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

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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

Disclosures

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

Systemic Lupus Erythematosus: 1982 classification criteria

- 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


Feraz et al
Highest prevalence - Asian followed by African-American, Native American and Hispanic children (2800-350 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 had increased prevalence of CNS disease vs. Asians (p=0.108).

- 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)

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

(Review by Silverman et al; Hiraki et al, The Rheumatologist)

<table>
<thead>
<tr>
<th>Table 1: Cumulative Incidence of Common SLE Manifestations</th>
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</thead>
<tbody>
<tr>
<td><strong>CSLE (%)</strong></td>
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<tr>
<td>------------</td>
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<tr>
<td>CONSTITUTIONAL - RHEUM</td>
</tr>
<tr>
<td>MALAR RASH</td>
</tr>
<tr>
<td>ORAL OR NASAL ULCERS*</td>
</tr>
<tr>
<td>PHOTODERMATOSIS</td>
</tr>
<tr>
<td>AORTHERS</td>
</tr>
<tr>
<td>NEPHRAL DISEASE*</td>
</tr>
<tr>
<td>NEUROLOGIC / COMATOSE</td>
</tr>
<tr>
<td>SEDUDES*</td>
</tr>
<tr>
<td>PSYCHOSIS</td>
</tr>
<tr>
<td>SEROSITES</td>
</tr>
<tr>
<td>HEMOPHILITIC ANEMIA</td>
</tr>
<tr>
<td>PHOTODERMATOSIS</td>
</tr>
</tbody>
</table>

*Refer to the literature for significance

Levy et al, The Rheumatologist
Review by Levy et al

Levy et al, The Rheumatologist

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

Bandeira et al, Lupus 2006

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

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

Increased and unique psychosocial stressors

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

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

More likely to meet ACR criteria for renal disease and have ESRD
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))
(56% vs. 24% and 21% vs. 8% (p=0.0001))

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

Mortality in childhood-onset SLE

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

Accumulate disease damage more quickly
More likely to meet ACR criteria for renal disease and have ESRD

19.5 vs. 16.5 years (p<0.0001)
(56% vs. 24% and 21% vs. 8% (p=0.0001))
Mean age at death 33 (childhood-onset; n=98) versus 52 years (n=859)

Childhood-onset SLE
Education
ESRD

Male sex
Cardiovascular disease
Medicare or Medicaid insurance

Constitutional symptoms in SLE
- Fever
- Fatigue
- Wt Loss
- Alopecia
- Arthralgias
- Diffuse generalized inflammation
- Lymphadenopathy
- Hepatosplenomegaly

Clinical Characteristics of Patients Who Have SLE

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

General
Hematologic disorder
• Hemolytic anemia—with reticulocytosis OR
• Leukopenia—less than 4,000/mm^3 on 2 or more occasions OR
• Lymphopenia—less than 1,500/mm^3 on 2 or more occasions OR
• Thrombocytopenia—less than 100,000/mm^3 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

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

• Immuneologic 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

<table>
<thead>
<tr>
<th>Organ System Involvement</th>
<th>At Diagnosis (%)</th>
<th>Within 1 Year After Diagnosis (%)</th>
<th>Ever (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantibody (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-ds-DNA</td>
<td>194 (72)</td>
<td>214 (84)</td>
<td></td>
</tr>
<tr>
<td>Anti-Smith antibody</td>
<td>84 (34)</td>
<td>124 (48)</td>
<td></td>
</tr>
<tr>
<td>Anti-DS antibodies</td>
<td>68 (27)</td>
<td>95 (37)</td>
<td></td>
</tr>
<tr>
<td>Anti-Ro</td>
<td>64 (25)</td>
<td>58 (23)</td>
<td></td>
</tr>
<tr>
<td>Anti-La</td>
<td>38 (15)</td>
<td>37 (15)</td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid (aP)</td>
<td>82 (33)</td>
<td>115 (46)</td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>67 (26)</td>
<td>102 (40)</td>
<td></td>
</tr>
<tr>
<td>LAC</td>
<td>53 (20)</td>
<td>32 (13)</td>
<td></td>
</tr>
<tr>
<td>Neutrophil factor</td>
<td>28 (11)</td>
<td>35 (14)</td>
<td></td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>141 (56)</td>
<td>161 (63)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>71 (29)</td>
<td>80 (31)</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>71 (29)</td>
<td>80 (31)</td>
<td></td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>58 (23)</td>
<td>63 (24)</td>
<td></td>
</tr>
</tbody>
</table>

