SHOULD I CALL?

A practical approach for calling a rheumatologist for inpatient consult

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DISCLOSURES

- I have participated in Advisory board for Silvergate pharmaceuticals for Xatmep

- I do not plan to discuss this medication or any unapproved or off-label use of this medication

- I will briefly discuss off-label use of FDA approved medications

OBJECTIVES

- Recognize when to consult inpatient vs. refer outpatient
- Identify when the hospitalist should call rheumatology
- Recognize emergencies in patient with rheumatologic conditions

CASE 1

6 y/o male admitted for observation for fever, abdominal pain and palpable purple rash on legs, buttocks

- h/o URI
- +nausea, +ankle pain and swelling; able to ambulate
- - weight loss, vomiting, dysuria or bloody stools
- Labs in ER: CBC/diff with wbc 14 but otherwise normal; ESR 35 (<=15), CRP 10 (<=7.9), CMP w/nl, strep negative

What is the diagnosis?

HSP

What do you want to do?

- UA and spot urine and spot protein: UA clear, UPC 0.18
- Dose of Toradol and feels better next day
- D/C Home to f/up with PCP in 2-3 days

CASE 1: HSP

Do not need to call rheumatology as long as patient responds to supportive care; HOWEVER make sure…

- UA
- Urine pr/cr
- Guidelines for follow up met…

UA, BP schedule

- Weekly x 4 weeks
- Every other week x 2 months
- Monthly x 3 months

NOT SO FAST….CASE2

3 year old female admitted

- Colicky abdominal pain
- b/l wrist and ankle pain
- No fever, no dysuria, no gross hematuria

Exam

- afebrile, BP: 120/95, wt: 50th percentile, height 50th percentile
- petechial rash on buttocks; fussy
- + abdominal tenderness, no rebound
- Edema in hands and feet

LABS/STUDIES

- + hemoccult
- UA with 1+ hematuria, 2+ protein
- First AM spot urine/protein = 2
- CBC/diff with leukocytosis, mild anemia otherwise unremarkable
- ESR elevated 65; CRP elevated 12
- ASO negative
- CMP with low albumin 2.1, Cr elevated at 1.1
- Abdominal u/s: bowel wall edema/thickness
- Renal u/s: increase in renal parenchymal echogenicity

DIAGNOSIS?

HSP

Who do you call for a consult?

- Nephrology
  - -renal biopsy: IgA nephropathy with mesangial proliferation, cellular crescents in 55% glomeruli, endocapillary proliferation, segmental sclerosis
  - Starts antihypertensive

- Rheumatology
  - Start IV solumedrol with plan to wean to oral
  - Additional immunosuppression started (?)

Hospital Course: 3 days of pulse Solu-Medrol → PO prednisone 2 mg/kg/dose until f/up

- 6 days to get BP under optimal control; ESR and CRP trending down; resolution of edema of hands/feet
- discharged home to f/up with rheum in 2 weeks and nephrology in 1 week and PCP

2010 CLASSIFICATION CRITERIA FOR HSP (ONSET < 16 YRS)

Palpable purpura or petechiae not related to thrombocytopenia

AND at least ¼

1) Diffuse, acute colicky abd pain
2) LCV with IgA deposits; or GN with IgA deposition
3) Arthritis and arthralgias
4) Renal disease (proteinuria and microscopic hematuria)

Ozen, et al. EULAR/PRINOT/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification crtieria, Ann. Rheum. .Dis. 69 (2010) 798-806.

EPIDEMIOLOGY OF HSP

- Estimated 13.5/100,000 children/year
- Slightly male predominant (1.6:1.0)
- Spring/Winter
- Infection antedates onset
- GABHS, Mycoplasma
- Adenovirus, parvovirus

Ozen, et al. EULAR/PRINOT/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification crtieria, Ann. Rheum. .Dis. 69 (2010) 798-806.
Saulsbury FT: Epidemiology of Henoch-Schonlein purpura. *Cleve. Clin.J.Med.* 69(suppl 2):SII87-SII89 2002.
-Calvino MC, Llorca J, Garcia-Porrua C, et al. Henoch-Schonlein prupura in children from northwestern Spain: a 20-year epidemioloic and clinical study. *Medicine(Baltimore*). 80:279-290 2001.

IMMUNOPATHOGENESIS

- Elevated IgA levels
- IgA immune complexes in capillary walls, post-capillary venules and mesangium
- Leukocytoclastic vasculitis
- Bleeding secondary to decrease in Factor XIII (fibrin stabilizing factor)

-Conley ME, Cooper MD, Michael AF: Selective deposition of immunoglobulin A1 in immunoglobulin A nephropathy, anaphylactoid purpura nephritis, and systemic lupus erythematosus. *J. Clin. Invest*. 66:1432-1436 1980.
-Vogler C, Eliason SC, Wood EG. Glomerular membranopathy in children with IgA nephropathy and Henoch Schonlein purpura. *Pedatr. Dev. Pathol*. 2:227-235 1999.
-Shin JI, Kim JH, Lee JS. The diagnostic value of IgA deposition in Henoch-Schonlein purpura. *Pedatr. Dermatol*. 25:140-141 2008.

CLINICAL MANIFESTATIONS

MSK:

- Presenting symptom 17-25% patients
- Knees, ankles > wrists, elbows, fingers
- Painful edema; articular, periarticular, Self-limited, nondeforming, nonerosive
- Muscle hemorrhage

Dermatologic

- Hallmark: palpable purpura
- Urticarial lesions early, Petechiae, target lesions
- Gravity dependent
- Acute hemorrhagic edema of infancy
- Skin necrosis

GI/RENAL MANIFESTATIONS

GI

- Abdominal pain
- Vomiting, melena (50%), hematemesis (15%)
- Anorexia
- Intussusception 1-5%, ileoileal, ileocolic
- Massive hemorrhage/perforation/infarction

RENAL

- 20-60% manifest hematuria+/- proteinuria
- 85% in first month, 97% by 6 months, but late (10 years) reported
- Hypertension
- Nephrotic syndrome
- Crescentic Glomerulonephritis
- End stage renal failure (<5%)

OTHER MANIFESTATIONS

Pulmonary

- Interstitial lung involvement
- Pulmonary hemorrhage

Neurologic

- Headache
- hemorrhage and retinal hemorrhages
- Seizures
- Peripheral neuropathies
- Optic neuritis, uveitis

LABS/IMAGING

- Normal CBC in most
- Decrease Factor XIII levels- bleeding
- Increased IgA 50%
- Normal or elevated sedimentation rate
- Throat swab + GABHS up to 75% (?)
- Abdominal ultrasound: R/o intussusception
- Renal/skin biopsies - selected indications- IgA deposition

DDX

- Acute abdomen- e.g. appendicitis
- Meningococcal meningitis or septicemia
- Idiopathic thrombocytopenic purpura
- ANCA+ vasculitis
- Systemic lupus erythematosus
- Child abuse
- Drug reactions
- Bacterial endocarditis

TREATMENT AND PROGNOSIS

Treatment

- Supportive
- Analgesics
- Corticosteroids: Severe abdominal pain, IgA nephritis, orchitis
- IVIG- severe skin rash
- Immunosuppressive - azathioprine, mycophenolate mofetil, cyclophosphamide (renal)

Prognosis

- Most cases resolve within 4-6 weeks
- Recurrences common - up to 33%- but typically milder
- End stage renal failure - 1-5%
- Death - ~ 1% - severe GI, neurologic, pulmonary, renal complications

CASE 3

- 2 year old male unable to ambulate, high fever and inconsolable with joint exam
- Xray shows effusion
- Who do you want to call?

a. Orthopedics
b. Rheumatology
c. Heme/onc
d. All of the above
e. Obtain further workup prior to consulting

WHAT ARE YOU CONCERNED FOR?

