Systemic Lupus Erythematosus in the young adult/adolescent- Approach to Management

American Academy of Pediatrics
New Jersey Chapter

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Systemic Lupus Erythematosus in the young adult/adolescent- Approach to management

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•Winter snow, By Moorthy LN

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Disclosures

- Site PI An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis- BMS

SLE

- Multisystem, episodic, chronic fluctuating autoimmune disease
- Extensive inflammation of blood vessels and connective tissues, with variable clinical manifestations, morbidity and course
- Causes multiple organ involvement and damage
- Requires multiple medications with unpleasant short-/long-term side-effects
- SLE-associated responsibilities significantly disrupt lifestyle

Systemic lupus erythematosus: 1982 classification criteria --4/11

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis
- Serositis
- Renal disorder
- Neurologic disorder
- Hematologic disorder
- Immunologic disorder
- Antinuclear antibody

Systemic lupus erythematosus: 1982 classification criteria

Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-1277.;

Feraz et al

SLICC† Classification Criteria for Systemic Lupus Erythematosus

RheumTutor.com

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

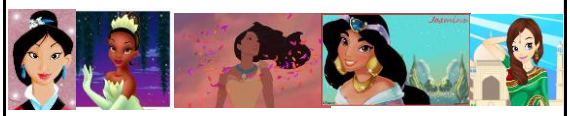
Clinical Criteria	Immunologic Criteria
1. Acute Cutaneous Lupus*	1. ANA
2. Chronic Cutaneous Lupus*	2. Anti-DNA
3. Oral or nasal ulcers *	3. Anti-Sm
4. Non-scarring alopecia	4. Antiphospholipid Ab *
5. Arthritis *	5. Low complement (C3, C4, CH50)
6. Serositis *	6. Direct Coombs' test (do not count in the presence of hemolytic anemia)
7. Renal *	
8. Neurologic *	
9. Hemolytic anemia	
10. Leukopenia *	
11. Thrombocytopenia (<100,000/mm³)	

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Petri M, et al. Arthritis and Rheumatism. Aug 2012

cSLE prevalence

- Highest prevalence -Asian followed by African–American, Native American and Hispanic children (cohort >30 million children over a 5-year period) (Hiraki et al 2012; Medicaid data).
- Highest incidence of lupus nephritis was in Asian children > Native American>African American and Hispanic>White children.
- Asians have the highest prevalence of SLE and SLE nephritis and have most severe disease (Hiraki et al, Levy et al)
  (Hiraki et al, Pluchinotta et al)



Ethnic differences in pediatric SLE

Non-Caucasians were younger at diagnosis (12.6 vs 14.6 yrs; p = 0.007

Non-Caucasians had more renal disease (62% vs 45%; p = 0.01)

Blacks - increased prevalence of CNS disease vs. Asians (p = 0.108).

- *Hiraki et al 2009*
- *Asians and S. Americans seemed to have a younger age of onset (Moorthy et al, 2012)*

Ethnic variations in cSLE

- Children of European/White ethnicity/race have a lower incidence and prevalence of
  - SLE
  - lupus nephritis
  - have milder disease
  - may sustain less damage than other ethnicities/races

(Review by Silverman et al; Levy et al, Watson et al, Hiraki et al, Hersh et al)

Childhood onset versus adult onset SLE

Adult onset SLE vs. Childhood onset SLE

- Malar rash, lymphadenopathy, cytopenias, and nephritis have a greater prevalence in cSLE.

(Brunner et al, Mina et al Papdimitraki et al, Livingston et al)
The Rheumatologist

Table 1: Cumulative Incidence of Common SLE Manifestations

	CSLE (%)	ASLE (%)
CONSTITUTIONAL – FEVER*	37–100	42–57
MALAR RASH	65–92	50–61
ORAL OR NASAL ULCERS*	14–49	14–42
PHOTOSENSITIVITY	35–50	41–56
ARTHRITIS	60–90	83–93
RENAL DISEASE*	50–80	31–65
NEUROPSYCHIATRIC SLE (ANY MANIFESTATION)	6–39	9–22
SEIZURES*	11–14	6–12
PSYCHOSIS	5–10	4–12
SEROSITIS	20–30	17–28
HEMOLYTIC ANEMIA	16–39	11–22
THROMBOCYTOPENIA*	15–37	14–38

*Manifestation has significantly greater prevalence in cSLE (odds ratio > 1 by meta-analysis).

•Levy et al, The Rheumatologist

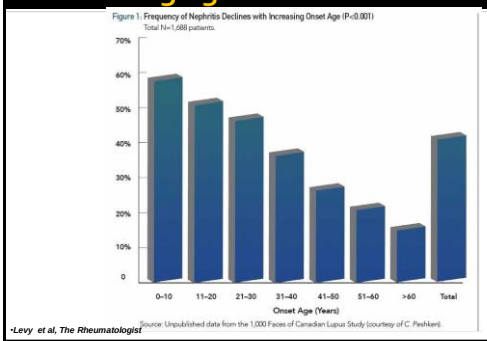
Common Clinical Features of cSLE

Clinical Feature	Prevalence of Involvement
Constitutional and generalized symptoms	
Fever	37 – 100%
Lymphadenopathy	13 – 45%
Weight loss	21 – 32%
Mucocutaneous	60 – 90%
Musculoskeletal	60 – 90%
Nephritis	48 – 78%
Neuropsychiatric disease (NPSLE)	15 – 95%
Gastrointestinal	24 – 40%
Hematologic	50 – 100%
Cardiovascular	25 – 60%
Pulmonary	18 – 81%

Data from 7, 12, 17,13,14-16

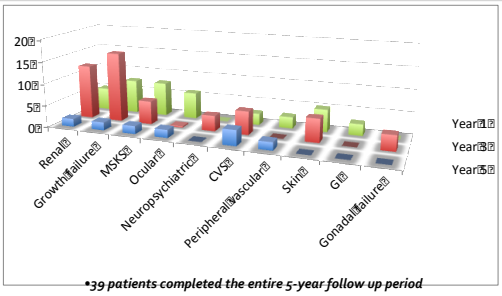
•**Review by Levy et al**

Frequency of nephritis declines with increasing age of onset



•*Levy et al, The Rheumatologist*

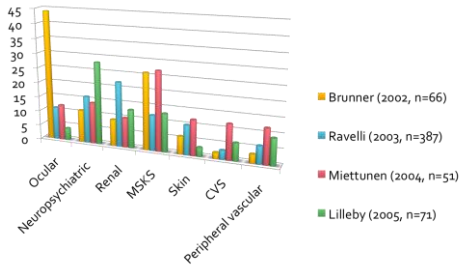
New damage in each organ system at years 1, 3 and 5 after diagnosis (n=57)



•*39 patients completed the entire 5-year follow up period*

•*Bandeira et al, Lupus 2006*

Percentage of patients with damage in the particular organ system



•Similar data from our cohort also, Moorthy et al, PRYSM 2011

Childhood –onset SLE versus adult onset SLE

Higher disease activity at onset and during the disease course (1)

↓

Significant and early damage
Increased exposure to steroids, Longer disease duration
Higher frequency of organ involvement cSLE (1-4)

↓

Cataracts, avascular necrosis, fractures, osteoporosis, low BMD (longer disease vs. steroids), premature atherosclerosis, persistent cognitive dysfunction in cSLE (1,2)

↓

Incurable, potentially devastating disease during a vulnerable period of psychosocial development in cSLE

Increased and unique psychosocial stressors

•(1) Brunner et al (2) Kamphius et al (3) Watson et al (4) Mok et al

Mortality in childhood-onset SLE

Young adults with SLE: SMR <u>20 times</u> higher than general population (vs. 2-5 fold in adults)

Accumulate disease damage more quickly

More aggressive course → increased exposure to immunosuppressive medications over a longer disease duration

