RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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Pediatric Rheumatology Basics for the Novice APP:

Childhood Juvenile Dermatomyositis and Systemic Lupus Erythematosus

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Faculty Disclosures

- Ingrid Pan, PharmD:
  - There are no relevant financial relationships to disclose

- Michelle Sutter, BSN, MSN:
  - There are no relevant financial relationships to disclose

Objectives

1. Review the epidemiology and clinical presentation of Juvenile Dermatomyositis and Systemic Lupus Erythematosus

2. Discuss diagnostics and diagnostic dilemmas specific to Juvenile Dermatomyositis and Systemic Lupus Erythematosus

3. Design an evidence-based pharmacotherapeutic regimen for a pediatric patient with Juvenile Dermatomyositis and Systemic Lupus Erythematosus

Abbreviations

- AVN = avascular necrosis
- cSLE = childhood-onset SLE
- HLA = human leukocyte antigen
- NSAID = Nonsteroidal anti-inflammatory drug
- SLE = Systemic Lupus Erythematosus

JUVENILE DERMATOMYOSITIS (JDM)

Overview

- Accounts for 80% of all children with Idiopathic Inflammatory Myopathies
- Typically affects skin and muscle
  - Most pronounced in proximal muscles
  - Disease manifestations are variable and can involve additional organ systems

Epidemiology

- Occurs in all regions of the world
- Estimated incidence rates in the United States
  - 1995 – 1998: 2.5 – 4.1 cases per million children per year
  - Similar rates among White, African American, non-Hispanics
  - Hispanics have a lower incidence rate
- Peak age of onset: 7 years
- F > M with ratio of 1.6 – 2.5:1

Causes

Etiology is unclear. It appears to be the result of genetic predisposition triggered by environmental factors.

Genetic Background	Environmental Factors
• Certain HLAs are associated and contribute to risk of disease (HLA DRB1*0301, DQA1*0301, DQA1*0501) • Non-HLA genes are also associated including genetic polymorphisms in tumor necrosis alpha (TNF-a-308A and TNF-a-238GG) and interleukin-1 receptor antagonist (IL-1-A1 and IL-1-A3)	• Unusual sun exposure • NSAID use in preceding 6 months • Hypertensive or psychiatric medications or HPV vaccine within 6 months • Infections: >50% with respiratory symptoms, 30% with GI symptoms in 3 months preceding

Baseline Characteristics from CARRA Registry

Enrollment started in 2019: 119 Subjects from 41 Sites

Table 1 Demographics and diagnostic features ($N = 119$)

Age at diagnosis in years, median (IQR)	8 (4.0–11.5)
Age at disease onset in years, median (IQR)	7 (3.5–7.5)
Time to diagnosis in months, median (IQR)	3 (1–6.5)
Female, N (%)	76 (63.4)
Race or Ethnicity[a], N (%)	
White	86 (72.3)
Hispanic, Latino, or Spanish origin	22 (18.5)
Black, African American, African, or Afro-Caribbean	9(7.6)
Asian	7(5.9)
Native American, American Indian or Alaskan Native	3 (2.5)
Middle Eastern	3 (2.5)
Unknown[b]	3 (2.5)
Other[c]	4 (3.4)
Concomitant Medical History, N (%)[d]	22 (16.8)
Family History of Autoimmunity, N (%)[e]	25 (21)
Skin Predominant JDM, N (%)	38 (31.9)
History of, N (%)	
Proximal Muscle Weakness	86 (72.3)
Rash (Heliotrope or Gottron's)	110 (92.4)
Elevated muscle enzymes	99 (83.2)
EMG performed	4 (3.4)
Muscle Biopsy performed	19 (16)
MRI performed	81 (68.1)
Autoantibodies, proportion[f]	
ANA	75/96 (78.1%)
Myositis-specific antibodies	
Anti-MJ/NXP2	11/49 (22.4%)
Anti-p155/140/TIF1-γ	7/53 (13.2%)
Anti-Mi2	6/55 (10.9%)
Anti-MDA5	4/51 (7.8%)
Anti-Jo1	2/67 (3.0%)
Myositis-associated antibodies	
Anti-PM-Scl	3/43 (7.0%)
Anti-Smith	1/56 (1.7%)

CARRA = Childhood Arthritis and Rheumatology Research Alliance

Pediat Rheumatol Online J. 2022 Jul 19; 20 (1): 50

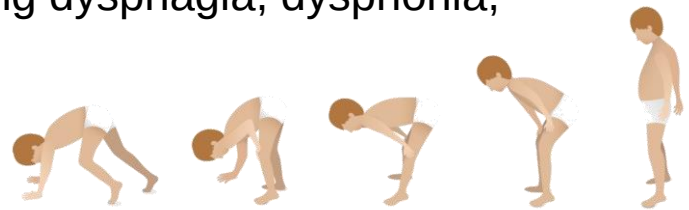
Clinical Manifestations

Constitutional Symptoms

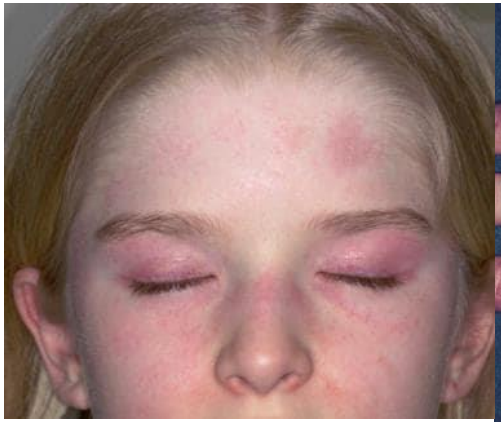
- Fever, fatigue, anorexia, and weight loss
- Occasional lymphadenopathy

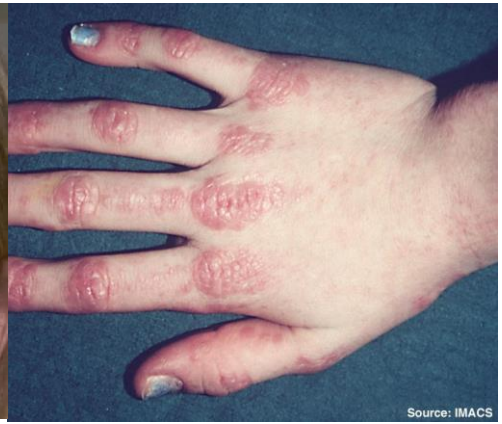
Musculoskeletal Symptoms

- Typically symmetrical
- Limb-girdle musculature, anterior neck flexors, and trunk muscle
- Muscle pain
- Muscle tenderness and edema of overlying subcutaneous tissue of affected muscles
- Palatal and pharyngeal muscle involvement causing dysphagia, dysphonia, aspiration, and reflux
- Respiratory muscle weakness
- Arthritis and tenosynovitis



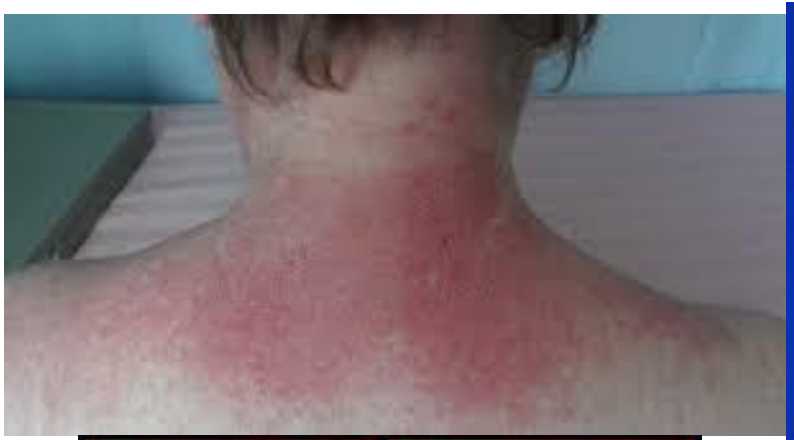
Clinical Manifestations: Mucocutaneous Disease