A. Juvenile Idiopathic Arthritis
B. Septic Arthritis
C. Legg-Calve-Perthes Disease
D. Toxic synovitis
E. B & D

TABLE 1. Age-specific Diagnosis in Patients Presenting With a Limp

TODDLER (<3 YEARS)	CHILD (3–10 YEARS)	ADOLESCENT (>10 YEARS)
Developmental dysplasia of the hip	Legg-Calvé-Perthes disease	Slipped capital femoral epiphysis
Congenital limb deficiencies	Stress fractures	Legg-Calvé-Perthes disease
Neuromuscular abnormalities	Tumors	Juvenile idiopathic arthritis
Painful gait	Osteochondrosis	Overuse syndromes
Toddler fracture	Kohler disease	Osteochondrosis
Septic arthritis	Osteochondritis dissecans	Tumors
Reactive arthritis	Osgood-Schlatter disease	Osteochondritis dissecans
Transient synovitis	Transient synovitis	Stress fractures
Osteomyelitis	Osteomyelitis	Tarsal coalition
Foreign object in knee or foot	Leg-length discrepancy	Discoid meniscus

Herman, MJ & M Martinek, *Ped in Review, 2015;36;184.*

KEY POINTS IN THE HISTORY

- Age of child important
- Sex
  - Developmental hip dysplasia- girls
  - Legg-Calve-Perthes & SCFE- boys
- Onset and duration
- Trauma history
- Systemic symptoms

Naranje, S, et al. *Am Fam Physician,* 2015;92(10):908-916.

Table 1
Differentiation of septic hip from other inflammatory causes of hip pain

	Transient Synovitis	Septic Hip	Legg-Calvé-Perthes Disease
Trauma	Mild at beginning of symptoms	Mild at beginning of symptoms	Less likely. May be some distance from onset of symptoms
Onset	Several days (3–5)	Several days (3–5)	Weeks/months/ intermittent
Fever	No. Sometimes low grade <38	Yes >38.5	No
Appears ill	No	Yes	No
Gait	Limp (sometimes not weight bearing)	Not weight bearing (sometimes limp)	Limp to normal gait
Pain	Mild to severe	Moderate to severe	Mild to moderate
Range of motion	Pain at the end of motion arc	Severe pain throughout motion arc	Guarding, with pain on flexion and internal rotation

Cook, PC, *Pediatr Clin N Am,* 61 (2014) 1109-1118.

KEY POINTS IN THE PHYSICAL EXAM

- Vital signs & general appearance
- Examine the skin- bruises, rashes
- Examine the nonpainful limb first
- Intra-articular hip pathology localizes to the groin, can refer to thigh & knee
- Assess leg lengths
- Observe gait if possible

Houghton, KM, *Ped Rheum,* 2009, 7:10.

WHAT IS YOUR NEXT STEP?

A. ANA and Rheumatoid Factor
B. CBC, ESR, CRP
C. Plain films of the knee and hip
D. Ultrasound of the hip
E. All of the above
F. B & C & D

KEY LABORATORY INVESTIGATIONS

- Primarily used to investigate for septic arthritis
  - CBC
  - ESR & CRP
  - Blood cultures

- Autoantibodies are not helpful for diagnosis
  - DO NOT order ANA, RF/CCP, HLAB27

Houghton, KM, *Ped Rheum,* 2009, 7:10.

KEY IMAGING STUDIES

- Plain films best initial test
  - AP & bilateral frog-leg laterals for hips
- US used to identify joint effusion
  - Pros: No sedation, cost, availability
  - Cons: Limited detail, tech dependent
- MRI
  - Pros: Increased soft tissue contrast, detailed eval of synovium, cartilage, periosteum and bone marrow elements
  - Cons: sedation, cost, availability

Houghton, KM, *Ped Rheum,* 2009, 7:10.

BACK TO OUR PATIENT

- Xrays of hips and knees normal
- WBC 11,000, rest of CBC normal
- ESR 35, CRP 2.9 (both elevated)
- US shows moderate sized left hip effusion

WHAT IS YOUR NEXT STEP?

A. Order MRI with/without contrast left hip
B. Ortho consult, to OR for left hip I&D
C. Make NPO, schedule IR guided arthrocentesis left hip for AM
D. Start IV cefazolin, ID consult in AM

KOCHER CRITERIA

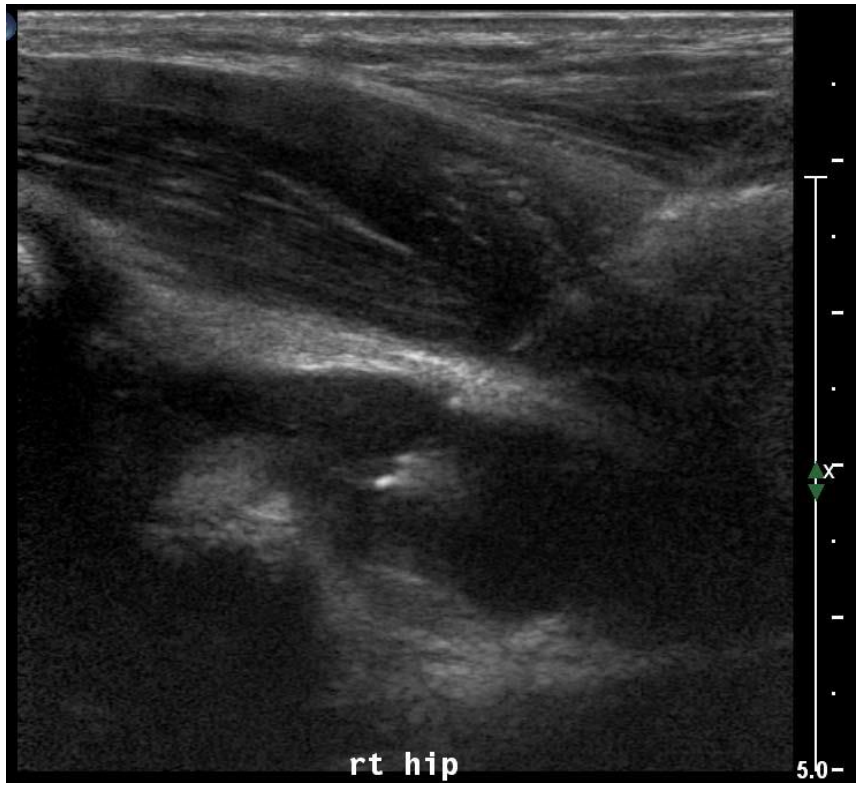
Non–weight bearing	
Erythrocyte sedimentation rate (ESR)	≥40 mm/h
White blood cell count (WBC)	>12 × 10^9/L
Temperature	>38.5°C
Probability of Septic Arthritis	
Presence of 0 predictors	<0.2%
Presence of 1 predictor	3.0%
Presence of 2 predictors	40%
Presence of 3 predictors	93.1%
All 4 predictors present	99.6%

- Our patient had 1 of 4 criteria
- 3% probability of septic arthritis
- IR guided arthrocentesis ordered

Kocher MS, et al. *JBJS (Am)* 1999;81(12):1662-70.

ARTHROCENTESIS

- Provides definitive diagnosis
- Send for cell count, GS & bacterial culture
- Prior antibiotic exposure makes a difference



SYNOVIAL FLUID CELL COUNT

	Normal	Non-Inflammatory	Inflammatory	Septic
Total WBC/mm3	<100	<2000	2000-50,000	>50,000
PMN (%)	<25	<25	>50	>75

Punzi L & F Oliviero. *Ann N Y Acad Sci*, 2009 Feb;1154: 152-8.

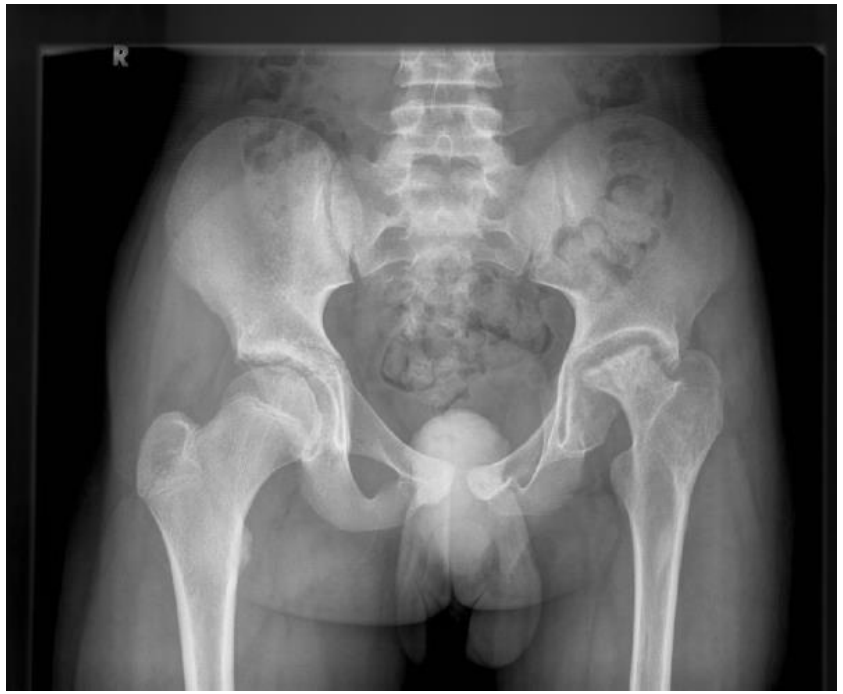
TRANSIENT/TOXIC SYNOVITIS

- Self-limited, inflammatory condition
- Unknown etiology
  - Often antecedent upper respiratory infection
- Primarily 2-10 years old, boys>girls
- Full recovery in 1- 4 weeks
- Conservative management: NSAIDs
- Recurrence in 15% of children

Houghton, KM, *Ped Rheum,* 2009, 7:10.
Cook, PC. *Ped Clin N Am,* 61 (2014) 1109-1118.

