RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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Pediatric Rheumatology Basics for the Novice APP:

Juvenile Idiopathic Arthritis and Periodic Fever/Autoinflammatory Syndromes

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Faculty Disclosures

- Ingrid Pan, PharmD:
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- Holly Reid, CPNP-C:
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Objectives

1. Review the epidemiology and clinical presentation of Juvenile Idiopathic Arthritis and Periodic Fever/Autoinflammatory Syndromes

2. Discuss diagnostics and diagnostic dilemmas specific to Juvenile Idiopathic Arthritis and Periodic Fever/Autoinflammatory Syndromes

3. Summarize current pharmacologic agents for the treatment of Juvenile Idiopathic Arthritis and Periodic Fever/Autoinflammatory Syndromes

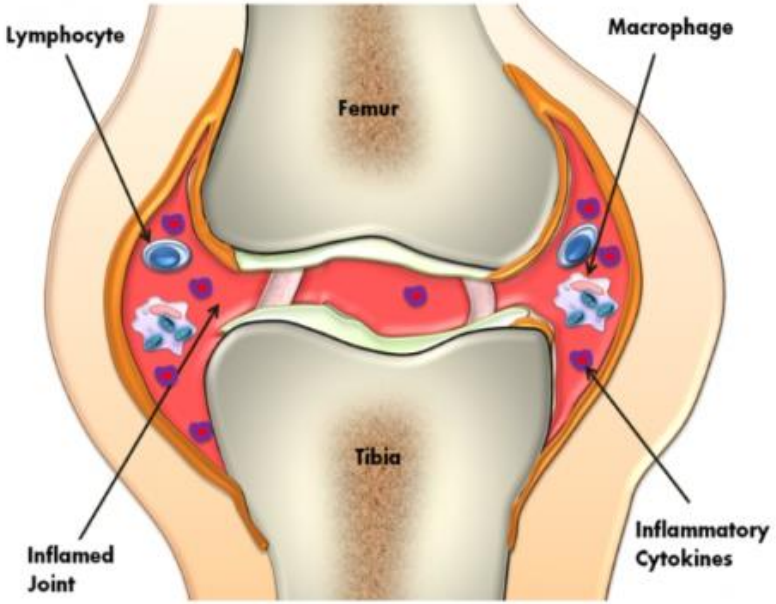
Pediatric Rheumatology Basics for the Novice APP:

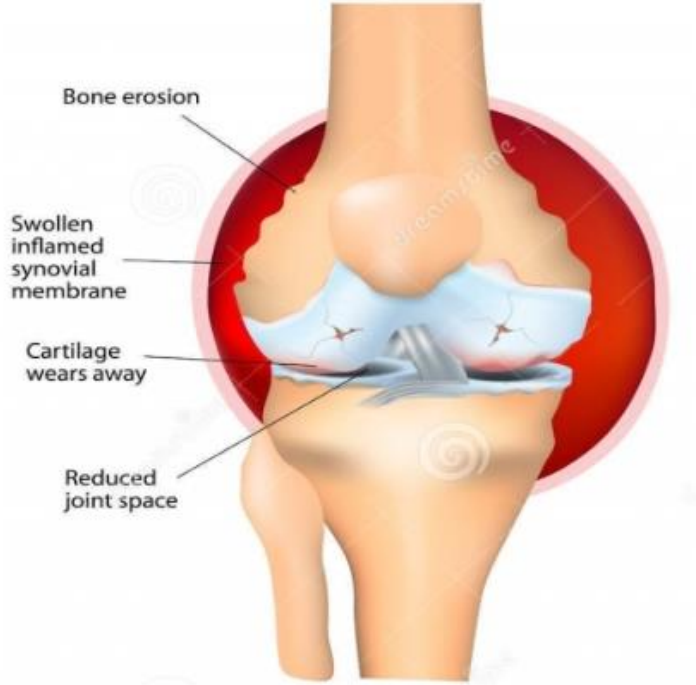
Juvenile Idiopathic Arthritis

Juvenile Idiopathic Arthritis (JIA) Epidemiology

- Most common pediatric rheumatologic disease
- Global distribution
- Prevalence: ~300,000 in USA
- Immune mediated inflammatory synovitis

JIA Pathophysiology





JIA Diagnosis

- Onset prior to 16 years of age
- Persistence of symptoms 6 weeks or greater
- No other cause of synovitis identified
- Further specifications for each of the classification types
- Presentation can be different from adults
- May not complain of pain
  - Stiffness is an abstract concept
  - Irritability in morning, after naps
  - Not walking on time, delay in milestones (i.e., pincer grasp), not playing at recess

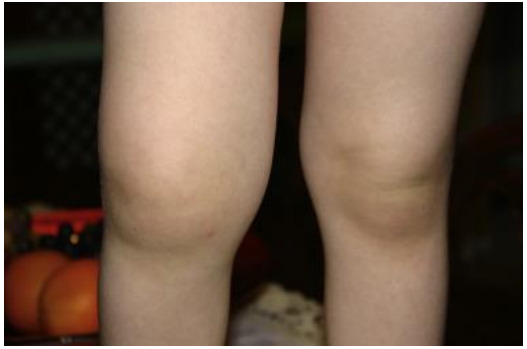
JIA Classification (ILAR)

- **Oligoarticular** (40-60%)
- **Polyarticular** (20-35%)
  - RF positive
  - RF negative
- **Enthesitis Related Arthritis (ERA)** (5-10%)
- **Psoriatic** (~5%)
- **Systemic** (10-20%)
- Undifferentiated

ILAR = International League of Associations for Rheumatology

Oligoarticular JIA

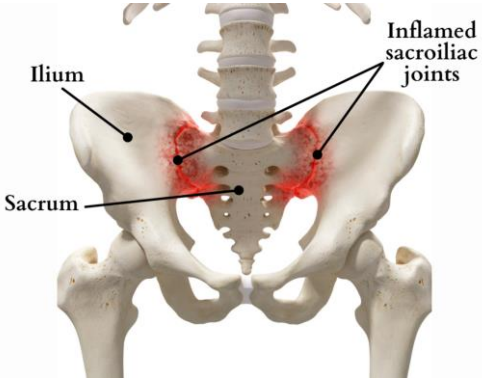
- Arthritis of <5 joints
- Sub-classification:
  - Persistent oligo JIA: never > 4 joints
  - Extended oligo JIA: eventually > 4 joints
- Peak incidence 1 – 3 years old
- Females more affected (3:1)
- Large joints (knees, ankles)
  - **Unilateral hip is rare; look for other cause!**
- Best overall prognosis of all JIA types
- Highest risk of uveitis

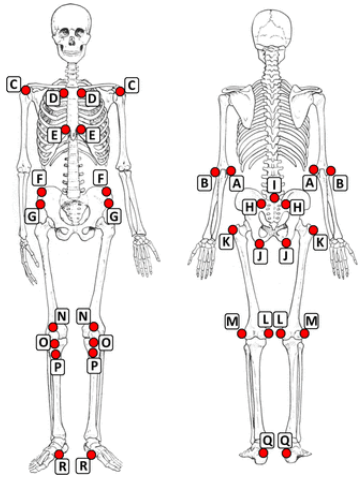


Enthesitis Related Arthritis

- Arthritis *and* Enthesitis
  OR
- Arthritis *or* Enthesitis, plus 2 of following:
  - SI tenderness or inflammatory back pain
  - HLA-B27+
  - Acute anterior uveitis
  - Onset of arthritis in boys > 6 years old
  - 1st degree relative with AS or ERA

- Mean age of diagnosis 10 – 13 years old
- Predominance of males





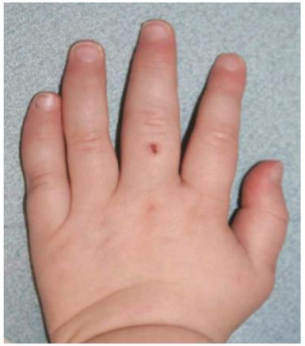
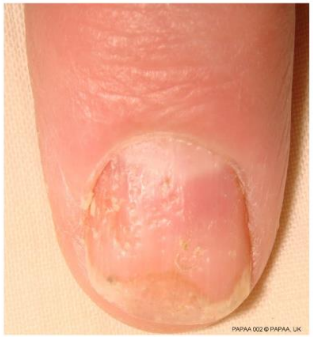
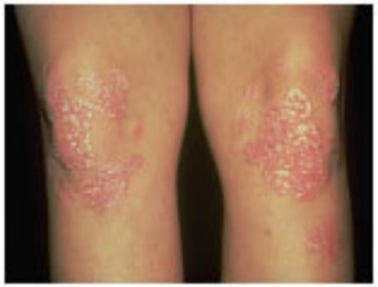
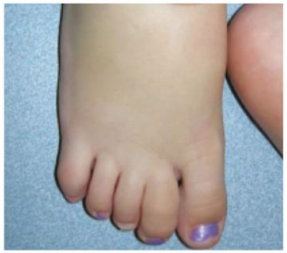
Polyarticular JIA

