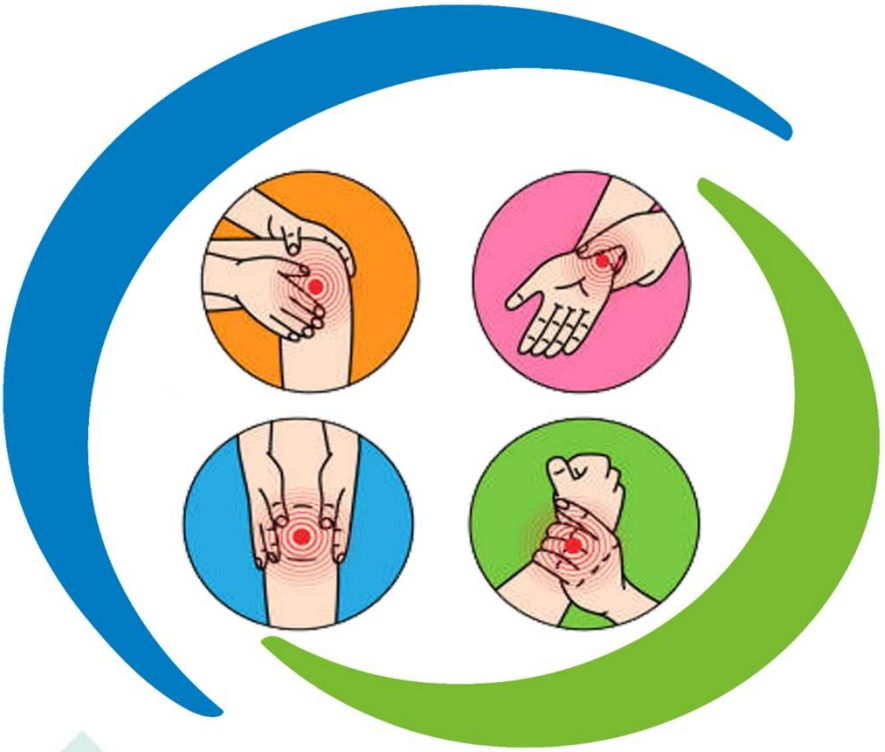
Pediatric Rheumatology Protocol of EHA



First Edition 2024

Egyptian Clinical Practice Protocols

in

Pediatric Rheumatology

for

Egypt Healthcare Authority

First Edition

2024

Prepared by

Working Group for Development of

Egyptian Clinical Practice Protocols

in

Pediatric Rheumatology

for

Egypt Healthcare Authority

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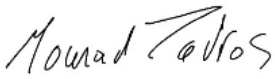

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PREFACE

Recently, there is an increasing need to provide programs with accurate competency-based assessments to ensure the delivery of high-quality healthcare. The aim of developing these Egyptian Clinical Practice Protocols in Pediatric Rheumatology is to unify and standardize the delivery of healthcare to any child at all health facilities.

Pediatric Rheumatology service is usually offered to children below 16 years of age in Egypt.

The current status of healthcare in which avoidable failures are abound. “We train longer, specialize more, use ever-advancing technologies, and still we fail.” Part of the problem, is that the ever-increasing complexity of medicine makes uniform care delivery impractical or impossible. That is, unless there are protocols, checklists, or care paths that are readily available to providers.

Regarding Pediatric Rheumatology, busy clinicians have all felt the need for a concise, easy-to-use resource at the bedside for evidence-based protocols, or consensus-driven care paths.

In this protocol, we offer comprehensive reviews of selected topics and comprehensive advice about management approaches based on the highest level of evidence available in each case. Our goal is to provide an authoritative practical medical resource for pediatricians.

We hope that such an approach will encourage clinicians to apply available evidence to their practice and also track compliance with desired practices. We hope that practicing pediatricians, fellows and practitioners will find this protocol useful in delivering high-quality clinical care to their patients. We remain open to feedback and suggestions about how to improve this resource and how to make it maximally useful to those delivering care at the bedside in for patients in Pediatric Rheumatology.

Members of the Working Group

For Development of the Egyptian Clinical Practice Guideline

In Pediatric Rheumatology

Table of Contents

General Referral Guidelines

When to refer to pediatric rheumatology?

Referral to paediatric rheumatology is indicated in the following cases:

1. Suspicion of inflammatory disease (joint or muscle).
2. Suspicion of multisystem disease (e.g., rash suggestive of vasculitis, Raynaud's, uveitis, fever of no apparent cause).
3. Limp that is not resolving.
4. Swollen joint(s).
5. Clumsiness (especially if changing from the child normal
6. Back pain.
7. Limb pain.
8. Joint pain that is not resolving.
9. Any red flags in each of the previous conditions.

