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Identification and Management of Systemic Juvenile Idiopathic Arthritis and Macrophage Activation Syndrome

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Faculty Disclosures

- The speakers have no relevant financial relationships with any commercial interests.
- The speakers will be discussing off-label medication use.

Objectives

1. Review the epidemiology and clinical presentation of Systemic Juvenile Idiopathic Arthritis and Macrophage Activation Syndrome
2. Discuss diagnostics and diagnostic dilemmas specific to Systemic Juvenile Idiopathic Arthritis and Macrophage Activation Syndrome
3. Appraise the differences between the 2012/2016 and 2022 American College of Rheumatology treatment guidelines

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)

Epidemiology

- Severe systemic inflammatory illness characterized by rash, arthritis, fever, and other systemic symptoms
- 5 – 15% of patients with JIA (North America & Europe)
- Autoinflammatory, not autoimmune
  - Autoantibodies and autoreactive T – cells are not present
  - Dysfunction of innate immune system & cytokine regulation
  - Different pathways involved from polyarticular or oligoarticular JIA
- Peak onset: 1 – 5 years, but can be seen in all ages
- Sex: M = F

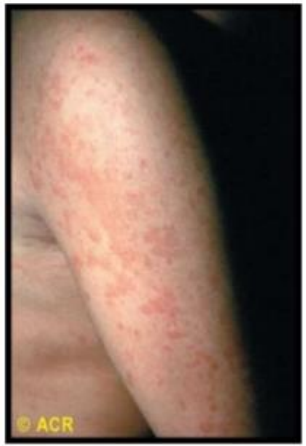
ILAR Classification Criteria

1. Fever for at least 2 weeks AND Quotidian for at least 3 days
2. Arthritis in 1 or more joint
   AND
3. One or more of the following:
   - Evanescent rash
   - Generalized lymphadenopathy
   - Enlarged liver or spleen
   - Serositis

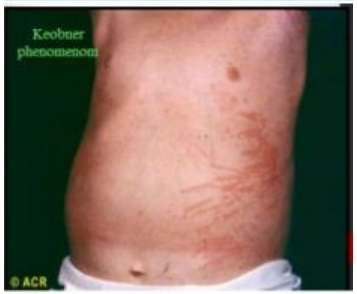
Exclusions: Psoriasis, ankylosing spondylitis, enthesitis-related arthritis, reactive arthritis, acute anterior uveitis in patient or 1st degree relative; arthritis in HLA-B27+ male > 6 years old, Rheumatoid factor positive x 2

SJIA Manifestations

- Fever
  - May initially be erratic without pattern
  - Eventually quotidian or bi-quotidian
  - Normothermic or hypothermic in between



- Evanescent rash
  - Discrete salmon-colored macules; sometimes in linear streaks (Koebner)
  - Often on trunk and proximal extremities or creases
  - Typically with fever spikes



SJIA Manifestations (Continued)

- Arthritis – typically polyarticular
- Myalgias common; myositis not common
- Cardiac: pericarditis, effusion, coronary artery dilation
- Pleural effusions
- LAD, splenomegaly > hepatomegaly
- Uveitis – rare

LAD = Lymphadenopathy

Lab Findings

- Leukocytosis
  - WBC often > 30,000/mcL
  - Predominance of PMNs
- Thrombocytosis
- Hgb: typically 7 – 10 g/dL
- ESR: usually very high
  - Exception is MAS
- Other elevated inflammatory markers: CRP, Ferritin, Fibrinogen, D-Dimer
- RF and ANA: typically negative

WBC = white blood cell; PMN = polymorphonuclear leukocytes; Hgb = hemoglobin; ESR = erythrocyte sedimentation rate; MAS = macrophage activation syndrome; CRP = C-reactive protein; RF = Rheumatoid factor; ANA = antinuclear antibodies

Prognosis

- 30 – 40%: monophasic with ultimate complete remission
- ~10%: polyphasic with multiple flares and remissions
- 50 – 60%: “persistent”
  - Systemic features typically monophasic
  - Persistent polyarticular arthritis: more resistant to treatment than typical polyarticular JIA