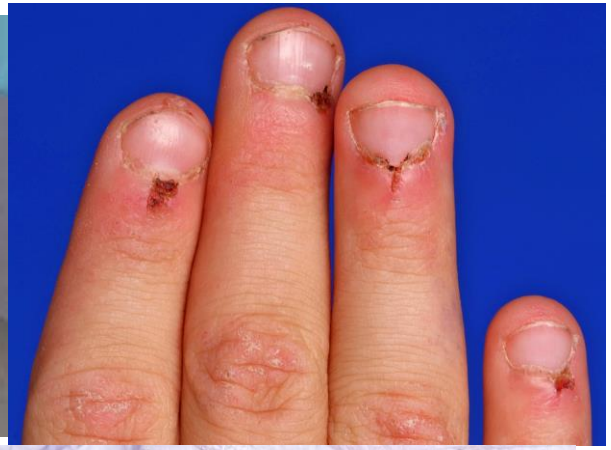


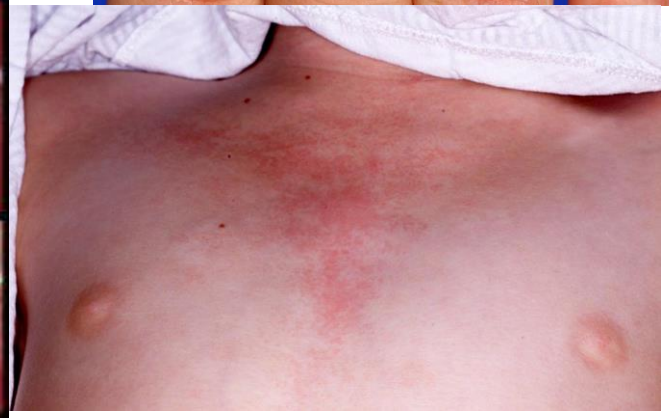


- Heliotrope rash
- Malar rash
- Gottron papules
- Shawl Sign
- V Sign
- Skin ulcerations
- Nailfold capillary change
  - Important diagnostic and prognostic roles
  - More normal nailfold capillary density is associated with shorter disease course
- Calcinosis: more common at pressure points
- Lipodystrophy: 3-10% Often associated with additional symptoms of metabolic abnormalities

Clinical Manifestations: Mucocutaneous Disease







Clinical Manifestations: Cardiopulmonary

Cardiac involvement is rare

- Asymptomatic
- SHARE initiative recommends ECHO and EKG on all new JDM patients

Interstitial lung disease is rare but one of the most serious complications

- Symptoms can be mild or absent
  - PFT's including carbon monoxide diffusion are recommended at baseline
  - High resolution CT is recommended for confirmation
  - Typical HRCT findings in ILD: consolidation, reticulonodular infiltration, ground glass opacities, and peribronchovascular opacities. .Findings are typically symmetrical and in lower lobe
- High association with anti-MDA5 antibodies

Clinical Manifestations: Other

Gastrointestinal Involvement

- Abdominal pain, ulceration, and hemorrhage
- Gut vasculopathy is rare but an important cause of death in JDM. Reports of perforation.
- Abdominal pain or change in stooling may be important clues to GI involvement

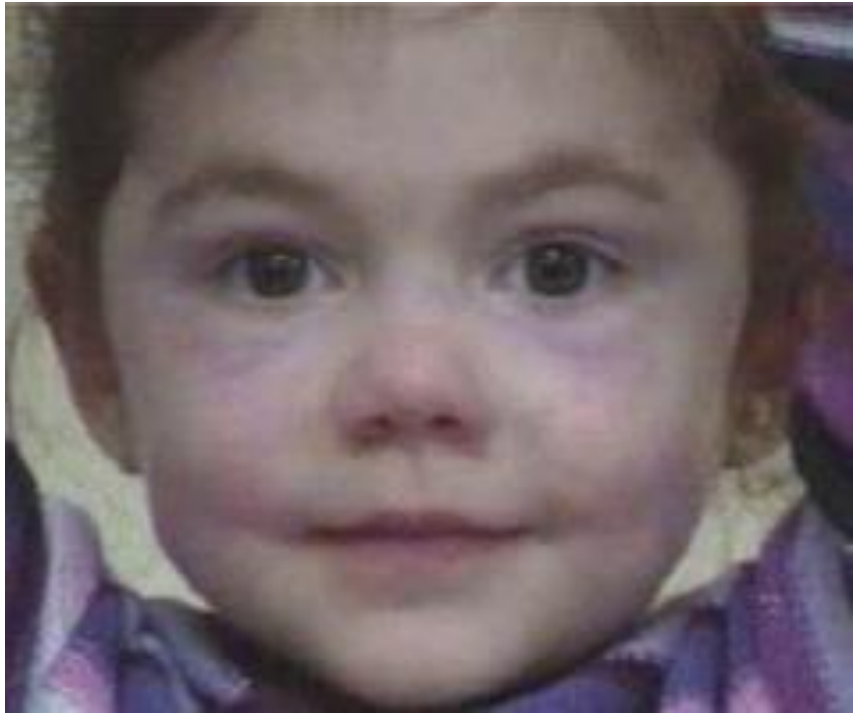
Rare Manifestation

- Neurological: seizures, pseudoseizures, sensory neuropathy, depression, fatal brainstem infarction
- Renal: more common in adults rare in pediatrics (should consider SLE with renal involvement)
- Eye and eyelid: scarring and blepharitis of eyelid, subcapsular cataract (corticosteroid use), retinopathy (rare)

Case Study: Call from Local PCP Office

3 y/o female with history of face and elbow rash not responsive to typical atopic dermatitis treatment.

- MOC has noticed that she will scoot to furniture and use it to help get up off the floor.
- She is also rolling out of bed instead of sitting up.
- She continues to walk without abnormality but seems more clumsy.
- No changes in eating, drinking, or voice quality.
- No recent illness or travel



Differential Diagnosis to Consider

Other Forms of Idiopathic Inflammatory Myopathies

- Amyopathic dermatomyositis
- Juvenile polymyositis
- Myositis with other connective tissue disease (overlap myositis)

Post Infectious Inflammatory Myopathies

- Bacterial: staphylococcal, streptococcal
- Viral: influenza, Coxsackievirus, HIV, adenovirus, Parvovirus B19, Dengue virus
- Fungal: candidiasis, cryptococcosis, histoplasmosis
- Parasitic: trichinosis, cysticercosis, toxoplasmosis

Differential Diagnosis to Consider

Non-Inflammatory Myopathies

- Muscular dystrophies: Duchenne, Becker muscular dystrophy
- Metabolic myopathies: glycogen storage disease, lipid myopathies
- Endocrinological disorders: hypothyroidism, hyperthyroidism, hyperparathyroidism, diabetes
- Toxins
- Drug induced
- Malignancy associated dermatomyositis (rare in pediatrics)

Cutaneous Lesions without Muscle Involvement

- Psoriasis
- Flat warts
- Lichen planus
- Sarcoidosis
- Cutaneous T-cell lymphoma

Making the Diagnosis

Muscle enzymes: CK, LDH, AST, ALT, and aldolase

- Elevated in 80-96% of JDM patients

Other Biomarkers

- CBC is often normal – anemia or leukocytosis is sometimes found
- ESR and CRP may be elevated
- Von Willebrand factor may be increased – not sensitive or specific for active disease

Autoantibodies

- +ANA in 76% of patients – not specific or diagnostic
- Myositis antibodies: anti-p155 and anti-p155/140 most common
- Commonly associated with malignancy in adults not linked with malignancy in pediatrics

Myositis Antibodies

Table 2 Overview of myositis specific antibodies and contribution to clinical decisions.