SEPTIC ARTHRITIS

- Orthopedic emergency
- Similar age distribution to TS, more common <2 years old
- Boys>girls
- *S aureus, S pneumoniae,* GBS, *Kingella kingae* most common organisms
- Surgical drainage and IV antibiotics



Houghton, KM, *Ped Rheum,* 2009, 7:10.
Cook, PC. *Ped Clin N Am,* 61 (2014) 1109-1118.

BACK TO OUR PATIENT

- Synovial fluid analysis: 1500 WBCs, 20% PMNs, culture negative
- Admitted, given IV ketorolac
- Rapid improvement, walking by the next day
- Diagnosed with Transient Synovitis and discharged home

The Next Day…..

CASE 4: 13 Y/O FEMALE: FEVER, FACIAL RASH, ARTHRITIS, FATIGUE

13 year old Hispanic female admitted for:

- Fever, rash on face
- arthritis in elbow, left knee, fingers,
- fatigue + 10 lb weight loss
- lower extremity swelling

You decide to initiate workup for systemic lupus – What do you order

LUPUS WORKUP

LABS	RESULTS
cbc/diff	WBC 2.1; hgb 9.6, platelets 200
Coombs	positive
CMP	Albumin 2.4, Cr w/nl, AST 65, ALT 60
UA and urine protein, urine Cr	2+hgb, 3+ protein; Urine Pr/cr = 2.015
C3/C4	C3=35, C4 = 4
ESR	85
CRP	7 mg/L (0-4.9 mg/L)
ANA	1:1280
dsDNA	>300
Anti smith Ab	negative
SSA/SSB	Positive/negative
Anti-RNP	negative
ANCA	negative

CRITERIA FOR SLE
Malar rash-fixed erythema; flat or raised
Discoid rash – erythematous raised patches
Photosensitivity – skin rash due to reaction sun (usu. Patient history)
Oral ulcers – oral or nasopharyngeal ulcers usu. painless
Arthritis – nonerosive arthritis in 2+ joints
Serositis – pleuritis – h/o pleuritic pain or rubbing heard on exam
Renal – persistent proteinuria >0.5g/day OR 3+ (quantitation), cellular casts
Neurologic – seizures; psychosis
Hematologic – hemolytic anemia w/ reticulocytosis or leukopenia < 4000/mm3 on >=2 times; lymphopenia < 1500/mm3 >=2x, or thrombocytopenia < 1,000,000/mm3
Immunological disorder: +dsDNA OR +antiSm nuclear Ag or +APL
ANA

Sensitivity of 96% and Specificity of 100%

Hochberg MC, Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, *Arthritis Rheum*. 40(1997) 1725.

NEXT STEP?

Call rheumatology – patient has SLE

Any other consults?

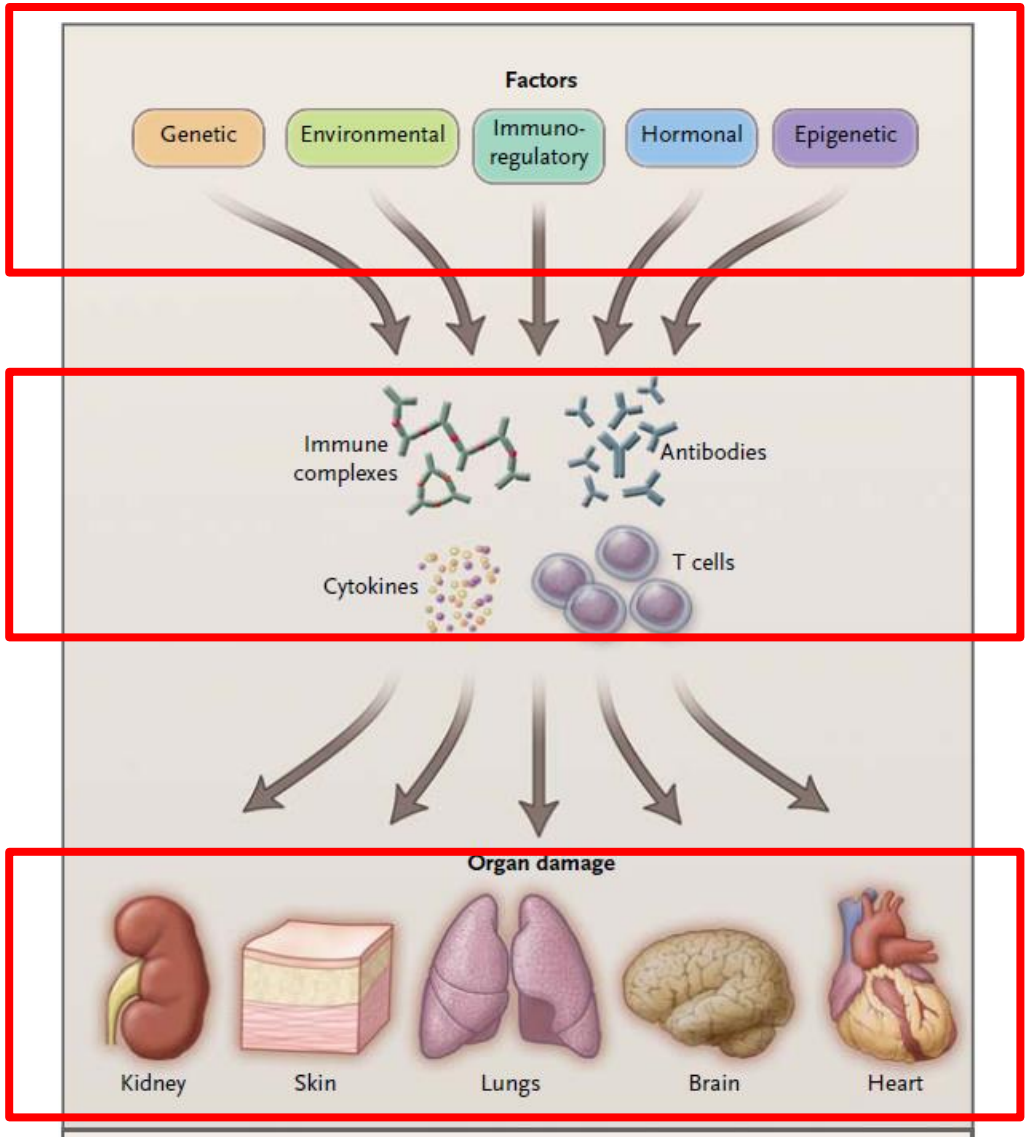
- Nephrology - patient will need renal biopsy
- Renal biopsy shows Class IIIA lupus nephritis – focal lupus nephritis: active or inactive focal, segmental or global endocapillary or extracapillary GN < 50% of all glomeruli w/ focal subendothelial immune deposits wit h or w/o mesangial alterations (text book)
- Patient is started on IV Solu-Medrol pulses x 3 days and then oral prednisone 2 mg/kg/day (max 60 mg), mycophenolate mofetil, hydroxychloroquine

EPIDEMIOLOGY OF SLE

- 20% of all SLE diagnosed before age 20 years
- Mean age at pSLE (pediatric SLE) diagnosis is 11-13 years
- Incidence
  - 0.4-0.9/100,000 per year in North America*
- Prevalence
  - 3-9/100,000 children in North America*
  - 6-19/100,000 white females **
  - 20-30/100,000 African-American females **
  - 11-30/100,000 Asian females±
- Incidence and prevalence vary by ethnicity and increase with age
- Gender differences

*Pineles D et al. *Lupus* 2011.
**Weiss JE. *Pediatr Rev* 2012.
±Huang JL et al. *Lupus* 2010.
Kurahara K, Tokuda A, Grandinetti, et al. Ehnic differences in risk for pediatric rheumatic illness in a culturally diverse population. *J. Rheumatol.* 29:379-383 2001.