- 5 or more joints affected
- Classified as:
  - **RF positive polyarticular JIA**
    - More severe, erosive
    - Most similar to adult RA
  - **RF negative polyarticular JIA**
    - CCP more specific; historic classifications have not caught up
- Females more affected
- Biphasic peak of onset
  - 1 – 4 years old: F>M
  - Pre-adolescence/adolescence: F >>>M

Juvenile Psoriatic Arthritis

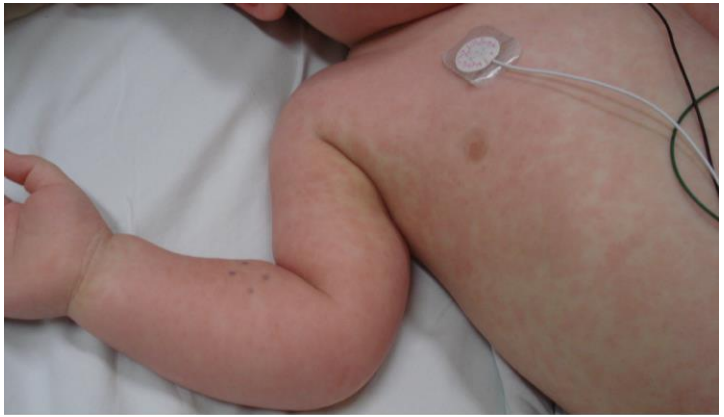
- Arthritis *and* Psoriasis
  OR
- Arthritis, plus 2 of following:
  - Dactylitis
  - Nail pitting or onycholysis
  - Psoriasis in a first-degree relative

- Age of onset bimodally distributed
  - 1st peak during preschool years
  - 2nd peak during middle to late childhood
- F > M

Systemic JIA

- Most severe JIA classification
- Behaves differently from other forms of JIA
- Autoinflammatory (as opposed to autoimmune)



The Role of Labs in JIA

Diagnosis is not based upon labs

- Labs help us track (sometimes)
  - Inflammatory markers are variable
- Labs help us categorize: RF, CCP, HLA-B27
- Labs help us with prognosis
  - RF/CCP = More erosive disease
  - ANA = Risk of uveitis

Most kids with JIA have normal labs!

ANA plays no diagnostic role

Differential Diagnoses

- Growing Pains
- Hypermobility
- Ortho: Trauma, Osgood Schlatter, Sinding-Larsen-Johansson, SCFE, Legg-Calve-Perthes, etc.
- Malignancies (leukemia, lymphoma)
- Infectious
  - Transient Synovitis/Post-viral Reactive Arthritis
  - Post-Streptococcal Reactive Arthritis, Rheumatic Fever
  - Septic Arthritis
  - Osteomyelitis
  - TB, Lyme Arthritis

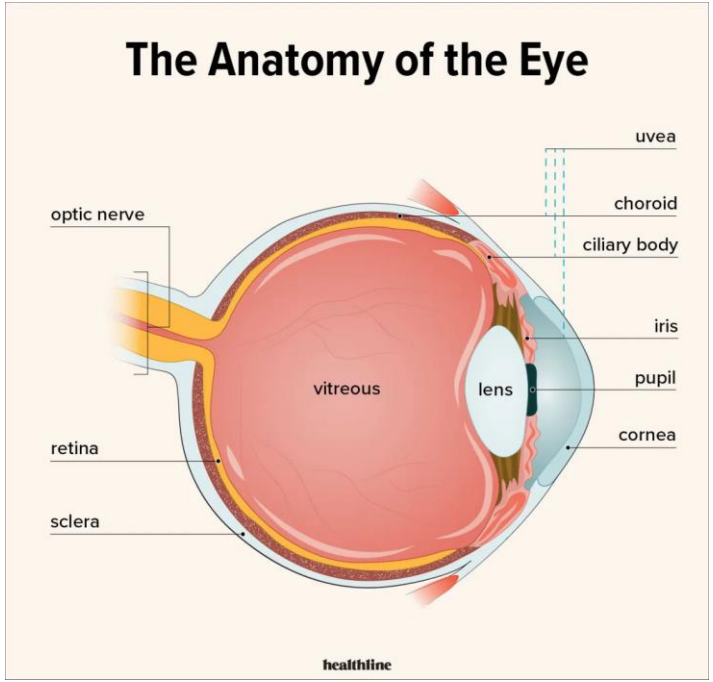
Differential Diagnoses (cont'd)

- GI: IBD, celiac disease
- Coagulopathy (hemophilia)
- PVNS
- Pain with no swelling: Amplified Musculoskeletal Pain Syndrome (AMPS), Vitamin D deficiency, Thyroid Dysfunction
- Rheumatologic disease
  - JIA
  - SLE
  - JDM
  - Vasculitis
  - Sarcoidosis
  - Autoinflammatory diseases

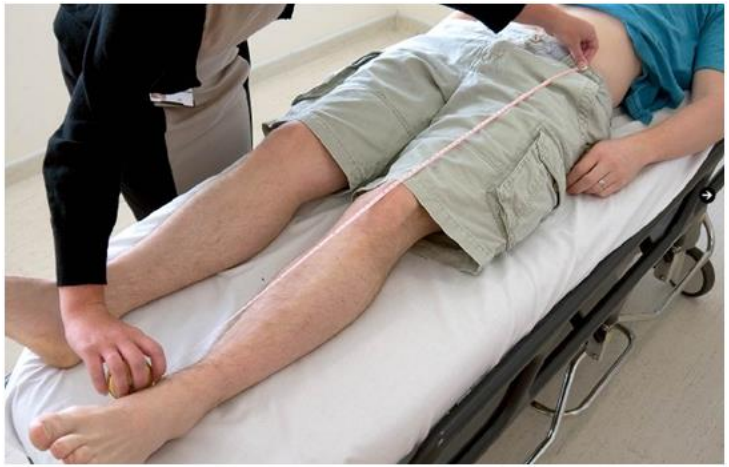
JIA Complications: Uveitis

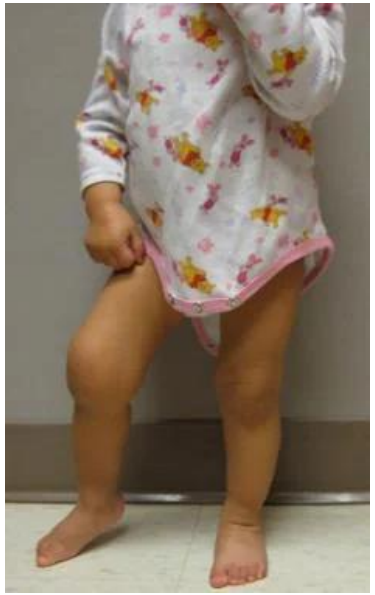
- **ERA/HLA-B27+:** Acute anterior uveitis
  - Symptomatic (painful red eyes, blurry vision, photophobia)

- **Oligoarticular (& sometimes polyarticular):** Chronic anterior uveitis
  - Most are asymptomatic
  - 4th leading cause of blindness in children
  - Positive ANA significantly increases risk
  - 20% of ANA+ oligoarticular JIA



JIA Complications: Leg Length Discrepancy and Thigh Atrophy

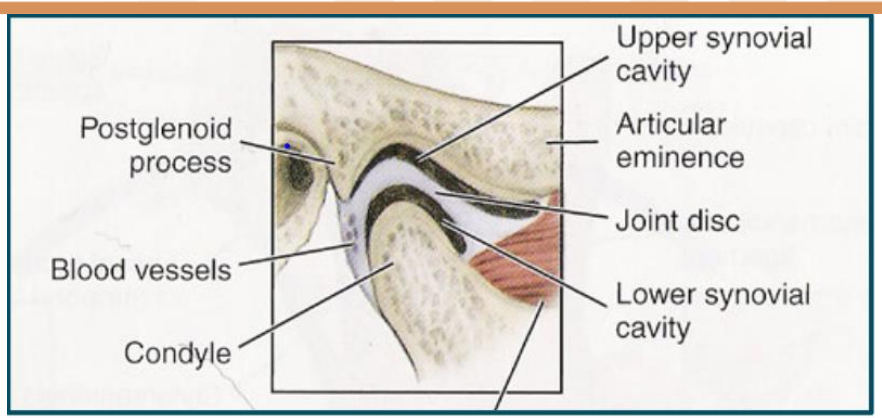




>1 cm difference: Refer to PT for shoe lift

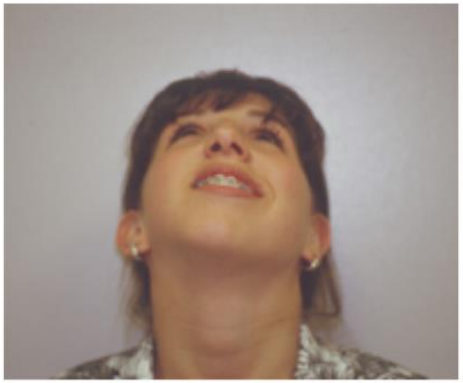
JIA Complications: TMJ Arthritis

- Common (30-60%)
- Destructive
- Often missed
- Difficult to treat
- Poor outcomes
  - Micrognathia, dentition problems, malocclusion, chronic pain
  - May need reconstructive surgery