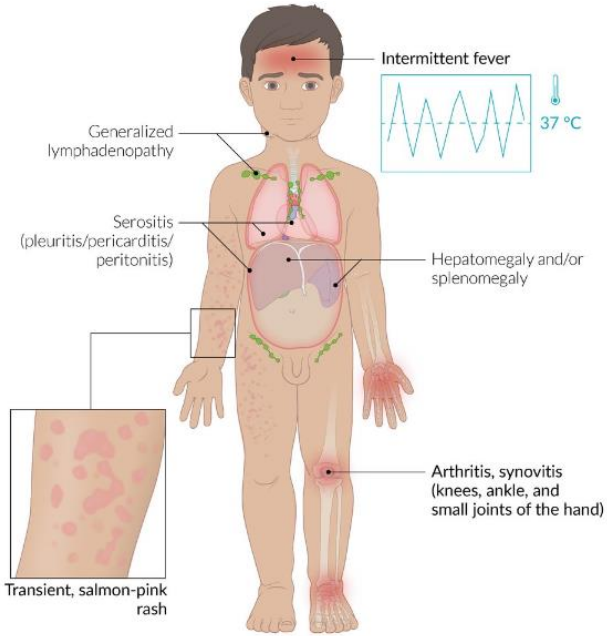
Differential Diagnoses

- MIS-C
- Infection: sepsis, endocarditis, acute rheumatic fever, leptospirosis, etc.
- Malignancy: large B-cell lymphoma, other hematologic malignancies
- Lymphoproliferative: Castleman, Rosai-Dorfman, Kikuchi, autoimmune lymphoproliferative syndrome
- Other rheumatological conditions:
  - Systemic Lupus Erythematosus
  - Vasculitis, including Kawasaki, Polyarteritis nodosa
  - Serum sickness-like illness
  - Autoinflammatory syndromes (e.g., Familial Mediterranean fever)

Case Study: P.H.

4-year-old female diagnosed with systemic JIA in September 2017

- Presented with 6 weeks of nightly fevers (Tmax 104°F) accompanied by pink rash- ill appearing
- Arthritis noted in bilateral ankles and knees
- Heme/onc evaluated while admitted - bone marrow biopsy unremarkable

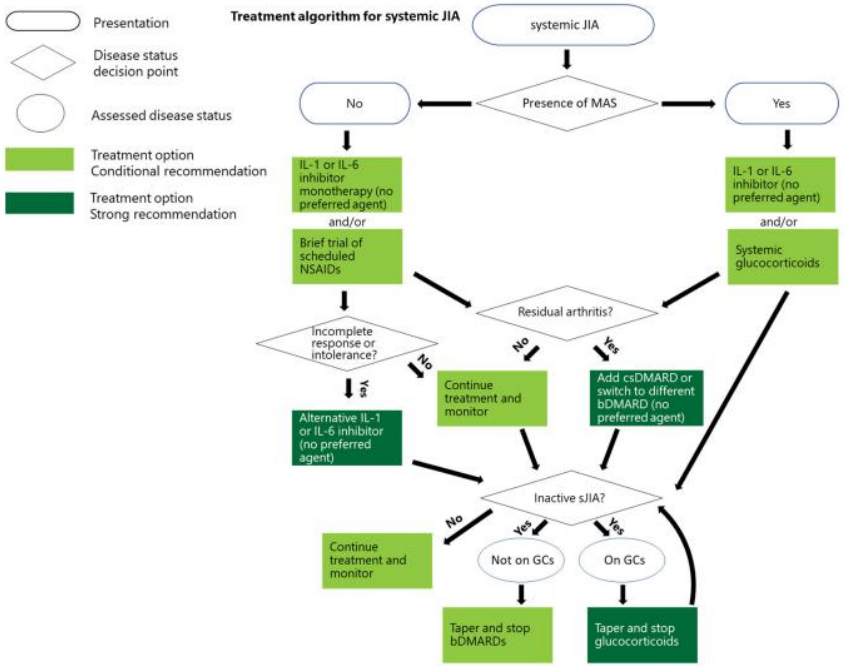


<u>Labs</u>

- WBC: 29,000/mcL
- Plt: 449,000/mcL
- ESR: 54 mm/Hr
- CRP: 17.5 mg/dL
- Ferritin: 889 ng/mL
- LDH: 493 U/L

What would you recommend as initial treatment?