ETIOLOGY AND PATHOGENESIS



Tsokos GC. *New Eng J Med* 2011.

GENETIC INFLUENCES

- Family history
- High concordance rate in monozygotic twins
- Complement deficiency
  - C1q
  - C2
  - C4
- TREX1
- HLA-DR2 and DR3

Gene	Chromosome	Published p value	Published OR
BANK1	4q24	3.7×10^{-10} (EU)	1.4
BLK	8p23.1	7.0×10^{-10} (EU)	1.22
C1q	6p21.32		~5–10
C2	6p21.32		~5–10
C4A/B	6p21.32		~5–10
CRP	1q23.2	6.41×10^{-7} (AA)	0.49
ETS1	11q24.3	1.77×10^{-25} (AS)	1.37
FcGR2A–FcGR3A	1q23.2	6.78×10^{-7} (EU)	0.74
FcGR3B	1q23.2	2.7×10^{-8} (EU)	–
HIC2-UBE2L3	22q11.21	7.53×10^{-8} (EU)	1.22
HLA-DR2 and DR3	6p21.32	1.71×10^{-52} (EU)	2.36
IKZF1	7p12.2	2.75×10^{-23} (AS)	0.72
IL-10	1q32.1	4.0×10^{-8} (EU)	1.19
IRAK1, MECP2	Xq28	1.2×10^{-8} (EU, AS)	1.39
IRF5	7q32	4.4×10^{-16} (EU)	1.45
ITGAM–ITGAX	16p11.2	1.61×10^{-23} (EU)	1.62
JAZF1	7p15.2	1.5×10^{-9} (EU)	1.19
KIAA1542/PHRF1	11p15.5	3.0×10^{-10} (EU)	0.78
LRRC18-WDFY4	10q11.22	7.22×10^{-12} (AS)	1.24
LYN	8q12.1	5.4×10^{-9} (EU)	0.77
NMNAT2	1q25	1.08×10^{-7} (EU)	0.85
PRDM1, ATG5	6q21	1.74×10^{-8} (EU)	1.19
PTPN22	1p13	9×10^{-5} (EU)	1.4
PTTG1	5q33.3	–	–
PXK	3p14.3	7.10×10^{-9} (EU)	1.25
RASGRP3	2p22.3	1.3×10^{-15} (AS)	0.7
SLC15A4	12q24.32	1.77×10^{-11} (AS)	1.26
STAT1, STAT4	2q32.3	1.9×10^{-9} (EU)	1.55
TNFAIP3	6q23.3	2.9×10^{-12} (EU)	2.3
TNFSF4	1q25.1	6.08×10^{-7} (EU)	–
TNIP1	5q33.1	3.8×10^{-13} (EU)	1.27
TREX1	3p21.31	4.1×10^{-7} (EU)	~25
UHRF1BP1	6p21.31	2.22×10^{-8} (EU)	1.17
XKR6	8p23.1	2.51×10^{-11} (EU)	1.23

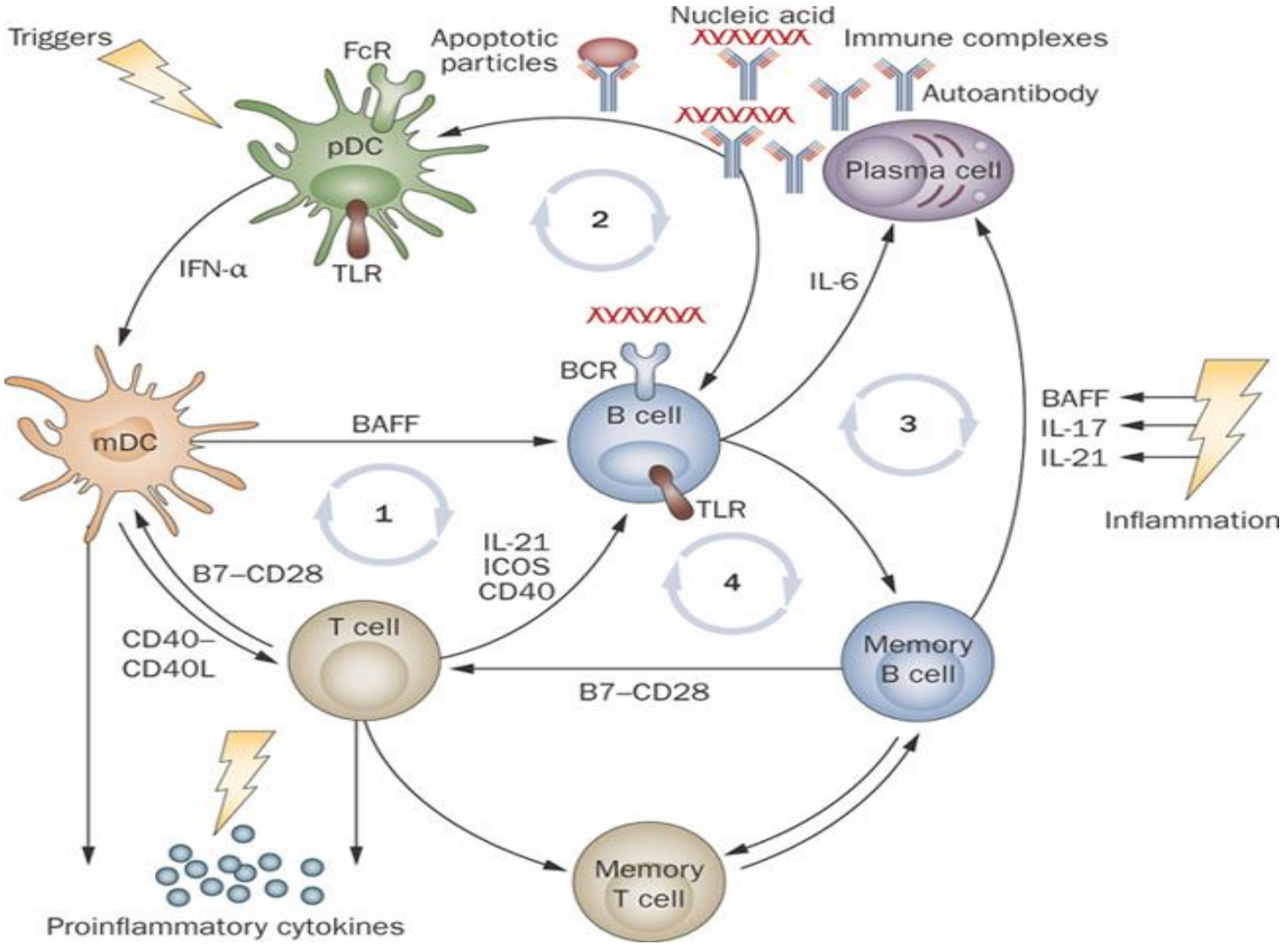
Sestak AL et al. *Ann Rheum Dis* 2011.

NONGENETIC FACTORS

- Environmental Factors
  - Ultraviolet radiation
  - Viral infection
  - Drugs and chemicals
- Hormonal Factors
  - Differential gender ratios
    - Prepubertal children 3-5:1
    - Childbearing years 7-15:1
    - Postmenopausal 5-8:1
  - Estrogen-induced flares
  - X chromosome
    - Increased prevalence of Klinefelter's syndrome (XXY)
    - Decreased prevalence of Turner syndrome (XO)

Edwards CJ, Cooper C. Early environmental exposure and the development of lupus. Lupus. 15:814-819 2006.

IMMUNE DYSREGULATION



Davidson A et al. *Nature Rev Rheum* 2010.