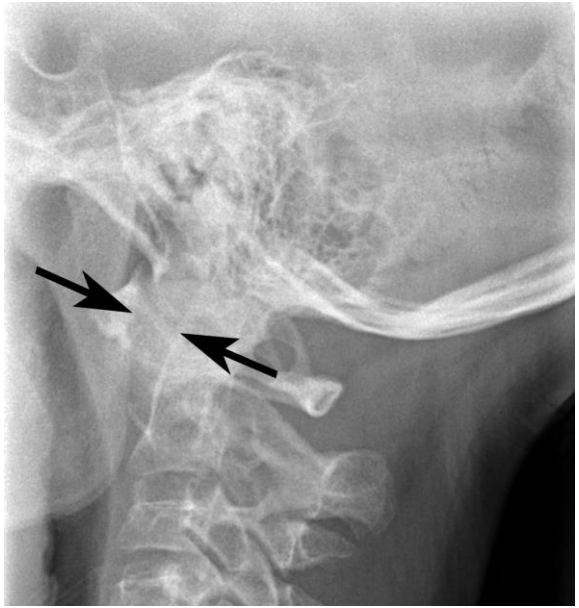
TMJ Monitoring

- Ask about jaw pain, pain chewing, avoiding certain foods
- Palpation over TMJ with opening/closing – Pain? Crepitus?
- Jaw asymmetry
- Maximal Interincisal Opening – goal 4 cm or 3 fingers

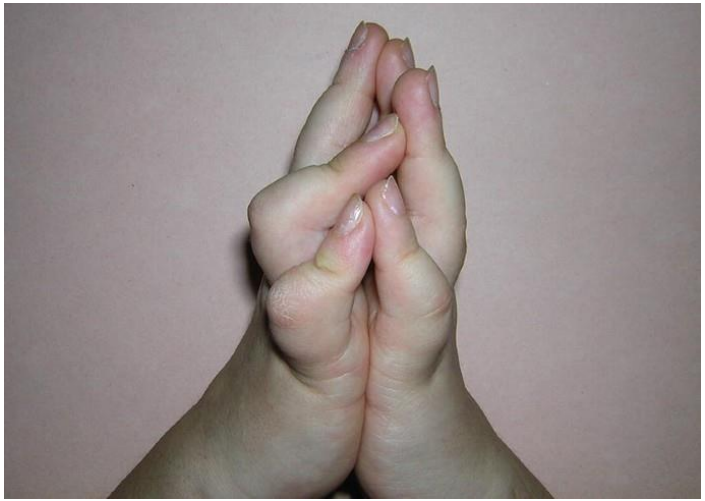


JIA Complications

C-Spine Subluxation

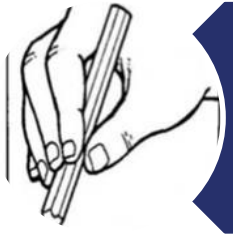


Flexion Contractures



JIA Complications

Impact on development



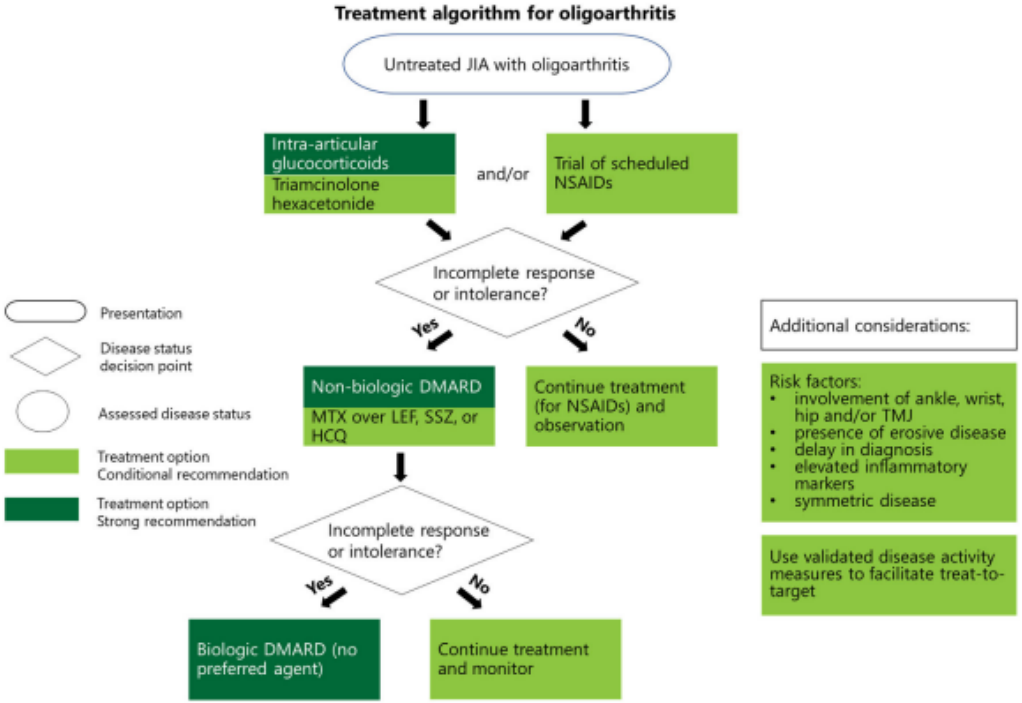
Impact on school performance

Social/ Emotional/ Bully

Treatment Goals

REDUCE PAIN, IMPROVE FUNCTION, PREVENT DAMAGE / DISABILITY

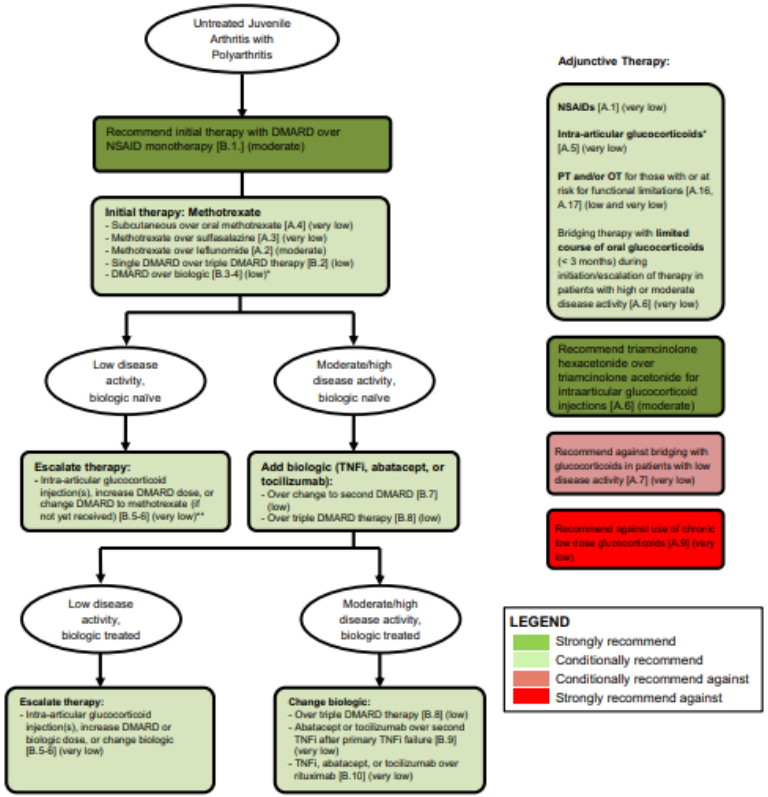
2021 ACR/AF Guidelines for the Treatment of Oligoarticular JIA



DMARD = disease-modifying antirheumatic drug, HCQ = hydroxychloroquine, JIA = juvenile idiopathic arthritis, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal antiinflammatory drugs, SSZ = sulfasalazine, TMJ = temporomandibular joint

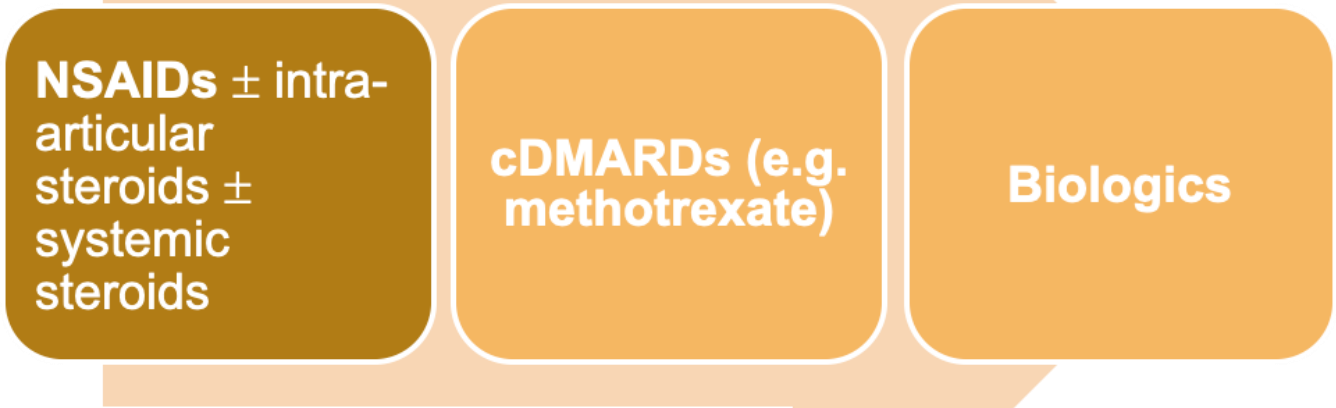
Figure 1. Treatment algorithm for oligoarthritis.