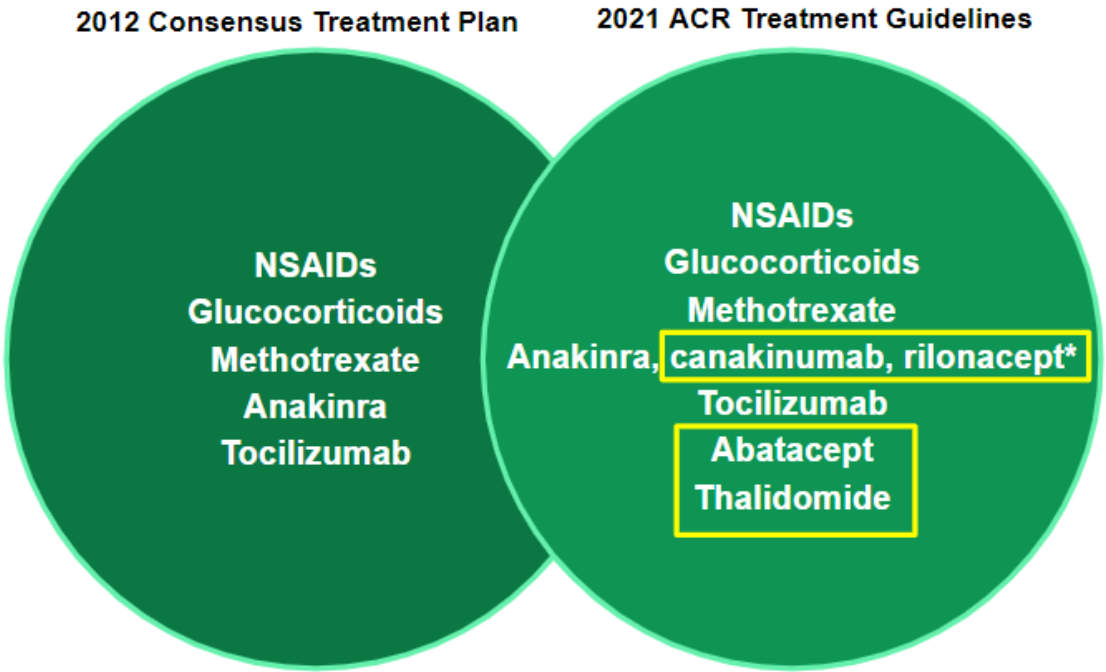
2021 ACR/AF Guidelines for the Treatment of Systemic-Onset JIA



bDMARD = biologic disease-modifying antirheumatic drug, csDMARD = conventional synthetic disease-modifying antirheumatic drug, GCs = glucocorticoids, IL = interleukin, JIA = juvenile idiopathic arthritis, MAS = macrophage activation syndrome, NSAIDs = nonsteroidal antiinflammatory drugs

Figure 3. Treatment algorithm for systemic juvenile idiopathic arthritis.