MSA	Criticality/comment	Relevance/criticality
HMGCoA reductase	The presence of anti-HMGCR antibodies predicts poor response to corticosteroid and immunosuppressant therapy. This anticipation is relevant for the clinician.	Relevant, not critical; however, false negative might lead to omission of biopsy
TIF1y	Strong association with malignancy in elderly patients. Extensive screening for malignancy is necessary prior to treatment of IIM.	Critical, false negative result might lead to delayed diagnosis of cancer
SRP	Associated with severe treatment resistant myopathy, leading to long term immunosuppressive therapy The presence of SRP antibodies predicts poor response to corticosteroid and immunosuppressant therapy. This anticipation is relevant for the clinician.	Relevant, not critical; however, false negative might lead to omission of biopsy
MDA5	Positive result should trigger screening for ILD and if confirmed more aggressive treatment and clinical vigilance	Critical, False negative result may lead to less intensive (respiratory) monitoring with a delay
PM/Scl	In general, associated with a milder disease course	Not critical, low relevance
Ku	Often associated with SLE and/or SSc. Requires monitoring and treatment to coexisting SLE and/or SSc, especially when other antibodies are present (eg, anti-dsDNA).[12]	Relevant, not critical
SAE	Severe cutaneous disease that classically precede DM with severe dysphagia and systemic symptoms.	Relevant, not critical
NXP2	Juvenile DM, diffused calcinosis. Cancer associated DM triggers consideration for screening for concurrent malignancy prior to treatment initiation.	Critical, similar to TIF1y, however, less pronounced
Mi-2	In general, associated with a milder disease course. If present without other MSA, reassures relatively mild disease phenotype.	Relevant, not critical; false positive can lead to a wrong perception of milder disease (no monitoring for ILD)
Jo-1, EJ, OJ, PL-7, PL-12	Positive result triggers the clinician to screen for ILD and to prospectively follow-up pulmonary function; often requires long-term immunosuppressive treatment ► Predicts better therapeutic response to rituximab[13] ► Influences patient management when pulmonologists identify these antibodies in patients with unexplained ILD ► Consider immunosuppressant strategies ► Follow-up for appearance of extra-pulmonary manifestations of the antisynthetase syndrome[14]	Relevant, not critical; False negative results might have a negative effect on optimal therapy choice in severe myositis (more arguments for rituximab) and patients with unexplained ILD (as single manifestation) might experience delay in diagnosis.

DM, dermatomyositis; IIM, idiopathic inflammatory myopathies; ILD, interstitial lung disease; MSA, myositis specific antibodies; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

Textbook of Pediatric Rheumatology

Muscle Biopsy: Gold Standard

- Should always be considered especially in the absence of typical rash
- A muscle biopsy scoring tool has been developed and validated by International Juvenile Dermatomyositis Biopsy Consensus Group
  - Consists of four domains: inflammatory, vascular, muscle fiber, and connective tissue
  - Can be used on biceps and quadriceps muscle biopsy

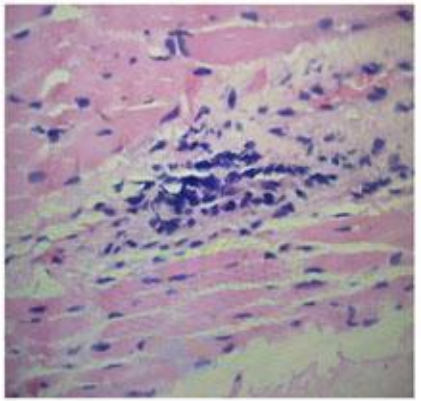
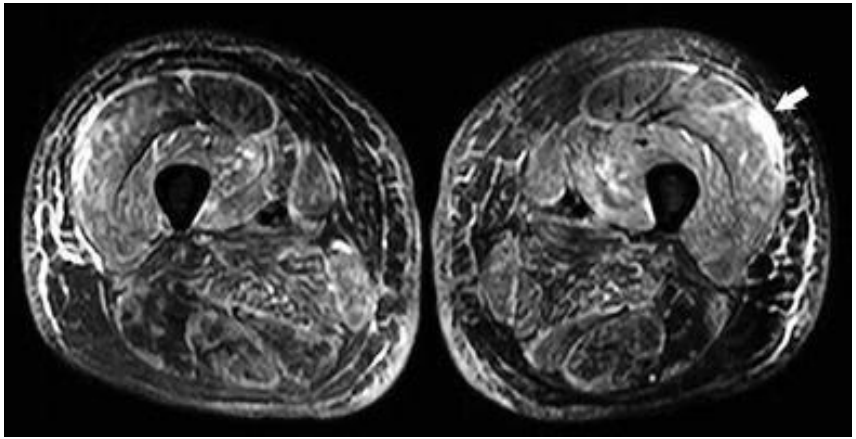


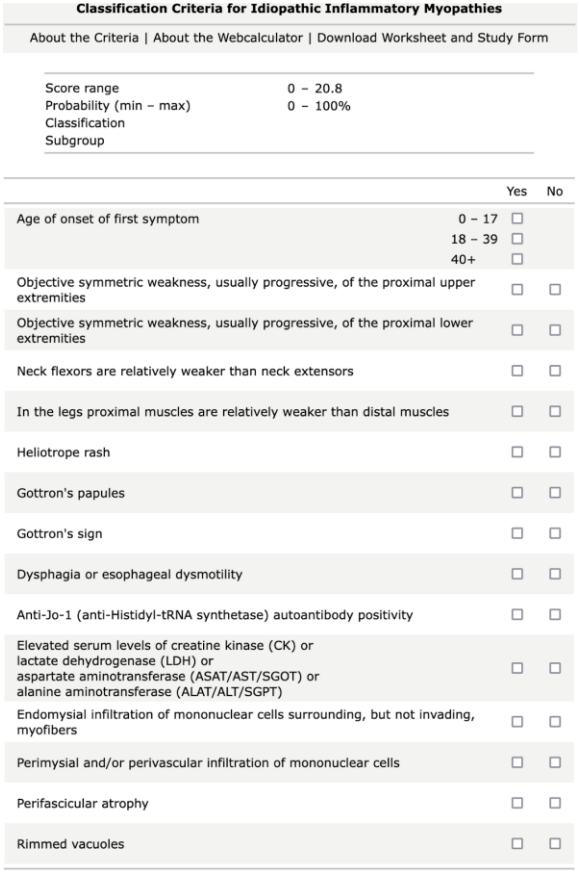
Fig. 2. Juvenile dermatomyositis: skeletal muscle biopsy with characteristic perivascular mononuclear cell infiltrate (HE, x400)

Imaging



- Plain radiographs: identifying and determining the extent of calcinosis, screening for pulmonary involvement
- MRI: important for diagnosing and monitoring myositis activity
  - IV contrast is not necessary
  - T2 weighted imaging and fat suppression reveal soft tissue edema and active disease
  - T1 weighted sequences detect muscle atrophy and fatty infiltration of chronic disease
  - STIR whole body sequences can also visualize subcutaneous tissue and myofascial tissue abnormalities in areas that are clinically undetected
- HRCT: used to diagnose ILD

2017 EULAR/ACR Classification Criteria for Idiopathic Inflammatory Myopathies



Classification Criteria for Idiopathic Inflammatory Myopathies

About the Criteria | About the Webcalculator | Download Worksheet and Study Form

Score range	0 – 20.8
Probability (min – max)	0 – 100%
Classification	
Subgroup	

		Yes	No
Age of onset of first symptom	0 – 17	☐	
	18 – 39	☐	
	40+	☐	
Objective symmetric weakness, usually progressive, of the proximal upper extremities		☐	☐
Objective symmetric weakness, usually progressive, of the proximal lower extremities		☐	☐
Neck flexors are relatively weaker than neck extensors		☐	☐
In the legs proximal muscles are relatively weaker than distal muscles		☐	☐
Heliotrope rash		☐	☐
Gottron's papules		☐	☐
Gottron's sign		☐	☐
Dysphagia or esophageal dysmotility		☐	☐
Anti-Jo-1 (anti-Histidyl-tRNA synthetase) autoantibody positivity		☐	☐
Elevated serum levels of creatine kinase (CK) or lactate dehydrogenase (LDH) or aspartate aminotransferase (ASAT/AST/SGOT) or alanine aminotransferase (ALAT/ALT/SGPT)		☐	☐
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		☐	☐
Perimysial and/or perivascular infiltration of mononuclear cells		☐	☐
Perifascicular atrophy		☐	☐
Rimmed vacuoles		☐	☐