N.B:

"Pediatric rheumatology referral guidelines depending on the complaints and the suspected rheumatologic disease"

Guidelines for diagnosis and treatment of systemic lupus Erythematosus in children

Introduction

- Juvenile systemic lupus erythematosus (JSLE) is a chronic, systemic autoimmune disease that has great impact on the child or young person affected. It shares its pathogenesis with adult-onset SLE, but generally has a more severe clinical phenotype (1).
- Clinical heterogeneity, unpredictable course and flares are characteristics of this disease.
- Tissue damage caused by autoantibodies or immune-complex depositions occurs in kidneys, heart, vessels, central nervous system, skin, lungs, muscles and joints leading to significant morbidity and increased mortality (2).
- Evidence-based guidelines are often based on clinical expertise. New data have emerged on treatment strategies and validated goals of treatment, alternative regimens of glucocorticoids (GC) and the approval of the first biological therapy for SLE.
- **Aim in management** of JSLE is to have a high index of suspicion in diagnosis and give an effective treatment with the least side effects possible (3).

When to suspect JSLE?

- A high degree of suspicion is warranted (especially if female above 8 years), and it should be considered in:

  a. Any child with **fever** of unknown origin.
  b. **Thrombocytopenia or autoimmune** hemolytic anemia.
  c. **Neuropsychiatric manifestations** including delirium, psychosis and seizures in absence of offending agents or metabolic derangement.
  d. **Mucocutaneous manifestations** as nonscarring alopecia, malar rash or persistent oral ulcers.
  e. **Serositis** as pleural or pericardial effusion.
  f. **Arthritis** non-deforming in two or more joints.
  g. **Renal** affection in the form of proteinuria more than 0.5 g/24 hrs.

N.B:

"Pediatric rheumatologist should be consulted upon suspicion of a case of JSLE after exclusion of infection and malignancy"

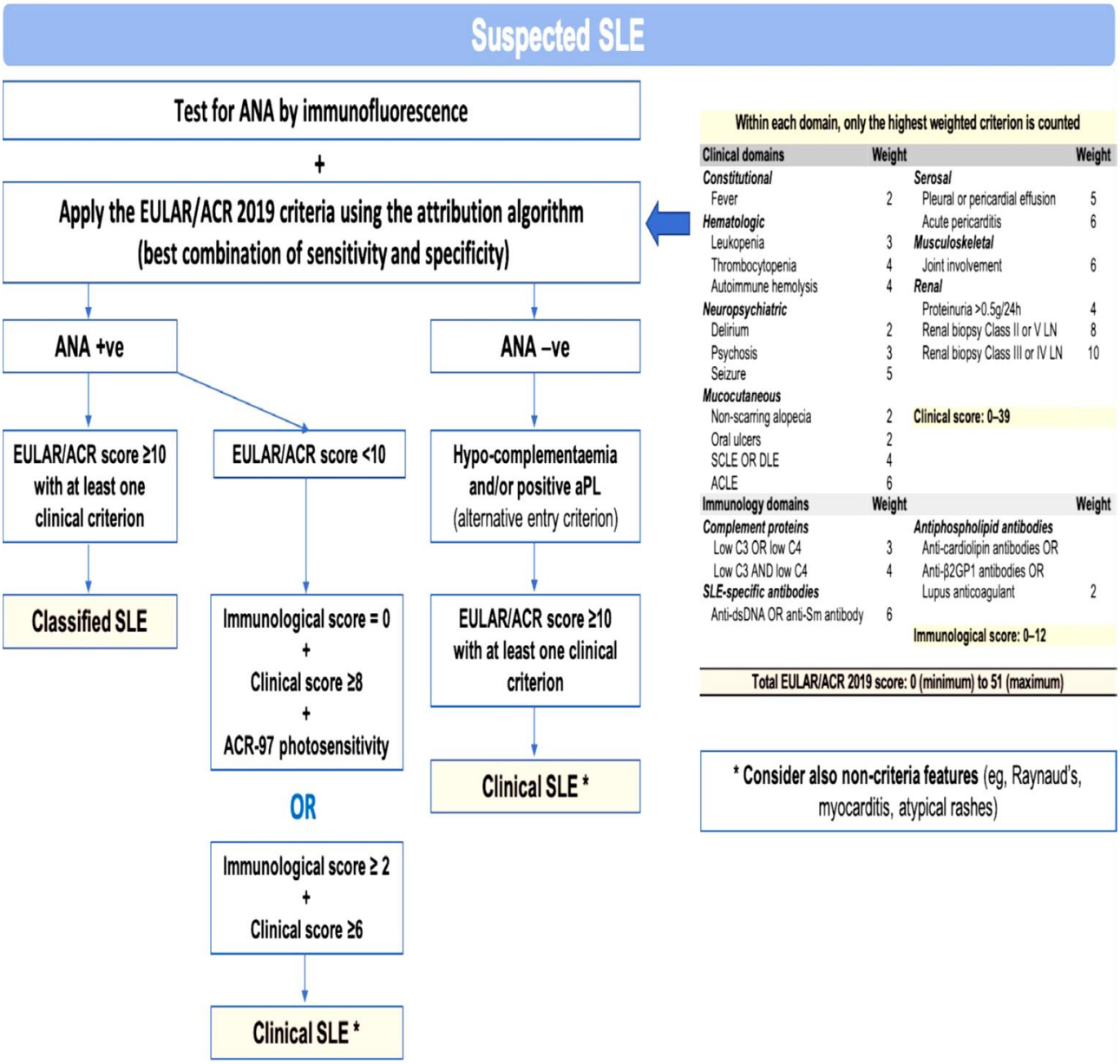
Before referral to pediatric rheumatologist, request these investigations:

a. CBC with differential, ESR, CRP with titer
b. ANA with titer and pattern
c. Anti-dsDNA, C3, C4
d. BUN, creatinine, urine analysis, microalbumin in urine
e. Liver transaminases
f. Direct Coomb's
g. Serum ferritin

Positive ANA specially with titer 1/80 or more is an important entry criterion in diagnosis of JSLE

- ANAs are present in over 99% of children with SLE.
- However, ANAs are also associated with **other rheumatic diseases, infections, malignancies, drug exposure and first-degree** relatives of patients with autoimmune disease. Also, **33% of normal** children may have a positive test for ANA (4).

Classification criteria for SLE (EULAR/ACR 2019) (2)



Within each domain, only the highest weighted criterion is counted

Clinical domains	Weight		Weight
Constitutional		*Serosal*	
Fever	2	Pleural or pericardial effusion	5
Hematologic		Acute pericarditis	6
Leukopenia	3	*Musculoskeletal*	
Thrombocytopenia	4	Joint involvement	6
Autoimmune hemolysis	4	*Renal*	
Neuropsychiatric		Proteinuria >0.5g/24h	4
Delirium	2	Renal biopsy Class II or V LN	8
Psychosis	3	Renal biopsy Class III or IV LN	10
Seizure	5		
Mucocutaneous			
Non-scarring alopecia	2	**Clinical score: 0–39**	
Oral ulcers	2		
SCLE OR DLE	4		
ACLE	6		
Immunology domains	**Weight**		**Weight**
Complement proteins		*Antiphospholipid antibodies*	
Low C3 OR low C4	3	Anti-cardiolipin antibodies OR	
Low C3 AND low C4	4	Anti-β2GP1 antibodies OR	
SLE-specific antibodies		Lupus anticoagulant	2
Anti-dsDNA OR anti-Sm antibody	6		
		Immunological score: 0–12	

Total EULAR/ACR 2019 score: 0 (minimum) to 51 (maximum)

*** Consider also non-criteria features** (eg, Raynaud's, myocarditis, atypical rashes)

Treatment of JSLE

- JSLE care is multidisciplinary, based on a shared patient-physician decision, and should consider individual, medical and societal costs.

►► Treatment of organ-threatening/life-threatening SLE includes an initial period of high-intensity immunosuppressive therapy to control disease activity, followed by a longer period of less intensive therapy to consolidate response and prevent relapses.

►► Treatment goals include long-term patient survival, prevention of organ damage and optimization of health-related quality of life.

Medications

1. **HCQ** is recommended for all patients with JSLE, unless contraindicated, at a dose not exceeding 5 mg/kg.
2. Pulses of intravenous **methylprednisolone** (10-30mg/kg/dose, max 1 gram for 1–3 days) provide immediate therapeutic effect and enable the use of lower starting dose of **oral glucocorticoids** (GC).
3. For chronic maintenance treatment, GC should be minimized to less than 7.5 mg/day and, when possible, withdrawn.
4. Prompt initiation of **immunomodulatory agents** can allow the tapering/discontinuation of GC.
5. **Cyclophosphamide** can be used for severe organ-threatening or life-threatening SLE as well as 'rescue' therapy in patients not responding to other immunosuppressive agents.
6. lupus nephritis: refer to specific guidelines.
7. Antiphospholipid syndrome
    a. All patients with SLE should be screened at diagnosis for aPL.
    b. Patients with SLE with high-risk aPL profile (persistently positive medium/high titres or multiple positivity) may receive primary prophylaxis with antiplatelet agents.
    c. For secondary prevention (thrombosis, pregnancy complication/loss), the therapeutic approach should be the same as for primary antiphospholipid.