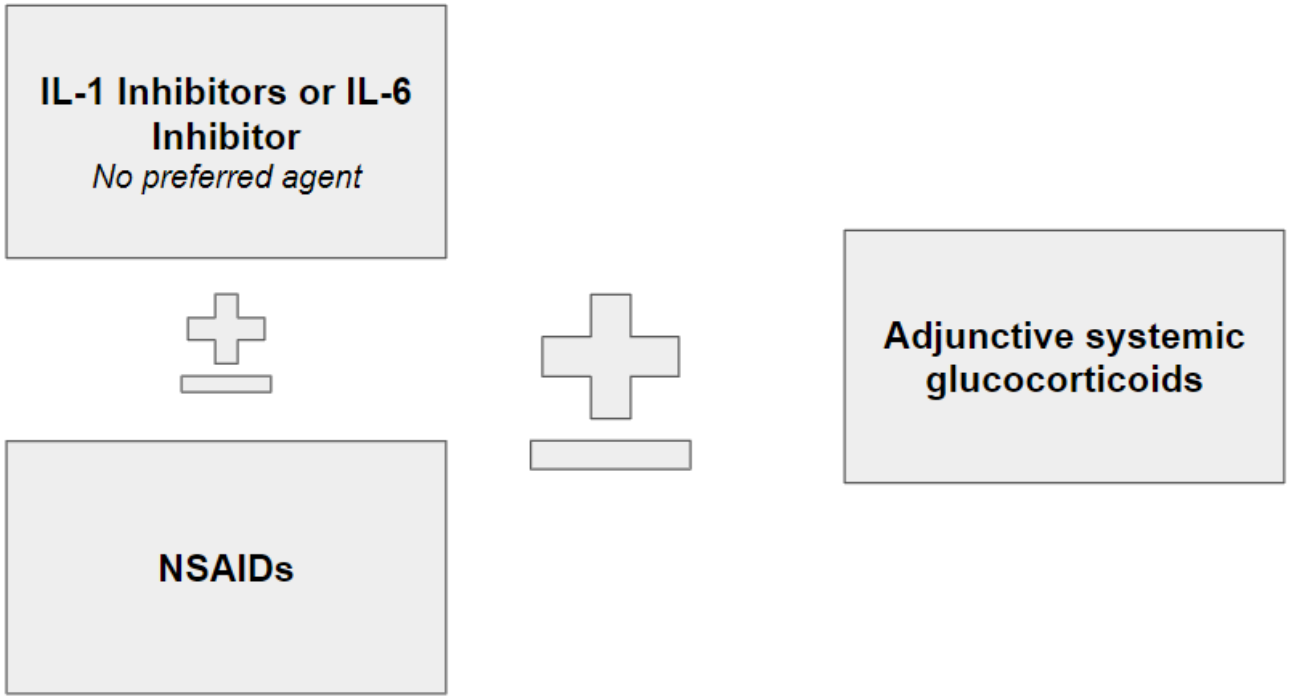
Treatment Guideline Updates



*Not FDA-approved for systemic JIA

DeWit EMt. *Arthritis Care Res (Hoboken)*. 2012 Jul;64(7):1001-10.
Onel KB. *Arthritis Rheumatol*. 2022 Apr;74(4):553-569

