Pediatric Systemic Lupus Erythematosus

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Objectives

- Definition
- Classification criteria
- Epidemiology
- Etiology & pathogenesis
- Clinical presentation
- Workup & labs
- Principles of treatment

Definition

- A chronic, multisystem, autoimmune disorder
- Has a wide variability in presentation
  - "The great imitator", "The disease with 1000 faces"
- "Lupus"- "wolf" in Latin; skin lesions' resemblance to wolf bites.

Classification

- Not for diagnostic purposes but useful for documenting key features.
- Mainly for purposes of inclusion in research

1. ACR criteria 1997 (Americal College of Rheumatology)
2. SLICC criteria 2012 (Systemic Lupus International Collaborating Clinics)
3. EULAR 2019 (The European Alliance of Associations for Rheumatology)

ACR criteria 1997

- 4 of 11 to fulfill classification of SLE- definite lupus
- In children:
  - Sensitivity 96%
  - Specificity 100%

- Tip to remember:
  - 4 skin/mucocutaneous
  - 4 (-itis)
  - 3 labs

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Non-erosive arthritis	Involving two or more peripheral joints, characterised by tenderness, swelling or effusion
6. Pleuritis or pericarditis	a. Pleuritis—convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR b. Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	a. Persistent proteinuria > 0.5 g/d or > than 3+ if quantisation not performed OR b. Cellular casts—may be red cell, haemoglobin, granular, tubular or mixed
8. Neurological disorder	a. Seizures—in the absence of offending drugs or known metabolic derangements; e.g. uraemia, ketoacidosis or electrolyte imbalance OR b. Psychosis—in the absence of offending drugs or known metabolic derangements; e.g. uraemia, ketoacidosis or electrolyte imbalance
9. Haematological disorder	a. Haemolytic anaemia—with reticulocytosis OR b. Leucopaenia—<4000/mm^3 on ≥ 2 occasions OR c. Lymphopenia—<1500/mm^3 on ≥ 2 occasions OR d. Thrombocytopaenia—<100,000/mm^3 in the absence of offending drugs
10. Immunological disorder	a. Anti-DNA: antibody to native DNA in abnormal titre OR b. Anti-Sm: presence of antibody to Sm nuclear antigen OR c. Positive finding of antiphospholipid antibodies on 1. An abnormal serum level of IgG or IgM anticardiolipin antibodies 2. A positive test result for lupus anticoagulant using a standard method, or 3. A false-positive test result for at least 6 months confirmed by Treponema pallidum immobilisation or fluorescent treponemal antibody absorption test
11. Positive anti-nuclear antibody	An abnormal titre of anti nuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

SLICC 2012

- Include 11 clinical and 6 immunological items
- To classify as SLE:
  - 4 items with as least 1 clinical + 1 immunological

    Or
  - Biopsy proven nephritis compatable with lupus in the presence of ANA or anti-dsDNA

- Slightly higher sensitivity compared to ACR criteria- 98%
- Slightly decreased specificity- 85%

EULAR 2019

- Require the presence of ANA 1:80 or greater as an entry criterion
- Clinical and lab criteria are weighted- a total score of 10 or more meets SLE classification requirements

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Suspicion of SLE		
ACR	SLICC	EULAR/ACR
any 4 of 11	Histology compatible with lupus nephritis and ANA or anti-dsDNA OR any 4 of 17 (at least one immunological)	ANA positive 10 points weighted items (highest in each domain counted only)

Epidemiology

- Incidence and prevalence 0.36-2.5 per 100,000
  - – no reports published in Jordan
- Females > males 5:1--> in adults 9:1
- Average age at diagnosis: 12 y.o. (rarely <5)
  - According to a retrospective descriptive study in JRMS- Avg age- 10 y.o

- Ethnicity

Etiology & Pathogenesis

A 15 year old girl was recently diagnosed with SLE her labs show a +ANA, anti-dsDNA, and anti-smith. She asks you how are these antibodies are made?

Of the following cells, which are MOST likely responsible for producing this patient's autoantibodies?

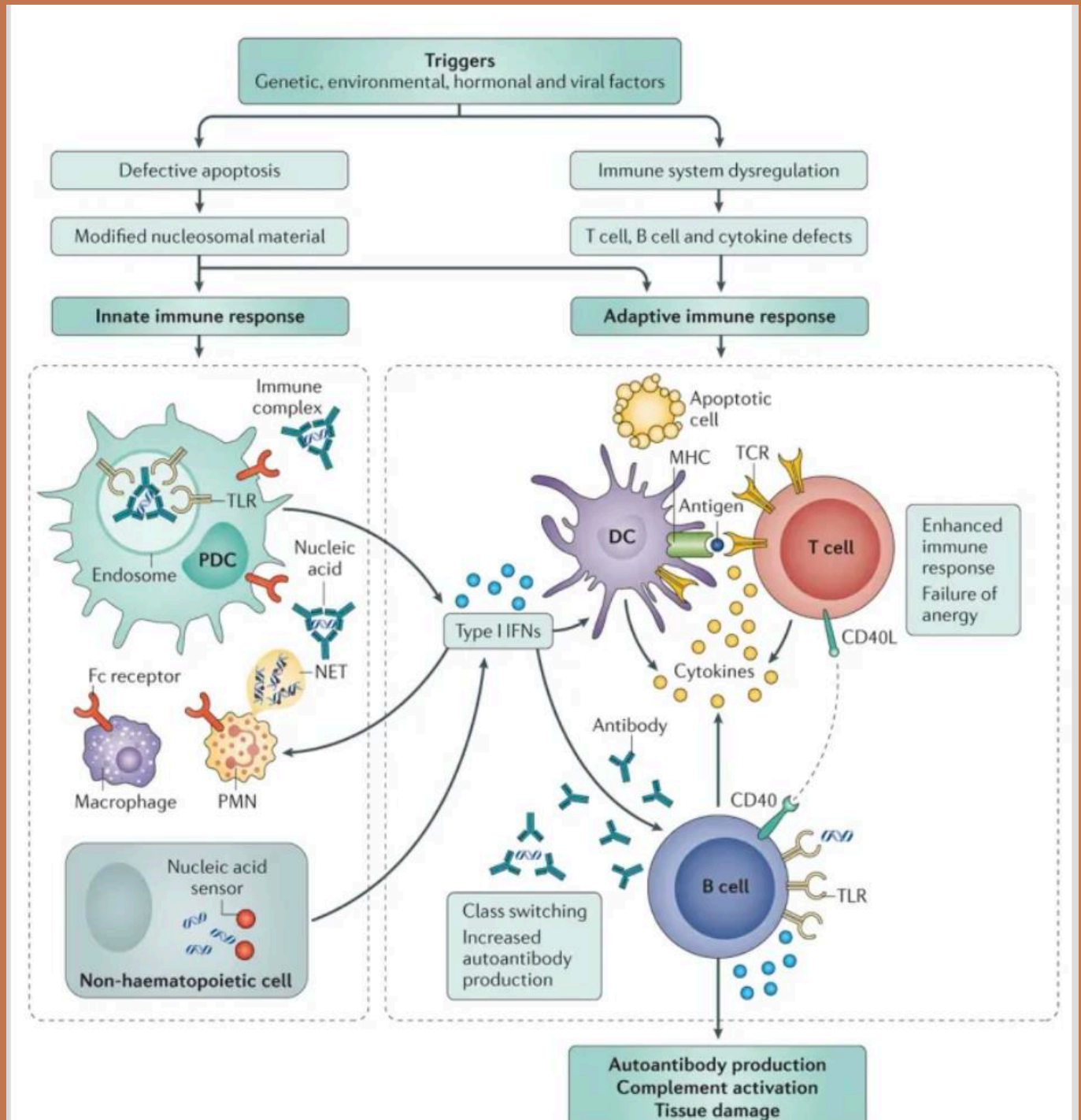
a. Plasma cells
b. Memory cells
c. Immature B cells
d. Mature naïve B cells

