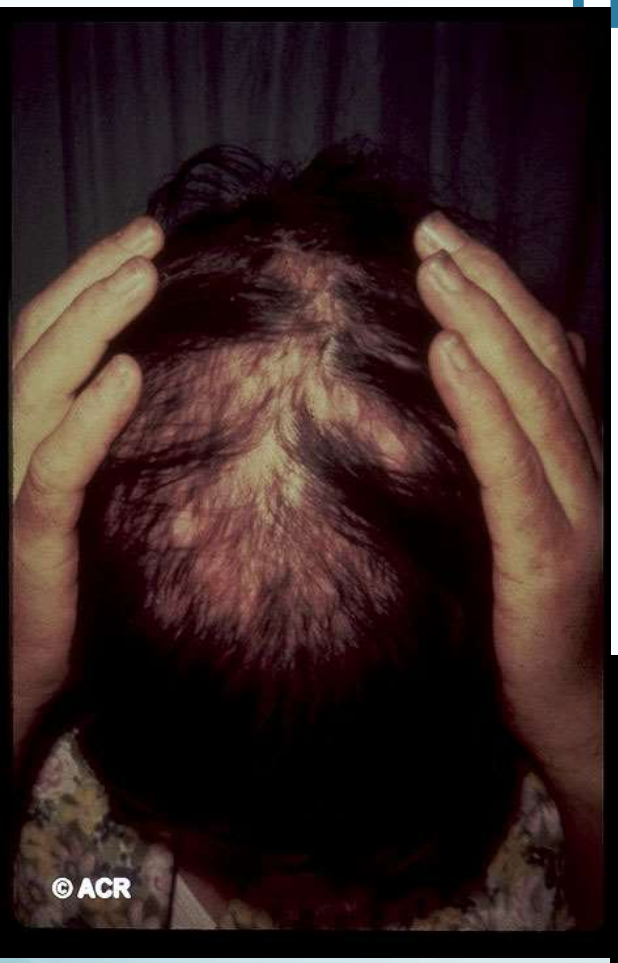


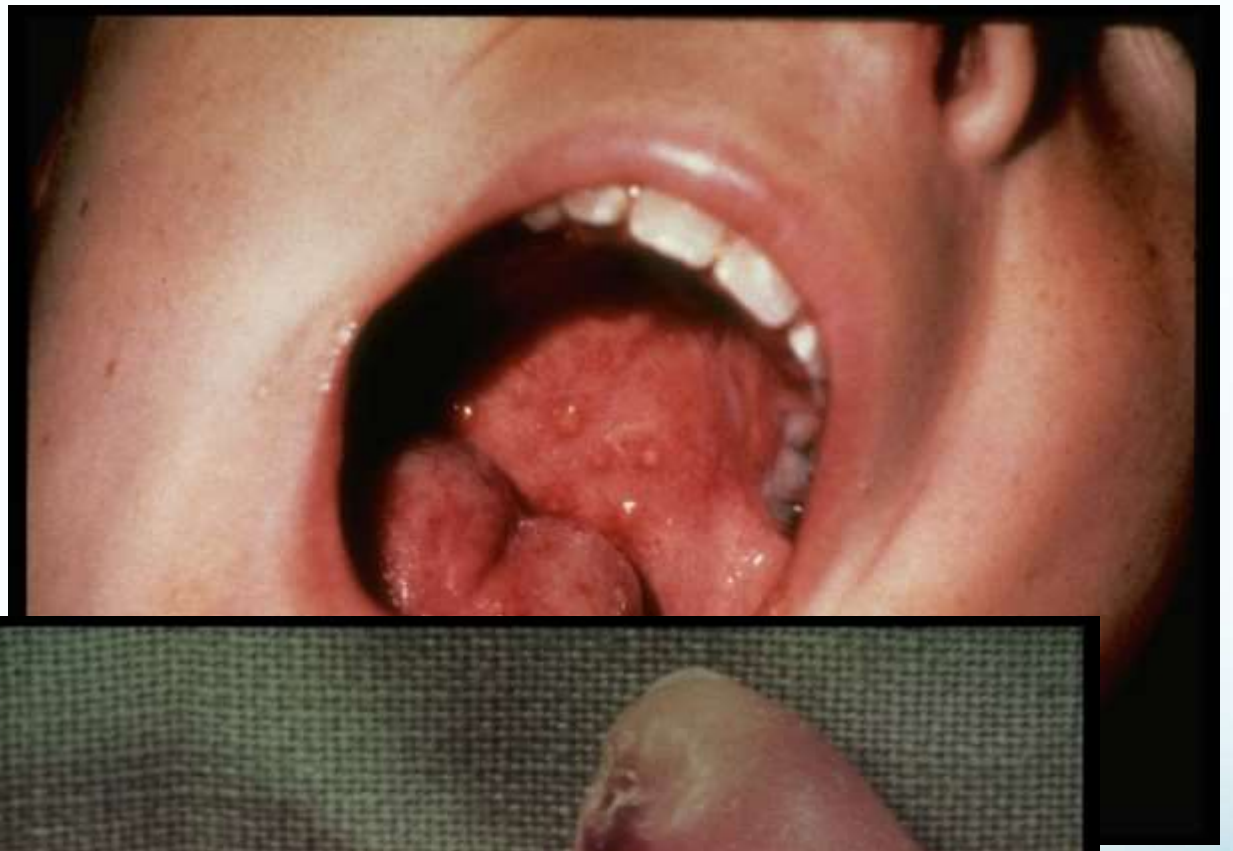
Rashes of SLE: anti-phospholipid antibodies