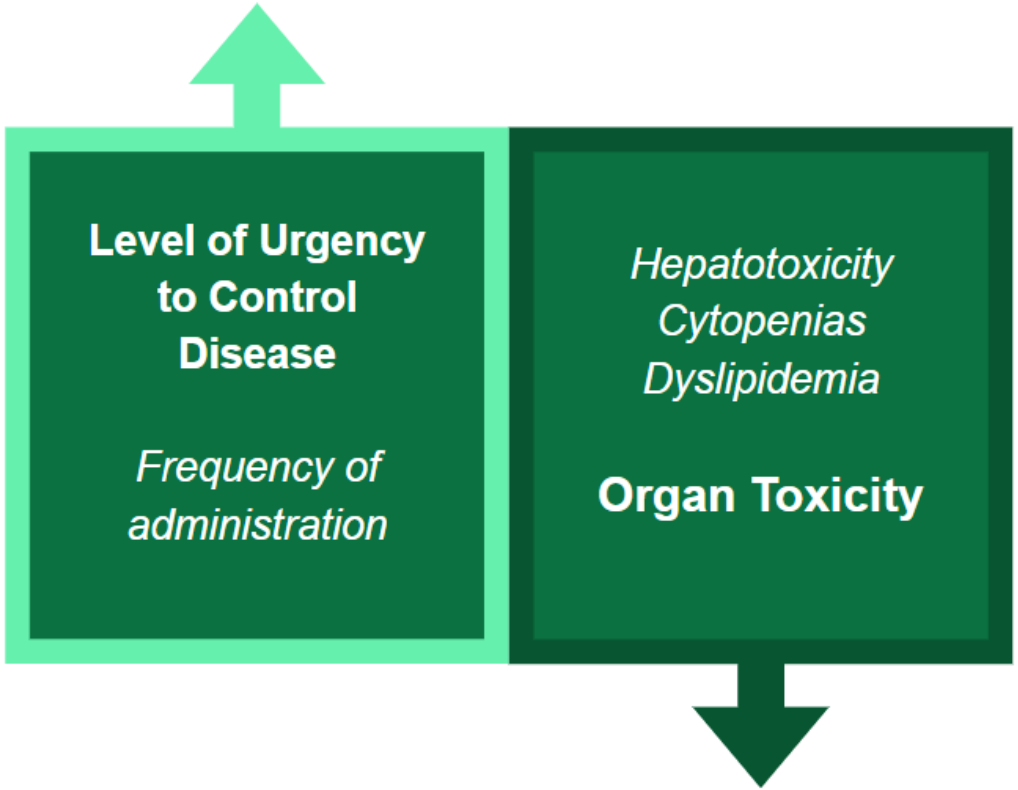
Initial Treatment



IL = interleukin; NSAD = nonsteroidal anti-inflammatory drugs

Onel KB. *Arthritis Rheumatol*. 2022 Apr;74(4):553-569

Picking an Interleukin Inhibitor



Avoiding Long – Term Glucocorticoid Use

1 Alternative bDMARDs

- Tumor-necrosis factor inhibitors
- Abatacept
- Rituximab

2 Alternative csDMARD

- Methotrexate
- Cyclosporine
- Thalidomide
- Cyclophosphamide

bDMARD = biologic DMARD, csDMARD = conventional DMARD

Onel KB. *Arthritis Rheumatol*. 2022 Apr;74(4):553-569

P.H.’s Treatment Course

September 2017

- Initial diagnosis
- Treatment with IV methylprednisolone, prednisone, naproxen, anakinra
- Transitioned from anakinra to canakinumab

June 2019

- Inflammatory markers and physical exam stable
- Trial off canakinumab

August 2019

- Experienced arthritis flare
- Canakinumab restarted

September 2019

- Admitted for flare, consisting of fevers and ongoing arthritis
- Canakinumab switched to tocilizumab

P.H.’s Treatment Course

December 2019

- Continued to experience ongoing arthritis, but systemic features are well-controlled
- Added oral methotrexate

April 2020

- Optimized oral methotrexate dose

April 2021

- Arthritis and systemic features well controlled
- Oral methotrexate discontinued. Tocilizumab continued.

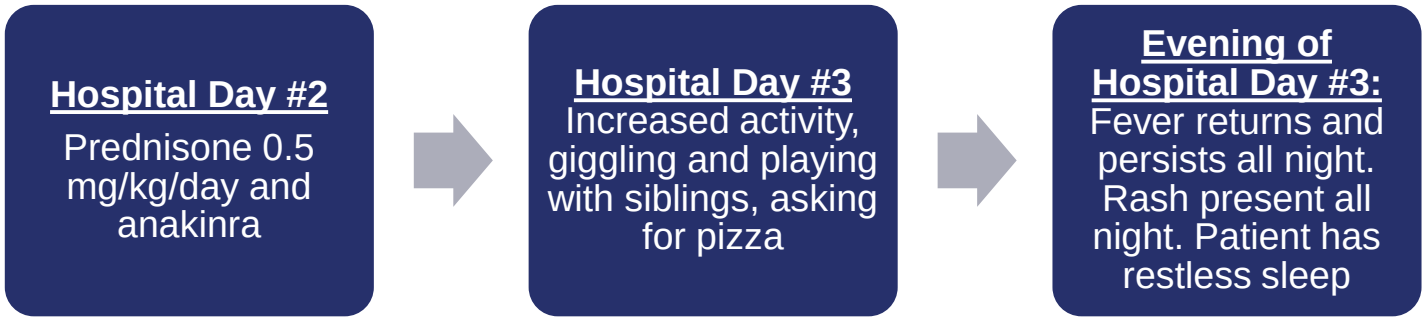
July 2022

- Patient continues to be stable.
- Tocilizumab discontinued
- Monitoring closely off medications

Case Study: G.A.

4-year-old male admitted for 8 days of evening high fevers

- Presents with fevers, malaise, evanescent rash
- Infections and malignant etiology ruled out
- Rheumatology consulted
- PE: LAD, splenomegaly, quotidian fever pattern, erythematous macular rash on back and upper thighs, no arthritis
- PMH: diagnosis with sJIA and started on scheduled naproxen



Case Study: G.A.