Etiology/ pathophysiology

- Main concepts:
  - Immune dysregulation of the innate and adaptive immune systems.
  - Defective apoptosis
  - Direct cellular injury and immune complex disease

- Main players:
  - Plasmacytoid dendritic cells--> produce IFN I alpha
  - B & T cells (autoantibodies & cytokines)
  - Immune complexes

- Trigger***---> activate innate immune system --> abnormal regulation of type I IFN (IFN alpha)--> pro-inflammatory response, cell death.
- Defective apoptosis- Cell debris that is not cleared --> phagocytic cells --> APC to the adaptive immune system (T cells) --> activate:
  - T cells ---> proinflammatory cytokines (IL1, IL6, TNFa)
  - B cells ---> autoantibodies ---> complement to form IC --> organ damage


Triggers
Genetic, environmental, hormonal and viral factors
Defective apoptosis
Immune system dysregulation
Modified nucleosomal material
T cell, B cell and cytokine defects
Innate immune response
Adaptive immune response
Immune complex
TLR
Endosome
PDC
Nucleic acid
NET
Fc receptor
Macrophage
PMN
Nucleic acid sensor
Non-haematopoietic cell
Type I IFNs
Apoptotic cell
MHC
TCR
Antigen
DC
T cell
Enhanced immune response
Failure of anergy
CD40L
Cytokines
Antibody
CD40
B cell
TLR
Class switching
Increased autoantibody production
Autoantibody production
Complement activation
Tissue damage

Etiology and pathophysiology

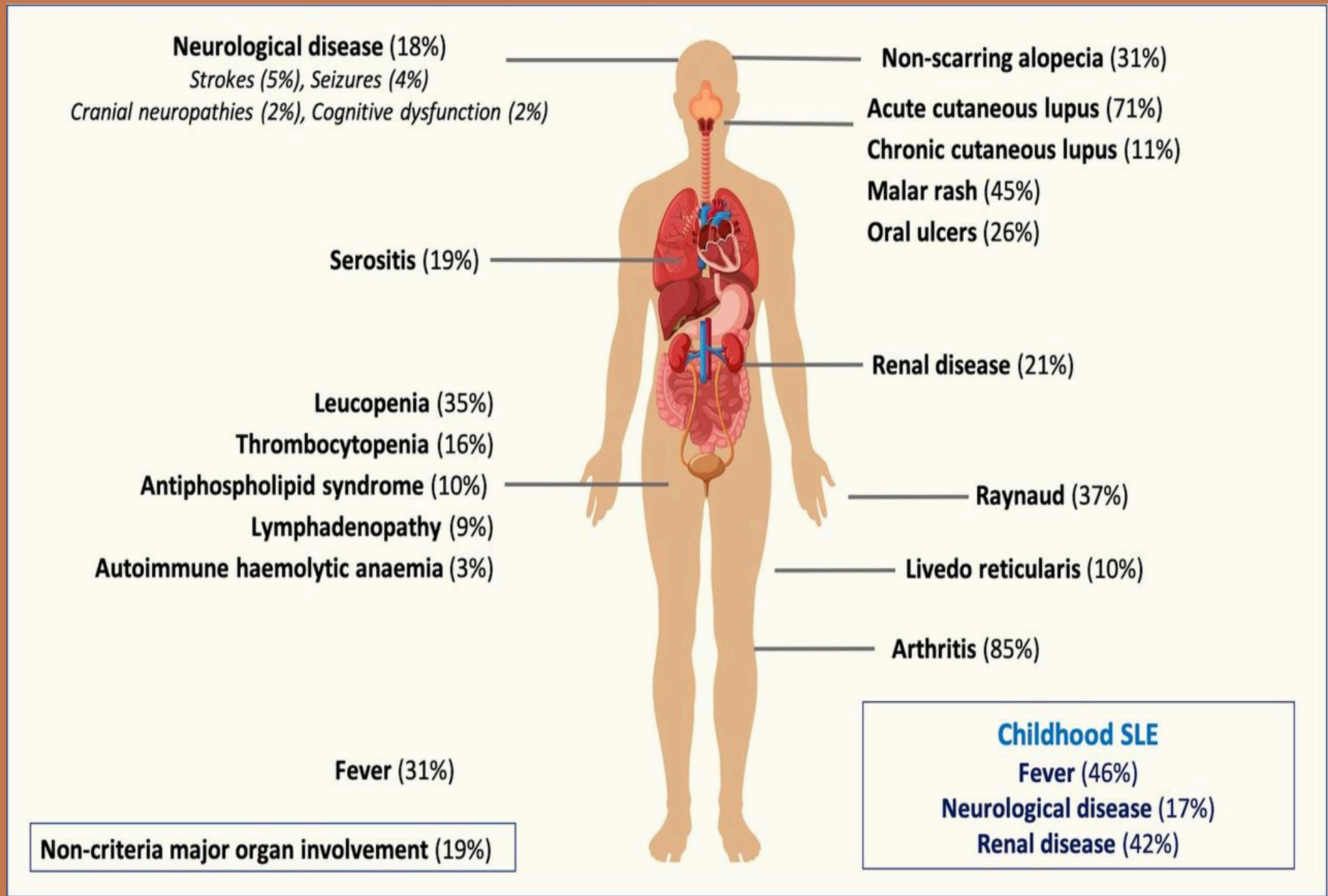
- Multifactorial
  - Genetic role:
    - 10% of first degree relatives of patients who have SLE are more likely to potentially have SLE Vs 1% I those with NO family hxt of SLE.
    - 20-fold increased risk in siblings
    - 24% concordance in monozygotic vs 2% in dizygotic twins
    - Single gene mutations are rare, but can happen – monogenetic lupus presentation (mostly complement def such as C1q, C2, C4)
  - Hormones:
    - Increased estrogen and low androgen play a role in(menarche to menopause)
    - Increased incidence incidence in Klinefleters