Classification	Probability	Score
Definite	> 90%	• > 7.5 without biopsy • > 8.7 with biopsy
Probable	55 – 90%	• 5.5 – 7.5 without biopsy • 6.7 – 8.7 with biopsy
Possible	50 – 55%	• <5.3 without biopsy • <6.5 with a biopsy

- Patients who meet criteria and have rash are classified as JDM
- Those <u>without</u> required rash criteria are classified as juvenile myositis other than JDM

Monitoring Disease Activity

- Muscle strength
  - Manual muscle testing (MMT8)
  - Childhood Myositis Scale (CMAS)
- Functional Ability: Childhood Health Assessment Questionnaire (CHAQ) = 30 item self report survey regarding activities of daily living
- Global Disease Activity: Physician (Provider) and Patient Global Assessments of Disease Activity

Monitoring Disease Activity

MMT-8 for RIM Trial

Muscle Groups	Right (0 – 10)	Left (0 – 10)	Axial (0 – 10)
Axial Muscles (0 – 10)			
Neck Flexors			0-10
Proximal Muscles			
Deltoid	0-10	0-10	
Biceps brachii	0-10	0-10	
Gluteus maximus	0-10	0-10	
Gluteus medius	0-10	0-10	
Quadriceps	0-10	0-10	
Distal Muscles (0 – 40)			
Wrist Extensors	0-10	0-10	
Ankle dorsiflexors	0-10	0-10	
MMT-8 score (0 – 150)	**0-70**	**0-70**	

MMT-8 is a set of 8 designated muscles with a potential score = 150

IMACS FORM 05c:
CHILDHOOD MYOSITIS ASSESSMENT SCALE (CMAS) SCORING SHEET

Subject's IMACS number _____
Assessor _____
Date of assessment (mm/dd/yy) _____
Assessment number _____

1. **HEAD LIFT:**
0 = Unable 3 = 30-59
1 = 1-9 sec 4 = 60-119 sec
2 = 10-29 5 = ≥ 2 min # of sec ___

2. **LEG RAISE/TOUCH OBJECT:**
0 = Unable to lift leg off table.
1 = Able to clear table, but cannot touch object (examiner's hand).
2 = Able to lift leg high enough to touch object (examiner's hand).

3. **STRAIGHT LEG LIFT/DURATION:**
0 = Unable 3 = 30-59 sec
1 = 1-9 sec 4 = 60-119 sec
2 = 10-29 sec 5 = ≥ 2 min #of sec ___

4. **SUPINE TO PRONE:**
0 = Unable. Has difficulty even turning onto side; able to pull right arm under torso only slightly or not at all.
1 = Turns onto side fairly easily, but cannot fully free right arm and is unable to fully assume a prone position.
2 = Easily turns onto side; has some difficulty freeing arm, but fully frees arm and fully assumes a prone position.
3 = Easily turns over, fully frees right arm with no difficulty.

5. **SITS-UPS:**
Hands on thighs, with counterbalance ___
Hands across chest, with counterbalance ___
Hands behind head, with counterbalance ___
Hands on thighs, without counterbalance ___
Hands across chest, without counterbalance ___
Hands behind head, without counterbalance ___
Total Sit-up Score (0-6) ___

6. **SUPINE TO SIT:**
0 = Unable by self.
1 = Much difficulty. Very slow, struggles greatly, barely makes it. Almost unable.
2 = Some difficulty. Able, but is somewhat slow, struggles some.
3 = No difficulty.

7. **ARM RAISE/STRAIGHTEN:**
0 = Cannot raise wrists up to the level of the A-C joint.
1 = Can raise wrists at least up to the level of the A-C joint, but not above top of head.
2 = Can raise wrists above top of head, but cannot raise arms straight above head so that elbows are in full extension.
3 = Can raise arms straight above head so that elbows are in full extension.

8. **ARM RAISE/DURATION:** Can maintain wrists above top of head for:
0 = Unable 3 = 30-59 sec
1 = 1-9 sec 4 = ≥ 60 sec
2 = 10-29 sec #of sec ___

The **maximum possible total score** for the 14 maneuvers is **52** (52 "points of muscle strength/function").

TOTAL CMAS SCORE: _____

9. **FLOOR SIT:** Going from a standing position to a sitting position on the floor:
0 = Unable. Afraid to even try, even if allowed to use a chair for support. Child fears that he/she will collapse, fall into a sit, or harm self.
1 = Much difficulty. Able, but needs to hold onto a chair for support during descent. Unable, or unwilling to try if not allowed to use a chair for support.
2 = Some difficulty. Can go from stand to sit without using a chair for support, but has at least some difficulty during descent. May need Gower's. Descends somewhat slowly and/or apprehensively; may not have full control or balance as maneuvers into a sit.
3 = No difficulty. Requires no compensatory maneuvering.

10. **ALL FOURS MANEUVER:**
0 = Unable to go from a prone to an all-fours position.
1 = Barely able to assume and maintain an all-fours position. Unable to raise head to look straight ahead.
2 = Can maintain all-fours position with back straight and head raised (so as to look straight ahead). But, cannot creep (crawl) forward.
3 = Can maintain all-fours, look straight ahead and creep (crawl) forward.
4 = Maintains balance while lifting and extending one leg.

11. **FLOOR RISE:** Going from a kneeling position on the floor to a standing position:
0 = Unable, even if allowed to use a chair for support.
1 = Much difficulty. Able, but needs to use a chair for support. (Unable if not allowed to use a chair.)
2 = Moderate difficulty. Able to get up without using a chair for support, but needs to place one or both hands on thighs/knees or floor. (Unable without using hands.)
3 = Mild difficulty. Does not need to place hands on knees, thighs or floor, but has at least some difficulty during ascent.
4 = No difficulty.

12. **CHAIR RISE:**
0 = Unable to rise up from chair, even if allowed to place hands on sides of chair seat.
1 = Much difficulty. Able, but needs to place hands on sides of seat. Unable if not allowed to place hands on sides of seat.
2 = Moderate difficulty. Able, but needs to place hands on knees/thighs. Does not need to place hands on sides of seat.
3 = Mild difficulty. Does not need to place hands on seat, knees or thighs but has at least some difficulty during ascent.
4 = No difficulty.

13. **STOOL STEP:**
0 = Unable.
1 = Much difficulty. Able, but needs to place one hand on exam table (or examiner's hand).
2 = Some difficulty. Able, does not need to use exam table for support, but needs to use hand on knee/thigh.
3 = Able. Does not need to use exam table or hand on knee/thigh.

14. **PICK-UP:**
0 = Unable to bend over and pick up pencil off floor.
1 = Much difficulty. Able, but relies heavily on support gained by placing hands on knees/thighs.
2 = Some difficulty. Has some difficulty (but not "much-difficulty"). Needs to at least minimally and briefly place hand(s) on knees/thighs for support. Is somewhat slow.
3 = No difficulty. No compensatory maneuver necessary.

Disease Course, Prognosis, and Outcome

Disease Course

- ⅓ of patient have a monocyclic course and reach remission without relapse
- 3 – 30% have polycyclic course
- 30 – 60% continue to have active disease despite treatment
- Median time to remission is 4.7 years
- MSK involvement typically resolves sooner than skin involvement