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 ophthalmological evaluation
  - Color vision and visual field testing
  - Benefits-disease activity, survival, and improvement in organ damage, thrombosis, atherosclerosis, BMD, and lipid profile
  - Used in combination with steroids and other medications

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

- **Avoid sun exposure**

**Mild SLE**

- **No renal or life threatening organ involvement**
- **NSAIDS for musculoskeletal manifestations**
- **Hydroxychloroquine up to 200mg/day (400mg/day for adults)**
- **Avoid Sulfas drugs (such as Sulindac): Sulfur 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 >0.35mg/kg/day**

**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 agents:**
  - 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)

**The girl with fevers and weight loss**

- **22 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-DNA ab+, Anti-Smith ab +ve; -ve anti-Ro, La and RNP ab**

**Treatment:** Oral steroids, Hydroxychloroquine

- Rash, fatigue and alopecia improved

**Mucocutaneous manifestations- Malar rash**

- **Acute cutaneous lupus erythematous (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 manifestations- Discoid rash and SCLE**

- **Discoid - inflammatory plaques evolving into atrophic disfiguring scars**
- **Subacute cutaneous lupus erythematous (S克莱) - erythematous scaly papules or annular plaques 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

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

Systemic therapy

Hydroxychloroquine, Chloroquine, Quinacrine

Refactory Disease

Methotrexate, MMF, Dapsone, Isotretinoin, Acitretin, Thalidomide, Azathioprine, Rituximab, IVIG, Clofazimine

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

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 0.5mg/kg/day)
  - Rash (43%), fatigue (39%), arthritis (14%), accompanied by worsening serologic activity (increasing anti-dsDNA titers and hypocomplementemia)

Vascular lesions
- Periungual erythema
- Raynauds
- Telangiectasias
- Livedo reticularis
- Chilblain LE
- Urticaria or purpuric vasculitis
- Check for antiphospholipid antibody
- Treatment individualized - may need anticoagulation

Musculoskeletal manifestations and treatment
- Synovial involvement
  - NSAIDS
  - Glucocorticoids
  - Hydroxychloroquine
  - Methotrexate
  - Belimumab
  - Rituximab
  - Subcutaneous nodules
  - Osteonecrosis (3-40% in SLE)
  - Activity restriction, surgical intervention
  - Osteoporosis
  - Vld, Calcium, Bisphosphonates
  - Myalgias
  - Fibromyalgia

Corticosteroids
- Belimumab
  - At the last follow-up average SLEDAI decreased from 6.4 to 4.
  - Able to taper steroids in 57% of patients, with 37 (43%) able to discontinue steroids.
  - The average complement levels increased from 71 to 74 (C3) and 8 to 10 (C4)
  - 67 clinically responded to belimumab within 3 months, with marked improvement in rash, arthritis, and fatigue.