Etiology/ pathophysiology

- Environmental
  - UV radiation- flares of cutaneous and systemic lupus-
    - UVB--> keratinocytes to release different chemokines and cytokines which cause necrosis and apoptosis---> decreased DNA methylation & release of intracellular molecules ---> autoantibody production
- Molecular mimicry: CMV, EBV, and herpes viruses- T cell activation
- Medications- drug induced lupus.
  - 80 different meds

Clinical Manifestations

1. Mucocutaneous
2. Organ
3. Lab/ immunologic



Clinical Manifestations

Note that childhood SLE:

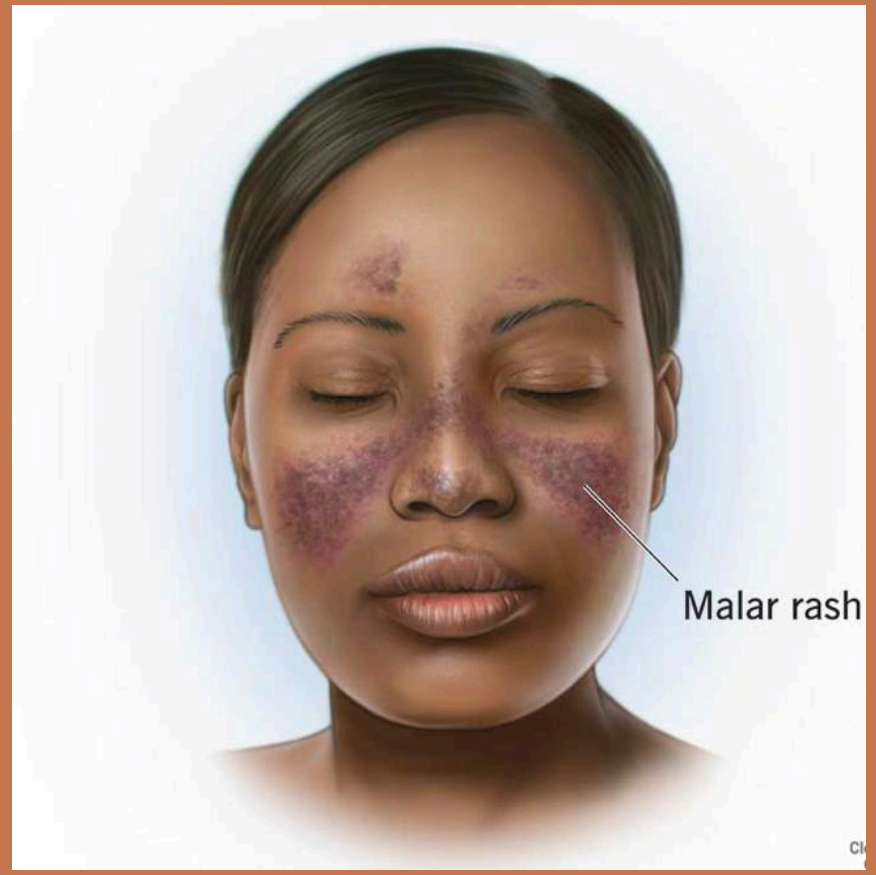
- Has higher activity at presentation
- More likely to have active renal disease
- Is more likely to be severe and to receive more aggressive therapy, as well as accumulate damage.
- **Children are NOT small adults.**

Mucocutaneous

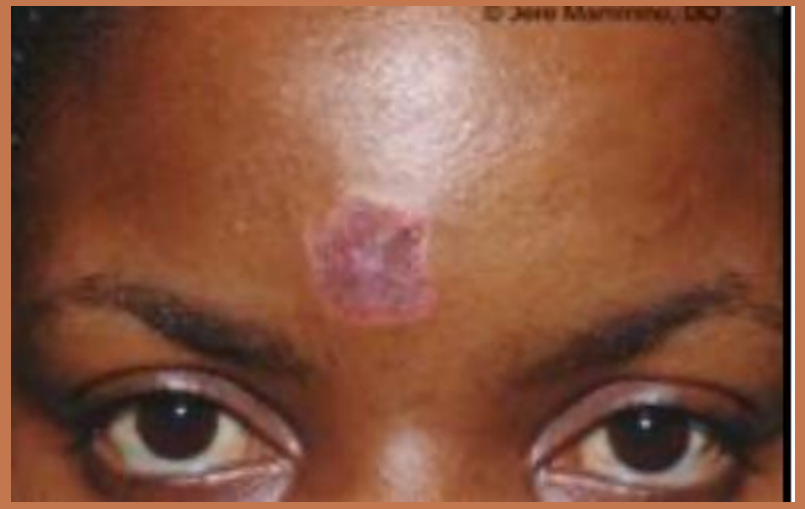
- Ulcers
- Rashes- 85% during the course of the disease
- photosensitivity

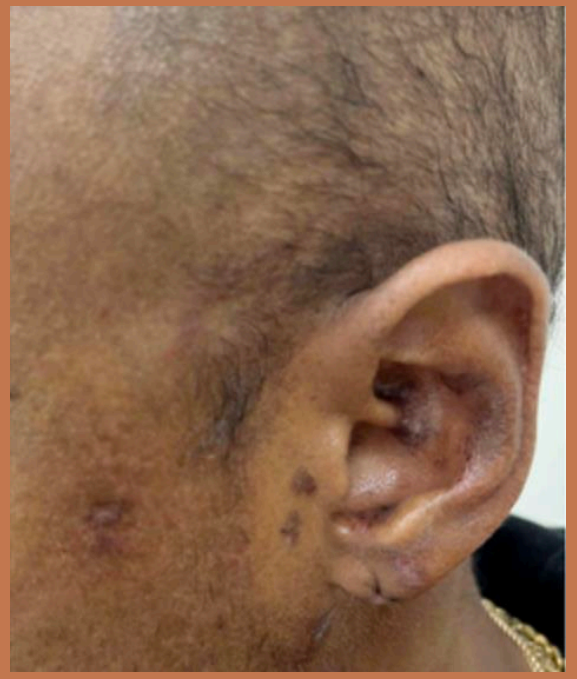
Mucocutaneous manifestations

- Malar rash "butterfly rash"- is the most common rash in peds
  - Maculopapular, erythematous, photosensitive
  - Nose and cheeks, chin & forehead
  - Spares nasolabial fold
  - **Non**-scarring