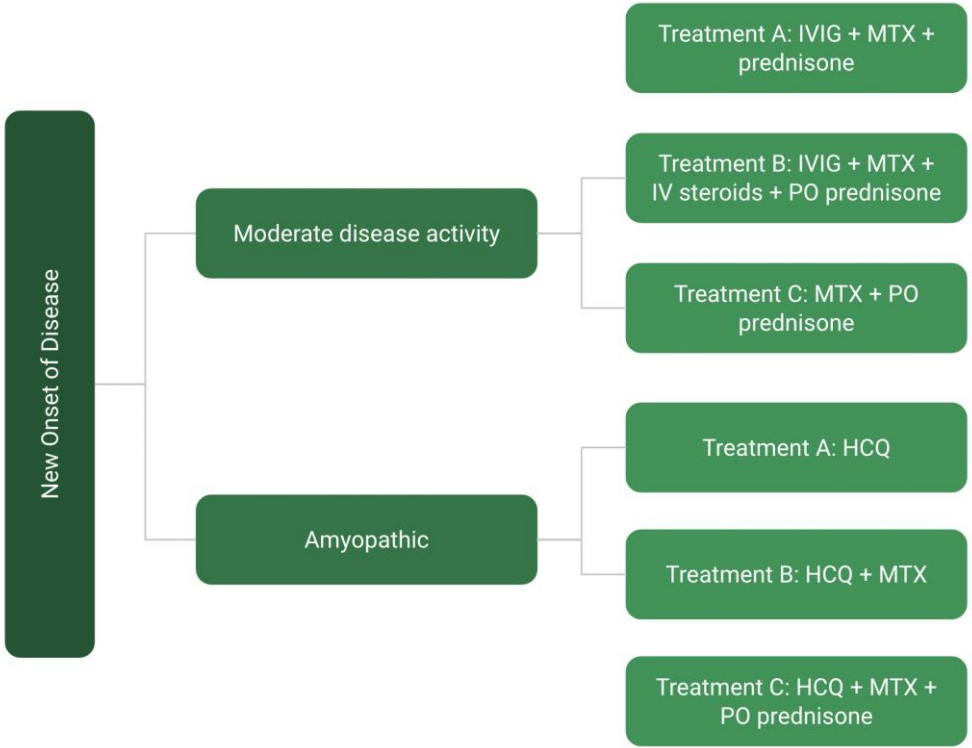
Prognosis and Outcomes

- Presence of rash 3 months after diagnosis and abnormal nailfold capillaries and rash at 6 months are predictor of longer time to remission
- Mortality rate has decreased from >30% to less than 5%
- Causes of death: GI vasculopathies, pulmonary disease, cardiovascular events, superimposed infections

Non – Pharmacological Treatment

- Sun avoidance
  - Sunscreen protective against UVA and UVB rays: SPF 30 or higher
  - Sun protective clothing
- Vitamin D and calcium Supplementation
- Physical Therapy and Occupational Therapy

Initial Treatment



MTX = methotrexate, IV = intravenous, PO = oral, HCQ = hydroxychloroquine

Arthritis Care Res. 2010 Feb;62(2):219-25
Pediatr Rheumatol Online J. 2017 Jan 11;15(1):1.
Ann Rheum Dis. 2017 Feb;76(2):329-340.

Corticosteroid – Sparing Agents

Medication Name	Dosing	Clinical Pearls
IVIG	2 g/kg/dose (Max: 70 g) every 2 weeks x 3 doses, then monthly	• 2 g/kg/dose is typically given over a period of 2 days to minimize risk for infusion reaction and adverse effects • Adverse effects are typically associated with individual IVIG product
Mycophenolate mofetil	10 mg/kg/dose BID OR 600 mg/m^2/dose BID	• Used if patient is intolerant to MTX • Preferred agent for persistent skin disease
Cyclosporine	3 – 5 mg/kg/day BID	• Used if patient is intolerant to MTX • Therapeutic goal: no current consensus • Adverse effects: hypertrichosis, hypertension, hirsutism, abdominal pain
Rituximab	• BSA ≤1.5 m^2: 575 mg/m^2 • BSA > 1.5 m^2: 750 mg/m^2 (Max: 1 g/dose)	• Dosing frequency variable • Effects lasts ~ 6-9 months • Timing of vaccinations

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Corticosteroid – Sparing Agents (Continued)

Medication Name	Dosing	Clinical Pearls
Cyclophosphamide	500 mg/m^2/dose (Max: 500 mg) IV every 2 weeks x 3, then 750 mg/m^2 (Max: 1.2 g) every 3 – 4 weeks	• Role in therapy: severe or refractory disease • Demonstrated to result in improvement in global disease, muscle disease, and skin disease activity
Hydroxychloroquine	5 mg/kg/day (Max: 400 mg)	Reserved for skin-predominant disease
Tacrolimus	Topical: Apply to affected area twice daily Oral: 3 – 5 mg/kg/day every 12 hours	• Topical: recalcitrant cutaneous lesions • Oral: aim for therapeutic trough goal of 5 – 15 mcg/mL
JAK inhibitors	Variable	• Agents: ruxolitinib, baricitinib, tofacitinib • Black Box Warning: increased risk of major cardiovascular events

Rheumatol (Oxford). 2004. 43:491-496
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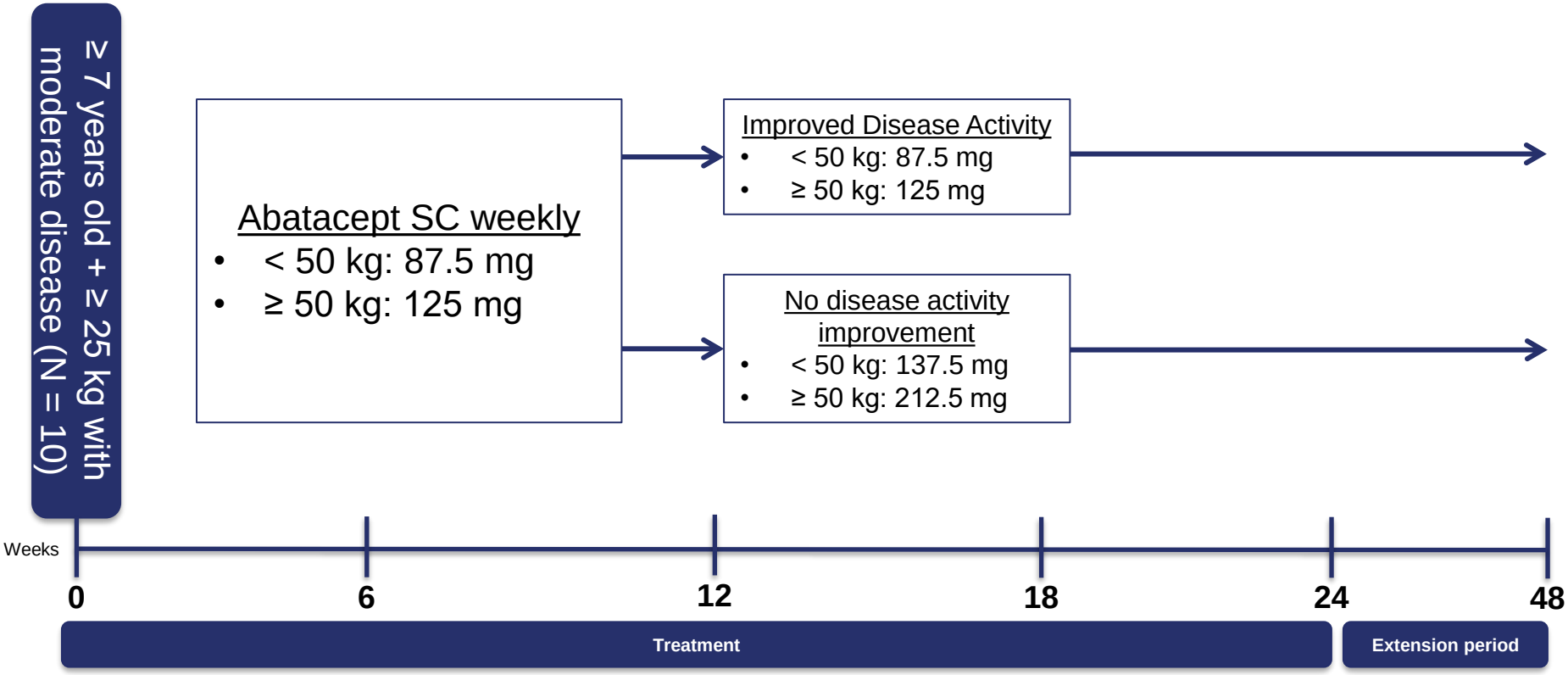
Ann Rheum Dis. 2017 Feb;76(2):329-340.
Clin Rheumatol. 2008 Nov;27(11):1469-71.
Rheumatology (Oxford). 2021 Dec 1;60(12):5801-5808.