•*19.5 vs. 16.5 years (p<0.0001)*

More likely to meet ACR criteria for renal disease and have ESRD

•*56%vs.24% and 21% vs. 8% (p<0.0001)*

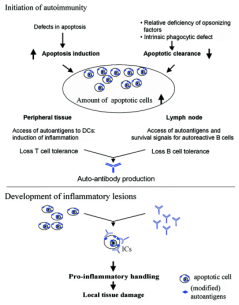
•*(Brunner 2008, Tucker 1995, Tucker 2008, Hersh 2009, Hersh 2010)*

Predictors for early mortality

Mean age at death 33 (childhood-onset; n=98) versus 52 years (n=859)	
Childhood-onset SLE	Male sex
Education	Cardiovascular disease
ESRD	Medicare or Medicaid insurance

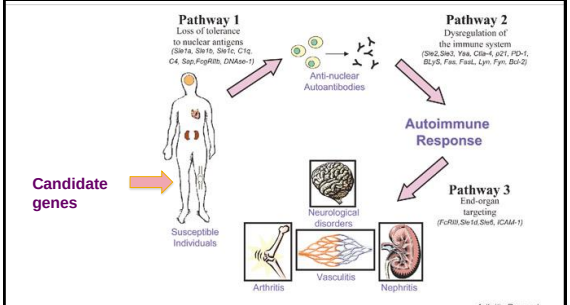
•Hersh 2010

SLE- Pathogenesis



Impaired apoptosis

SLE- Pathogenesis



Clinical manifestations, treatment and prognosis

Constitutional symptoms in SLE

- Fever
- Fatigue
- Wt Loss
- Alopecia
- Arthralgias
- Diffuse generalized inflammation
- Lymphadenopathy
- Hepatosplenomegaly

Clinical Characteristics of Patients Who Have SLE

Organ System Involvement	At Diagnosis (%) (*n* = 256)	Within 1 Year After Diagnosis (%) (*n* = 256)	Ever (%) (*n* = 256)
Diffuse lymphadenopathy	48 (19)	50 (20)	51 (20)
Other			
Raynaud phenomenon	35 (14)	45 (18)	49 (19)
Thrombotic thrombocytopenic purpura	2 (0.8)	2 (0.8)	2 (0.8)
Constitutional symptoms			
Fatigue	129 (50)	136 (53)	142 (55)
Fever	101 (39)	104 (41)	106 (41)
Weight loss	74 (29)	79 (31)	82 (32)
Anorexia	51 (20)	72 (28)	72 (28)
Headache[b]	34 (13)	39 (15)	46 (18)

- Dry eyes and mouth (Sjogrens)
- Stomach, liver, pancreas
- Thyroid, diabetes
- Irregular or absent periods

Pediatric Systemic Lupus Erythematosus : More Than a Positive Antinuclear Antibody
Jennifer E. Weiss
Pediatrics in Review 2012;33;62
DOI: 10.1542/pir.33-2-62

Laboratory exam

General

Hematologic disorder

- Hemolytic anemia--with reticulocytosis OR
- Leukopenia--less than 4,000/mm3 total on 2 or more occasions OR
- Lymphopenia--less than 1,500/mm3 on 2 or more occasions OR
- Thrombocytopenia--less than 100,000/mm3 in the absence of offending drugs

Evidence of immune dysfunction

Bleeding and clotting abnormalities

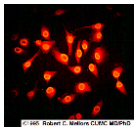
Liver functions

Increased ESR

Urine--Blood and protein in urine

Laboratory abnormalities

Anti-ds-DNA



- **Low complements**- C3, C4
- **Autoantibodies -**ANA, Anti-ds-dna, ENA
- **Antiphospholipids**

- *Immunologic disorder*
  - *a) Anti-DNA: antibody to native DNA in abnormal titer OR*
  - *b) Anti-Sm: presence of antibody to Sm nuclear antigen OR*
  - *c) Positive anti-phospholipid antibody*

Clinical Characteristics of Patients Who Have SLE

Organ System Involvement	At Diagnosis (%) (n = 256)	Within 1 Year After Diagnosis (%) (n = 256)	Ever (%) (n = 256)
Autoantibody (%)			
Anti-dsDNA	184 (72)		214 (84)
Anti-Smith antibody	88 (34)		124 (48)
Anti-ribonucleoprotein antibody	68 (27)		95 (37)
Anti-Ro	69 (27)		84 (33)
Anti-La	34 (13)		37 (15)
Antiphospholipid (any)	82 (32)		115 (45)
ACLA[c]	67 (26)		102 (40)
LAC	22 (9)		32 (13)
Rheumatoid factor	28 (11)		35 (14)
Hematologic (any)	141 (55)		161 (63)
Thrombocytopenia	75 (29)		80 (31)
Lymphopenia	73 (29)		93 (36)
Coombs positive hemolytic anemia	58 (23)		63 (25)

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Goals of treatment

- Ensure long-term survival
- Achieve the lowest possible disease activity
- Prevent organ damage
- Minimize drug toxicity
- Improve quality of life
- Educate patients and family about their role in disease management

Reviewed in UpToDate, TJA Lehman, last updated April 2015

Principles of management

- >90% of patients with cSLE require prednisone at some point in their disease course
  - Unacceptable side effects: weight gain, acne, cushingoid facies, striae, increased facial hair, and mood alterations may be devastating to the adolescent and child alike (Levy et al, Watson et al)
- Chemotherapy and related effects
- Fatigue, joint pain, and "lupus fog" make school and extracurricular participation difficult.
- Greater involvement of the physician and other healthcare providers.

Principles of management

- Mindful of –
  - normal expected growth and development
  - pubertal status
  - age and stage of adolescence, maturity
  - self-management capacity
  - education and involvement of the family
  - self-esteem, suicidal tendencies
- Usual adolescent issues are magnified by the chronic disease
- Impact on the ability and confidence to establish new friendships and intimate relationships
- Alteration of "sex, drugs, and rock 'n roll" phase of adolescence (i.e., periods of normal experimentation)
- Abnormal socialization and mood disorders
- Contraception, Pregnancy

Initial therapy

Hydroxychloroquine
- ≤7mg/kg/day during entire course of the disease including pregnancy
- Regular opthalmological evaluation
- Color vision and visual field testing
- Benefits-disease activity, survival and improvement in organ damage, thrombosis, atherosclerosis, BMD and lipid profile (Ruiz-Irastorza et al 2010)
- Used in combination with steroids and other medications

Glucocorticoids
- Individualized
- Lower initial dose and rapid taper – prednisone 0.25mg/kg/d for mild disease
- Pulse steroids for severe CNS disease followed by oral prednisone 2mg/kg/d and tapered over several months.

Avoid sun exposure

Reviewed in UpToDate, TJA Lehman, last updated April 2015

Mild SLE

- **No renal or life threatening organ involvement**
- NSAIDS for musculoskeletal manifestations
- Hydroxychloroquine up to 200mg/day (400mg/ day for adults)
- Avoid Sulfa drugs (such as Sulindac)- Sulfa antibiotic allergy more common in SLE (Pope et al, Aceves et al)
- Dapsone in some dermatological manifestations (David et al)
- Low dose glucocorticoids (< 0.35mg/kg/day of prednisone
- Dose above 0.2mg/kg/dose may impact longitudinal growth (David et al)
- Add 2nd line agent, Mycophenolate mofetil if glucocorticoid dose is >0.35/kg/day

Reviewed in UpToDate, TJA Lehman, last updated April 2015

Moderate SLE

- **Clinically significant but not life threatening organ involvement of kidneys or other vital organs/systems**
- Daily higher dose glucocorticoids (or alternate day/intermittent IV therapy) (Guiducci et al) with hydroxychloroquine
- Steroid sparing agent:
  - Mycophenolate mofetil
  - Azathioprine
  - Methotrexate (aware of renal toxicity, toxic levels if renal function deteriorates)
  - Cyclophosphamide and Rituximab as steroid sparing agent

(Buratti et al, Ravelli et al)