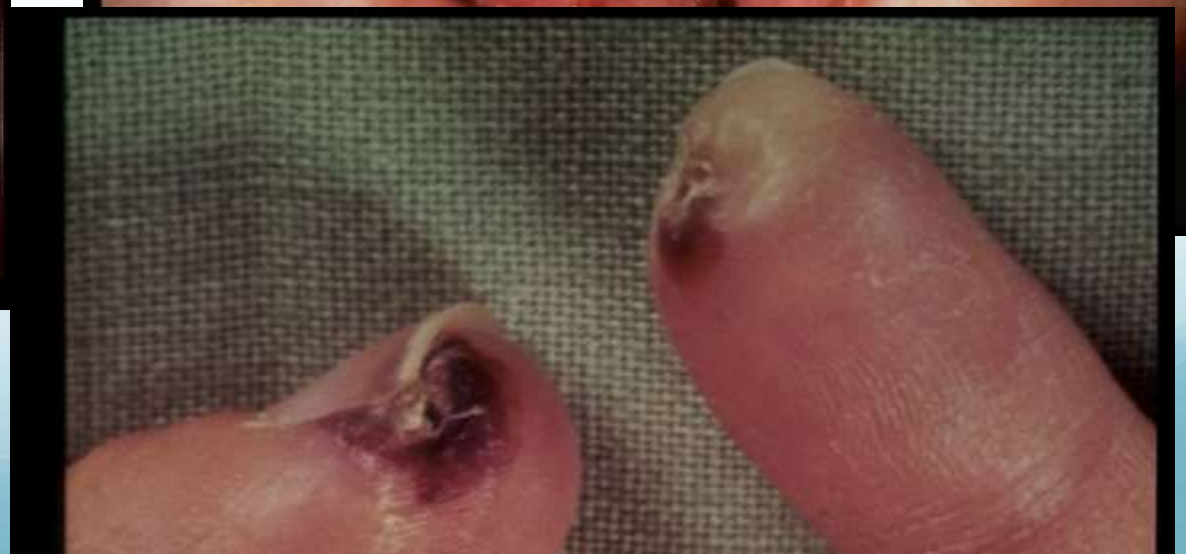




SLE: other mucocutaneous manifestations







cSLE and renal disease

- Higher frequency of renal involvement at time of diagnosis in cSLE then aSLE
- Inflammation in the kidneys may cause:
  - Blood in urine
  - Elevated blood pressure (headaches)
  - Swelling around ankles
  - Swelling around eyes
  - Belly pain

cSLE and blood cell lines

- Anemia
- Low white cells
- Low platelets

cSLE and CNS

- cSLE patients may present with inflammation in the brain at time of diagnosis (more than aSLE)
- Seizures
- Change in mental status
- Hallucination
- Limb weakness