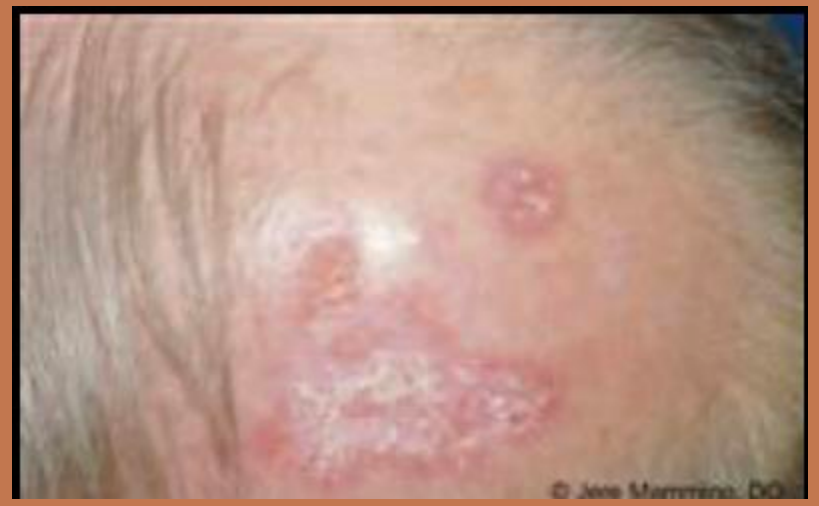


Mucocutaneous

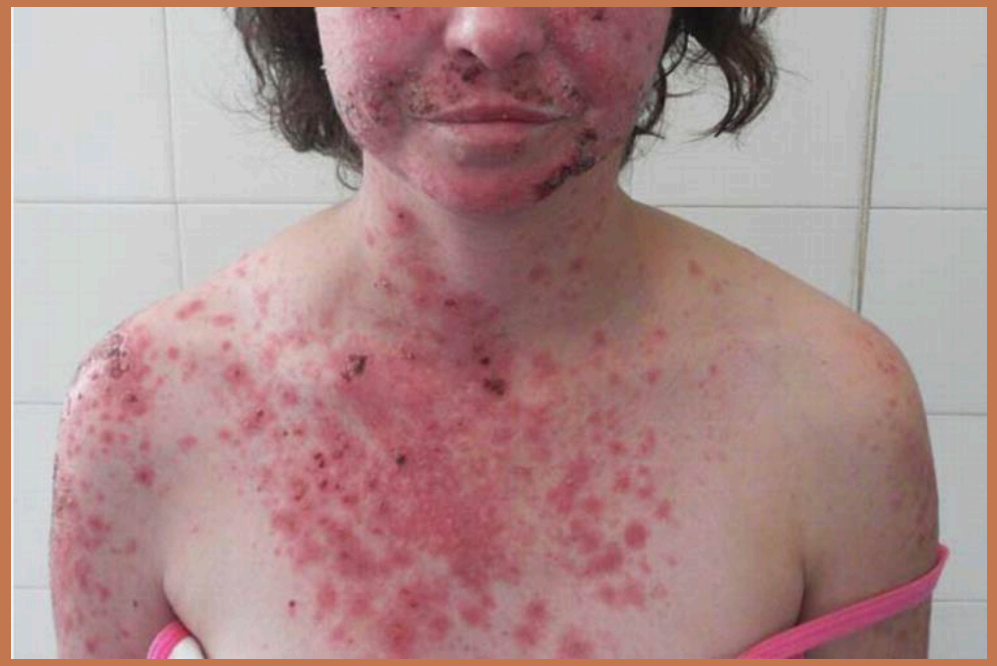


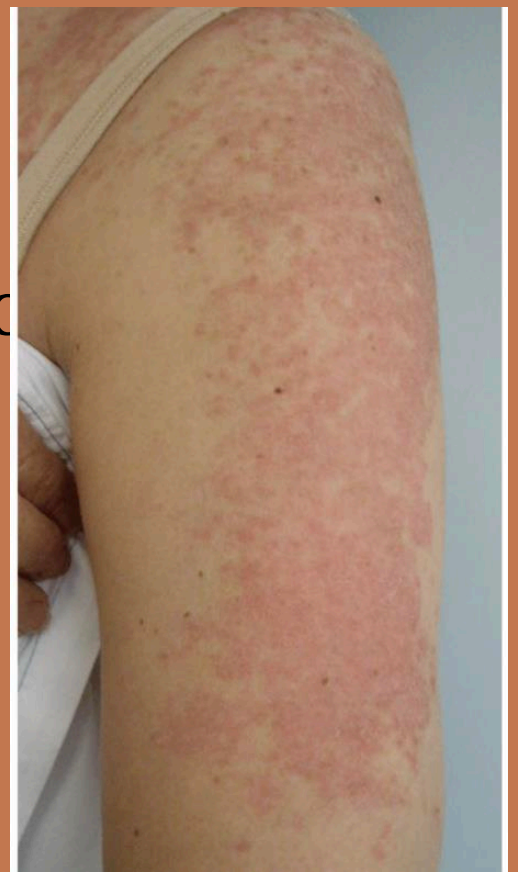


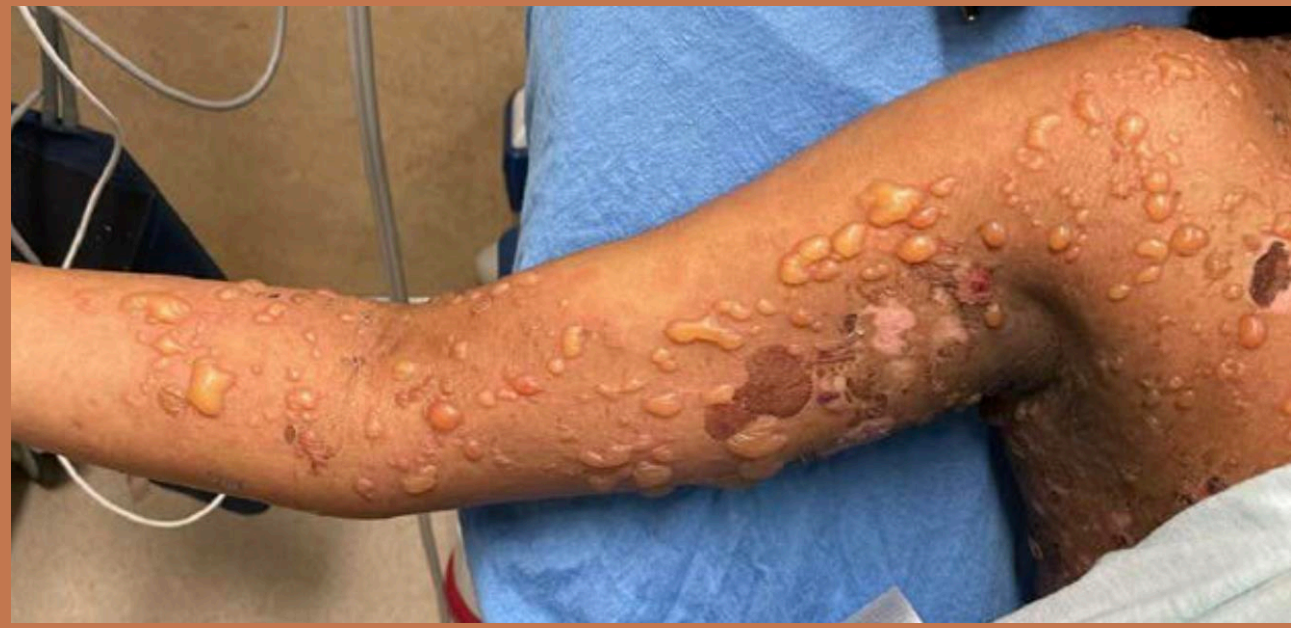
- Discoid rash
  - Less common in peds
  - Thick adherent scaling
  - Follicular involvement- hair loss at the lesion
  - Usually hyperpigmented- can be hypopigmented
  - Around the eyes, ears, face, and scalp- can be more generalized
  - Scarring