Reviewed in UpToDate, TJA Lehman, last updated April 2015

The girl with fevers and weight loss

11 year old girl is feeling very tired and has a malar rash that is worsening. It is maculopapular erythematous with brownish plaques. She also has some photosensitivity and alopecia. For the last 2 months she has had intermittent fevers, fatigue, weight loss, and irritability

- CBC and diff, CMP, UA NL
- ESR 30 mm/hr
- ANA positive
- Anti-DS-DNA ab+, Anti-Smith ab +ve;
- -ve anti-Ro, La and RNP ab

Treatment: Oral steroids, Hydoxychloroquine
Rash, fatigue and alopecia improved

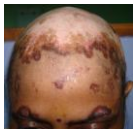
Mucocutaneous manifestations- Malar rash

- Acute cutaneous lupus erythematosus (ACLE) -facial rash or generalized eruption (disseminated ACLE)
- Localized ACLE (Butterfly rash) usually after UV light exposure, mistaken for a sunburn
  - Malar rash-fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds

Mucocutaneous manifestions- Discoid rash and SCLE

Discoid – inflammatory plaques evolving into atrophic disfiguring scars

Subacute cutaneous lupus erythematosus (SCLE)– erythematous scaly papules or annular plaqunes over neck, upper trunk and arms



J Clarke, Initial management of discoid lupus and subacute cutaneous lupus, UpToDate updated May 2015

Mucocutaneous manifestations

- Other lesions
  - Bullous lesions
  - Lupus erythematosus tumidus (anti-malarials)
  - Cutaneous and reticular erythematosus mucinosis
  - Lichen planus-LE overlap
  - LE panniculitis (Lupus profundus)
  - Nail pitting, ridging, onycholysis
  - Photosensitivity

Mucocutaneous manifestations

Table 2. Clinical Characteristics of Patients Who Have SLE

Organ System Involvement	At Diagnosis (%) (n = 256)	Within 1 Year After Diagnosis (%) (n = 256)	Ever (%) (n = 256)
Arthritis	157 (61)	159 (62)	171 (67)
Mucocutaneous involvement			
Malar rash	155 (61)	161 (63)	169 (66)
Other rash	96 (38)	106 (41)	111 (43)
Oral ulcers	55 (21)	59 (23)	76 (30)
Alopecia	56 (22)	62 (24)	73 (29)
Photosensitivity	44 (17)	45 (18)	52 (20)
Nasal ulcers	21 (8)	25 (10)	26 (10)
Digital ulcers	9 (4)	10 (4)	13 (5)

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Treatment of skin disease

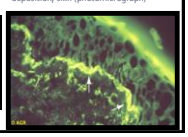
Prevent long-term skin sequelae, alopecia, scarring

Non-pharmacological:

- Photoprotection (avoid UV light)
- Sunscreens lead to decrease in disease activity, SPF clothing
- Avoid exacerbating drugs
- Stop smoking
- Low levels of Vit D
- Cosmetics

Skin Lesion-hyperkeratosis

Discoid lupus erythematosus: Ig deposition, skin (photomicrograph)



J Clarke, Initial management of discoid lupus and subacute cutaneous lupus, UpToDate updated May 2015

Treatment

- Local therapy:
  - Topical corticosteroids (Clobetasol, flucinonide); maintenance regimen- low potency- hydrocortisone (Cutaneous atrophy- adverse effect)
  - Calcineurin inhibitors: Pimecrolimus (burning/stinging)
  - Intra-lesional corticosteroids
  - Topical retinoids (Tazarotene)
- Systemic therapy
  - Hydroxychloroquine, Chloroquine, Quinacrine
- Refractory Disease
  - Methotrxate, MMF, Dapsone, Isotretinoin, Acitretin, Thalidomide, Azathioprine, Rituximab, IVIG, Clofazimine

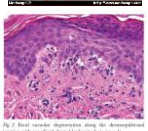
J Clarke, Initial management of discoid lupus and subacute cutaneous lupus, UpToDate updated May 2015
And Management of refractory discoid lupus and subacute cutaneous lupus, UpToDate, updated Jul 2015

Neonatal Lupus Erythematosus

- **1 to 2% percent of babies born to mothers with autoimmune disease**, primarily SLE, Sjögren's syndrome, and antibodies to SSA/Ro and/or SSB/L
- A considerable proportion of mothers of affected infants are asymptomatic (40%).
-
- If a anti-Ro (SS-A)-positive mother has one child with NLE, risk of recurrence is close to 20%

NLE

- Skin lesions are transient, lasting weeks to months
- Usually resolve without scarring—mild epidermal atrophy
- Hypopigmentation
- Rarely, remnant telangiectasias can occur at previously affected sites. Cutaneous telangiectasia 6-12 mo (10% of cases)—temples near hairline
- ~ to Subaculte cutaneous LE (SCLE)
- Treatment
  - Reassurance
  - Sun avoidance
  - Usually heal w/o scarring
  - Low potency topical mild steroid (increased risk of telangiectasia), Pulse dye laser



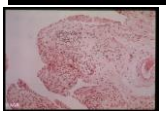
Alopecia - treatment

- Scarring- complication of cutaneous DLE
- Non-scarring (telogen effluvium, Lupus hair)
- Hair loss in active SLE responds to treatment for disease
- Minoxidil

Musculoskeletal manifestations and treatment

- Synovial involvement
  - NSAIDS
  - Glucocorticoids
  - Hydroxychloroquine
  - Methotrexate
  - Belimumab
  - Rituximab
- Subcutaenous nodules
- Osteonecrosis (3-40% in SLE)
  - Activity restriction, surgical intervention
- Osteoporosis
  - VitD, Calcium, Bisphosphonates
- Myalgias
- Fibromyalgia

(Schur and Wallace, Musculoskeletal manifestations of SLE, UpToDate Last updated 8.4.15)



Nonerosive synovitis in SLE. Note the inflammatory exudate of occasional neutrophils and numerous lymphocytes immediately beneath the surface layer of synoviocytes.

Belimumab

- 7 with childhood-onset SLE treated with belimumab, mean F/u 9.3 months on belimumab, Hui-Yuen et al (2014)
- Mean age 18.5 years and mean disease duration 5.8 years
- 86% female, 57% African American, 28% Hispanic, and 14% Caucasian.
- All patients were taking other background medications prior to initiation of belimumab (hydroxychloroquine 7/7, prednisone 7/7, azathioprine 2/7, mycophenolate mofetil 3/7)
- The most common indications for initiation of therapy were:
  - Inability to taper steroids (100%, mean prednisone equivalent dose 0.54mg/kg/day)
  - Rash (43%), fatigue (29%), arthritis (14%), accompanied by worsening serologic activity (increasing anti-dsDNA titers and hypocomplementemia)

Belimumab

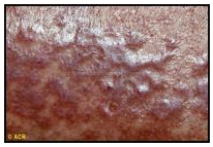
- At the last follow-up average SLEDAI decreased from 6.4 to 4.
- Able to taper steroids in 57% of patients, with 3/7 (43%) able to discontinue steroids.
- The average complement levels increased from 71 to 74 (C_3) and 8 to 10 (C_4)
- 6/7 clinically responded to belimumab within 3 months, with marked improvement in rash, arthritis, and fatigue.
- 6/7 tolerated infusions and 1 patient discontinued treatment due to recurrent vaginal moniliasis. Hui-Yuen et al (2014)

Pediatric Lupus Trial of Belimumab Plus Background Standard Therapy (PLUTO)

Vascular lesions

- Periungual erythema
- Raynauds
- Telangiectasias
- Livedo reticularis
- Chilblain LE
- Urticaria or purpuric vasculitis

Check for antiphospholipid antibody!
Treatment individualized- may need anticoagulation