Table 1 Key differences between juvenile and adult SLE

Features		*JSLE*	*Adult SLE*
Demographics[2]	Female : Male ratio	5 : 1	9 : 1
Organ manifestations[2,8,73]	Renal disease	60–80%	35–50%
	Constitutional symptoms	Fever ≥ 60%, Fatigue ≥ 75%	Less
	Haematological involvement	> 70%	Less frequently seen
	Neurological involvement	20–45% (especially seizures)	Less common (10–25%)
	Cardiorespiratory involvement	Rare	Frequently seen
	Other	Malar rash (70%) and mouth ulcers more common	Arthralgia, Raynaud's and sicca more common
Disease activity[2,8]	Overall activity	Higher mean disease activity scores	More controlled disease activity
	Anti-dsDNA antibodies	61–93%	25–78%
Disease damage[2,8]	Overall damage	Increased mean damage scores – especially early renal damage	Less damage accrued early in the disease
	Major organ associated morbidity	Neurological, renal	Cardiovascular
Medications[2]	Steroid use	Over 90%	Up to 70%
	Cyclophosphamide use	25%	10%
Other[2]		Poor growth and potential pubertal delay with active disease	Malignancy more common

Morgan et al, Children and Adolescents with SLE: not just little adults
Lupus (2013)22, 1309-1319

Some labs the rheumatologist will check

- CBC (low white cell count, anemia, low platelets)
- CMP (elevated creatinine, liver enzymes, low albumin)
- ESR/ CRP (for inflammation)
- Urinalysis (protein or blood in urine)
- Complements (if low may suggest flare)
- ANA (95-99% of SLE patients)

Some labs the rheumatologist will check

- Anti-dsDNA antibodies: renal disease
- Anti-chromatin antibodies: skin/ renal disease
  - Seen more often in children
- Anti-SSA/ SSB antibodies: dry eyes or mouth
- Anti-smith antibodies: very specific for lupus
- Anti-RNP antibodies: lung disease
- Anti-phospholipid antibodies:
  - Migrain headaches
  - Blood clots
  - Miscarriage
  - Should not take estrogen containing birth control pills
- Anti-thyroid antibodies: 30% of thyroid patient has + ANA

Labs to be monitored regularly

- CBC
- CMP
- Complements C3, C4
- Urinalysis
- Anti-dsDNA antibodies
- ESR/ CRP

Treatments used in cSLE

- Steroids
- Hydroxychloroquine: stabilizes the cell membrane
  - Minimizes flares
  - Helps to decrease steroid dose
  - Decrease autoantibody load
  - Decreases atherosclerosis risk
  - Helps with joint pains and rash
- Methotrexate: may be used for joint disease
- Azathioprine:
  - Skin disease
  - Lung disease
  - Maintenance therapy for kidney disease

Treatments used in cSLE

- Mycophenolate mofetil:
  - Used for achieving and maintaining clinical remission esp in renal disease
- cyclophosphamide:
  - Used for major organ involvement
  - Risk of infertility: ? Role of gonadotrophin releasing hormone agonists/ cryopreservation of eggs
- Belimumab: first SLE medication approved in 50 years for adult SLE
  - Trials ongoing for cSLE: Saint Louis University involved
- Rituximab: has been used off label in cSLE with favorable response esp in refractory cytopenia

Treatment

- Sunscreen SPF 50
- Exercise 20-50min every other day for cardiopulmonary health, joint health

Complications of cSLE and it's treatment

- Infections: vaccinations are important
- Cosmetic: steroids may cause weight gain/ stretch marks
  - Referral to dietition
  - Minimizing steroid dose if possible
- Growth and puberty:
  - 15% of cSLE may experience growth failure
    - Close monitoring of height/ BMI
    - Referral to endocrinologist if needed
  - Puberty may be delayed in female cSLE by 1 year
  - Female cSLE patients may temporarily stop menstruating if there is high disease activity