Newer Agent: Abatacept



Arthritis Rheumatol. 2023 Jul;75(7):1229-1237

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Overview

- Childhood-onset SLE is a heterogeneous autoimmune inflammatory condition
- Any organ system is fair game
  - Organ damage can occur all at once or sequentially
  - Flares of the disease can be unpredictable
- Morbidity and mortality is **higher in cSLE** than in adult-onset SLE
- Requires a multi-disciplinary approach to care
  - Involving patient/family in management is key

Epidemiology

Incidence

- 0.36-2.5 per 100,000 persons
- Varies by ethnicity and location

Prevalence

- 4-250 cases per 100,000 persons
- Greater prevalence in Native Americans, Asian Americans, Latin Americans and African Americans

Females > Males: 4.5:1

- Compared to 10:1 in adult population
- Difference is attributed to hormone status differences in childhood
- 10 – 20% of all people who develop SLE are diagnosed in childhood
- Average age of onset: 12 years – rare cases occurring age < 5 years old

Pathophysiology

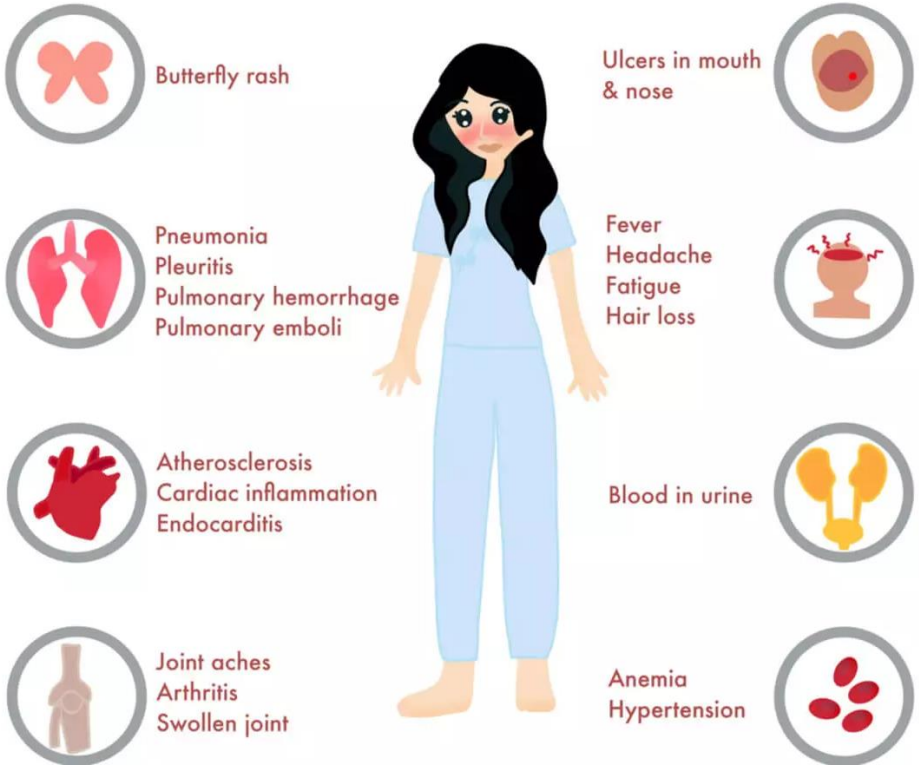
- Complex disease of immune dysregulation with alterations in both innate and adaptive immunity
- Monogenic causes include complement deficiencies, genetic overproduction of interferon alpha, and apoptosis defects
- Genetics, hormones, environmental factors (UV radiation, viral infection, drugs, smoking, pesticides, heavy metals) play a role

Clinical Presentation

Presenting signs and symptoms can vary widely

- Insidious onset with worsening over weeks to months
  - Persistent fever, weight loss, fatigue, arthralgia
- If onset <10 years of age may have more severe disease and poor prognosis
- Major organ involvement usually occurs in 1st 2-3 years of disease onset
- Severe/life-threatening presentations:
  - Macrophage activation syndrome (MAS)
  - Severe renal disease
  - Severe neuropsychiatric manifestations
  - Acute thromboemolic disease

Systemic LUPUS Erythmatosus (SLE)



Systemic Manifestations

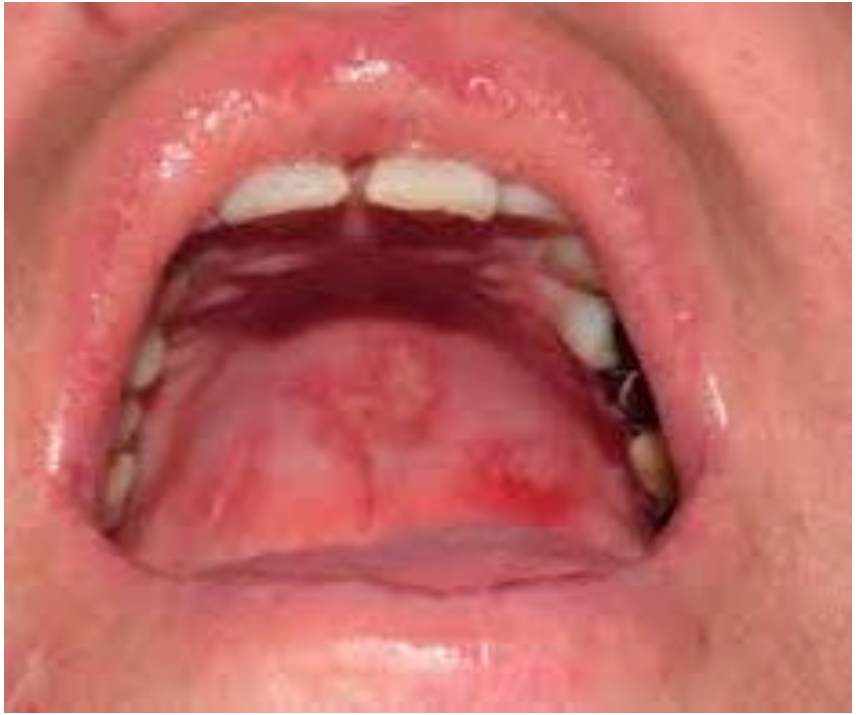
- Low grade fever
- Fatigue
- Anorexia
- Lymphadenopathy
- Persistent high fever (>101.5) – *Consider infection and/or MAS*

Hematologic Clinical Manifestations

- Anemia: 50 – 75%
- Leukopenia
  - ⅔ of cSLE affected at some point
  - Usually due to a fall in the absolute lymphocyte count
  - Neutropenia is less common
- Thrombocytopenia: 10 – 50%
  - **ITP** may pre-date the diagnosis of SLE by many years

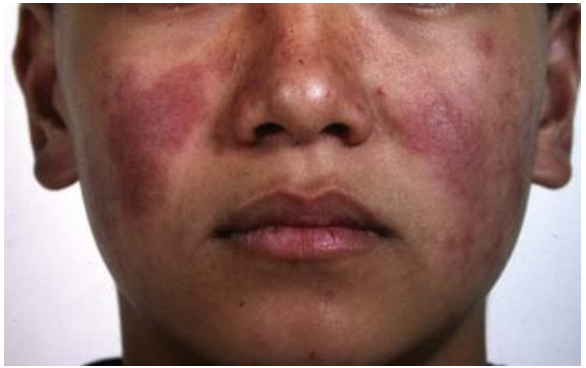
Mucocutaneous Manifestations

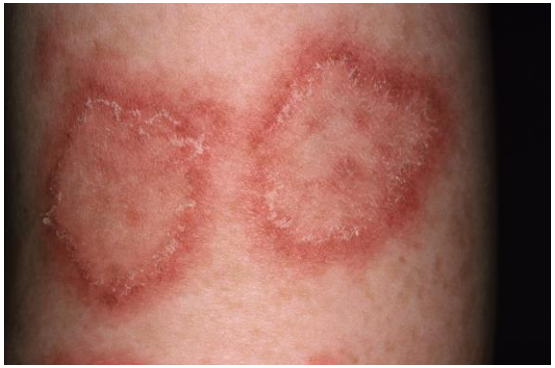
- **Occurs in 70% of cSLE patients**
- **Oral and/or nasal ulcers**
  - Palatal erythema
- **Alopecia –** common manifestations
  - Thinning of hair in the frontotemporal areas
  - “Lupus Hair”: unruly hair that fractures easily
  - ≥ 1 localized patches of alopecia areata