Case: Girl with a vasculitic rash

15 yo Hispanic girl presents with vasculitic rash over her finger tips and funny feeling over her toes.
Has fatigue, joint swelling and pain and joint swelling
CBC and diff- WBC 2.8K, Hgb 10g/dl
ESR 70mm/hr
UA nl
C_3 50 C_4 <7
ANA 1:5120
dsDNA 1:300
Anti-SM ab reported as highly positive

Antiphospholipid syndrome

- Low dose ASA if no thrombosis
- If thrombosis- warfarin (INR 2-3)
- Lovenox (antifactor Xa 0.5-1 units/ml)

Severe SLE

- Substantial Renal (worst DPGN) and CNS involvement
- Glucocorticoids (often high dose IV)
- Cyclophosphamide (IV monthly/ po)
- Rituximab with Cyclophosphamide regimen
- Mycophenolate mofetil
- Azathioprine
- Length may vary with organ involvement (longer for renal vs. 1 year for extra-renal manifestations)

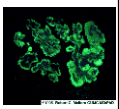
(Guiducci et al, Ravelli et al, Buratti et al, Lehman et al) (Lehman et al 1991, Lehman et al 1989, Lehman et al 2000, Ginzler 20045, Austin et al, Lehman et al 2014)

The girl with tea colored urine

- 14 yo girl has tea-colored urine, low grade fever and edema over face and feet in the past 2 weeks.
- UA 3+ protein
- CBC and diff – NL
- CMP- low albumin 2.5
- ESR 50mm/hr
- C3= 50, C4 = 7, ANA 1:1280, DS-DNA 1:160

Table 3. **International Society of Nephrology/Renal Pathology Society 2003 Classification of Lupus Nephritis**

Class I	Minimal mesangial lupus nephritis Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	Mesangial proliferative lupus nephritis Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	Focal lupus nephritis[a]
	Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	Diffuse lupus nephritis[a]
	Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	Membranous lupus nephritis
	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
	Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed
	Class V lupus nephritis show advanced sclerosis
Class VI	Advanced sclerosis lupus nephritis ≥90% of glomeruli globally sclerosed without residual activity



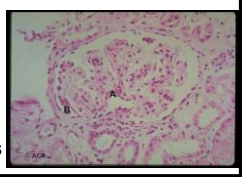
Clinical Characteristics of Patients Who Have SLE

Organ System Involvement	At Diagnosis (%) (n = 256)	Within 1 Year After Diagnosis (%) (n = 256)	Ever (%) (n = 256)
Nephritis[a]	95 (37)	117 (46)	141 (55)
Mesangial (class II)	14 (15)	21 (18)	25 (18)
Focal proliferative (class III)	27 (28)	36 (31)	41 (29)
Diffuse proliferative (class IV)	45 (47)	50 (43)	65 (46)
Membranous (class V)	15 (16)	20 (17)	29 (21)
Nephrotic syndrome	20 (22)	22 (19)	25 (18)
Central nervous system	40 (16)	53 (21)	68 (27)
Lupus headache	23 (58)	31 (58)	42 (62)
Psychosis	14 (35)	21 (40)	25 (37)
Cerebrovascular disease	13 (33)	14 (26)	20 (29)
Cognitive dysfunction	9 (23)	13 (25)	15 (22)
Cardiac			
Pericarditis	30 (12)	33 (13)	39 (15)
Myocarditis	3 (1)	5 (2)	6 (2)
Endocarditis	0	0	1 (0.4)
Pulmonary			
Pleuritis	30 (12)	32 (13)	37 (14)
Pneumonitis	1 (0.4)	1 (0.8)	2 (0.8)

Pediatric Systemic Lupus Erythematosus : More Than a Positive Antinuclear Antibody
Jennifer E. Weiss
Pediatrics in Review 2012;33:62
DOI: 10.1542/pir.33-2-62

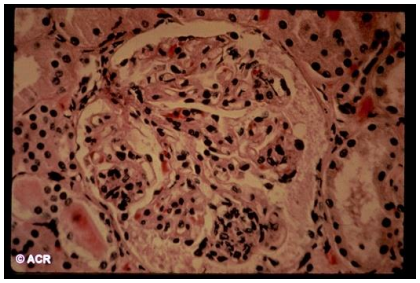
Renal involvement

- Clinical nephritis in 75% of children, blood in the urine (hematuria- not always gross hematuria -need to get urine tests with your physician), swelling, high BP
- Renal disorder
- a) Persistent proteinuria greater than 0.5 grams per day or grater than 3+ if quantitation not performed
  - OR
- b) Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
- Creatinine in <10 year olds is 0.5mg/dl 1.1 is abnl in that age group!



Mesangial nephritis

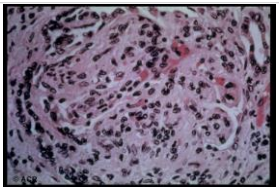
Focal Proliferative Glomerulonephritis

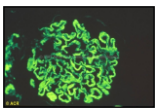


In one glomerular tuft there is marked hypercellularity and obliteration of capillary lumina; another tuft shows similar but less pronounced changes. The remainder of the glomerulus is normal or minimally altered. (hematoxylin-eosin, high power)

Diffuse Proliferative GN

- "Wire loop" lesions
- Enlarged glomerulus with increased cellularity
- Characteristic GBM thickening and bright red staining of the GBM of peripheral capillary loops ("wire loop" lesion)

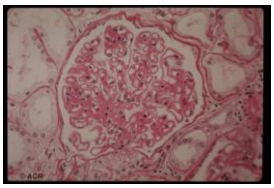




Immunofluorescence micrograph of glomerulus stained for human IgG-- - Note the fine and coarsely granular deposits of IgG along the GBM of peripheral capillary loops.

Note the granular and massive "lumpy-bumpy" deposits of IGs along the GBM of peripheral capillary loops.

Membranous GN



Widespread, uniform thickening of capillary basement membranes is particularly striking because the section is very thin (2 mm). (periodic acid-Schiff, high power)

In most areas of this glomerulus, the capillary walls are thickened by pink-staining deposits (corresponding to immune complexes) on the outer (epithelial) surface of the black-staining basement membrane. Between deposits are protrusions of black basement membrane material (arrows, S). Mesangium also stains black (single arrow). (periodic acid-silver methenamine stain, high power)

Severe SLE – Renal involvement

- Cyclophosphamide for induction typically
  - Maintenance with mycophoenolate mofetil or azathioprine
  - Poor adherence – every 3 monthly cyclophosphamide for 30 months
  - Reduces proteinuria and increases creatinine clearance, prevented scarring
  - Toxicity-increased risk in sexually mature males; lowest in prepubertal children; Girls rarely become infertile (fertility based on cumulative CTX dose)
  - Decreased bladder toxicity with MESNA

Adjunctive measures: Antihypertensives, Hydroxychloroquine, Avoid live viral vaccines, Calcium and Vitamin D

(Guiducci et al, Ravelli et al, Buratti et al, Lehman et al) *(Lehman et al 1991, Lehman et al 1989, Lehman et al 2000, Ginzler 20045, Austin et al, Lehman et al 2014)*

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CONSENSUS TREATMENT PLANS FOR INDUCTION THERAPY OF NEWLY-DIAGNOSED PROLIFERATIVE LUPUS NEPHRITIS IN JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS

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SELECTION OF IMMUNOSUPPRESSIVE AGENT (pick 1 of these 2)
Cyclophosphamide IV q 4 weeks for 6 months
-OR-
Mycophenolate mofetil 600 mg/m2/dose PO BID (max 3,000 mg/d) for 6 months
(may substitute Mycophenolate sodium 400 mg/m2/dose PO BID (max 1,080 mg BID) for 6 months

SELECTION OF STEROID REGIMEN (pick 1 of these 3)