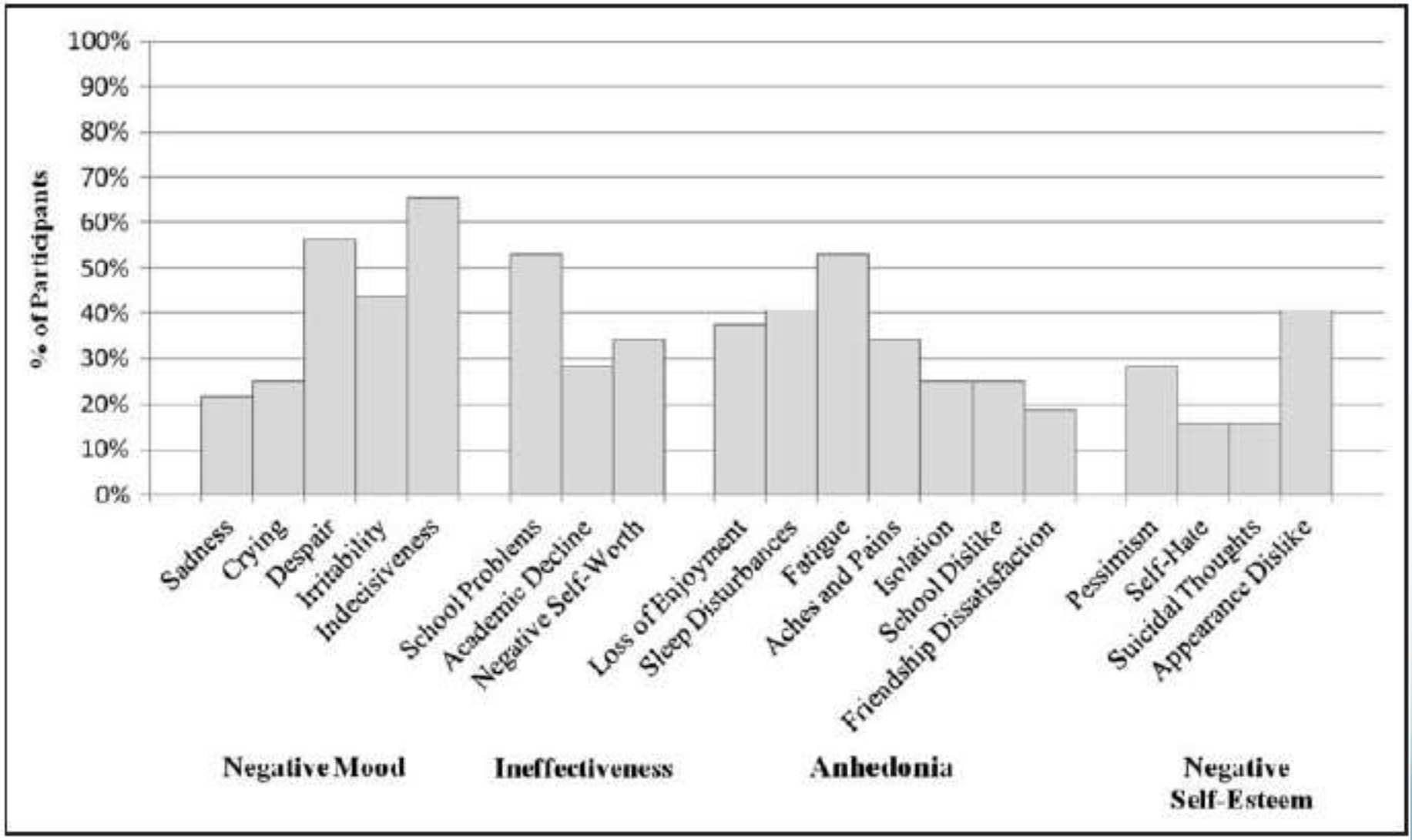
Complications of cSLE and it's treatment

- Infertility: low risk with current regimens
  - Esp in younger females < 21 years of age
  - Prepubertal girls protected from cyclophosphamide related ovarian side effects
  - * for successful pregnancy there is should be good disease control thus the need for aggressive management
  - * pregnancy may cause SLE flare
    - Good education regarding contraceptions/ reproductive health should be provided to adolescents
- If anti-phospholipid antibodies present
  - Risk of blood clots
  - Start baby aspirin
  - No estrogen containing oral contraceptives if high levels of APLA