IMMUNOSEROLOGY

- Positive antinuclear antibody test
- Other positive immunoserology:
  - Antibodies to double-stranded DNA
  - Antibodies to Smith nuclear antigen
  - Antiphospholipid antibodies
    - IgG or IgM anticardiolipin antibodies
    - Lupus anticoagulant test
    - False positive RPR

ANTINUCLEAR ANTIBODIES

- Anti-double stranded DNA antibodies
- Anti-single stranded DNA antibodies
- Anti-chromatin antibodies
- Anti-histone antibodies
- Anti-Smith antibodies
- Anti-Ro (SSA) antibodies
- Anti-La (SSB) antibodies
- Anti-U1 RNP antibodies

DISORDERS ASSOCIATED WITH ANA

ANA very useful for diagnosis
- Systemic lupus erythematosus
- Systemic sclerosis

ANA somewhat useful for diagnosis
- Sjögren's syndrome
- Polymyositis-dermatomyositis

ANA very useful for monitoring or prognosis
- Juvenile chronic arthritis
- Raynaud's phenomenon

ANA is a critical part of the diagnostic criteria
- Drug-associated lupus
- Mixed connective tissue disease
- Autoimmune hepatitis

ANA not useful or has no proven value for diagnosis, monitoring or prognosis
- Rheumatoid arthritis
- Multiple sclerosis
- Thyroid disease
- Infectious disease
- Idiopathic thrombocytopenic purpura
- Fibromyalgia

Solomen et al. *Arthritis Rheum* 2002.

MALAR RASH

PICTURE HERE

DISCOID RASH

PICTURE HERE

PHOTOSENSITIVITY

PICTURE HERE

SLE: ORAL ULCERS

PICTURE HERE

NONEROSIVE ARTHRITIS

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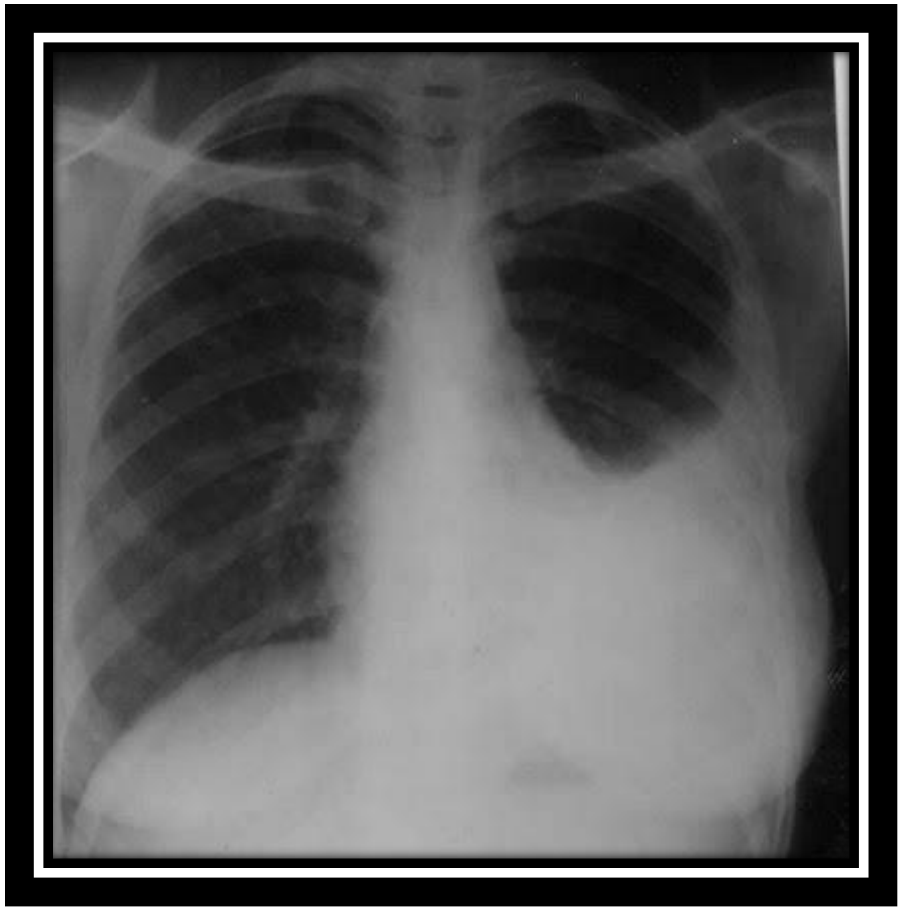
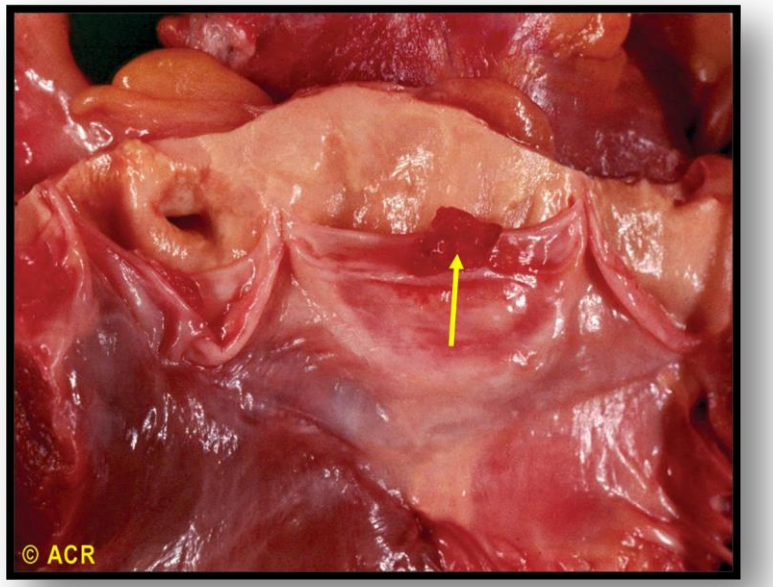
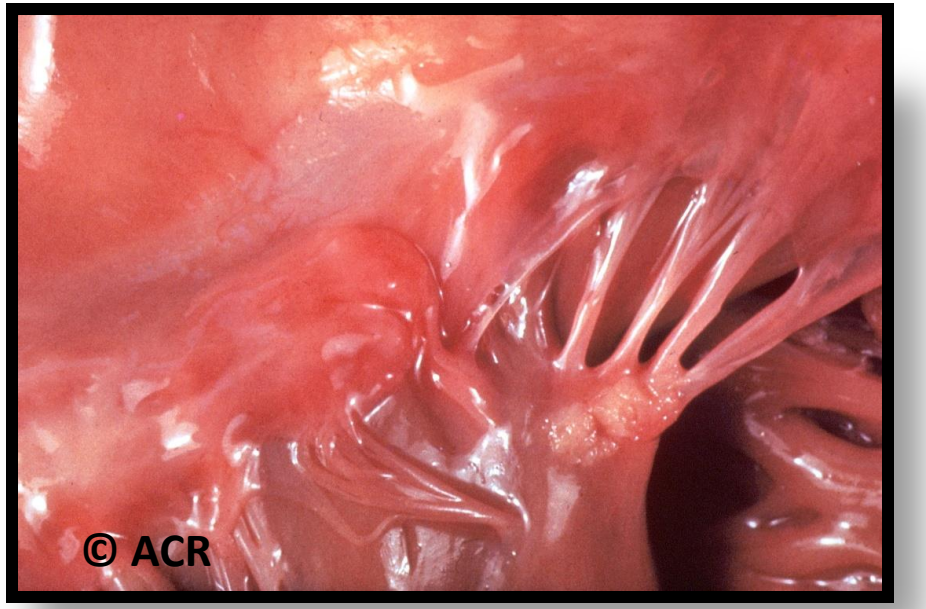
PLEUROPULMONARY DISEASE



- Pleural effusions
- Acute lupus pneumonitis
- Pulmonary hemorrhage
- Pneumothorax
- Diffuse interstitial disease
- Shrinking lungs
- Pulmonary hypertension
- Pulmonary infections