*Primarily ORAL**			OR	*PRIMARILY INTRAVENOUS (IV)*				OR	*MIXED ORAL/IV*			
Week (wk)	Daily dose >30kg (mg)	Daily dose ≤30kg		Week	# Steroid pulses†	Daily dose >30kg (mg)	Daily dose ≤30kg (mg)		Week	# Steroid pulses†	Daily dose >30kg (mg)	Daily dose ≤30kg (mg/kg/d)
1-4	60-80	2mg/kg/d		1	3/wk	20	10		1	3/wk	60	1.5
5-6	60	2mg/kg/d		2	1-3 wk	20	10		2	1/month (mo)	60	1.5
7-10	50	↓ by 5-10 mg		3	1-3 wk	20	10		3		50	1.2
11-12	40	↓ by 5 mg		4	1-3/wk	20	10		4		40	1
13-14	40	↓ by 5 mg		5-7	1-3/wk	20	10		5-8	1/mo	35	0.9
15-18	30	↓ by 5 mg		8-11	1/mo	20	10		9-12	1/mo	30	0.8
19-22	25	↓ by 2.5-5 mg		12-18	1/mo	15	7.5		13-16	1/mo	25	0.7
23-24	20	↓ by 2.5-5 mg		19-24	1/mo	10	5		17-20	1/mo	20	0.6
									21-24	1/mo	15	0.5

*Optional 3 day pulse in week 1 is permitted

†Pulse methylprednisolone: 30 mg/kg/dose, maximum: 1000 mg/dose

Figure 3.

Maintenance therapy

Table 2. Maintenance therapy in childhood lupus nephritis.

Drug	Suggested Dose
Oral prednisolone	10-15 mg /day or alternate days (where possible)
Oral azathioprine (AZA)	2-2.5 mg/kg/day
Oral mycophenolate mofetil (MMF)	0.6-1.2 g/m2/day, maximum 3 g/day in two divided doses
Oral hydroxychloroquine	4-6 mg/kg/day (up to 10 mg/kg/day)

Demircin et al 2013 Annals of Peds Rheum

Refractory Disease- MMF

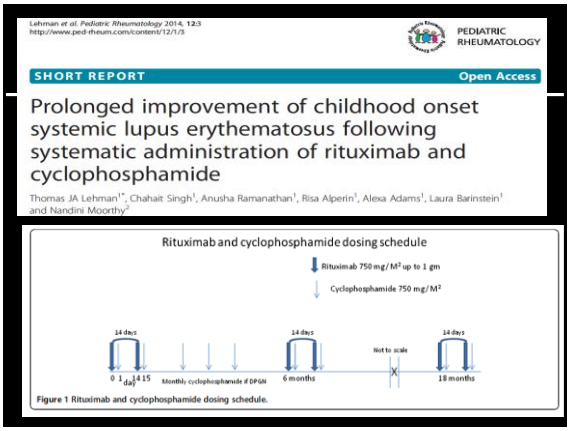
- Mycophenolate mofetil
- 4/11 with MGN improved (Buratti et al 2001)
  - SLE disease activity index (SLEDAI) reduced in 10
  - Glucocorticoid dose reduced in 6
- 13/16 got mycophenolate mofetil + cyclosporine (Aragon et al 2010)
  - Remission in 44% and 75% at 6 and 12 months
  - Common side effect infection
- Increased incidence of "stomach feeling upset"
- Use enteric coated formulation
- Compliance

Reviewed in UpToDate, TJA Lehman, last updated April 2015Kazyra et al 2010, Buratti et al 2001, Aragon et al 2010

Rituximab

- Useful in combination with cyclophosphamide in treating severe SLE refractory to conventional therapy (Marks et al 2005, Willems 2006, Tambralli et al 2015)
- Combination resulted in decreased steroids and CTX
- Efficacy of RTX alone in adult studies (Merill et al 2010)

- N=63 children given 2 doses of RTX 2 wks apart (Watson et al 2015)
  - 19 got more than one course of RTX
  - ¾ treated earlier with CTX
  - All received prior immunotherapy
  - Decreased oral steroid dose and clinical biomarkers improved
  - Adverse events – neutropenia (1), decreased IGG levels (2), infections (2) and anaphylaxis (2)



Cyclophosphamide and Rituximab

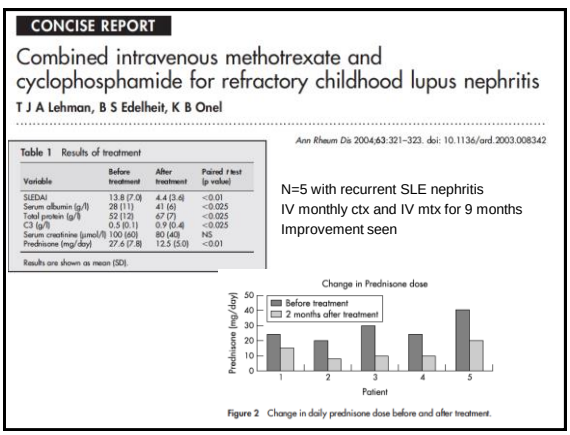
- N=12
- SLE nephritis or corticosteroid resistant SLE
- Combination of Rituximan 750mg/m2 up to 1 gm and cyclophosphamide 750mg/m2
- Dramatic improvement seen and maintained over a 60 month period.

Table 1 Sustained improvement at 12 and 60 months

	Month 0	Month 12	Month 60
Prednisone (mg/day)	29.7 ± 24[‡]	12.7 ± 4.1[#]	7.0 ± 2.5*
C3 (mg/ml)	55.5 ± 27	113 ± 32**	107.5 ± 36**
ESR (mm/hr)	42.3 ± 27	17.8 ± 22*	11.8 ± 12**
Hb (gms/dl)	11.3 ± 1.8	12.1 ± 1.7[#]	13.2 ± 1.4[#]
SLEDAI	10.10 ± 5.9	1.0 ± 1.8*	0*
IgG (mgs/ml)	1272 ± 526	819 ± 200*	977 ± 505*
IgM (mgs/ml)	107 ± 52	45 ± 24*	51 ± 28[#]

[‡]All values represent mean ±1 Standard deviation.
#p<0.05 *p<0.005 **p<0.001.

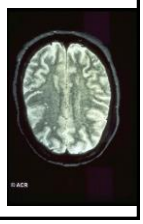
Lehman et al



Central Nervous System

- 20-40% of affected children, depression, difficulty in concentrating, cognitive impairment (~52% of children), lupus headache, seizures etc.

- ***Neurologic disorder***
- *a) Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance*
  - *OR*
- *b) Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance*



Neuropsychiatric Syndromes observed in SLE (NPSLE)

CENTRAL NERVOUS SYSTEM	PERIPHERAL NERVOUS SYSTEM
Aseptic meningitis	Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome)
Cerebrovascular disease	
Demyelinating syndrome	
Headache	Autonomic disorder
Movement disorder (chorea)	Mononeuropathy, single/multiplex
Myelopathy	Myasthenia gravis
Seizure disorder	Neuropathy, cranial
Acute confusional state	Plexopathy
Anxiety disorder	Polyneuropathy
Cognitive dysfunction	
Mood disorder	
Psychosis	

Adapted from American College of Rheumatology : Nomenclature and case definitions for neuropsychiatric lupus syndromes. *A* 1999; 42:599-608.