Complications of cSLE and it's treatment

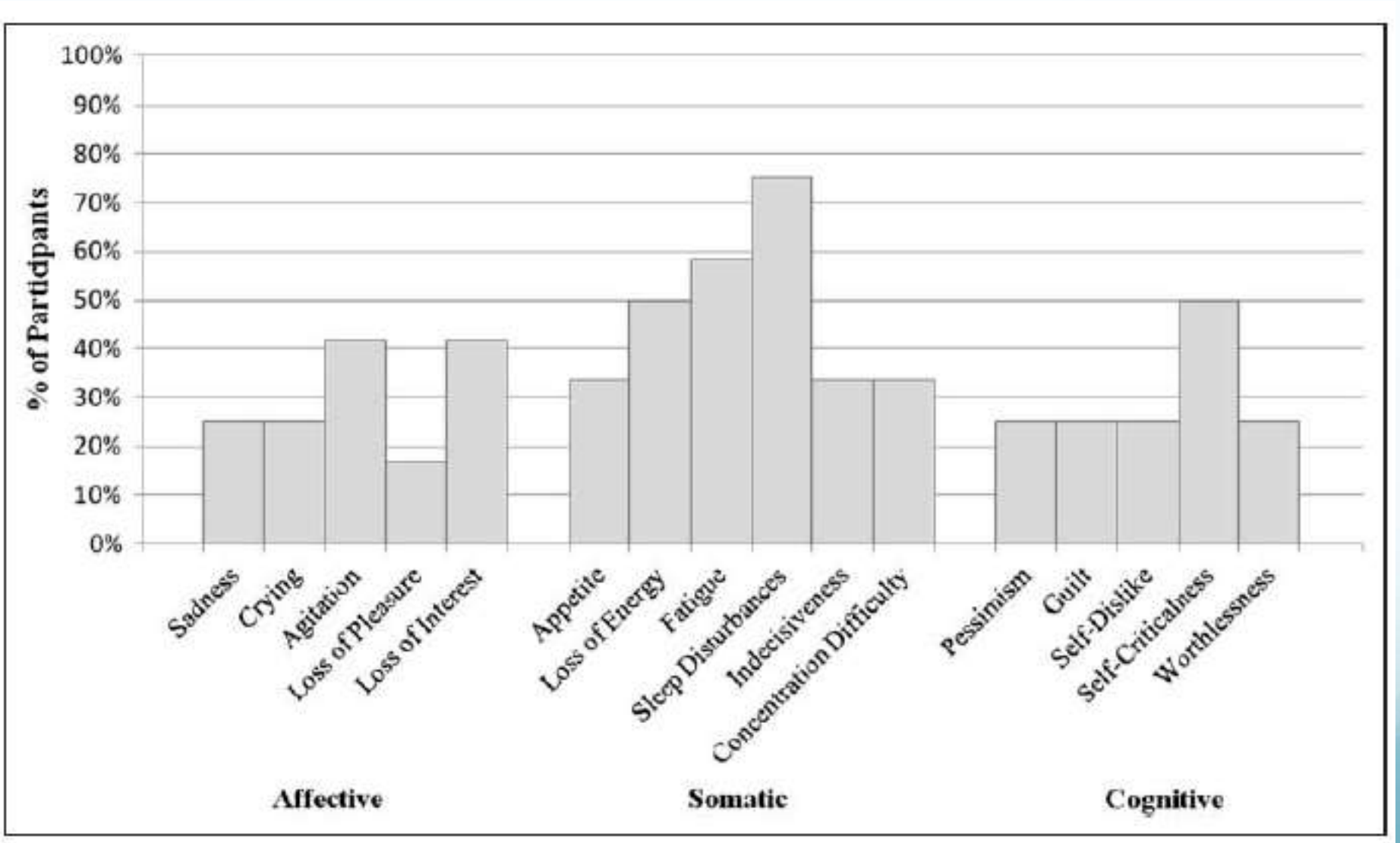
- Risk of earlier atherosclerosis
  - Better control of disease
  - Healthy diet/ exercise/ weight control/ BP control/ lipid control/ avoiding smoking
- Lower bone density:
  - Osteopenia in 40%
  - Calcium and vitamin D
  - Weight bearing exercises
- Risk of malignancy: hematologic possibly increased