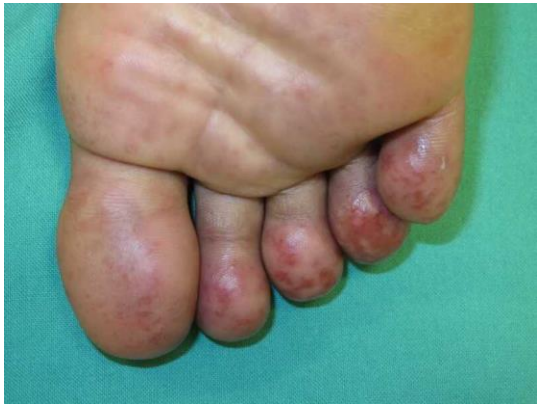


Mucocutaneous Manifestations: Cutaneous Lesion Classifications

- **Acute cutaneous (ACLE)** - *most common lesion in children*
  - Malar rash, generalized maculopapular rash
- **Subacute cutaneous (SCLE)**
  - Subacute cutaneous, polycyclic rash
- **Chronic cutaneous**
  - Discoid lupus (DLE), lupus profundus, Chilblain lupus lesions
  - DLE progresses to SLE in 25% of patients







Musculoskeletal Manifestations

Arthritis & Arthralgias (61-64%)

- Large and small joints
- May be asymptomatic
- Typically non-destructive, unless associated with a +RF (“Rhupus”)

Osteonecrosis/AVN

- Common areas: vertebrae and hip

Renal Manifestations

Renal involvement is a significant cause of morbidity and mortality (adults and children)

- Incidence: 20-75% of children with cSLE
- Prevalence: 50-67% (vs. 24-48% in adults)
- 90% develop within 1st year of diagnosis
- 18-50% progress to end-stage kidney disease

Renal Manifestations

- Proteinuria
  - Spot urine protein:creatinine ratio alternative to 24-hr collection
- Renal insufficiency
  - Increased creatinine or reduced estimated glomerular filtration rate (eGFR)
- Hematuria
- Renal biopsy required for accurate diagnosis

Classification of Lupus Nephritis

Classification	
Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis
Class IV	Diffuse lupus nephritis
Class V	Membranous lupus nephritis
Class VI	Advanced sclerotic lupus nephritis

Arthritis Care Res (Hoboken). 2012 Jun;64(6):797-808.

Neuropsychiatric Manifestations

Most Common

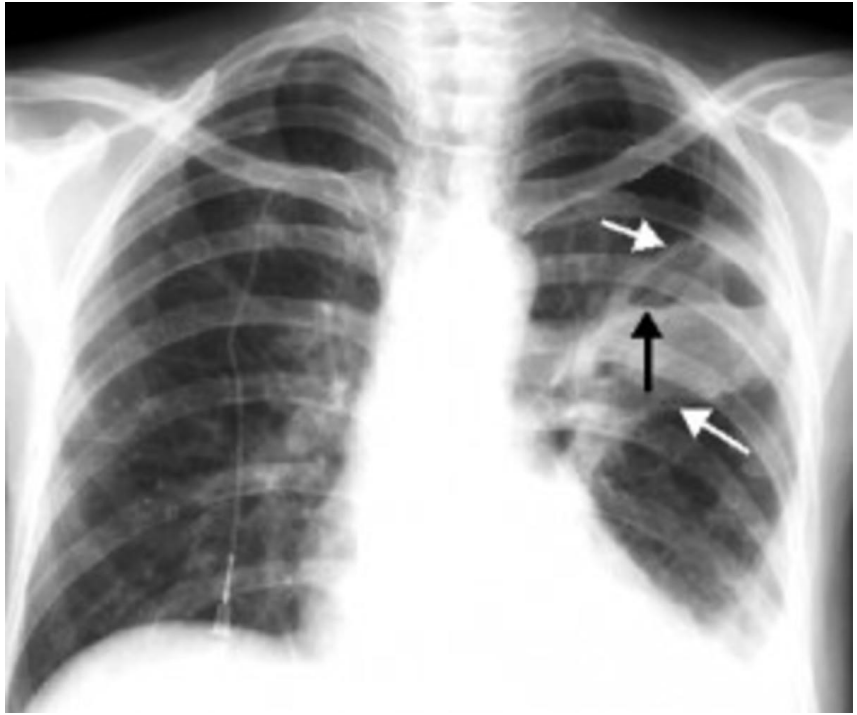
- Headache
- Cognitive impairment
- Psychosis
- Seizure
- Mood disorder
- Anxiety disorders
- Cerebrovascular disease

Less Common

- Acute confusional state
- Peripheral neuropathy
- Chorea
- Cranial nerve palsy
- Transverse myelitis

Pulmonary Manifestations

- 30-50% of patients
- Pleuritis (30-35%) - most common
- Sharp and stabbing localized chest pain, may be severes, worse with deep inspiration
- Plain radiographs - pleural fluid on one or both sides
- Elevated CRP



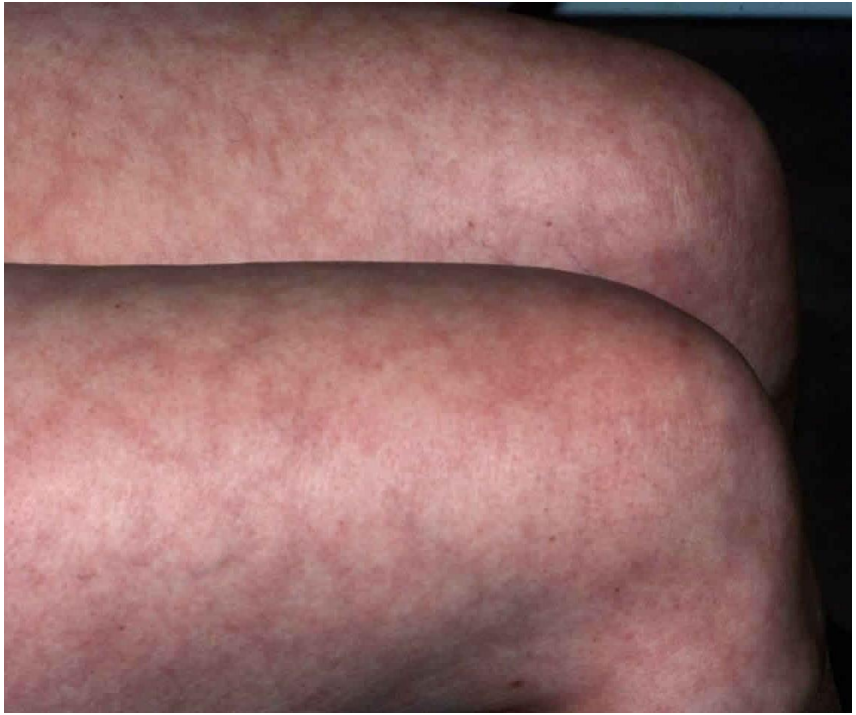
Pulmonary Manifestations

- **Acute pulmonary hemorrhage** (<5%)
  - Acute emergency
  - Fever, cough, fatigue, pallor, tachypnea, epistaxis or hemoptysis
  - Consider if acute SOB and sudden drop in hemoglobin
    - Can include infection and pulmonary embolism
- **Pulmonary hypertension** (<2%)
  - Multifactorial etiology
  - Dyspnea on exertion, fatigue, lethargy, chest pain, exertional syncope, cough, hemoptysis, hoarseness
  - Increasing tricuspid insufficiency on echocardiogram
- **Shrinking lung syndrome**
- **Pneumonitis**

Thromboembolic Manifestations

Antiphospholipids (aPLs)

- ¼ -⅔ of patients with cSLE are positive
- < ½ will have a thrombotic event
- Lupus anticoagulant (LA/LLI): *greatest risk factor for future thrombosis*
- Venous thromboembolic event
  - More common than arterial
  - DVT > Cerebral sinus venous thrombosis (CSVT) > Pulmonary embolism > Arterial stroke