- Photosensitivity
  - Raised
  - Erythematous
  - Reaction to sunlight & flourescent lights
  - It is NOT "easily
- Subacute cutaneo
- Bullous lupus

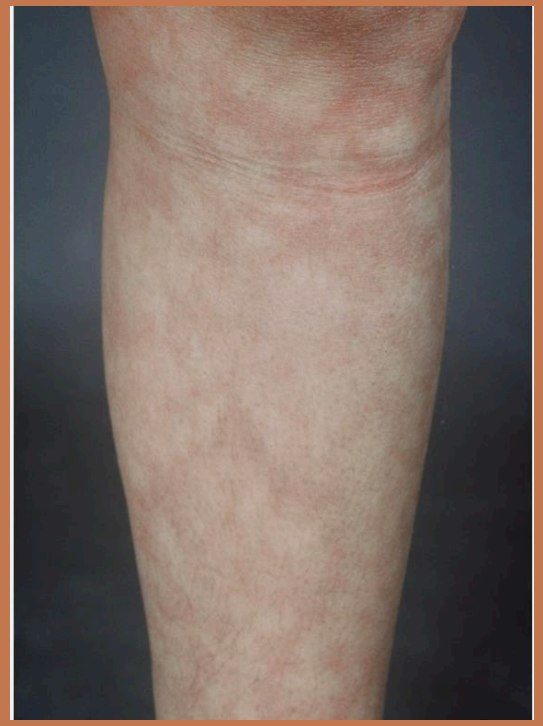


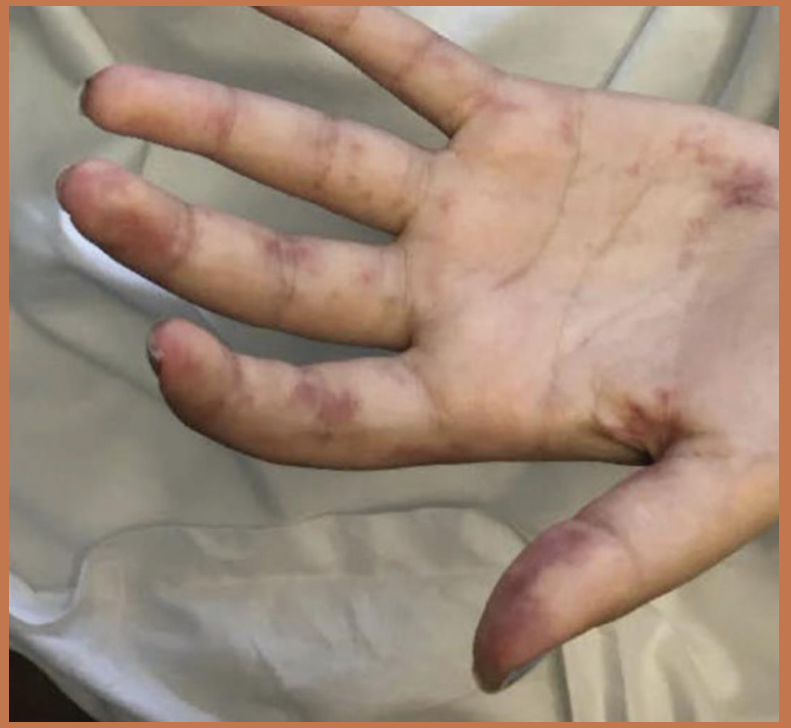


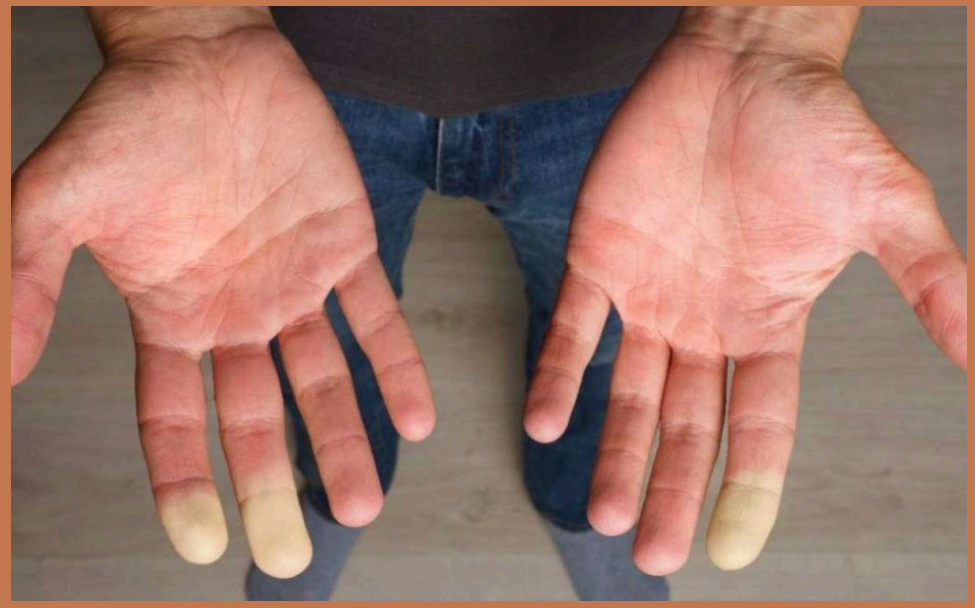


Mucocutaneous

- Livedo reticularis
- Alopecia
- Digital ulcers
- Raynauds

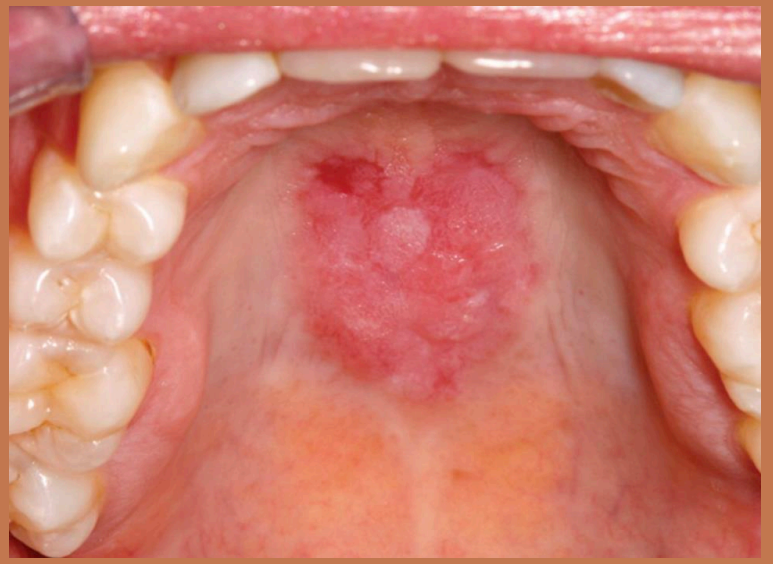


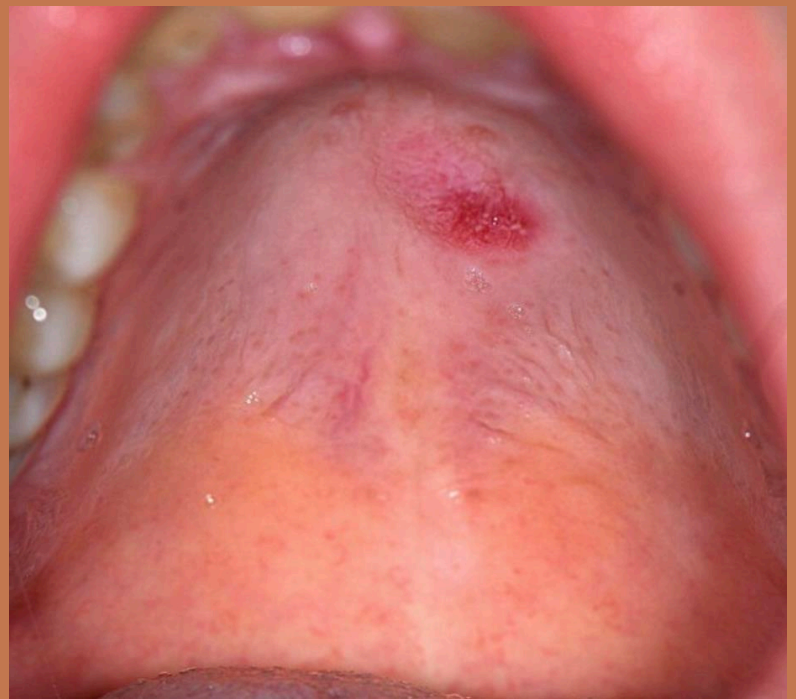




Mucocutaneous

- Mucosal ulcers
  - Oral; hard palate- painless erythema