2019 ACR/AF Guidelines for the Treatment of Polyarthritis



Therapy Escalation

Dependent on disease activity



cDMARD = conventional DMARD

Ringold S. *Arthritis Care Res (Hoboken)*. 2019 Jun;71(6):717-734.

NSAIDs

- Role: mostly for symptomatic relief
- Mechanism of action: COX inhibition
- Clinical pearls
  - Celecoxib: only FDA-approved NSAID in pediatrics
  - Naproxen: available as oral suspension, but rarely covered by insurance
  - Drug-drug interaction with methotrexate: not clinically significant with rheumatologic ”low-dose” of methotrexate used
  - Avoid aspirin due to Reye’s Syndrome, excluding Kawasaki Disease

Corticosteroids

1. Intra-articular steroid injections
   - Role: symptomatic relief
   - Agents: Triamcinolone acetonide, triamcinolone hexacetonide
   - Joint injections can be due either without or with sedation depending on patient's age and number of joints requiring injections
   - Duration of effect: 3-6 months, up to 12 months

2. Systemic steroids
   - Role: quick control of initial disease presentation, disease flare
   - Goal is to always minimize long-term exposure given established short-term and long-term consequences of chronic corticosteroid exposure in pediatric population

Conventional DMARDs: Clinical Pearls

1. Methotrexate: first-line DMARD
    a. Preferred route of administration: Subcutaneous
    b. Supportive care
        i. Oral sores, GI side effects: folic acid
        ii. Nausea: folic acid, antiemetic
        iii. Major surgeries: Hold 1 week before and 2 weeks after
2. Leflunomide
    a. Typically used if patient is intolerant to methotrexate
    b. No specific pediatric dosing
3. Sulfasalazine
    a. Minimal evidence for use in JIA
    b. Used in spondyloarthritis/ERA

Biologic DMARDs

Drug Class	Clinical Pearls
TNF inhibitors • Adalimumab (Humira®) and biosimilars • Etanercept (Enbrel®) • Infliximab (Remicade®) and biosimilars	• Adalimumab: FDA approved indications for polyarticular JIA and pediatric uveitis • Infliximab: additional role in treatment of uveitis • Adalimumab and infliximab: commercially available method to measure drug level and development of antidrug antibodies • Warnings and precautions (select): malignancies, new-onset or worsening heart failure, new-onset or worsening of CNS demyelinating disease • Can cause pustular and palmoplantar psoriasis
Tocilizumab (Actemra®)	• Additional role in treatment of uveitis • Dose adjustments necessary in the setting of neutropenia, thrombocytopenia, and hepatotoxicity • Dyslipidemia: no current guidance in pediatric patients
Abatacept (Orencia®)	• Intravenous route of administration requires a loading dose period vs. subcutaneous • Post marketing adverse effects: new or worsening psoriasis, angioedema reactions, vasculitis, non-melanoma skin cancers

Humira. Package insert. AbbVie Inc; 2021.
Enbrel. Package insert. Amgen; 2022.
Remicade. Package insert. Janssen Pharmaceutical Companies; 2021.
Actemra. Package insert. Genentech, Inc.; 2022.
Orencia. Package insert. Bristol-Myers Squibb Company; 2022.
Klein A. *ACR Open Rheumatol.* 2020 Jan;2(1):37-47.

Biologic DMARDs

Medication Name	Clinical Pearls
Golimumab (Simponi Aria®)	• Requires a dosing load period • No maximum dose • Antidrug antibodies were found to not be clinically significant • Off-label use for non-infectious uveitis
Tofacitinib (Xeljanz®)	• Available as oral solution and tablet (immediate-release, extended release) • Black Box Warning of cardiovascular risk • Numerous drug-drug interactions • Dose adjustments necessary in the setting of neutropenia, lymphopenia, and anemia
Secukinumab (Cosentyx®)	• FDA-approved age for use is different based on types of JIA • Requires a dosing loading period • Auto-injector (Sensoready pen) is only available in 150 mg strength and takes ~15 seconds for total administration
Ustekinumab (Stelara®)	• Requires a dosing loading period. Can dose up to 90 mg (2 separate injections) • Only FDA-approved for jPsA

Simponi Aria. Package insert. Janssen Pharmaceutical Companies; 2021.
Xeljanz. Package insert. Pfizer Laboratories Div Pfizer Inc; 2022.
Cosentyx. Package insert. Novartis Pharmaceuticals Corporation; 2021.
Stelara. Package insert. Janssen Pharmaceuticals Corporation; 2022.

Pediatric Rheumatology Basics for the Novice APP:

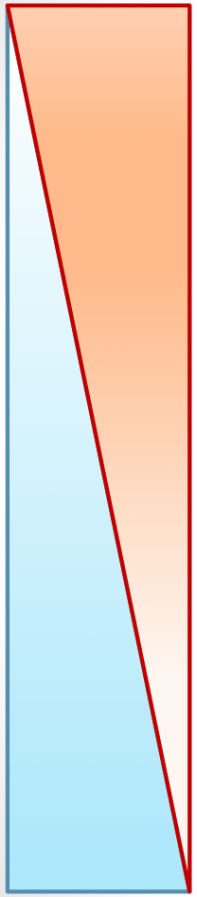
Autoinflammatory/Periodic Fever Syndromes

Overview

I. Autoimmune vs Autoinflammatory
II. Systemic JIA (sJIA)
III. Macrophage Activation Syndrome (MAS)
IV. Brief overview of select autoinflammatory conditions
    I. Periodic Fever Syndromes
    II. CRMO

Adapted from: Scrambler T, Brit Soc Imm, & McGonagle D, PLoS Med

AUTOINFLAMMATION



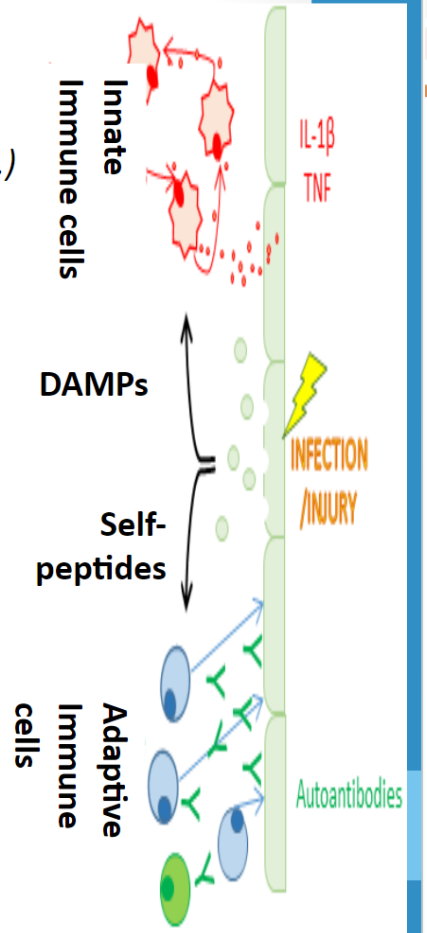
Rare monogenetic autoinflammatory dz — *FMF, CAPS, HIDS, TRAPS, Blau, NLRC4*

Polygenic Autoinflammatory dz — *IBD; OA, Uveitis (idio.) Takayasu, GCA, PAN PFAPA, Sarcoidosis CRMO*

Mixed pattern dz *(partially MHC class I-assoc; partially autoinflamm)* — *Behcet's; Gout; SpA, AS, ERA, PsA Reactive Arthritis HLA-B27 uveitis*

Polygenic Autoimmune dz — *RA, JIA, Celiac, PBC, Graves/Hashi, vitiligo, MG, Addison, SSc, JDMS, ANCA-vasc, Sjogren, T1DM, SLE*

Rare Monogenic Autoimmune dz — *ALPS, APECED, IPEX*



AUTOIMMUNITY

Systemic Juvenile Idiopathic Arthritis

- Currently classified under ILAR under the autoimmune JIA umbrella
- In reality, the pathogenesis and clinical phenotype are more in line with polygenic autoinflammatory syndromes

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

SJIA ILAR Classification Criteria

- Fever for at least 2 weeks AND Quotidian for at least 3 days
- Arthritis in 1 or more joint
  AND
- 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

Labs not part of criteria

- They help exclude other dx
- Trend & recognize complications

DO NOT have to wait for 2 weeks to treat; Once other dx are excluded, start treating ASAP