Labs	Hospital Day #3	Hospital Day #4
WBC*	16 x10*3/mcL	4.5 x10*3/mcL
Hgb	11 g/dL	10 g/dL
Plt*	535 x10*3/mcL	103 x10*3/mcL
ESR	65 mm/Hr	10 mm/Hr
CRP	10.8 mg/dL (normal <1)	11.4 mg/dL

WHAT IS NEXT?

Case Study: G.A.

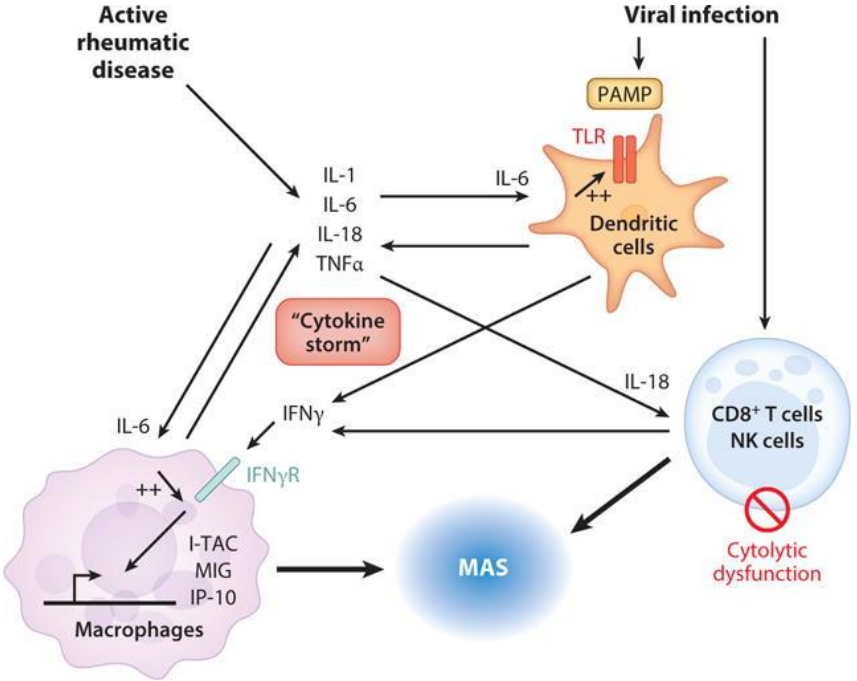
- D-dimer: 11.7 mcg/mL
- Fibrinogen: 82 mgs/dL
- Albumin: 2.1 g/dL
- Triglycerides: 380 mg/dL
- LDH: 970 U/L
- AST
- mg/dL
- Ferritin: 9000 ng/mL

MEDICAL EMERGENCY!

MACROPHAGE ACTIVATION SYNDROME (MAS)

Overview

Hyperinflammatory complication of sJIA caused by severe hypercytokinemia due to dysregulation of immune response