  - Nasal; very rare. May cause septal perforation





Organ involvement

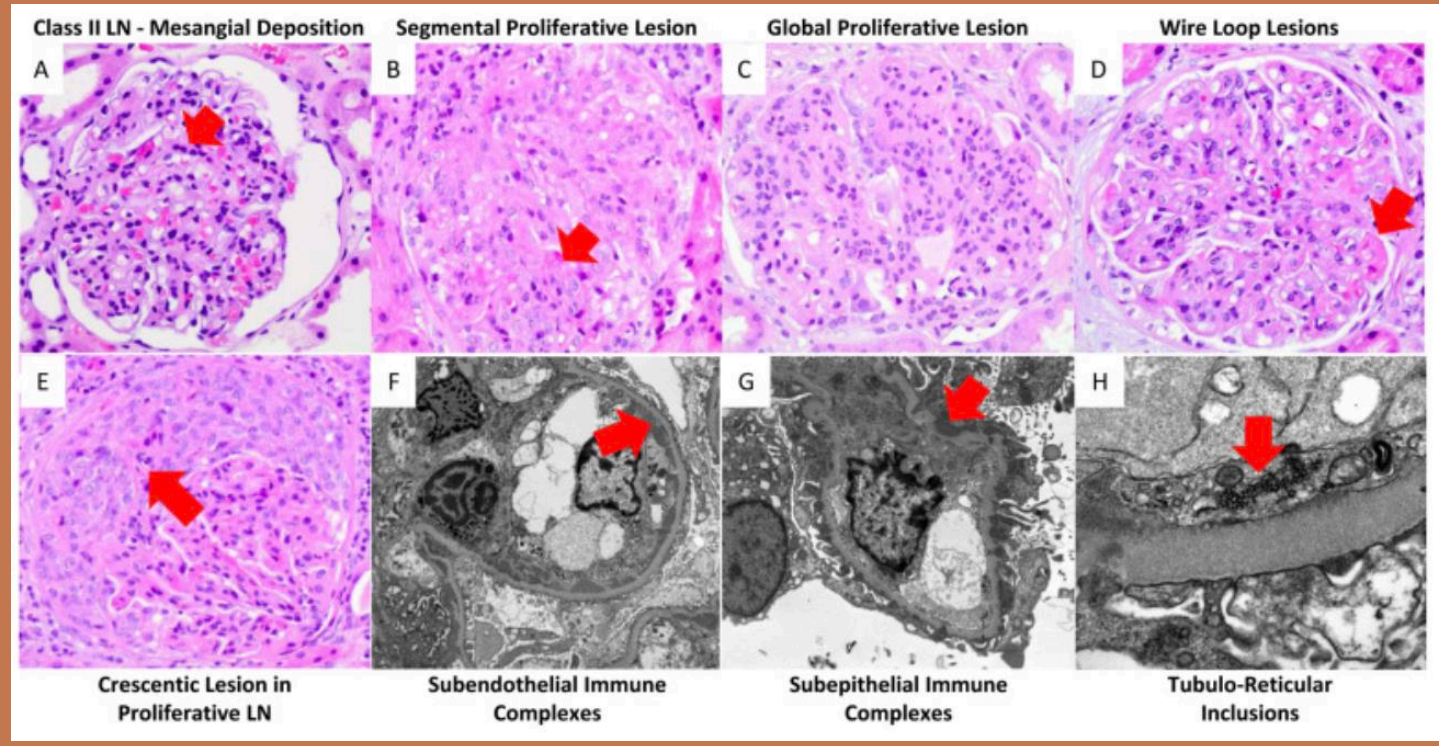
- Renal- the most common besides the skin involvement in kids
- Cardiac
- Pulmonary
- GI
- CNS
- MSK

Lupus Nephritis (LN)

- Significant cause of M&M
- 25-75% of children with SLE will develop LN
  - 18-50% progress to ESRD
  - 80-90% childhood LN develops w/in the 1st year of diagnosis
  - 10-20% of patients, the LN occurs between year 1-2 after diagnosis