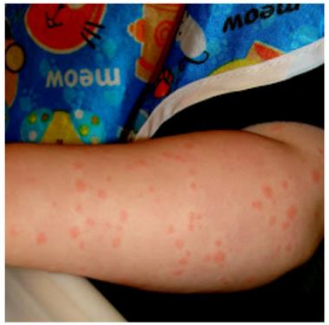
SJIA Manifestations

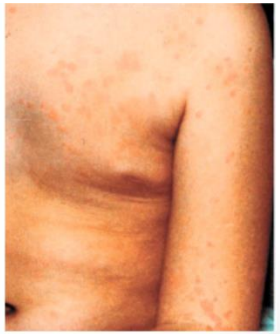
Fever

- 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

SJIA Laboratory 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

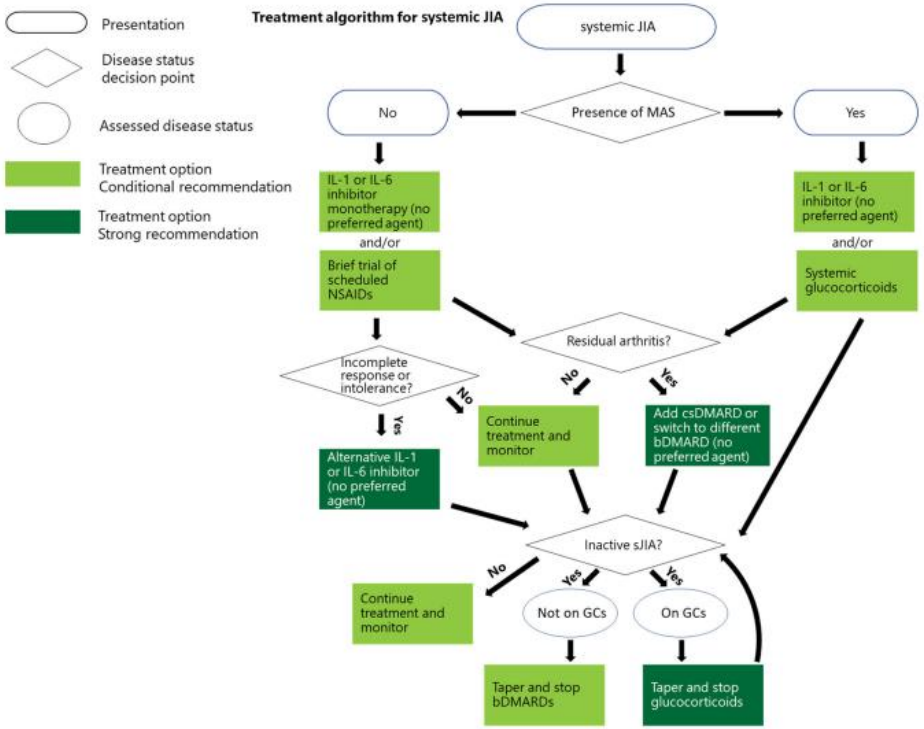
Differential Diagnoses

- 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)

SJIA 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

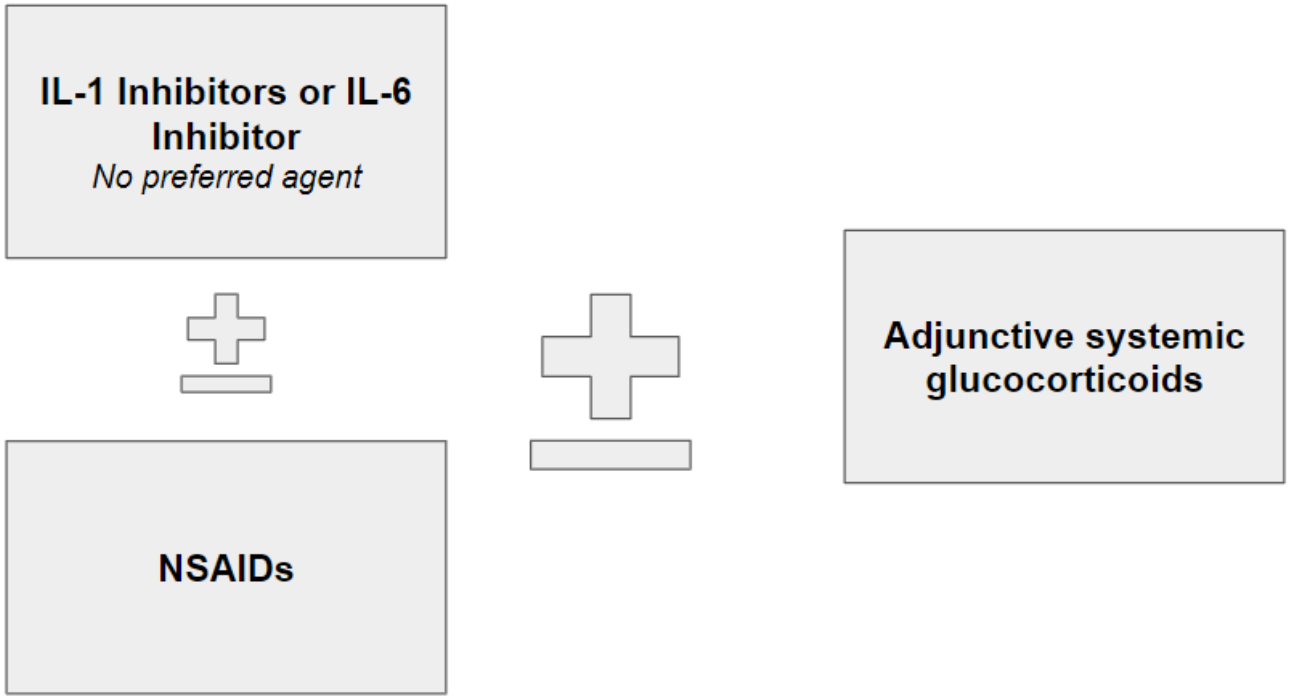
2021 ACR/AF Guidelines for the Treatment of Systemic-Onset JIA



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.

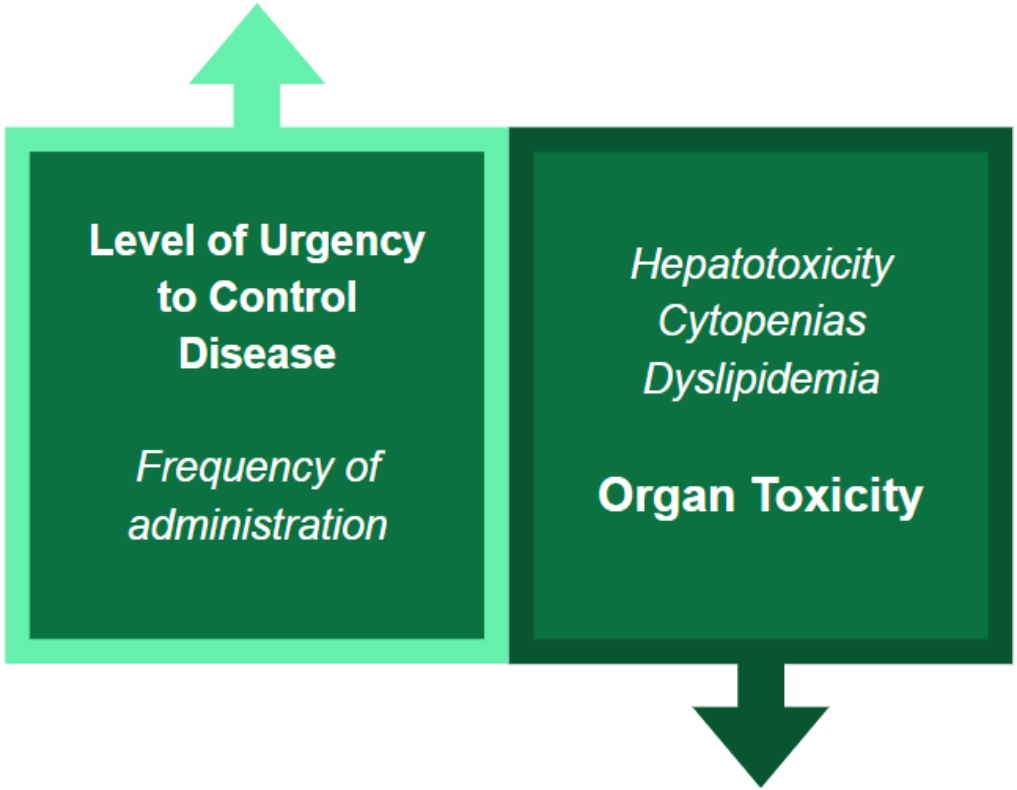
Initial Treatment



IL = interleukin; NSAD = nonsteroidal anti-inflammatory drugs

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

Picking an Interleukin Inhibitor



Cytokine Storm

- Cytokine storm = the physiology behind the condition called Hemophagocytic Lymphohistiocytosis (HLH)

- A final common pathway of uncontrolled inflammation
  - Fever
  - Hemodynamic instability
  - End organ dysfunction

- Multiple routes to end up at this final destination

Hemophagocytic Lymphohistiocytosis (HLH)