Gastrointestinal manifestations

- 25-40% of SLE patients
- Abdominal pain
- Pancreatitis
- Hepatitis
- Protein-losing enteropathy
- Mesenteric vasculitis and infarction

Massarotiand Schur, Gastrointestinal manifestations of SLE, UpToDate, Last updated Jan 2014

Hematological manifestations

- Leukopenia- resolves as disease activity is brought under control
- Neutropenia is the exception- may need GCSF
- Anemia of chronic disease resolves as disease is brought under control
  - Iron not helpful
  - If Iron deficiency anemia , 3-4mg/kg/day or elemental Iron orally
  - Parenteral iron is rarely required
- AIHA -Systemic glucocorticoids
  - Mild/moderate- prednisone
  - Severe/rapidly progressive-IV methylprednisolone pulse
  - Supplemental folate
  - Danazol, IVIG, Plasmapheresis, Rituximab
  - Splenectomy if life threatening

(Euler et al 1997, McDougall et al 2000, Ahn et al 1985, Majer et al 1988, Von Keyserlingk et al 1987, Gomard-Mennenson 2006 et al, Rivero 1979et al)

Thrombocytopenia

- Glucocorticoids
- Prednisone/pulse methylprednisolone
- Rituximab (Cobo-Ibanez Semin Arthritis Rheum 2014; Ale'ed A et al, Rheumatol Int 2014)
- Hydroxychloroqine and Danazol (Hepburn et al Cutis 1997)
- TTP- plasmapheresis (Strickler et al, J Rheumatol1992) and Rituximab (Niewold J Rheumatol 2006)

Case: Girl with eye pain

21 year old girl with SLE is complaining of blurry vision and eye pain

C3 70

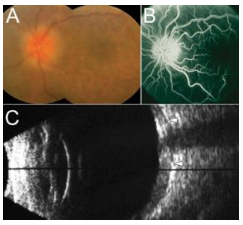
C4 14

CBC, CMP and ESR nl

UA – nl

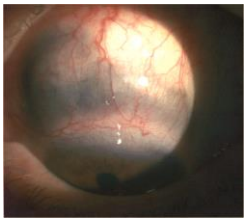
She sees opthalmology- has loss of vision

She says now that she has severe pain at 6 o' clock position in the L eye.



Posterior scleritis in a patient with systemic lupus erythematosus. Optic disc hyperemia and retinal striae were evident clinically (A, B). B-scan ultrasonography showed posterior eye wall thickening with retrobulbar fluid producing the so-called "T-sign" (C).

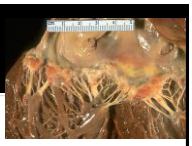
Ocular involvement



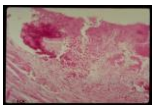
Necrotizing anterior scleritis
resulting in scleral thinning. Areas of scleral thinning appear dark due to visualization of the underlying uveal tissue.

Cytoid bodies

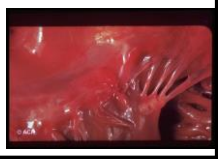
Cardiac abnormalities



- Pericardial disease
  - Subclinical pericarditis- usually requires no therapy
  - Symptomatic pericarditis- NSAIDS (indomethacin), glucocorticoids (sometimes pulse doses); tamponade-pericardiocentesis
    (Mandell et al, Semin Arthritis Rheum 1987, De Inocencio et al 1994,)
  - Activity self restricted due to pain
- Myocarditis- treated with glucocorticoids, activity restriction, serial ECHOs
- Endocarditis-If prior infective endocarditis, antibiotic prophylaxis as recommended by AHA



Fibrinoid and Histiocytes



Cardiac abnormalities

- Coronary artery disease
  - Non pharmacological measures- diet low in saturated fat and cholesterol with omega 3 fatty acides and routine exercises
  - Antihypertensives, statins (routine use not justified) Schanberg et al Arthritis Rheum 2012
  - Hydroxychloroquine can improve lipid profile (Ardoin et al, Lupus 2007)
- Heart failure- Ace inhibitors, address underlying comorbidity (Brown et al, Circulation, 1998)

Pulmonary disease

- Pleuritis- treatment depends of severity
  - If tachypneic and in severe pain, require oxygen, analgesics, IV methylprednisolone
  - Chronic cases- talc pleurodesis/tetracycline- rarely needed (Kaine et al, Ann Rheum Dis 1985, McKnight et al, Arthritis Rheum 1991)
- Pulmonary hemorrhage- ventilation, high dose IV glucocorticoids, pheresis, Cyclophosphamide, Rituximab
- Pulmonary hypertension- Epoprostenol, Bosentan
- Acute pneumonitis- Glucocorticoids

Beresford et al Lupus 2005, Samad et al South Med J 2003, Mok et al Lupus 207, Jacods et al 1982

Medication Side effects

- NSAIDS (Motrin, Aspirin, Relafen) - Liver and kidney function, gastritis
- Antimalarial drugs (Plaquenil)- Retinal damage
- Steroids-Cushingoid appearance, thinning of skin, acne, short stature, suppresses immunity, osteoporosis, diabetes, HTN, avascular necrosis (may need joint replacement), cataracts, etc.

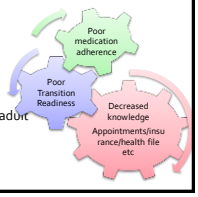
  Very important to not miss any doses/ or drastically change without speaking to your physician!
- Other immunosuppressive agents -risk of infection, liver and kidney function, blood counts, risk for cancer, risk for infertility (consider Lupron), affects bladder

Complications

- Organ Damage
- Atherosclerosis
- Infections
  - Pneumonia with opportunistic infections (CMV, aspergillosis)
  - Administer pneumococcal and influenza vaccine
- Macrophage activation syndrome
  - 1-4.6%
  - High fever, pancytopenia, hepatosplenomegaly, hepatic dysfunction

Can I take care of myself?

- In the 1st 6 months after diagnosis, teens with SLE report-
  - ~7 medications a day
  - ~5 pediatric rheumatology visits
  - laboratory testing on (up to) 8 separate days (Valente, Moorthy et al, 2012)
- 17% took 8 or more medications daily; 46% had 3-4 doctor visits per year and 34% had 8-12 doctor visits per year (Applebaum, 2013)
- 51 adolescents (Hersh et al)
  - moderate negative effect on their life
  - moderate understanding of their condition
  - were worried about change to adult providers
  - moderately prepared to manage on their own
  - large gaps in care with delayed presentation to the adult clinic of up to 33 months (mean 7 months)



•Applebaum et al
•Lawson et al

Team approach to management

General

- Routine/flare-worsening
- Adequate rest
- Sun-protection
- Immunizations
- Prompt management of infection
- Call doctor prior to any procedure-may need extra antibiotics or steroids
- Appropriate transitioning

from pediatric to adult care

- Require medical home
- Reproductive health
- No piercing/tattos
- Subspecialty visits
- Evaluate mood (patients may get depressed!!!)
- Medication interactions
- Exercise
- VitD and Ca

Prognosis

- Most children do well (Lehman et al Pediatrics 1989)
- Primary causes of an unsatisfactory outcome (McCurdy et al Pedaiatrics 1992, Taddio et al J Pediatr 2010, Amaral et al Rheumatol 2014)
  - Poor compliance
  - Neurological complications
  - Renal disease, esp DPGN
  - Delay in diagnosis
  - Intercurrent infections
- N=34 followed for 2.8 years (median) had (Otten et al, Lupus 2010)
  - Chronic active (49%)
  - Relapsing remitting (14%)
  - Long quiescence (37%)
- Chronic active disease associated with +ve anti-Sm ab
- Survival rate in 1980s 100% at 5 years and 85 % at 10 yrs (Platt Am J Kid Dis 1982, Glidden et al, Clin Immunol Immunopathol1983)

Renal Disease

- Degree of involvement impacts on morbidity and mortality
- Retrospective study of 66 Canadian children (Hagelberg J Rheumatol 2002)
  - 10- and 19- yr mortality rates were 9% and 12% in pts with DPGN
  - ESRD in 25 %-40%
  - Caucasian children fared better than others
  - 14/16 (87%) such alive w/o ESRD at last f/u versus 9/16 (56%) non-Caucasian children
- Mesangial disease (n=15) and FPGN (n=8) no deaths and none had ESRD over 11 years f/u

Reproductive Health

Sexual function and reproductive health in adolescent females with systemic lupus erythematosus

Clovis Artur Almeida da Silva[1], Marília Vieira Febrônio[2], Eloísa Bonfá[3], Rosa Maria Rodrigues Pereira[4], Elsa Aida Gay de Pereira[5], Albertina Duarte Takiuiti[6]