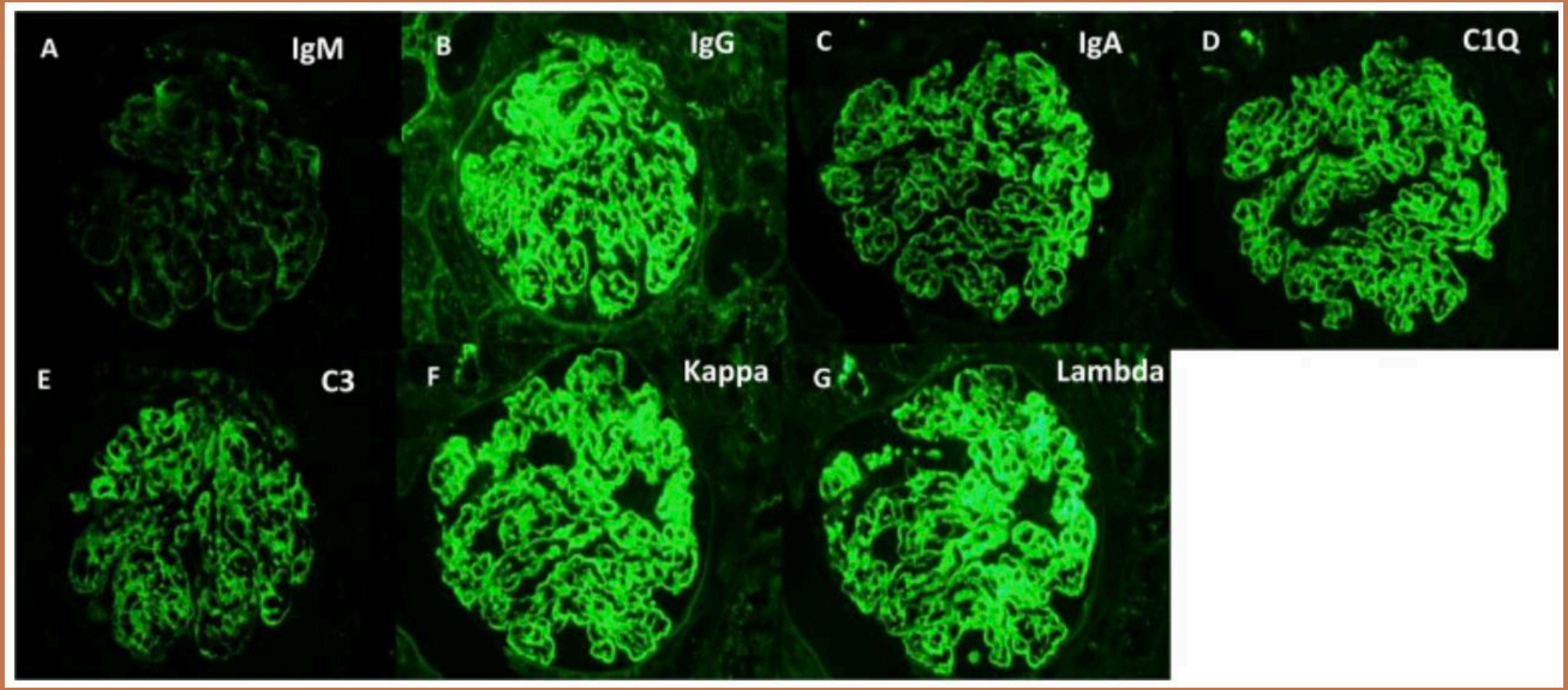
Staging Lupus Nephritis

1. Minimal mesangial
   - Normal Light microscopy
   - Ig or Complement deposits on IF
2. Mesangial proliferative
3. **Focal proliferative GN**
4. **Diffuse proliferative GN**
5. Membranous GN
6. Advanced sclerotic



Classes may overlap
Classification per the ISN and RPS

Lupus Nephritis



- Pathogenesis of LN:
  - Renal formation of ICs (form directly in the kidney and deposit there) not from another site or the blood

Clinical manifestations of LN

- Isolated asymptomatic hematuria and/or proteinuria
- Acute nephritic syndrome – commonly class III & IV
- Nephrotic syndrome- class III, IV, & sometimes V
- CKD

Note:

- Creatinine can be normal at presentation
- Always check UA with urine Pr/Cr ratio at every visit

- Proteinuria
  - > 0.5 g/day or > 3+
  - or
- Urinary Cellular casts
  - red cell, hemoglobin, granular, tubular, mixed
    - Hematuria >5 RBC/Hpf
    - Pyuria > 5 WBC/hpf

Cardiac

- ~ 30-40% in children
- Pericarditis- The most common
- Myocarditis
- Coronary artery disease-
  - the risk of myocardial infarction in patients with SLE is increased between 9- and 50-fold over that in the general population !!
- Endocarditis:
  - Libman Sachs is rare: sterile- non infectious- vegetations of IC on the valves (most commonly the mitral valve) within the heart.
  - Usually in pts with high disease activity, long ds duration, +APLs

Pulmonary

- Pleuritis- the most common
  - Dyspnea, chest/abdominal pain, pleural effusions on CXR- exudative fluid
- Pneumonitis- rare, life threatening mortality rate 50%
  - Usually with infections, diffuse LL infiltrates. CT- ground glass opacities
- Pulmonary Arterial Hemorrhage- rare, mortality 50%
  - Symptoms vary from mild cough and dyspnea to hemoptysis.
- Pulmonary Embolism
- Pulmonary HTN
- Shrinking lung syndrome

Gastrointestinal

- Pancreatitis
- Mesenteric vasculitis/ lupus enteritis
- Hepatitis- is it lupus or med-related?
- Protein losing enteropathy
  - Suspect if low total protein and albumin, no protein in UA

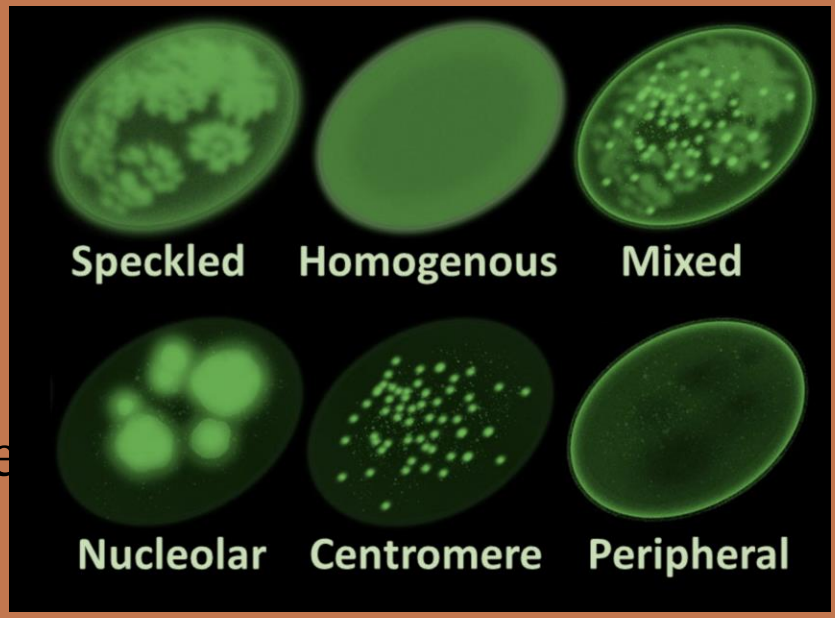
CNS

- Headache
  - Usually severe requiring narcotics
- Psychosis/ lupus cerebritis
  - Hallucinations; visual or auditory
  - Rule out steroid-induced psychosis first
- Stroke and cerebral vein thrombosis
  - Small vessel vasculitis
  - Seizures
  - Focal deficits
  - Need imaging; CT/CTA, MRI/MRA