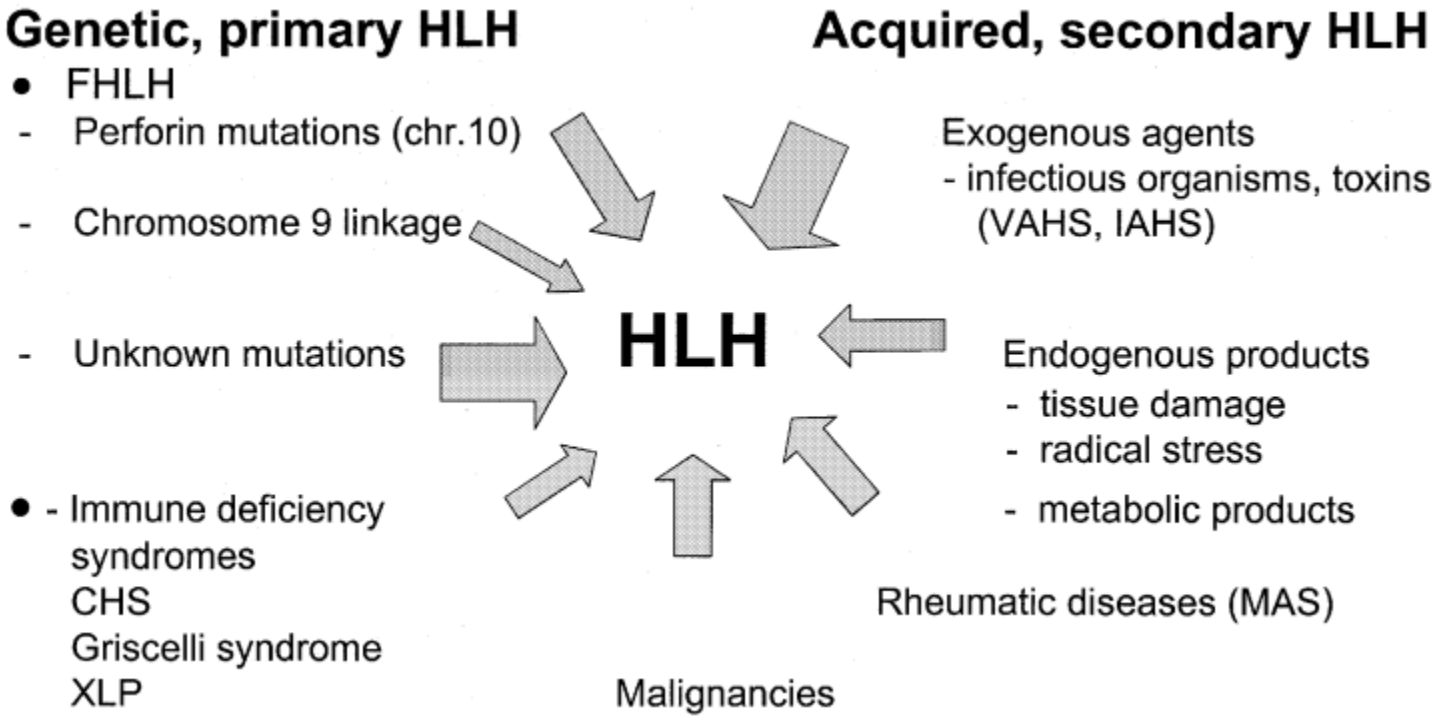


Overview

- Most devastating complication of sJIA
- It occurs in 7% of patients during the disease course
- Closely resembles HLH
- Associated with serious morbidity and mortality: 8% in a series of 350 patients with MAS associated with sJIA
- Most often occurs during periods of active disease, especially early in the disease course
- 20% of MAS present at initial diagnosis
- Patients well-controlled by IL-1 or IL-5 can develop MAS

HLH = Hemophagocytic lymphohistiocytosis

Triggers of HLH



Clinical Presentation

Rapid development of:

- Unremitting fever (not quotidian pattern associated with SO-JIA)
- Hepatosplenomegaly
- Lymphadenopathy
- Hepatic dysfunction (sometimes with jaundice or liver failure)
- Encephalopathy
- Purpura, bruising, or mucosal bleeding

Severely affected patients may develop:

- Respiratory distress
- Renal failure
- Disorientation
- Seizures
- Hypotension
- Shock