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Guidelines for treatment of Pediatric Lupus Nephritis

Introduction

- Childhood SLE is rare, with a prevalence of 1.9–25.7 per 1 00 000 children and incidence of 0.3–0.9 per 1 00 000 children-years worldwide.1
- Childhood SLE in general has a more severe phenotype than adult-onset disease.2
- Fifty to sixty per cent of patients with cSLE will develop lupus nephritis (LN).2,3,4
- Timely and accurate recognition of renal involvement combined with appropriate treatment choices will optimize clinical outcome and decrease renal-associated morbidity and mortality.5
- The long-term aim for treatment of LN should be complete renal response, with early morning urine protein: creatinine ratio of <50 mg/mmol (or urine albumin: creatinine ratio of <35 mg/mmol) and normal renal function (estimated glomerular filtration rate >90 mL/min/1.73 m2).6 Within 6–12 months after initiation of treatment, partial renal response, defined as ≥50% reduction in proteinuria to at least sub nephrotic levels and normal or near-normal renal function should be achieved.[7].

Treatment

ISN/RPS class I and II LN

Class I LN:

Is more common in cSLE compared with adult-onset SLE, and it could be treated with low-dose oral corticosteroid therapy.

Class II LN:

- Generally, responds well to low-dose oral corticosteroid therapy (starting dose 0.25–0.5 mg/kg/day, maximum of 30 mg/day; often 0.25 mg/kg/day is sufficient), tapered over a 3–6 months period.
- If proteinuria is persistent after 3 months or corticosteroid dose cannot be effectively weaned, renal biopsy should be re-evaluated.
- Adding a DMARD to the treatment or switching to another DMARD effective for LN (e.g., MTX to AZA) is recommended

ISN/RPS class III and IV LN with or without class V LN

Class III and IV LN (proliferative LN) are the most common and severe forms of LN in cSLE. Combination of class III or IV LN with class V LN is prevalent.

Induction treatment

- Low-dose intravenous CYC (fixed dose 500 mg/pulse, six pulses given every 2 weeks)-euro lupus-, and high-dose CYC (500–750 mg/m2/pulse, if tolerated increase to 750 mg/m2/pulse, maximum dose 1000–1200 mg/pulse, 6 monthly pulses), adjusted appropriately in cases of renal dysfunction.
- MMF (standard dose 1200 mg/m²/day, maximum 2000 mg/day; when poor response option to increase to maximum of 1800 mg/m²/day, maximum dose 3000 mg/day, but toxicity increases with higher dose) or intravenous CYC combined with high-dose prednisone (1–2 mg/kg/day, maximum 60 mg/day) should be considered for induction treatment of proliferative LN in cSLE.

Maintenance treatment

Duration of maintenance treatment in LN in the cSLE from the literature search was variable (1–5 years).

- MMF and AZA are good options for maintenance treatment although a higher relapse rate is seen in patients treated with AZA
- Intravenous CYC can be effective as maintenance treatment, but is not advised due to higher toxicity when compared with MMF or AZA (e.g., increased risk of a reduced ovarian reserve/premature ovarian failure, inhibition of spermatogenesis, increased risk of bladder carcinoma).

Corticosteroid

- Use as oral prednisone 1–2 mg/kg/day (maximum 60 mg/day) as initial dosing.
- Intravenous methylprednisolone pulse therapy (30 mg/kg/dose intravenous for three consecutive days, maximum 1000 mg/dose) may be added to induction treatment before start of oral prednisone, especially in case of severe disease (e.g., impaired GFR (<80 mL/min/1.73 m2); nephrotic range proteinuria (>3.5 g/24 hours); biopsy-proven crescentic glomerulonephritis).
- Prednisone-tapering schedule that may be used is tapering by 10%–20% at 1-week or 2-week interval based on clinical improvement.

ISN/RPS class V LN

- MMF in combination with low-dose oral prednisone (0.5 mg/kg/day) as induction treatment for pure class V LN in cSLE.
- MMF or AZA are recommended as maintenance treatment. CNI (ciclosporin, tacrolimus), rituximab or intravenous CYC are recommended as alternative options or for non-responders, with consideration of their respective toxicity.