Musculoskeletal

- Arthritis/ arthralgias- very common
  - Nonerosive, nondeforming arthritis
  - Unless they have “Rhufus” (RA + Lupus)
  - Peripheral joints
- Myositis/ myalgia

Labs/ investigations



- **ANA- antinuclear antibody**
  - Developed to screen for SLE
    - 99% of children with SLE have a positive
    - Very sensitive
  - Can be positive in other conditions:
    - 25% healthy population
    - Thyroid disorders
    - Infections, malignancies
  - Different patterns
  - The level of ANA is not that important as long as it is positive >1:80

Labs

- **Hematologic**
  - Anemia- the most common is anemia of chronic disease
    - AIHA, +coombs test
  - Leukopenia- commonly lymphopenia
  - Thrombocytopenia

Labs

- **<u>Antibodies</u>**:
  - DsDNA
    - High specificity
  - ENA- Extractable Nuclear Antigens:
    - SSA/B, RNP, and smith
    - Smith high specificity
    - SSA/B- neonatal lupus
    - RNP- MCTD, and SLE
  - **<u>Complement</u>**
    - NPV for disease activity
    - C3, C4

- **<u>Antiphospholipid antibodies</u>**
  1. Lupus anticoagulant; misnomer- more specific in predicting risk of thrombosis
  2. Beta 2 glycoprotein
  3. Anticardiolipin
- Can be transiently positive in:
  1. 25% of healthy peds
  2. Infections, malignancy, & with certain medications.
- *Should be repeated in 3 months.*

Question

- You have a patient with a new diagnosis of SLE in your clinic and need to discuss with the family a medication that is frequently given in management of SLE. This medication has the ability to reduce inflammation, prevent disease flares, and protect organ damage. What medication is this?
  a) Steroids
  b) Plaquenil/ hydroxychloroquine
  c) Methotrexate
  d) IVIG
  e) Cyclophosphamide

Management

- Sun protection
- Antimalarials- for all SLE patients
    - Need regular eye exams due to risk of retinal toxicity
- Steroids (PO, IV, topicals)
- Immunosuppressants/anti-inflammatory
    - Cytotoxics/ DMARDs
    - Calcineurin inhibitors
    - Biologics

Management Principles

- Treat acute events
- Prevent flares- maintenance

Guided by:

Type & degree of organ involvement

- Steroids
  - Dose depends on disease activity
    - High dose with slow taper
- Steroid-sparing immunosuppression
    - Plaquenil (skin)
    - Azathioprine (cytopenias)
    - Methotrexate (joints)
    - Mycophenolate (GN)
    - Cytoxan (DPGN, cardiac, CNS)
    - Biologics (CNS, DPGN, AIHA)

Question

- A **6-week-old** girl is noted to have multiple **annular, erythematous, scaly plaques** on the head and neck. On physical examination, a **heart rate of 40 bpm** is noted.
- **These findings are most likely the result of which of the following complications during pregnancy?**

A. Maternal transfer of rubella virus .
B. Maternal transfer of anti-SSA/anti-SSB antibodies
C. Asymptomatic primary maternal toxoplasmosis
D. Vertical transmission of HIV-1 from mother to child
E. Maternal transfer of varicella virus

Neonatal lupus- pearls

- The name is misleading because the affected newborn does not have SLE and the mother is frequently healthy
- Clinical manifestations:
  - Cardiac
  - Dermatologic
  - Hepatic/ heme

- **Cardiac**: the most clinically significant manifestation of neonatal lupus.
  - The most frequent cause of congenital heart block (CHB).
  - 3rd degree--> pace maker
  - High titer of anti-Ro rather than the presence of these abs is a requirement for cardiac NLE.
  - Incidence of fetal CHB - 1-2% in mothers who had anti-Ro abs and a known AI disease. I
  - Incidence increased to 15% for those with a previously affected child with CHB
  - Mortality 20%

- **Cutaneous lesions** -> noted at birth or first few weeks
  - photosensitive
  - Annular, papulosquamous (discoid lesions)
  - Transient, usually resolve by 6 months

- **Liver/heme**
  - elevated serum transaminases, hepatomegaly
  - leukopenia, thrombocytopenia (most common), and anemia
  - caused by transplacental passage of maternal Ro (SSA), La (SSB)

SLE emergencies

- Pericardial effusion with tamponade
- Macrophage activation syndrome
- Infections
  - Suspect with high CRP, high fever
- Pulmonary hemorrhage
- PRES (posterior reversible encephalopathy syndrome)
- AVN- steroid induced
- Stroke/ PE

pSLE morbidity and mortality

- Morbidity
  - Infections
  - Steroids

- Mortality
  - Infection
  - Renal failure
  - Cardiac

Is this SLE?

- 13 year old female with a 1-month history of weight loss and intermittent fever. Exam showed: palatal ulcers and swelling of the joints of her hands and knees.
- Labs:
  - +ANA (1:640)
  - +anti-smith
  - Low complements C3/C4

Is this SLE?

- 12 year old male with a 1-year history of hypertension, 2-week history of bilateral ankle swelling.
- His labs showed:
  - +ANA (1:640)
  - Low C3/C4
  - UA with +2 protein, numerous RBCs, +hyaline casts, Pr/Cr 1
  - ECHO: pericardial effusion

Question

- 14 year old female with anxiety and depression, presents with arthralgias for 3 months. She has pain all over with swelling in her face, hands, and feet for a few hours at a time. She has lost 3 kg in the last year with no GI symptoms.
- Exam: palatal petechiae, bilateral wrist swelling, faint erythematous cheeks, +2 pitting edema of LL.
- Labs show +ANA, +dsDNA ab, smith ab, low C3 & C4, and anemia.
- What is another important/urgent study to obtain based on this patient's presentation?
    a) ECHO
    b) Direct coombs
    c) ESR
    d) UA with Pr/Cr

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