- Primary (a.k.a. ‘genetic’) HLH
  - Familial
  - Immunodeficiency syndromes
- Secondary (a.k.a. ‘reactive’) HLH
  - Infections
    - Viral Hemorrhagic fever (Dengue, Ebola)
    - Sepsis / SIRS
    - Endotoxin mediated (TSS)
    - EBV, CMV
  - Malignancy
  - Rheumatologic disease → Macrophage Activation Syndrome

Macrophage Activation Syndrome (MAS)

- Reported in virtually all pediatric rheumatologic conditions
- Most common in sJIA
  - **Prevalence of MAS in sJIA ~10%**
- Next most commonly seen in
  - SLE
  - JDM
  - Kawasaki (“Kawasaki Shock”)

MAS = Medical Emergency

In a febrile patient with a known and active rheumatologic condition,

- Fall in ESR and platelet count
- Ongoing elevation of CRP
- Increasing D-dimer

SHOULD RAISE SUSPICION FOR MAS

- Especially if hyperferritinemia is present
- Ferritin >10,000 has a very limited differential diagnosis in peds
  - 88-90% sensitive and >98% specific for MAS in SJIA

High Ferritin = High Mortality

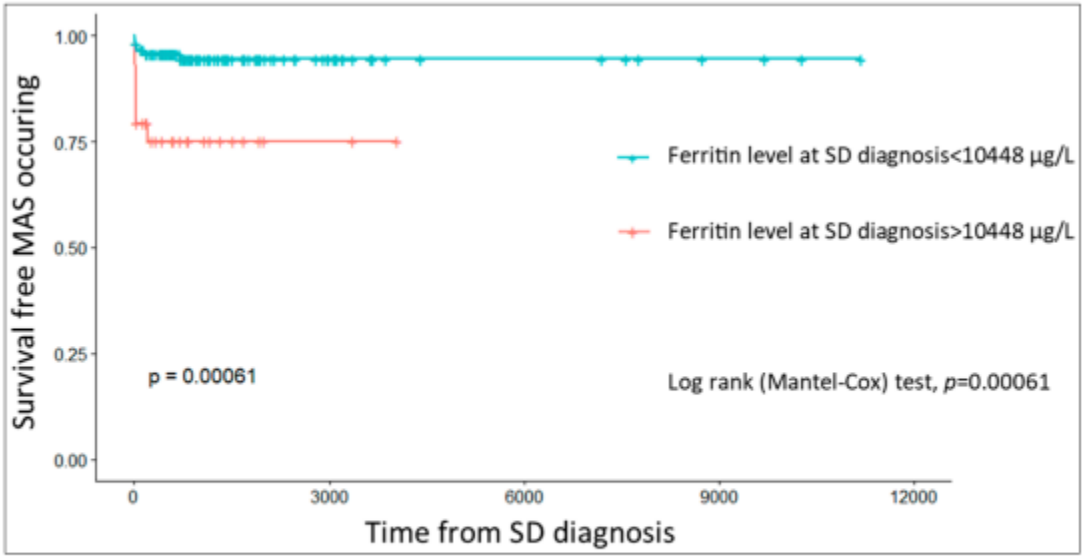


Figure 1. Kaplan–Meier curves showing the probability of MAS-free survival as a function of ferritin level at the time of SD diagnosis (MAS, macrophage activation syndrome; SD, Still's disease).

J Clin Med. 2021 Dec 31;11(1):206.

Lab Findings in 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

Clinical Presentation of MAS

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

2016 ACR/EULAR Criteria for Classification of MAS in SJIA

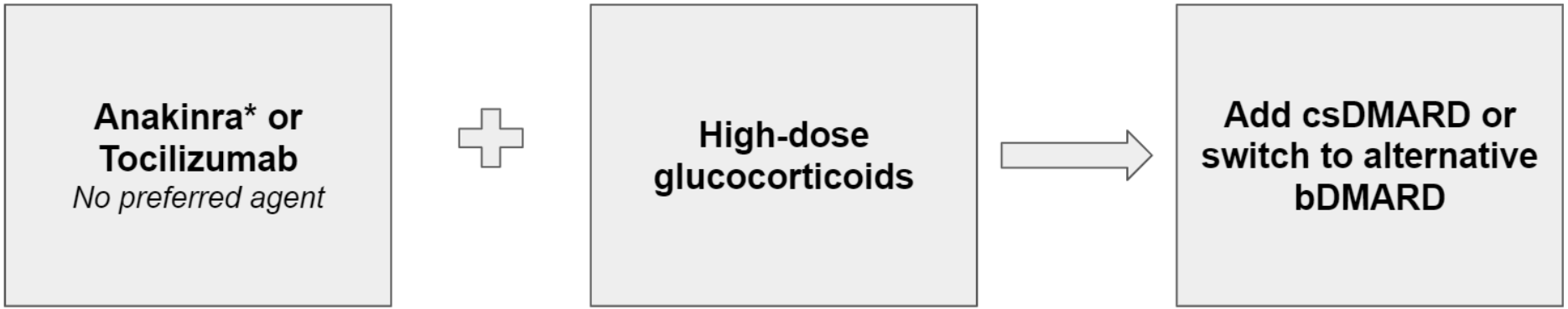
- A **febrile** patient with **known or suspected sJIA** is classified as having MAS if the following are met:

- **Ferritin** > 684 ng/ml

- And **any 2** of the following:
  - Platelets < 181k
  - AST > 48 U/L
  - Triglycerides >156 mg/dl
  - Fibrinogen < 360 mg/dl

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

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

Arthritis Rheumatol. 2022 Apr;74(4):553-569
EULAR Annual Meeting 2019. Abstract.
J Allergy Clin Immunol. 2017;139:1698-1701.
Ann Rheum Dis. 2023 Jun;82(6):857-865.

Adapted from: Scrambler T, Brit Soc Imm, & McGonagle D, PLoS Med

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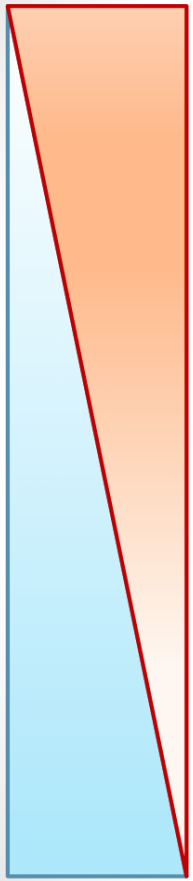


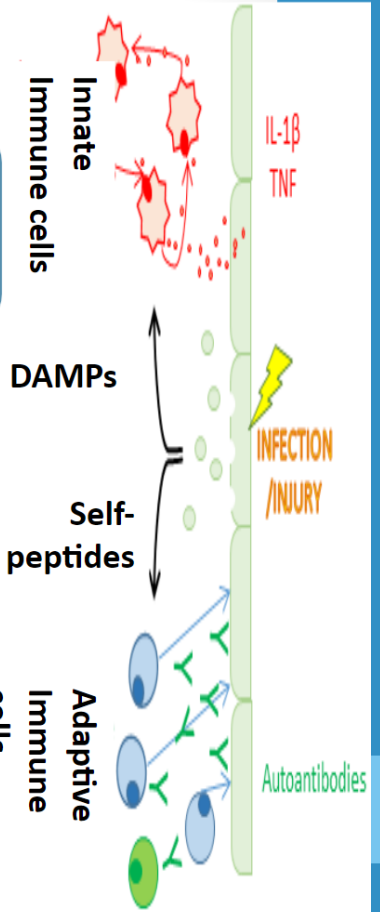
Rare monogenetic autoinflammatory dz — *FMF, CAPS, HIDS, TRAPS, Blau, NLRC4*

Polygenic Autoinflammatory dz — *IBD; OA, Uveitis (idio.) Takayasu, GCA, PAN PFAPA, Sarcoidosis CRMO*

Mixed pattern dz *(partially MHC class I-assoc; partially autoinflamm)* — *Behcet's; Gout; SpA, AS, ERA, PsA Reactive Arthritis HLA-B27 uveitis*

Polygenic Autoimmune dz — *RA, JIA, Celiac, PBC, Graves/Hashi, vitiligo, MG, Addison, SSc, JDMS, ANCA-vasc, Sjogren, T1DM, SLE*

Rare Monogenic Autoimmune dz — *ALPS, APECED, IPEX*



AUTOIMMUNITY

Non-Hereditary Periodic Fever Syndrome: PFAPA

PFAPA = Periodic Fever, Aphthous stomatitis, Pharyngitis, Adenitis

- **Periodic Fevers**
  - Frequency: Every 3-6 weeks (mean 28 days)
  - Duration: 3-6 days (mean 5 days)
  - VERY predictable; often identifiable prodrome
- **Aphthous stomatitis** (38-75%)
- **Pharyngitis** (75-100%)
- **Adenitis** (61-100%) - cervical

Clinical Features of PFAPA

- ***Most common Periodic Fever Syndrome***
- Onset typically before age 5, self-resolves by late school-age
- No long-term sequelae from inflammation
  - Major quality of life implications: missed school/work, unnecessary antibiotics, etc.
- Completely well between episodes
- Other symptoms – HA, abdominal pain, arthralgias
- Often managed by PCPs