Depression in cSLE



Kohut et al. Depressive symptoms are prevalent in childhood-onset systemic Lupus erythematosus. Lupus (2013) 22;712-720

Depression in cSLE



prognosis

- Overall better outcomes since diagnosis is being made earlier and more treatment options are available
- 5 year survival > 90%
- 10 year survival 90%
- 15 year survival 80%
- Risk factors for poor outcomes:
  - Lower socioeconomic status
  - Presence of end stage renal disease

Brunner H et al. Pediatric SLE-Towards a comprehensive Management plan. Nat Rev Rheumatol. (2011);7:225-233

Box 4 | Clinical disease surveillance, health maintenance and education

At every visit

Disease activity

Physician global assessment of disease

Patient assessment of well-being and pain

Every 12 months

Eye screening

- Especially in patients treated with antimalarial drugs and/or corticosteroids; more frequent if pSLE-associated eye disease and/or keratoconjunctivitis sicca is present

Health-related quality of life

- Use a validated measure; implementation may not be possible in certain clinical settings

Bone health assessment

- Dual-energy X-ray absorptiometry at diagnosis and then every 1–2 years; treat abnormal bone density as per current recommendations

Influenza vaccinations

- Avoid attenuated live-virus vaccine

Review need for other immunizations

- Patients with SLE are at an increased risk for infection by encapsulated organisms: immunizations against pneumococcus, meningococcus and *Haemophilus influenzae* type b are suggested
- Discuss risks and benefits of potential cancer prevention with vaccination against human papilloma virus and hepatitis B; discuss potential risks and benefits of varicella zoster virus vaccination

At least once every 12 months

Review of risk factors for coronary artery disease

- Tobacco use, obesity, hypertension, hypercholesterolemia and family history

Review importance of weight management

- Dietary counseling may be warranted

Assist with exercise regimen

- Physical therapy assessment may be warranted

Review reproductive health issues

- The following are recommended in postpubertal patients: cervical Papanicolaou smear test; contraception assessment; education about teratogenic medications, including mycophenolate mofetil, angiotensin inhibitors, methotrexate and warfarin; pregnancy risks and fertility in relation to clinical features and antibody status

Education about photoprotection

- Rationale and options: use of sun screen, sun avoidance and sun-protective clothing

Abbreviation: pSLE, pediatric systemic lupus erythematosus.

Table 3 Transition in practice – suggested planning checklist.[74]

Self advocacy

- Ensuring an understanding of the condition and education on how to access information and support groups
- Encouraging the patient and parents to participate and ask questions
- Providing details about adult care options, discussing differences between adult and paediatric care, and help to facilitate the choice of adult care providers

Independent health care behaviour

- Understanding medications and how to take them
- Ensuring the patient maintains a system such as a personal health record book to record health information and details of appointments, transport arrangements, medications and treatments
- Discussing potential side effects/problems with medications and barriers to good concordance
- Understanding of where to get help
- Understanding of the principles of confidentiality
- Facilitating transition clinics and/or meetings with adult consultants and specialist nurses

Sexual health

- Discussing pubertal changes and the implications of the condition and medications upon puberty and sexual health
- Ensuring patient and parents know how to access information and help regarding puberty, sex and sexuality
- Discussing sexual health (including fertility, safe sex and potential genetic issues) giving the patient and their parents opportunities to discuss their concerns alone

Psychosocial support

- Giving the patient and parents the opportunities to discuss their ideas and concerns regarding transition
- Discussing the role of friends, social groups and supportive relationships
- Identifying available options and any need for assistance with regards to self care, living arrangements and finances
- Encouraging the setting of positive goals