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
C3 50, C4 <7
ANA 1:5120
dsDNA 1:300
Anti-SM ab reported as highly positive
Low dose ASA if no thrombosis
- If thrombosis- warfarin (INR 2-3)
- Lovenox (antifactor Xa 0.5-1 units/ml)

### 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 50 mm/hr
- C3 = 50, C4 = 7, ANA 1:1280, DS-DNA 1:160

### Clinical Characteristics of Patients Who Have SLE

<table>
<thead>
<tr>
<th>Organ System Involved</th>
<th>At Diagnosis (%)</th>
<th>Within 1 Year After (n = 214)</th>
<th>Ever (%) (n = 276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephritis*</td>
<td>14 (17)</td>
<td>119 (96)</td>
<td>141 (102)</td>
</tr>
<tr>
<td>Mesangial (class II)</td>
<td>14 (11)</td>
<td>29 (10)</td>
<td>52 (156)</td>
</tr>
<tr>
<td>Focal nephropathy (class III)</td>
<td>27 (13)</td>
<td>60 (11)</td>
<td>61 (39)</td>
</tr>
<tr>
<td>Diffuse proliferative (class IV)</td>
<td>45 (47)</td>
<td>50 (43)</td>
<td>60 (44)</td>
</tr>
<tr>
<td>Membranous (class V)</td>
<td>14 (16)</td>
<td>20 (17)</td>
<td>28 (23)</td>
</tr>
<tr>
<td>Nephritic syndrome</td>
<td>36 (16)</td>
<td>52 (23)</td>
<td>60 (17)</td>
</tr>
<tr>
<td>Cortical necrosis</td>
<td>21 (10)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Membranous disease</td>
<td>14 (15)</td>
<td>12 (10)</td>
<td>26 (157)</td>
</tr>
<tr>
<td>Periarteritis nodosa</td>
<td>13 (12)</td>
<td>14 (13)</td>
<td>21 (23)</td>
</tr>
<tr>
<td>Cerebral dysfunction</td>
<td>8 (7)</td>
<td>13 (15)</td>
<td>15 (233)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>5 (5)</td>
<td>5 (5)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>5 (5)</td>
<td>5 (5)</td>
<td>6 (62)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>2 (2)</td>
<td>0</td>
<td>1 (84)</td>
</tr>
<tr>
<td>Arthralsy</td>
<td>34 (15)</td>
<td>22 (18)</td>
<td>23 (16)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>34 (15)</td>
<td>1 (1)</td>
<td>2 (16)</td>
</tr>
</tbody>
</table>

*Pediatric Systemic Lupus Erythematosus: More Than a Positive Antinuclear Antibody

### 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)

### 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 years old is 0.5 mg/dl
- 1.1 is abnl in that age group!

Mesangial nephritis
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)

"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)

Membranous GN

In most areas of the glomerulus, the capillary walls are thickened due to deposits (corresponding to immune complexes) or the basement membrane. Between deposits are protrusions of black-staining mesangial material. (hematoxylin-eosin, high power)

Severe SLE – Renal involvement

- Cyclophosphamide for induction typically
- Maintenance with mycophenolate mofetil or azathioprine
- Poor adherence – every 3 monthly cyclophosphamide for 3 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

Maintenance therapy

**Table 2: Maintenance therapy in childhood lupus nephritis.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Suggested Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>10-15 mg/day</td>
</tr>
<tr>
<td>Azathioprine (AZA)</td>
<td>2-2.5 mg/kg/day</td>
</tr>
<tr>
<td>Mycophenolate mofetil (MMF)</td>
<td>0.6-1.2 g/m²/day, maximum 3 g/day in two divided doses</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>4-6 mg/kg/day (up to 10 mg/kg/day)</td>
</tr>
</tbody>
</table>

Demircin et al 2013 Annals of Peds Rheum

**Refactory 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 2015

**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 (2), decreased IgG levels (2), infections (2) and anaphylaxis (2)

**Cyclophosphamide and Rituximab**

- N=12
- SLE nephritis or corticosteroid resistant SLE
- Combination of Rituximab 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**

<table>
<thead>
<tr>
<th>Month 0</th>
<th>Month 12</th>
<th>Month 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone (mg/day)</td>
<td>20-70</td>
<td>20-70</td>
</tr>
<tr>
<td>C3 (mg/dl)</td>
<td>95-275</td>
<td>95-275</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>10-40</td>
<td>10-40</td>
</tr>
<tr>
<td>HB (mg/dl)</td>
<td>10-12</td>
<td>10-12</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>1-5</td>
<td>1-5</td>
</tr>
<tr>
<td>IgM (mg/dl)</td>
<td>170-300</td>
<td>170-300</td>
</tr>
</tbody>
</table>