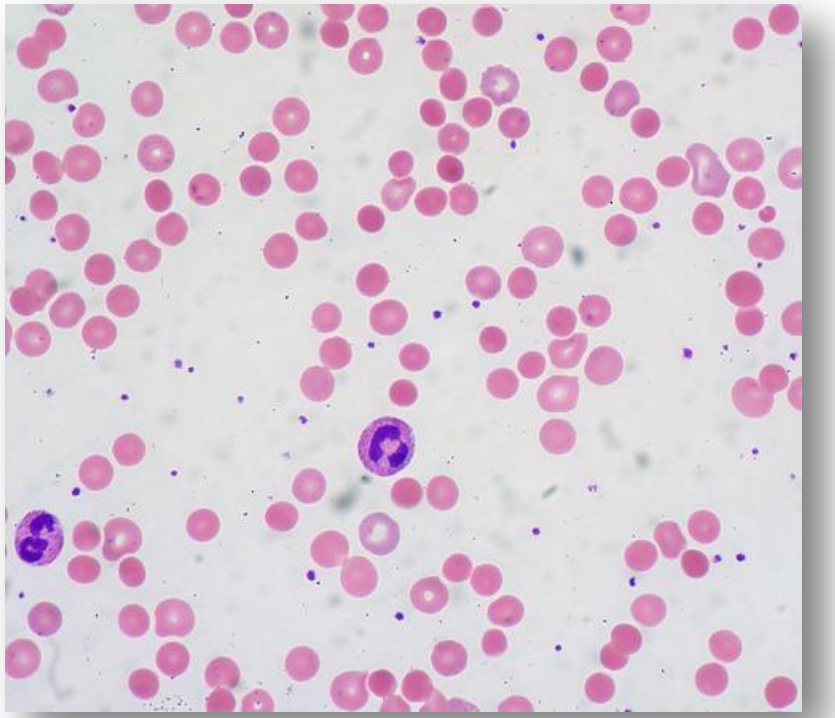
PLEURITIS OR PERICARDITIS



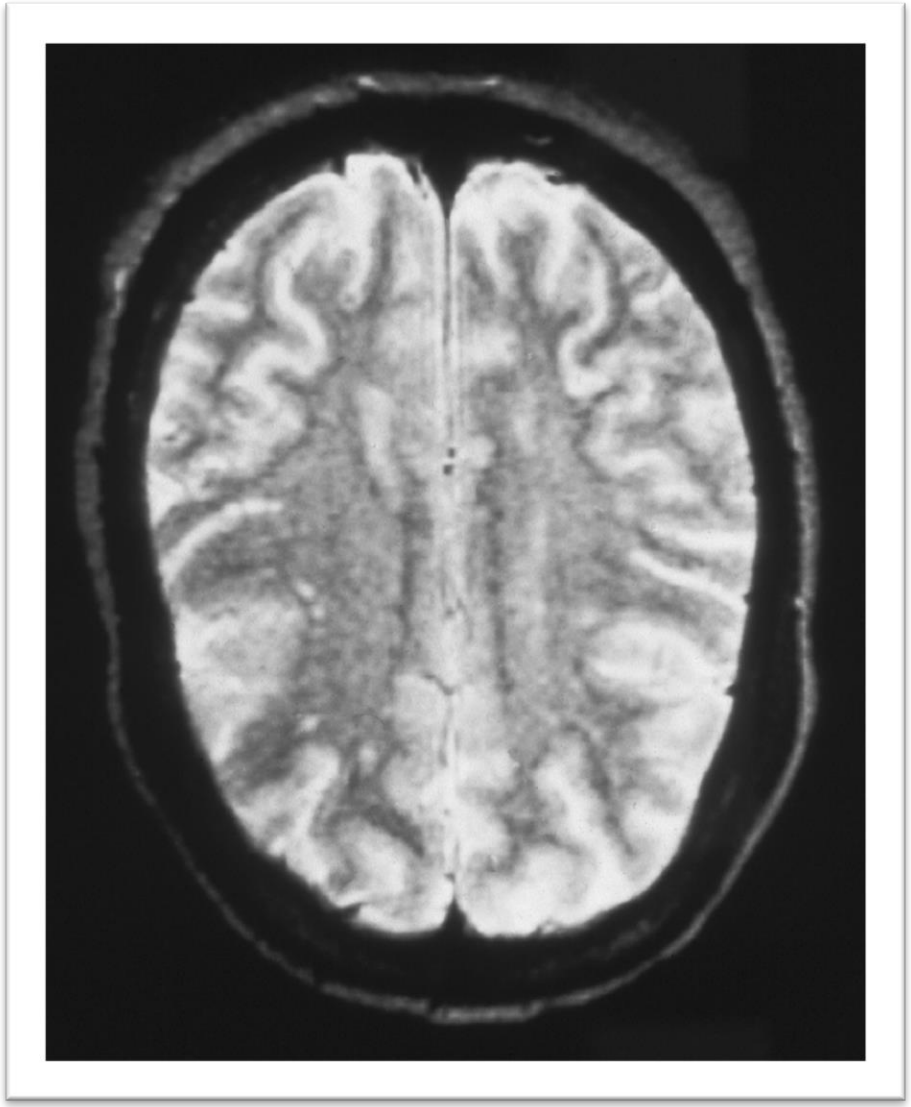


CYTOPENIA

- Coomb's positive, hemolytic anemia
- Thrombocytopenia
- Leukopenia
- Lymphopenia
- Neutropenia



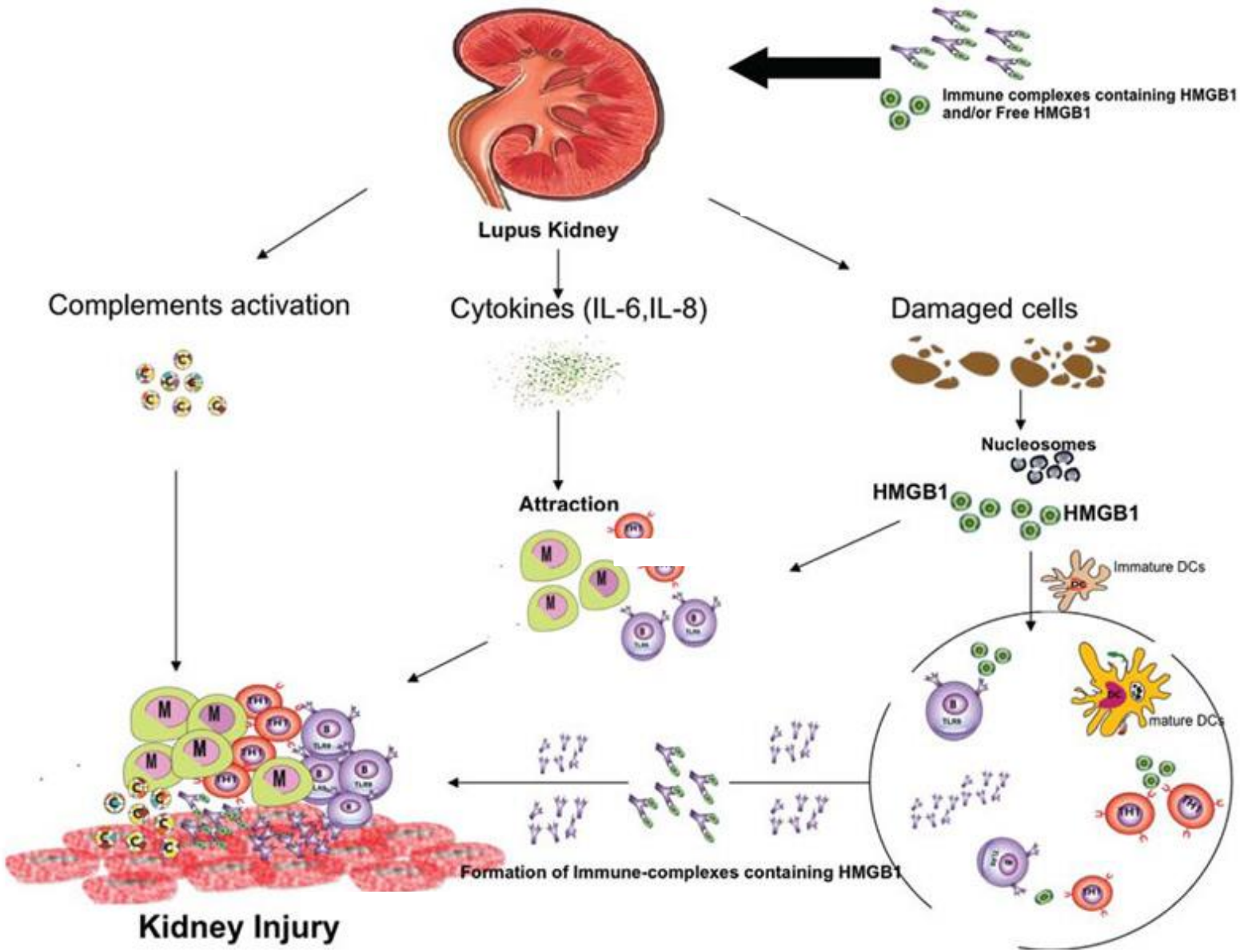
CNS MANIFESTATIONS



© ACR

- Headache
- Cognitive dysfunction
- Psychosis
- Seizures
- Transverse myelitis
- CNS vasculitis
- Stroke

LUPUS NEPHRITIS



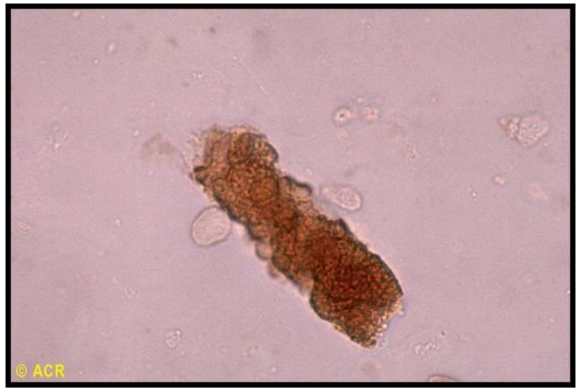
Abdulahad DA et al. *The Rheumatologist* 2011.