PFAPA

Diagnosis = Clinical

- Fever/Symptom Diary – Predictable pattern emerges
- Labs: acute phase during flares (leukocytosis, hypergammaglobulinemia, ESR, CRP); normal labs in between
- Exclude other etiologies (immunodeficiency with frequent infection, cyclic neutropenia, genetic autoinflammatory) – degree of workup based upon degree of suspicion

Treatment

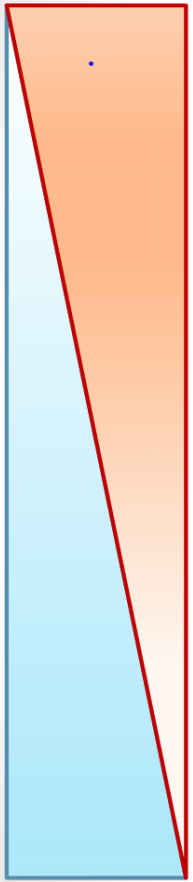
- Prednisone 1-2 mg/kg as a single dose at onset of fever
  - Can repeat in 24 hours if still febrile
  - Typically will abort entire episode and be life-changing
  - Episodes can start to be more frequent
- Cimetidine, colchicine
- Tonsillectomy

Chronic Nonbacterial Osteomyelitis

- Bone inflammation in absence of identifiable trigger
  - Pain periarticular or non-articular; often worse at night
  - Labs may be normal or abnormal
- Imaging – looks like infectious osteo, but lesions are sterile
  - Some say that it is triggered by infectious exposure
- Precise immunologic basis unclear
- Some have overlap with HLA-B27+ spondylitis, but most HLA-B27 neg
  - Association w IBD
- Classic teaching is that most resolve by adolescence
  - Some more recent cohorts report persistence

Adapted from: Scrambler T, Brit Soc Imm, & McGonagle D, PLoS Med

AUTOINFLAMMATION



Rare monogenetic autoinflammatory dz — *FMF, CAPS, HIDS, TRAPS, Blau, NLRC4*

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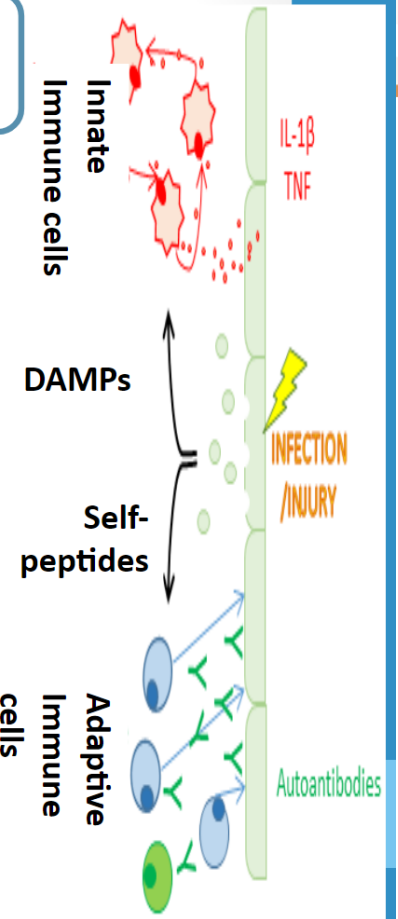
Rare Monogenic Autoimmune dz — *ALPS, APECED, IPEX*



AUTOIMMUNITY

Rare Monogenetic Autoinflammatory Syndromes

1. **IL-1β Activation Disorders (inflammasomopathies)**
   - CAPS (Cryopyrin Associated Periodic Syndrome)
   - FMF (Familial Mediterranean Fever)
   - PAPA (Pyogenic Arthritis, PG & Acne)
   - HIDS (Hyper Ig-D Syndrome)
   - DIRA (Deficiency of IL-1 Receptor Antagonist)
   - NLRC4-associated MAS
2. **Protein Folding Disorders of the Innate Immune System**: TRAPS (TNF receptor-associated Periodic Syndrome)
3. **Interferonopathies**
   - SAVI (STING-associated Vasculopathy of Infancy)
   - CANDLE (Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy & Elevated Temperature)
4. **Other**: DADA-2 (Deficiency of Adenosine Deaminase 2)

Rare Monogenetic Autoinflammatory Syndromes

Many different types, but collectively are manifest by:

- Dysregulated innate immune system
- Flares of inflammation with variable frequency & duration
- Untreated, adverse health outcomes from inflammation
  - MAS, amyloidosis/renal failure, hearing loss, …

Some unique differences in treatment amongst them

- Many respond to colchicine
- Nearly all respond to anti-IL1
- Some respond to anti-TNF
- Steroids have a roll in some situations; not good long-term

Genetic testing confirms diagnosis

Comparing Select Monogenetic Periodic Fever Syndromes

	Cryopyrin-Associated Periodic Syndromes (CAPS)			Pyrin	Protein Folding	Mevalonate Kinase Deficiencies		*ADA2 deficiency*
	Familial Cold Autoinflammatory Syndrome*	Muckle-Wells Syndrome*	Neonatal-Onset Multisystem Autoinflammatory Disease—aka Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA)*	Familial Mediterranean Fever*	Tumour Necrosis Factor (TNF)-Associated Periodic Sydrome —aka Familial Hibernian Fever*	Hyperimmunoglobulinemia D with Periodic Fever Syndrome (HIDS)*	Mevalonate Aciduria (MA) (Mevalonate Kinase Deficiencies, such as HIDS & MA are also referred to as MKD)	Deficiency of Adenosine Deaminase 2 (DADA2) —aka Fever w/Early Onset Stroke (FEOS)
ACRONYM	FCAS	MWS	NOMID/CINCA	FMF	TRAPS	HIDS	MA	DADA2
GENE	*NLRP3*	*NLRP3*	*NLRP3*	*MEFV*	*TNFRSF1A*	*MVK*	*MVK*	*CECR1*
INHERITANCE	Autosomal Dominant. Large familial groups, some spontaneous mutations.[1]	Autosomal Dominant. Spontaneous mutations, some familial groups.[1]	Autosomal Dominant. Spontaneous mutations, few familial cases.[1]	Autosomal Recessive. Some cases are gene-dosage-dependent autosomal dominant.[10]	Autosomal Dominant. Spontaneous mutations, some familial groups.[1]	Autosomal recessive. Some cases w/only one mutation found.[33]	Autosomal recessive.	Autosomal recessive.
ETHNICITY	Affects all races, but many are of European descent.[1]	Affects all races, but many are of European descent.[1]	Any–present in all races.[1]	Turk, Armenian, Arab, Sephardic Jew, Italian.[1] Most common inherited periodic fever syndrome.	Affects all races. 2nd most common inherited SAID (after FMF.)[1]	Mostly of Dutch descent, or Northern European.[1]	Mostly of Dutch descent, or Northern European.[1]	Unknown.
FREQUENCY IN THE WORLD	1:1 million, or more. In USA 300+ diagnosed–most cases are from large family groups.[2,5]	1:1 million, maybe more. Some large family groups.[5] Frequency of CAPS in France is 1:360,000.[55]	Estimated frequency 1:1 million, mostly due to spontaneous genetic mutations.[5]	In specific ethnic groups, the carrier frequency of *MEFV* variants is up to 1:5 people.[1]	Unknown. TRAPS affects 0.01:10,000 people in the European Union.[51] >1000 pts. worldwide.[52]	Unknown, but very rare. >200-300 known patients worldwide, (>300, when suspected cases are also included.)[12]	Unknown, but very rare. <100 known patients worldwide.[11]	Unknown but rare.
TIMING OF SYMPTOMS OR ATTACKS	12-24 hours, or longer. Onset of fever & flares is often 1-3 hours after exposure to cold or cooling temperatures.[1]	Often lasts 2-3 days. Random onset–flares of fever & symptoms are often triggered by cold or cooling temperature.[1]	Continuous w/increased symptoms & fever during flares.[1] Chronic inflammation noted between flares.	12-72 hours.[1,9] Recurrent fever & flares can occur weekly, or only a few times a year.	Days to weeks. Average flare is 3 weeks.[1,9]	3-7 days. Recurrent bouts of fever & flares every 2-12 weeks.[1,9] Some flares occur after vaccines.[9]	4-5 days. Recurrent flares & fever every 2-3 weeks. Patients have chronic inflammation noted between flares.[11]	Intermittent, recurrent fevers, livedo reticularis rash, vasculopathy, & high risk for early-onset lacunar stroke.[73,74]
AGE OF ONSET	Infancy, but a few present w/symptoms later in childhood or adolescence.[1]	Infancy, but a few present w/symptoms later in childhood or adolescence.[1]	Neonatal/early infancy. Rash, symptoms, & abnormal labs are often present at birth.[1,6]	Infancy, to under 20 years of age for the first symptoms.[9]	Most first attacks by 3 yrs, & almost all begin by 20 yrs. of age; a few start later in life.[9]	>90% present w/symptoms in infancy.[9]	Most present w/symptoms at birth, or in early infancy. Most have facial features noted at birth.[11]	Onset of symptoms in infancy–early childhood. w/recurrent fevers, livedo reticularis rash, & vasculopathy.[73,74]