N=5 with recurrent SLE nephritis
IV monthly ctx and IV mtx for 9 months
Improvement seen

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

Gastrointestinal manifestations

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

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-μg/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

Thrombocytopenia

- Glucocorticoids
- Prednisone/pulse methylprednisolone
- Rituximab
- Hydroxychloroquine and Danazol
- TTP—plasmapheresis

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 ophthalmology—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. Ocular disc hyperemia and central ulcer were evident clinically A. B. B-scan ultrasonography showed posterior eye wall thickening with intraocular 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.

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

Cardiac abnormalities

- Coronary artery disease
  - Non pharmacological measures: diet low in saturated fat and cholesterol with omega 3 fatty acids 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)

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

Pulmonary disease

- Pleuritis - treatment depends of severity
  - If tachypneic and in severe pain, require oxygen, analgesics, IV methylprednisolone
  - Pulmonary hemorrhage - ventilation, high dose IV glucocorticoids, plasmapheresis, Cyclophosphamide, Rituximab
  - Pulmonary hypertension - Epoprostenol, Bosentan
  - Acute pneumonitis - Glucocorticoids


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

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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)
- 37% took 8 or more medications daily, 68% had 3-4 doctor visits per year and 34% had 8-12 doctor visits per year (Applebaum, 2013)
- 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)

51% of patients had poor transition readiness, poor appointment adherence, decreased knowledge, insurance, and other factors.

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/tattoos
- Subspecialty visits
- Evaluate mood (patients may get depressed!!)
- Medication interactions
- Exercise
- VitD and Ca

Most children do well (Lehman et al Pediatrics 1989)
- Poor compliance
- Neurological complications
- Renal disease, esp DPGN
- Delay in diagnosis
- Intercurrent infections

N=34 followed for 2.8 years (median) had chronic active disease (43%), relapsing (14%), long quiescence (37%)
Chronic active disease associated with +ve anti-Sm ab
Survival rate in SLE is 100% at 5 years and 85% at 10 yrs (Platt Am J Kid Dis 1981, Golden et al Clin Immunol Immunopathol 1981)

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

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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

ESRD in 25%-40%
- Mesangial disease (5-15%) and FPGN (8-15%) no deaths and none had ESRD over 11 years f/u

Retrospective study of 66 Canadian children (Hagelberg J Rheumatol 2002)

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 = 0.004).
- 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 patients (58% versus 21%, P = 0.03; 50% versus 16%, P = 0.04; 58% versus 23%, P = 0.03; 50% versus 26%, P = 0.04, respectively).
- Demographic data, pubertal changes, abnormalities in menstrual cycle, and cervicovaginal cytology were similar in JSLE patients and the control group.
Contraception for adolescents with lupus

- 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

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 an 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, preclampsia, 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

<table>
<thead>
<tr>
<th>Medications</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDS</td>
<td>Avoid in 1st and 3rd trimester</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Continue (better outcomes and decreased risk of CHB in Ro and La+ve cases)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>&lt;1mg/kg/day (in 1st trimester, associated with cleft lip, with and without cleft palate).</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Relatively safe during pregnancy, not exceed 2 mg/kg/day</td>
</tr>
<tr>
<td>Cyclosporine and Tacrolimus</td>
<td>If benefit outweighs risk</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Methyldopa, labetalol, hydralazine (avoid ACE inhibitors and ARB)</td>
</tr>
<tr>
<td>Biologics</td>
<td>Discourage Rituimab B cell lymphocytopenia in infant</td>
</tr>
<tr>
<td></td>
<td>Limited data on Belimumab</td>
</tr>
</tbody>
</table>