CLINICAL MANIFESTATIONS LN

- Microscopic hematuria and/or proteinuria
- Hypertension
- Generalized edema
- Decreased GFR ± elevated creatinine

LUPUS NEPHRITIS: WHO CLASSIFICATION

- Class I: Normal
- Class IIA: Minimal change
- Class IIB: Mesangial glomerulitis
- Class III: Focal and segmental proliferation
- Class IV: Diffuse proliferative glomerulonephritis
- Class V: Membranous glomerulonephritis
- Class VI: Glomerular sclerosis



Weening JJ et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited, J. Am. Soc. Nephrol. 15 (2)2004. 241-250.
J Am Soc Nephrol 2004.

OTHER CLINICAL MANIFESTATIONS

- Cutaneous manifestations: alopecia, Raynaud's phenomenon, livedo reticularis, vasculitis, panniculitis
- GI manifestations: serositis, vasculitis, pancreatitis, enteritis, liver disease/autoimmune hepatitis
- Endocrine: hypothyroidism, diabetes, delayed growth, osteoporosis
- Early coronary artery disease and MI
- Myalgias and myositis
- Functional asplenia

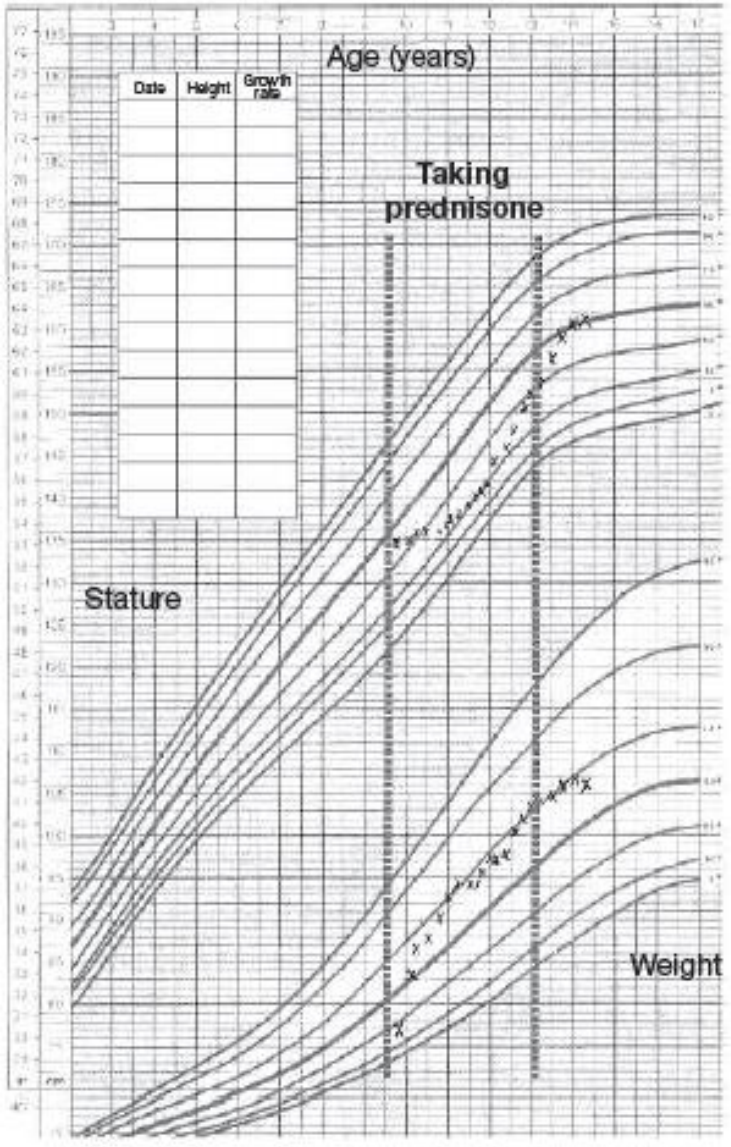
MANAGEMENT

- Sun protection
  - Sunscreen SPF > 30 and against both UVA and UVB light
- Proper nutrition and exercise counseling
- Optimize bone health
- Plaquenil (5-7 mg/kg)
  - Prevention of disease flares
  - Improves rash
  - Improves lipid profiles
  - Risk of retinal toxicity
  - Risk of skin darkening

Table of medications/management in SLE

OUTCOMES

- 5 year survival rate > 95%
- 10 year survival rate ~ 81-92%
- Predictors of poor outcome:
  - Low SES
  - Black race
  - Male gender
  - Young age
  - Renal and CNS disease
  - High overall disease activity
- Malignancy
- Osteoperosis & osteonecrosis
- Premature atherosclerosis



Ardoin SP et al. *Nat Clin Pract Rheumatol* 2005.

CASE 5: SYSTEMIC JIA – IT'S 2 AM

3 y/o M- history of sJIA: 5 days PTA- treatment switch from IL-1 → IL-6 inhibition for increased arthritis

- preliminary labs prior to calling rheumatology since it is 2 AM
- Cbc/diff, CMP, ferritin, ESR, CRP
- You recall previous case and add: LDH, TG, …..

Results

CBC/diff with wbc 2, hgb 8.7, platelets 75000, ESR 78, CRP 56, Ferritin 8700, CMP with AST and ALT in 200s, albumin 1.3, TG 575

LDH 950

IS THIS JUST SYSTEMIC JIA FLARE?

What is your main concern?

Macrophage Activation Syndrome (MAS)

- Do you call rheumatology now? or wait for results

YOU DECIDE TO CALL RHEUMATOLOGY

Recommendations:

- IV solumedrol 30 mg/kg q24 hours x 3 days
- Ferritin added to labs

SJIA EXTRA-ARTICULAR FEATURES

- Fevers
- Rash
- Serositis
- Hepatosplenomegaly
- Lymphadenopathy

ILAR CRITERIA

(INTERNATIONAL LEAGUE OF ASSOCIATIONS FOR RHEUMATOLOGY)

Fever x 2 weeks, daily x $\geq$ 3 days (quotidian) + arthritis
+ 1 or more:

- Evanescent rash
- Generalized lymphadenopathy
- Hepatomegaly/splenomegaly
- Serositis

About 1/3 of patients meet criteria at diagnosis

Behrens EM, Beukelman T, Gallo L, et al. Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR)

SJIA EPIDEMIOLOGY

- Incidence = 0.5 – 1.3/100,000 persons under age 16 annually
- 5-15% of all JIA patients have sJIA
- Peak between 1 – 5 years but can occur anytime.
- Males=Females

CLINICAL PRESENTATION

Ill at time of diagnosis

- Fatigue
- Fever
- Arthralgia/Arthritis
- Weight loss
- Chest pain

80% present with triad fever, arthritis, rash

Correll CK, Binstadt BA. Advances in the pathogenesis and treatment of systemic juvenile idiopathic arthritis Pediatr Res 2014;75:176-83.

CLINICAL COURSE

Monocyclic – presents with typical features; eventually remits with treatment (~40%)

Polycyclic – relapses of disease with periods of remission (~7%)

Remission = off all meds x 12 months, asymptomatic, and normal labs.

Unremitting/Persistent No remission, require long-term treatment (~53%)

.

Correll CK, Binstadt BA. Advances in the pathogenesis and treatment of systemic juvenile idiopathic arthritis Pediatr Res 2014;75:176-83

- Temp to 39◦C or higher
- 2 weeks or more with daily (*quotidian*) or twice daily spikes x 3 days or more (64%)
- Temps return to normal between spikes
- Correlates with inflammatory cytokines
- More obvious pattern once on NSAIDs

De Bendetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2385-95.