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Comparing Select Monogenetic Periodic Fever Syndromes

	FCAS	MWS	NOMID/CINCA	FMF	TRAPS	HIDS	MA	DADA2
SKIN/ CUTANEOUS	Cold induced urticaria-like rash w/increased neutrophils at the eccrine coils.[4] Almost daily rash that increases w/flares.[1]	Urticaria-like rash w/increased neutrophils at the eccrine coils.[4] Most w/daily rash that increases w/flares.[1]	Ever-present[1] Urticaria-like rash w/increased neutrophils at the eccrine coils. Rash increases w/flares.[4]	Erysipeloid erythema on the ankle–foot–below knee region–lasts 2-3 days during flares of symptoms.[1]	Migrating rash w/deep pain under rash areas. Severe pain follows the rash path from the trunk out to the limbs.[9]	Diffuse maculopapular rash. Some w/petechiae or purpura present. A few w/apthous ulcers.[1,9]	Diffuse maculopapular or morbilliform rash. Some w/petechiae or purpura present. A few w/apthous ulcers.[1,8,11]	Livedo reticularis rash, few w/polyarteritis nodosa. Diffuse vasculopathy, w/impaired endothelial integrity & endothelial cellular activation.[73,74]
NEUROLOGIC	Some have headaches, fatigue w/fever after cold exposure. Unknown if there are notable CNS affects at this time.[1]	Some have headaches, fatigue w/fever & flares. Uncommon to have many other CNS symptoms.[1] A few pts. have MWS/NOMID crossover of symptoms.	Headaches, fever, fatigue, chronic aseptic meningitis, & high CNS pressure (ICP). Many with mental &/or cognitive impairments. Papilledema is common.[8]	Fevers. Acute aseptic meningitis is rare & can occur during flares, but is never chronic.[1] Other neurological involvement is very rarely seen in FMF.	Fevers lasting >3 days at over 38°C w/flares. Some have headaches w/flares of symptoms.[1,9]	Headaches & fevers w/flares of symptoms are common.[1,9] More severe neurological symptoms are rarely present in HIDS.[9]	Fevers w/flares. Microcephaly, dolichocephaly, mental retardation, developmental delays, cerebellar ataxia, cerebellar atrophy & epilepsy often develop over time.[11]	Recurrent fevers & early-onset lacunar strokes. Possible adult stroke risk. Brain biopsies: diffuse vasculopathy, w/impaired endothelial integrity & endothelial cellular activation.[73,74]
AUDITORY	Some pts have mild hearing loss–not currently known if it's from CAPS inflammation.[1]	Many have increased sensorineural hearing loss, starting in adolescence.[1]	Many have increased sensorineural hearing loss, from infancy/childhood.[1,8]	Uncommon–not believed to be caused by a FMF disorder.[1]	Uncommon–not believed to be caused by TRAPS.[1]	Uncommon–not believed to be caused by HIDS.[1,9]	Uncommon–not believed to be caused by MA.[1,8,11]	Unknown.[73,74]
OPHTHALMIC	Conjunctivitis (non-infectious) during flares.[1]	Conjunctivitis (non-infectious) during flares,[1] or corneal haze.[20] MWS/NOMID crossover pts. may have more eye involvement.	Papilledema, uveitis, iritis, conjunctivitis. Some w/retinal scarring, corneal haze or vision loss.[8,20]	Very rare to uncommon.[1]	Conjunctivitis, & periorbital edema during flares.[1,9]	Very rare to uncommon.[9]	Uveitis, central cataracts, blue sclerae & tapetoretinal degeneration are often present, even in less severe cases.[11]	Unknown.[73,74] Strokes have the potential to cause blindness.
CARDIO-PULMONARY	Not noted.[1]	Rare.[1]	Some have clubbing of fingers. Some cases of pericardial effusions, or pericarditis.[1]	45% have pleuritis, painful respiration, w/flares. Some w/pericarditis.[1]	Common, including pleurisy.[1]	Rare.[1] Some pts. have developed severe respiratory infections. Higher risk for issues w/*S. pneumoniae* infections.[78]	Rare.[1,11]	Unknown.[73,74]
ABDOMINAL	Uncommon.[1]	Some have abdominal pain w/flares or other gastrointestinal issues.[1]	Nausea, vomiting & abdominal pain w/flares, or w/high CNS pressure.[4]	Sterile peritonitis, pain, and/or constipation with flares.[1]	Peritonitis, diarrhea, & constipation w/flares.[1]	Extreme pain, vomiting & diarrhea w/flares.[1,9] Some w/enlarged liver/ spleen, other GI issues.[78]	Enlarged liver &/or spleen. Cholestatic liver disease. Pain, vomiting & diarrhea w/flares.[1,8,11]	Enlarged liver & spleen; diffuse vasculopathy noted in the liver.[73,74]
LYMPHATIC	Not noted.[1]	Rarely noted.[1]	Some pts. with enlarged liver and/or spleen, many have enlarged lymph nodes.[1]	Enlarged spleen is common, some have enlarged lymph nodes.[1]	Enlarged spleen is common; some have enlarged lymph nodes.[1]	Enlarged cervical lymph nodes w/flares.[1] Few w/enlarged spleen.[78]	Enlarged spleen, &/or lymph nodes are common.[1,11]	Not noted.[73,74]
JOINTS/BONES MUSCLES & CARTILAGE	Arthralgias, stiffness & swelling with flares.[1]	Arthralgias, recurrent arthritis, stiffness & swelling with flares.[1]	Joint pain, knee valgus or varus. Some w/frontal bossing, saddleback nose, contractures, clubbing.[1] <50% of patients knees have bony overgrowth. Short stature, growth delays failure to thrive, arthritis, & osteopenia noted.[1,20]	Mono/Polyarthritis, oligoarthritis & clubbing are common. Ankle arthralgias are common. Severe arthritis of the hip or ankle is rare.[1]	Intermittent or chronic arthritis in large joints w/muscle pain & swelling.[1]	Arthralgias common, symmetric polyarthritis frequently noted.[1]	Congenital defects are often noted: microcephaly, dolichocephaly, wide irregular fontanels, low set and posteriorly rotated ears, downslanted palpebral fissures. Hypotonia, myopathy, & failure to thrive are common.[11]	Not noted.[73,74]
VASCULITIS	Not noted.[1]	Not noted.[1]	Vasculitis rarely develops.[1]	HSP, polyarteritis nodosa.[1]	HSP, lymphocytic vasculitis.[1]	Cutaneous vasculitis common, HSP is rare.[1]	Not noted.[11]	Diffuse vasculopathy in the skin, liver & brain.[73,74]
AMYLOIDOSIS	Elevated serum amyloid (SAA). Secondary amyloidosis in some patients.[1,9]	Elevated SAA. >25 % w/secondary amyloidosis.[1,9]	Elevated SAA. Secondary amyloidosis in <2% pts.[1,8]	Common >50% in untreated patients, it depends on genotype.[9]	10-20% occurrence–higher risk w/cysteine mutation.[9]	<5-10%–uncommon.[9]	Not noted-unknown.[9,11]	Not noted.[73,74]
ABNORMAL LABS	High: ESR, CRP, SAA. Leukocytosis with flares.[1]	High: ESR, CRP, SAA. Leukocytosis,with flares.[1]	Chronically high: ESR, CRP, SAA, anemia, granulocyte leukocytosis.[1,8]	High: ESR, CRP, SAA between flares. Fibrinogen, Leukocytosis present with flares.[1]	High: ESR, CRP, SAA. Elevated PMNs, polyclonal gammopathy, leukocytosis.[1]	High: ESR, CRP, SAA w/flares. High IgD w/IgA in 80% pts. Mevalonate aciduria noted during flares.[1]	Anemia, leukocytosis, thrombocytopenia. High: ESR, CRP, SAA, CK, IgD, IgA, IgE; chronically high Mevalonate aciduria.[1,11]	High: CRP, ESR w/flares. Cytopenia. Blood: 10-fold decrease in ADA2. Low ADA2-specific adenosine deaminase activity: blood & CD14+ monocytes.[73,74]

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Pharmacological Agents

Group	Subtype	IL-1 Inhibitors			TNF-α inhibitors	Other		
		Anakinra	Canakinumab	Rilonacept		Colchicine	CS	JAKi
IL-1β Activation Disorders	CAPS	✓	✓	✓				
	FMF		✓		✓*	✓*		
	PAPA	✓*			✓*		✓*	
	HIDS		✓					
	DIRA	✓	✓*	✓			✓*	
	NLRC4-associated MAS	✓*	✓*				✓*	
TRAPS			✓		✓* Etanercept		✓*	
Interferonopathies	SAVI							✓*
	CANDLE							✓*
Other	DADA2				✓*			

CS = Corticosteroids; JAKi = JAK inhibitors; ✓* = Off-label use

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QUESTIONS?