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. 8-21)
  - More likely to be black (34% vs. 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SLE N = 4,142</th>
<th>Non-SLE N = 9,121,082</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Outcomes N (%)</td>
<td>P*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia and Eclampsia</td>
<td>627 (16)</td>
<td>4,455,529 (6.6)</td>
<td>&lt;0.0001 3.9 (3.3 4.7)</td>
</tr>
<tr>
<td>Death during hospitalization</td>
<td>15 (0.37)</td>
<td>490 (0.005)</td>
<td>&lt;0.0001 69.7 (22.6 211.6)</td>
</tr>
<tr>
<td>Fetal Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td>843 (20)</td>
<td>736,665 (8.1)</td>
<td>&lt;0.0001 2.9 (2.5 3.4)</td>
</tr>
<tr>
<td>Low birth weight or fetal</td>
<td>0 (0)</td>
<td>20 (0.005)</td>
<td>&lt;0.0001 1.0 (0.0004 0.0005)</td>
</tr>
<tr>
<td>growth retardation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous abortion or</td>
<td>179 (4.3)</td>
<td>93,486 (1.1)</td>
<td>&lt;0.0001 4.1 (2.9 5.8)</td>
</tr>
<tr>
<td>intrauterine death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induced abortion</td>
<td>90 (2.2)</td>
<td>11,229 (0.013)</td>
<td>&lt;0.0001 12.1 (10.4 13.8)</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>720 (17.4)</td>
<td>30,093 (0.3)</td>
<td>&lt;0.0001 0.7 (0.62 0.78)</td>
</tr>
</tbody>
</table>

Allen et al 2014, ACR abstract
Medications during breastfeeding

- Long-acting NSAIDs are inadvisable; use short-acting NSAIDs-displace bilirubin and cause kernicterus
- Hydroxychloroquine-displace bilirubin and cause kernicterus
- Azathioprine, cyclosporine, 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 1-20 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, Esmus UpToDate, last updated July 2015

Considerations during pregnancy

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

SLE monitoring

Preeclampsia vs SLE nephritis flare

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

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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>
<thead>
<tr>
<th>Clinical situation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third-degree block, no hydrosalpinx</td>
<td>Tissue biopsy, surgical treatment</td>
</tr>
<tr>
<td>Second-degree block or alternating second/third-degree block</td>
<td>Tissue biopsy, surgical treatment</td>
</tr>
<tr>
<td>Prognostic mechanical PR interval</td>
<td>Repeat echocardiography in 24h. If first-degree block persists, treatment with 0.4 mg/kg/day desmopressin. If progression to second-degree block occurs-desmopressin dose to discontinuation. If referral to NRP or lesser forms of block occurs, continue to delivery at term.</td>
</tr>
<tr>
<td>Block associated with signs of myocarditis, CHF and/or hydronephrosis</td>
<td>Treatment with 0.4 mg/kg/day desmopressin until improvement</td>
</tr>
<tr>
<td>Severe hydropic fetus</td>
<td>Consider termination. Treatment with 0.4 mg/kg/day desmopressin plus spironolactone to rapidly remove maternal antibodies</td>
</tr>
</tbody>
</table>

Cardiac manifestations of neonatal lupus: contraception guidelines and management, integrating data from the bench and bedside

Medscape, Esmus UpToDate, last updated July 2015
**SLE (activity and damage) involvement of systems and Health Related Quality of Life (HRQOL)**

- **Renal**
  - SLEDAI, SDI
- **Fatigue**
  - MSKS
  - Vasculitic (Raynaud's phenomenon)
  - Neurologic (headaches & migraines, ocular)
  - BILAG

**Low HRQOL**

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**

**HROQOL scores in children with SLE using a SLE-specific scale (SMILEY®)**
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, deoxyribonucleoprotein
Nucleolar | Scleroderma | Nucleolar RNP
Speckled | Sjogren’s, MCTD, Scleroderma | Nonhistone proteins, Nuclear RNP

### Sensitivity and specificity of ANA

### Significance of a +ve ANA test

#### Differential Diagnosis

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