Educational and vocational planning

- Discussing the options and availability of careers counselling, work experience
- The implications of going to college or university if planned
- Discussing employment options and if applicable the impact and any restrictions the condition may impose
- Raising awareness of any healthcare benefits and rights available through, for example, the Disability Discrimination Act

Health and lifestyle

- Discussing issues regarding smoking, alcohol and illicit substances
- Discussing body images and concerns regarding weight management issues
- Providing the opportunity to discuss feelings of low mood, depression or difficulties adjusting to or managing their condition

Neonatal lupus

- Very rare (< 2% of all pregnancy)
- Anti-SSA antibodies are transmitted via placenta to baby's blood (SSA antibodies present in 2% of individuals)
- Affected infant may have
  - Rash presents at birth to few weeks of life
    - usually disappears within weeks to months
    - On face/ scalp
    - Around eyes: "owl eye" "eye mask"
    - Worsening of rash when exposed to sunlight

Neonatal lupus

- Also effects the heart
  - Most common finding: 3rd degree heart block
    - Develops in 2nd trimester of pregnancy
    - Irreversible
    - Treatment of mom in early pregnancy with steroids may prevent heartblock
- Anemia/ low white cells/ low platelets may be found in baby
- Hepatobiliary disease
  - Liver enzyme elevation
  - Elevated bilirubin (jaundice)

cSLE and vaccination

- Center for disease control defines profound immunosuppression if
  - Current use of or in the past 3 months use of methylprednisolone, mycophenolate mofetil, or cyclophosphamide (any dose)
  - Methotrexate > 0.4mg/kg
  - Azathioprine > 1.5mg/kg
  - Corticosteroid 2mg/kg or > 20mg daily for > 1 week
- LIVE vaccines are not recommended in patients with profound immunosuppression
- Seasonal influenza vaccine, tetanus vaccine, hepatitis B vaccine safe (supportive studies)
- Human Papilloma virus is well tolerated and did not cause SLE flare

In the next few years novel Biomarkers may become Available to monitor disease activity

Box 2 | Novel biomarkers of pSLE activity

Urinary biomarkers

CC-chemokine ligand 2 (monocyte chemotactic protein-1)

CC-chemokine ligand 5

CX_3C-chemokine ligand 1 (fractalkine)

CXC-chemokine receptor 3

Neutrophil gelatinase-associated lipocalin

Hepcidin-20 and hepcidin-25

Lipocalin-type prostaglandin D synthase

Alpha-1-acid-glycoprotein (orosomucoid)

Ceruloplasmin

Transferrin

Adiponectin

Interferon-gamma-induced protein 10

TNF-like weak inducer of apoptosis

Vascular cell adhesion molecule 1

Tumor necrosis factor receptor p55

Cell-bound complement-activated products

Erythrocyte-bound: C4d, C3d, fragment Bb, complement receptor type 1

Reticulocyte-bound: C4d, C3d, fragment Bb

Platelet-bound: C4d

Genomic Activity Score

Interferon-inducible genes

Neutrophil genes

Interferon-inducible genes

Ribosomal proteins

T-cell proteins

Abbreviation: pSLE, pediatric systemic lupus erythematosus.

On the horizon

- Childhood Arthritis & Rheumatology Research Alliance CARRA multicenter registry
  - Concensus treatment protocol for lupus nephritis
- Multi-center Randomized trial to evaluate the safety, efficacy, and pharmacokinetics of Belimumab plus standard therapy in pediatroc patients with systemic lupus erythematosus

Patient resources

- American College of Rheumatologywww.rheumatology.org/Practice/Clinical/Patients/Diseases_And_Conditions/Systemic_Lupus_Erythematosus_in_Children_and_Teens/
- The ACR's Lupus Initiative www.thelupusinitiative.org
- Lupus Foundationwww.lupus.org
- Lupus International www.lupusinternational.com
- Medline Plus www.medlineplus.gov
- For Lupus Use Interactive Tutorials (English and Spanish) PRINTO www.printo.it/pediatric-rheumatology/
- NIH www.niams.nih.gov/Health_Info/Lupus/default.asp
- Friends of CARRA / Childhood Arthritis & Rheumatology Research Alliance www.**friendsofcarra**.org/
- Clinicaltrials.gov

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