Cardiac Manifestations

Pericarditis

- Most common cardiac manifestation
- Usually presents within the first 6 months of diagnosis
  - Acute, sharp, anterior chest pain associated with dyspnea
  - Low grade fever, tachycardia, tachypnea
  - Pericardial rub
  - High CRP

Large pericardial effusions may be *without symptoms* until they cause *cardiac tamponade*

- Distant heart sounds, pulsus paradoxus, hepatosplenomegaly, jugular venous distention
- Enlarged cardiac silhouette on chest radiograph
- Confirm with ECG

Gastrointestinal Manifestations

GI involvement - 20% of cSLE patients

- Pancreatitis
- Asymptomatic/mild hepatitis
  - Liver enzymes 2-3 x ULN
  - May be present at time of diagnosis
  - Rule out infection
- Autoimmune hepatitis (AIH)
  - May be pre-date diagnosis
  - + Anti-smooth muscle antibodies but *without* anti-liver kidney microsomal antibodies

Case Study: Call from Local PCP Office

Previously healthy 14-year-old female

- 1 month of hand and foot swelling and activity impairment. Obvious ankle swelling and limp. Tenderness and guarding with bilateral wrist flexion
- Currently also being evaluated for idiopathic anemia. Hbg 11.4 with normal ferritin
- Increased epistaxis
- Recent 10lb weight loss
- Faint erythema over bilateral cheeks and nasal bridge
- ESR 54 and CRP <0.1

Differential Diagnosis to Consider

Infection

- Parvovirus
- CMV
- EBV

Malignancies

- Acute lymphoblastic leukemia

Other Rheumatic Conditions

- Mixed connective tissue disease (MCTD)
- Primary Sjögren's Syndrome
- JDM
- Scleroderma
- Granulomatosis with polyangiitis
- Polyarteritis nodosa

Amplified Pain Syndrome

Making the Diagnosis: Laboratory Tests

ESR and CRP

- ESR is typically highly elevated and CRP is normal
- CRP can be elevated with infection, serositis, and arthritis

Ferritin

- Typically elevated but not as significant as in MAS

ANA

- Present in 99% of children with SLE
- Also associated with other rheumatic disease, infections, malignancies, drug exposures, family history of autoimmune disease
- **33% of healthy patients have a positive ANA**

Anti-dsDNA

- High specificity for SLE

Making the Diagnosis: Laboratory Tests

Anti-histone antibodies

- Drug-induced SLE

Anti Ribosomal P antibodies

- Associated with neuropsychiatric lupus

Complements

- Approximately 60% of pediatric lupus patients have a C4 null allele and can not achieve C4 levels above half of the normal range

CBC

- Leukopenia, thrombocytopenia, and anemia are common
- Neutropenia is less common

Coombs

Rheumatoid Factor

Making the Diagnosis: Laboratory Tests

Electrolytes

Liver Function Tests

U/A with Micro

- Protein/Creatinine Ratio

Thyroid function and antithyroid antibodies

Antiphospholipid antibodies

- PTT, RVVT, Beta 2 Glycoproteins IgG, IgA, and IgM, Anticardiolipin Antibodies IgG, IgA, IgM

IgG

Making the Diagnosis: ANA Autoantibodies

Anti-ds DNA

- Specific for SLE
- Indicator of glomerulonephritis

Anti-Smith

- Specific for SLE

Anti-RNP

- Specific for MCTD

Anti-RO/SSA

- Associated with Neonatal SLE and subacute cutaneous lupus
- Present in 32% of SLE patients and 16% of general population
- Associated in Sjogren's disease

Anti-LA/SSB

- Associated with Sjögren's disease and Neonatal SLE

Making the Diagnosis: Imaging and Diagnostics

- Echocardiogram
- Chest X-ray
- Chest CT
- PFT with DLCO
- Kidney Biopsy
- Skin Biopsy
- MRI/MRA
- U/S with doppler

Classification Criteria for SLE

Classification criteria are designed to classify similar patients for *research studies*, not for diagnosis

Clinicians use these criteria to *aid in diagnosis*

Three sets of classification criteria exist:

1997 American College of Rheumatology (ACR)

2012 Systemic Lupus International Collaborating Clinic (SLICC) – more sensitive in early cSLE

2019 European Alliance of Association for Rheumatology & ACR (EULAR/ACR)

ACR Criteria (1997)

Role: Used in adults, can be used in children

≥ 4 of 11 criteria must be present, either serially OR simultaneously at any time *(without other explanation)*

- Malar rash
- Naso-oral ulcers
- Photosensitive rash
- Discoid rash
- Arthritis
- Pleuritis or pericarditis
- Proteinuria (>500 mg/d) or evidence of nephritis in urinalysis
- Hemolytic anemia, thrombocytopenia, leukopenia, or lymphopenia
- Seizure or psychosis
- Positive ANA finding
- Positive anti–double-stranded DNA, anti-Smith, or antiphospholipid antibody/lupus anticoagulant

SLICC Criteria

Requires 4 of 17 clinical criteria + 1 immunologic Criteria

OR

Biopsy Proven Nephritis with +ANA or +DS DNA

Clinical Criteria

- ✓ Acute Cutaneous Lupus
- ✓ Chronic Cutaneous Lupus
- ✓ Oral or nasal ulcers
- ✓ Non-scarring alopecia
- ✓ Arthritis
- ✓ Serositis
- ✓ Renal

Immunologic Criteria

- ✓ ANA
- ✓ Anti-dsDNA
- ✓ Anti-Sm
- ✓ Antiphospholipid
- ✓ Low complement: C3, C4, CH50
- ✓ Direct Coombs test

EULAR/ACR Criteria 2019

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

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

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

Total score:

↓

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

Clinical Outcomes

- Patients with cSLE continue to improve life expectancy
- Cause of death: infection, renal failure, cardiopulmonary disease
- Increased risk of poor cardiovascular outcomes
  - Abnormalities of CV perfusion and atherosclerosis
- Osteoporosis
- Osteonecrosis

Overview of Treatment

1. Treatment goal: minimize disease activity to prevent organ damage from inflammation

2. Treatment approach
   - Induce remission
   - Maintenance therapy

Therapeutic Agents

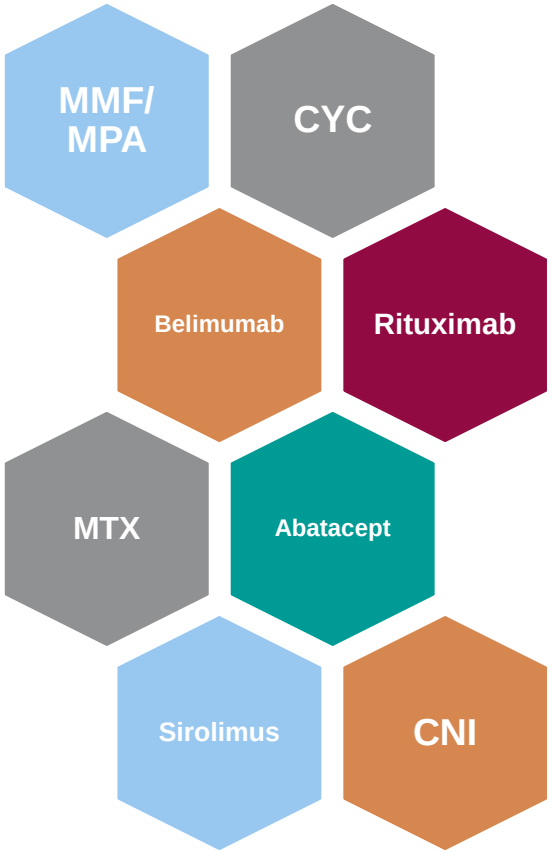
Hydroxychloroquine

±

Corticosteroids

+

Corticosteroid-Sparing Agents



AZA = azathioprine; CNI = calcineurin inhibitor; CYC = cyclophosphamide; MMF = mycophenolate mofetil; MPA = mycophenolate acid; MTX = methotrexate

Special Thanks to Michelle Hicks, FNP-C!!

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