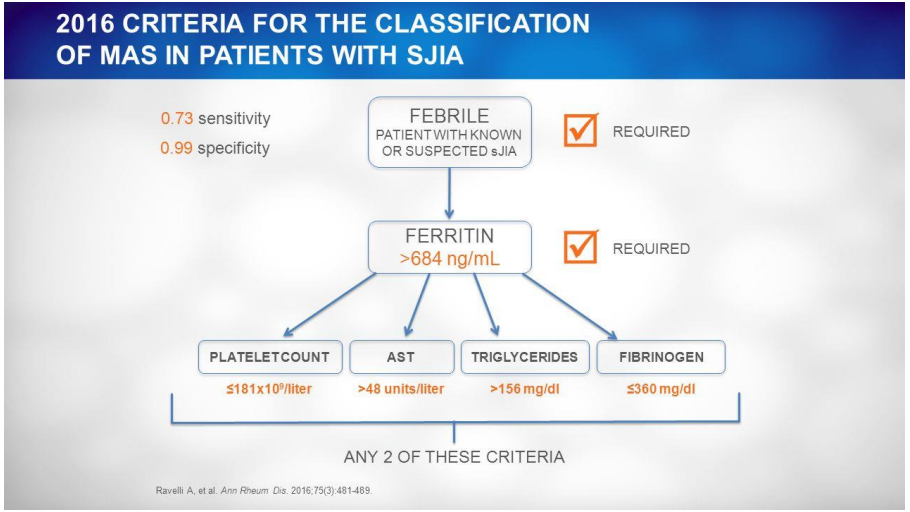
Laboratory Studies in Diagnosing MAS

- Hematocytopenia – especially thrombocytopenias
- Normal or slightly elevated neutrophils
- Elevated liver enzymes, LDH, triglycerides, and ferritin
- Low serum albumin
- Elevated D-dimer
- Prolonged PT and PTT
- ESR may drop sharply
- CRP elevated
- Increased soluble IL-2
- Hemophagocytosis in bone marrow or other tissues (lymph nodes, liver, spleen) is diagnostic

PRINTO, ACR, and EULAR Classification Criteria for MAS

Multistep consensus formation process

- Delphi survey
- Large scale data collection
- Patient profile completion
- Consensus conference
- Cross-sectional validation of classification criteria



Ravelli A. *Arthritis Rheumatol*. 2016 Mar;68(3):566-76.

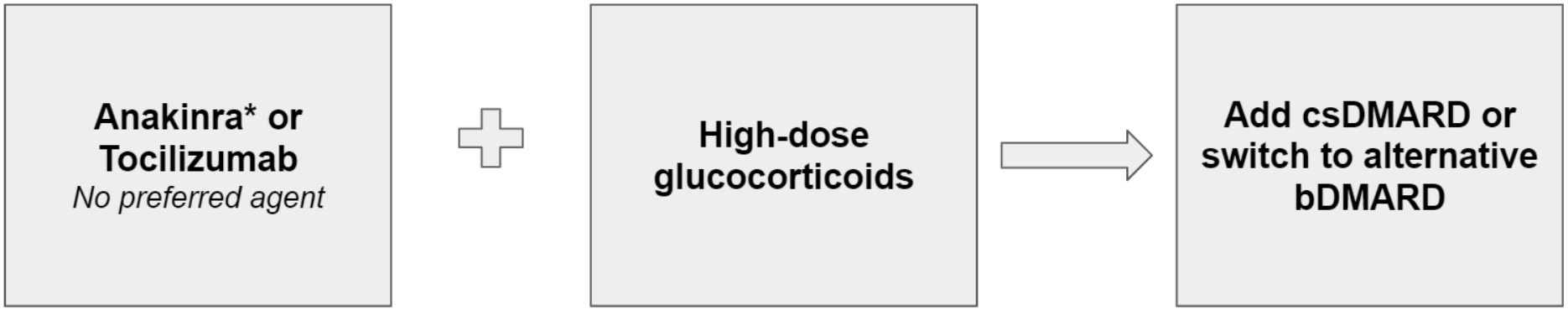
Diagnosing MAS: Special Considerations

- Patients with active sJIA often have elevated WBC, neutrophils, platelets, and fibrinogen
- Sudden and sustained reductions is often associated with MAS even in the absence of cytopenias and hypofibrinogenemia

Consider current treatment regimen

- Tocilizumab can cause cytopenias or elevated liver transaminases
- Treatment with IL-1 and IL-6 inhibitor can modify features of MAS

Interrupting the Cytokine Storm



*In the setting of hemodynamically instability, anakinra dosing can go up to 5 mg/kg/day

Onel KB. *Arthritis Rheumatol*. 2022 Apr;74(4):553-569

Therapeutic Agents for Refractory Disease

Medication	Dosing	Clinical Pearls
Cyclosporine	2 – 7 mg/kg/day IV	• Trough goal: not established • Level should not be drawn through IV line • Conversion from IV to PO = 1:2
Etoposide	50 – 10 mg/m^2 OR 150 mg/m^2 (HLH protocol)	• No controlled studies of etoposide in MAS • Hepatic and renal impairment • Cytopenias, sepsis • High mortality rate: up to 44%

Investigative Agents

- Emapalumab: IFNγ-blocking antibody
- rhIL-18BP: recombinant human IL-18BP

Onel KB. *Arthritis Rheumatol*. 2022 Apr;74(4):553-569
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Canna SW. *J Allergy Clin Immunol*. 2017;139:1698-1701.

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