RASH

- Occurs in > 90% of patients at onset
- Evanescent, 2-5 mm salmon-pink macules on face, palms/soles, trunk, arms/legs; migratory
- Usually coincides with fever
- Lesions can develop by scratching skin =*Koebner* phenomenon
- Rash & fever support diagnosis if arthritis not present

EVANESCENT RASH

- PICTURE HERE

KOEBNER PHENOMENON (ISOMORPHIC PHENOMENON)

- PICTURE HERE

ARTHRITIS

- Knees, wrists, ankles, cervical spine, hip, joints of hand, TMJ
- Myalgia and myositis at onset
- Polyarticular in ¼ cases
- May be absent at onset delaying diagnosis—~1/3 of cases at onset; can take years
- *Severe* w/ resistance to treatment → disability

LYMPHADENOPATHY & HEPATOSPLENOMEGALY

- LAD in b/l anterior cervical, axillary, inguinal
- Non-tender, firm, mobile
- Must r/o lymphoma

Organomegaly

- Mild hepatomegaly
- Splenomegaly in approximately 30% - mild
- Massive splenomegaly suggests malignancy

Szer IS, Kimura Y, Malleson PN, Southwood TR. Arthritis In Children & Adolescents Juvenile Idiopathic Arthritis. New York: Oxford University Press; 2006.

CARDIAC/PULMONARY

- Pericardial effusion or thickening
  - Asymptomatic vs. pain +/- dyspnea when supine
  - May precede development of arthritis
- Myocarditis rare
  - Cardiomegaly
  - Congestive heart failure
- Pleural effusions – usually incidental
- ILD, pulmonary fibrosis, PAH, lipoid pneumonia often associated with MAS

Szer IS, Kimura Y, Malleson PN, Southwood TR. Arthritis In Children & Adolescents Juvenile Idiopathic Arthritis. New York: Oxford University Press; 2006.

LABORATORY

- Leukocytosis (neutrophilia)
- Microcytic or normocytic anemia
- Thrombocytosis
- Elevated ESR
- Elevated CRP
- Elevated ferritin, fibrinogen, d-dimer
- NOT specific for sJIA

If MAS present at onset lab profile different

TREATMENT

- NSAIDs
- Corticosteroids
- DMARDs
- Biologics (IL-1, IL-1β and IL-6 inhibitors)

The Childhood Arthritis and Research Alliance (CARRA) developed 4 consensus treatment plans in 2010 to attempt to standardize treatment of sJIA

Morgan DeWitt E, Kimura Y, Beukelman T, Nigrovic PA, Onel K, Prahalad S, et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. Arthritis Care Res 2012;64:1001-10.

COMPLICATIONS

- Growth impairment
- Osteoporosis
- Avascular Necrosis
- Amyloidosis – rare in North America
  - 5-7% of children in Europe
  - Finnish and UK series showed significant mortality including renal insufficiency

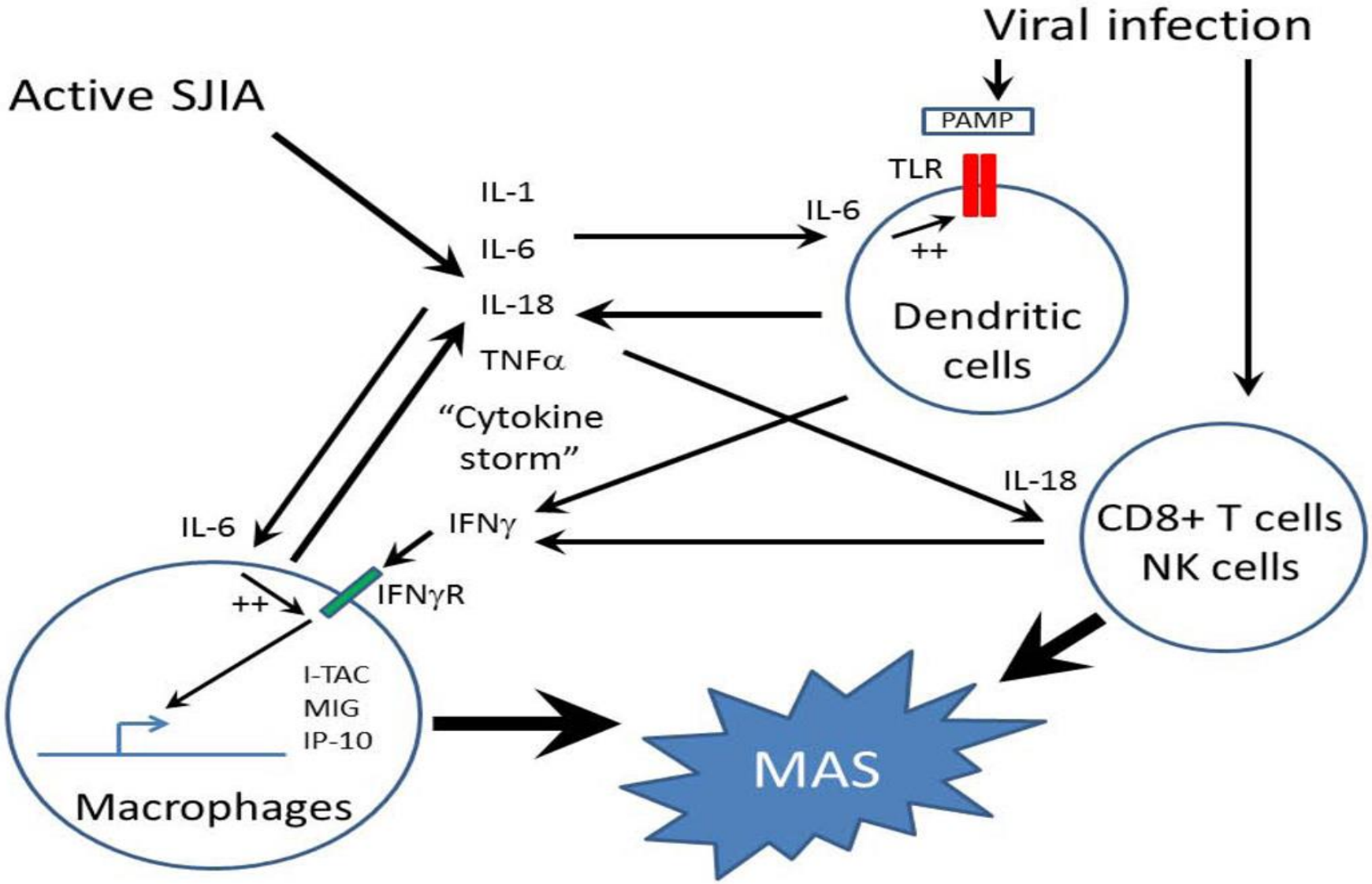
- **Macrophage Activation Syndrome (MAS)**

Petty RE, Laxer RM, Lindsley CB, Wedderburn LR., editors. Textbook of Pediatric Rheumatology. 7th ed. Philadelphia: Saunders Elsevier; 2016.

MACROPHAGE ACTIVATION SYNDROME

- Severe complication of sJIA
- Increased activation of macrophages and T cells → overwhelming inflammation
- Resembles HLH
- Occurs in about 7-10% of patients with sJIA
  - 25-30% may have subclinical MAS
  - 20% at time of diagnosis
- Also seen in SLE , Kawasaki and infection

Grom AA, Mellins ED. Macrophage activation syndrome: advances towards understanding pathogenesis. Curr Opin Rheumatol 2010;22:561-66.



Schulert GS, Grom AA. Macrophage activation syndrome and cytokine directed therapies. Best Pract Clin Rheumatol 2014;28:277-92.

MAS

- Fever
- Hepatosplenomegaly
- Lymphadenopathy
- Severe cytopenia
- Liver dysfunction/failure (coagulopathy/DIC)
- Multi-organ: respiratory distress, Renal failure, seizures hypotension, shock

MAS DIAGNOSIS

- Thrombocytopenia, leukopenia or relative ↓
- Elevated ferritin, LDH, TG, AST/ALT
- Low albumin, Drop in ESR with low fibrinogen
- Elevated CRP, increasing D-dimer
- Pathognomonic: macrophages demonstrating hemophagocytic activity
- sIL2Rα and sCD163 levels can aid in diagnosis

Grom AA, Mellins ED. Macrophage activation syndrome: advances towards understanding pathogenesis. Curr Opin Rheumatol 2010;22:561-66.

MAS TREATMENT

- High morbidity and mortality—early recognition and treatment essential
- IV methylprednisolone
- IL-1 inhibitor—anakinra
- Cyclosporine

BOTTOM LINE

- If not sure…call and have discussion rather than assume consultation needed