- Age matched controls for 52 SLE patients
- Mean age of menarche higher in JSLE patients (12.82 ± 1.62 versus 11.55 ± 1.45 years, P = 0.0004).
- Frequency of sex activity lower in patients with JSLE (23% versus 60%, P = 0.0003).
- Higher percentage of sexual dysfunction, reduced vaginal lubrication, decreased performance, reduced orgasm, and dissatisfaction with one's sex life in JSLE patents (58% versus 23%, P = 0.03; 50% versus 16%, P = 0.046; 58% versus 23%, P = 0.03; 50% versus 26%, P = 0.046, respectively).
- Demographic data, pubertal changes, abnormalities in menstrual cycle, and cervicovaginal cytology were similar in JSLE patients and the control group

Bras J Rheumatol 2009;49(6):690-702

Tesher et al. Pediatric Rheumatology 2010, 8:10
http://www.ped-rheum.com/content/8/1/10

PEDIATRIC RHEUMATOLOGY

REVIEW Open Access

Contraception for adolescents with lupus

Melissa S Tesher[1], Amy Whitaker[2], Melissa Gilliam[2], Linda Wagner-Weiner[1] and Karen B Onel*[1]

- Protect against STI
- Protect against Pregnancy
- GYN maintenance exam
- Antiphospholipid antibodies, history of thrombosis, smoking, BP,
- Male and female condoms (use rare in adolescents <40%; failure rate 15-21%)
- IUD
- Nuvaring (ethinyl estradiol)
- Combined estrogen-progesterone (very effective, low cost)
- Progestin only pill
- Depo-provera (decreased BMD)
- Emergency contraception- oral levonorgestrel – decreased thrombosis risk)

Adverse Pregnancy Outcomes in Adolescents and Young Women with SLE: A National Estimate

- NIS database
- SLE patients =4142
- Hospitalized women with SLE were:
  - Slightly older (mean age 19.4 with range 14-21 vs.19 with range 8-21)
  - More likely to be black (34% v. 21%)
  - More likely to carry a discharge diagnosis of nephritis (11% v. 0.02%) or aPL (2.7% v. 0.1%)
  - More likely to undergo hemodialysis (0.35% v. 0.0%), all p<0.0001.

Allen et al 2014, ACR abstract

Outcome	SLE N = 4,142	Non-SLE N = 9,121,082	P*	OR (95%CI) +
Maternal Outcomes	*N (%) unless noted*			
Pre-eclampsia and Eclampsia	657 (16)	417,676 (4.6)	<0.0001	3.9 (3.3 4.7)
Death during hospitalization	15 (0.37)	490 (0.005)	<0.0001	69.7 (22.6 214.6)
Fetal Outcomes				
Preterm	843 (20)	736,665 (8.1)	<0.0001	2.9 (2.5 3.4)
Low birth weight or fetal growth retardation	0 (0)	20 (0)	0.97	1 (0.0004 0.0005)
Spontaneous abortion or Intrauterine death	179 (4.3)	99,426 (1.1)	<0.0001	4.1 (2.9 5.8)
Induced abortion	90 (2.2)	11,749 (0.13)	<0.0001	17.2 (10.4 28.3)
Ectopic pregnancy	²10 (²0.24)^	30,293 (0.3)	0.61	0.7 (0.17 2.78)

Allen et al 2014, ACR abstract

Pregnancy -Preconception counseling

- Contraception/pregnancy contraindicated while they are taking methotrexate,leflunomide, cyclophosphamide, mycophenolate mofetil
- Educate patients that, because of prolonged half-lives, some medications may need to be discontinued several months before the planned conception.
- Women with SLE ane antiphospholipid antibody syndrome, and +ve SSA and SSB ab will require more frequent monitoring than those with SLE alone.

Risk assessment

Previous Obstetric history → SGA, preeclampsia, stillbirth, miscarriage, and preterm birth.

SLE activity
APLA(S)
Ro, La Ab → Evidence of active SLE, especially lupus nephritis, should be advised to defer pregnancy until the disease is well controlled for at least six months.

Selective use during pregnancy

Medications	Considerations
NSAIDS	Avoid in 1st and 3rd trimester
Hydroxychloroquine	Continue (better outcomes and decreased risk of CHB in Ro and La+ve cases)
Glucocorticoids	<10mg/day (In 1st trimester, associated with cleft lip, with and without cleft palate).
Azathioprine	Relatively safe during pregnancy, not exceed 2 mg/kg/day
Cyclosporine and Tacrolimus	If benefit outweighs risk
Antihypertensives	Methyldopa, labetalol, hydralazine (avoid ACE inhibitors and AII RB)
Biologics	Discourage Rituximab-B cell lymphocytopenia in infant Limited data on Belimumab

Medications during breastfeeding

- Long-acting NSAIDs are inadvisable; use short-acting NSAIDs-displace bili and cause kernicterus
- Hydroxychloriquine-displace bili and cause kernicterus
- Azathioprine, cylcopspoine, tacrolimus, low dose methotrexate
- Warfarin, and heparin seem to be safe.
- Prednisone (< 15-20 mg/d) -small amounts (5% of the glucocorticoid dose) are secreted in breast milk.
- Prednisone (> 20 mg once or twice daily), breast milk should be pumped and discarded 4 hours after the dose to minimize drug exposure to the infant

Medscape, Bermas UpToDate, last updated July 2015

Considerations during pregnancy

- SLE exacerbation-SLE nephritis
- APLA
- Preeclampsia
- SLE monitoring
- Fetal- preterm birth, fetal loss, growth restriction
  - Neonatal Lupus
  - Fetal monitoring

Laboratory

- Lupus anticoagulant, immunoglobulin G (IgG) and IgM anticardiolipin antibodies, and IgG and IgM anti-beta2-glycoprotein (GP) I antibodies
- Anti-Ro/SSA and anti-La/SSB antibodies
- Renal function (creatinine, UA with urine sediment, spot urine protein/creatinine ratio)
- Complete blood count
- Liver function tests
- Anti-double-stranded deoxyribonucleic acid antibodies
- Complement (typically C_3 and C_4)
- Uric acid

Preeclampsia vs SLE nephritis flare

Clinical and laboratory features	Active lupus nephritis	Preeclampsia
Hypertension	Onset before 20 weeks	Onset after 20 weeks
Proteinuria	≥300 mg/day	≥300 mg/dl
Urinary sediment	Active	Inactive
Uric acid	≤5.5 mg/dl	>5.5 mg/dl
DNA antibody levels	Rising	Stable or negative
24 h urine calcium	≥195 mg/day	<195 mg/day
Complement levels	≥25% drop	Normal

Reproduced with permission from [114].

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Autoimmune Congenital Heart Block Statistics Friedman and Buyon et al 2003

Incidence in +Ro/La pregnancies	3%
Recurrences after first index case	18%
Mortality	20%
Need for pacemaker	>60%
Late onset cardiomyopathy	10%

CHB-TREATMENT APPROACH

Table 1 Therapeutic approach for congenital heart block diagnosed *in utero*.

Clinical situation	Treatment
Third-degree block, no hydrops fetalis	Evaluation by serial echocardiography; no therapy
Second-degree block or alternating second/third-degree block	Treatment with 4 mg oral dexamethasone daily. If progression to third-degree block occurs, taper dexamethasone dose to discontinuation. If reversal to NSR or lesser forms of block occurs, continue to delivery at term
Prolonged mechanical PR interval (first-degree block)	Repeat echocardiography in 24 h. If first-degree block persists, treatment with 4 mg oral dexamethasone daily. If progression to third-degree block occurs, taper dexamethasone dose to discontinuation. If reversal to NSR occurs or first-degree block persists, taper or individualize therapy
Block associated with signs of myocarditis, CHF and/or hydropic changes	Treatment with 4 mg oral dexamethasone daily until improvement
Severely hydropic fetus	Consider termination. Treatment with 4 mg oral dexamethasone daily plus apheresis to rapidly remove maternal antibodies

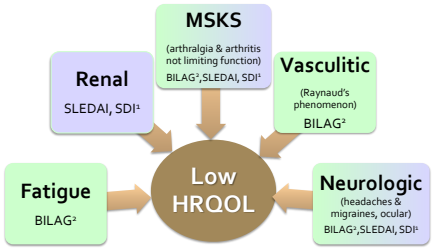
Abbreviations: CHF, chronic heart failure; NSR, normal sinus rhythm.

Cardiac manifestations of neonatal lupus erythematosus: guidelines to management, integrating clues from the bench and bedside

Thank you

Health related quality of life (HRQOL) in pediatric SLE

SLE (activity and damage) involvement of systems and Health Related Quality of Life (HRQOL)



1. Ruperto N, et al, Health-Related Quality of Life in Juvenile-Onset Systemic Lupus Erythematosus and its Relationship to Disease Activity and Damage, Arthritis Rheum 2004; 51 (3):458-464
2. Brunner et al. Health Related Quality of Life and Its Relationship to Patient Disease Course in Childhood-onset Systemic Lupus Erythematosus. J Rheumatol 2009, 36:7 (n=98)

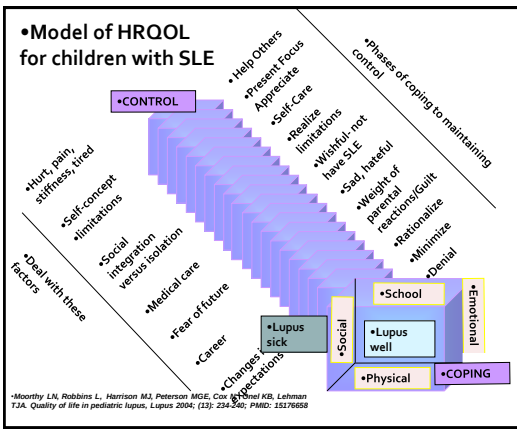
Quotes from my patients with SLE

"I do greatly worry about the future…. passing on this disease to my offspring… Many times I feel I don't have as much time as everyone else."

"I can't do the stuff that kids of my age do… Everything in my life has changed."

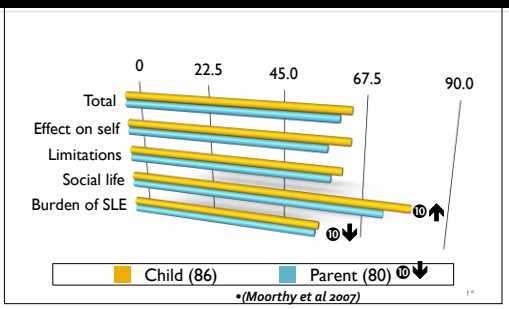
"I wish I never had lupus in my life."

•Model of HRQOL for children with SLE



•Moorthy LN, Robbins L., Harrison MJ, Peterson MGE, Cox S, Tonel KB, Lehman TJA. Quality of life in pediatric lupus, Lupus 2004; (13): 234-240; PMID: 15176668

HRQOL scores in children with SLE using a SLE-specific scale (SMILEY©)



•(Moorthy et al 2007)

Collaboration, Genetic Associations, and Lupus Erythematosus

Mary K. Crow, M.D.

Table 1. **New and Confirmed Genetic Variants Conferring a Significant Risk of Systemic Lupus Erythematosus in Two Genomewide Association Studies.***

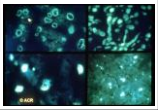
Gene	Genome Location	Proposed Function
HLA†	6p21.33	Presentation of antigen
HLA‡	6p21.32	Presentation of antigen
ITGAM‡	16p11.2	Adhesion of leukocytes to endothelial cells
IRF5‡	7q32.1	Production of interferon-α
KIAA1542†	11p15.5	Linkage disequilibrium with *IRF7*; production of type I interferon
PXK†	3p14.3	Unknown effect of serine–threonine kinase
PTPN22†	1p13	Inhibition of lymphocyte activation
FCGR2A†	1q23	Clearance of immune complexes
STAT4‡	2q32	Modulation of the production of cytokines in T cells and natural killer cells; activation of response of macrophages to interferon-α
BLK§	8p23.1	Activation of B cells

* Data are from Hom et al.[1] and from the International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN) study.[2]
† This variant meets the authors' criteria for association with systemic lupus erythematosus only in the SLEGEN study.
‡ This variant meets the authors' criteria in both Hom et al. and the SLEGEN study.
§ This variant meets the authors' criteria only in Hom et al., although the SLEGEN study provides suggestive evidence of an association at this locus.

ANA

- Antinuclear antibody-An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time

Pattern	Disease	Antibodies
Rim (peripheral)	SLE	DsDNA
Homogeneous (diffuse)	Drug induced LE, SLE	Histones, deoxyribonucleopr
Nucleolar	Scleroderma	Nucleolar RNPs
Speckled	Sjogrens MCTD Scleroderma	Nonhistone proteins Nuclear RNP



Sensitivity and specificity of ANA

Table 1: Sensitivity and specificity of ANA and its clinically important subtypes [18,19]

Autoantibodies	Associated CTD	Sensitivity	Specificity
ANA	SLE	93	57
	Sjogren's syndrome	48	52
	SS	85	54
	PM/dermatomyositis	61	63
	Raynaud phenomena	64	41
Specific ANA			
Anti-dsDNA	SLE	57	97
Anti-Sm	SLE	25–30	High*
Anti-SSA/Ro	Sjogren's syndrome, subacute cutaneous SLE, Neonatal lupus syndrome	8–70	87
Anti-SSB/La	Sjogren's syndrome, subacute cutaneous SLE, Neonatal lupus syndrome	16–40	94
Anti-U3-RNP	SS	12	96
Anticentromere	Limited cutaneous SS	65	99.9
Scl-70	SS	20	100
Jo-1	PM	30	95

Diagnostic Pathology 2009, **4**:1

Antinuclear antibodies and their detection methods in diagnosis of connective tissue diseases: a journey revisited
Yashwant Kumar*†, Alka Bhatia† and Ranjana Walker Minz†

Significance of a +ve ANA test

Table 2: Significance of positive ANA test in CTD and some non-autoimmune conditions [36]

Useful for diagnosis	Useful for monitoring or prognosis
1) Lupus erythmatosus (LE)	1) Juvenile chronic oligoarticular arthritis
SLE	2) Raynaud phenomenon
Discoid LE	**Not useful for diagnosis**
Subacute cutaneous LE	
Neonatal LE	1) Relatives of patients with CTD
Overlap of two or more LE subsets	2) Other autoimmune diseases (e.g., Rheumatoid arthritis, Idiopathic thrombocytopenia purpura, primary biliary cirrhosis, autoimmune thyroiditis)
Overlap of LE with other CTD	3) Drugs (e.g., procainamide, hydralazine)
2) SS	4) Silicone breast implant patients
Cutaneous SS (morphea)	5) Fibromyalgia
Systemic SS	6) Chronic infections
a) Limited disease	7) Neoplasms
b) Diffuse disease	8) Elderly persons
3) PM/Dermatomyositis	9) Pregnant women
4) Sjogren's syndrome (primary and secondary)	10) Healthy persons
5) Mixed CTD	
6) Overlap and undifferentiated CTD	

Antinuclear antibodies and their detection methods in diagnosis of connective tissue diseases: a journey revisited
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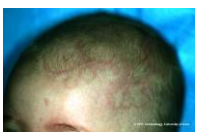
Diagnostic Pathology 2009, **4**:1

DIFFERENTIAL DIAGNOSIS

- Neonatal lupus erythematosus has a very characteristic appearance but the following are in the differential diagnosis-
  - For Polycyclic lesions: Urticaria, E marginatum, tinea, seborrheic dermatitis
  - For Annular erythema: E multiforme, Pityroisporum, Annular erythema of infancy
  - A photodistributed drug eruption