Renal flares and refractory disease

- Patient not responding to the prescribed treatment as expected or developing disease flare, medication non-compliance should first be explored. Lack of adherence to therapy can be as high as 50%, and has been associated with higher persistent disease activity and poorer renal outcomes.
- Measuring medication (trough) levels to unmask non-compliance is advisable. If a patient shows hardly any response within 3 months of induction treatment, it is generally accepted to change the principal induction agent.
- Renal flares can occur in up to 50% of patients with cSLE during maintenance treatment. After excluding non-compliance, restarting or increasing corticosteroid dose (oral prednisone or intravenous methylprednisolone pulses) and a switch of DMARD should be considered.
- In refractory cases Rituximab should be considered.
- CNI (tacrolimus, ciclosporin) can be considered as a treatment option for LN in selected cases, although with the consideration of potential nephrotoxicity especially related to ciclosporin after long-term use.

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Guidelines for diagnosis and management of antiphospholipid syndrome

Introduction

- Antiphospholipid syndrome (APS) is a ***systemic autoimmune*** disorder characterized by an increased risk of thrombotic events and pregnancy morbidity in the setting of persistently positive antiphospholipid antibodies (aPL) .
- The concept of "***pediatric APS***" is typically applied when the disorder occurs in individuals under the age of 18 years.
- APS may affect children from neonates to adolescents, and is likely underdiagnosed given that widely-used classification criteria were designed for adults.
- APS either "***primary* APS**" or in conjunction with another autoimmune condition "***secondary* APS**" which classically associated with lupus.

When to suspect APS?

Clinical presentation

1) **Vascular thrombosis:**

Venous: Lower-limb deep venous thrombosis (DVT), portal vein thrombosis, upper extremity DVT, and left atrial thrombus formation. There were also but rare jugular vein, inferior vena cava, renal vein, and retinal vein.

a. ***Arterial:*** ischemic stroke the most common, other rare forms of arterial thrombosis as peripheral artery thrombosis, retinal artery thrombosis, myocardial infarction, renal artery thrombosis, and splenic infarction.
b. ***Small-vessel thrombosis:*** in the form of digital ischemia or renal thrombotic microangiopathy

2) **Nonthrombotic manifestations:**

a. ***Neurologic*** manifestations including migraine headache, chorea/athetosis, epilepsy, pseudotumor cerebri, and mood disorder.
b. ***Hematologic*** abnormalities including Evans syndrome, thrombocytopenia and autoimmune hemolytic anemia.
c. ***skin*** disorders as livedo reticularis, Raynaud's phenomenon, skin ulcers, pseudo-vasculitic lesions, chronic urticaria and purpura fulminans.
d. ***kidney*** disease including CKD due to thrombotic microangiopathy.
e. ***Primary adrenal*** insufficiency secondary to adrenal infarction.
f. ***Antiphospholipid antibodies*** may be transiently positive in children, especially in the context of infections, and so confirmatory testing should always be performed.
g. ***Catastrophic APS*** (CAPS) is a life-threatening complication of APS typically characterized by widespread microvascular occlusions placing organs such as heart, lungs, and kidneys at significant risk.

N.B:

"So, new classification criteria for pediatric APS are needed that would incorporate non-thrombotic manifestations in children, in addition to thrombosis"

Investigations

a. Lupus anticoagulant (LA)
b. Anticardiolipin IgG and IgM
c. Anti-β2-glycoprotein-I IgG and IgM.

Treatment of APS

1. In patients with cSLE and aPL, ***antiplatelet agents*** could be considered for primary prevention of thrombosis in addition to hydroxychloroquine.
2. When a patient has suffered a *venous thrombotic* event associated with persistent aPL positivity, ***long-term anticoagulation*** therapy is indicated, low-molecular- weight heparin yielding a target anti-Xa.
3. In a patient with pediatric CAPS, immediate ***combination*** treatment with *anticoagulants*, *corticosteroids*, *plasma exchange* with or without intravenous immunoglobulins should be considered. rituximab or other immunosuppressive therapy may also be considered as a treatment option.

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Guidelines for diagnosis and management of Juvenile Dermatomyositis

Introduction

- Juvenile dermatomyositis (JDM) is a rare disease with a characteristic rash and symmetrical proximal muscle weakness.
- It is classified as a vasculopathy1; however, the pharmacokinetic data suggests that the microvascular damage may not be limited to the skin2 and muscle 3 and also may include the vasculature of the gastrointestinal tract.4
- The annual incidence of JDM by race in the USA is 3.4/million for white, non-Hispanic, 3.3/million for African Americans, and 2.7/million for Hispanic patients, with an overall girl-to-boy ratio of 2.3 girls:1 boy (11).5

When to suspect juvenile dermatomyositis disease?

- The Clinical features includes ***cutaneous*** and ***muscular***:

Cutaneous:

1. Gottron's sign—linear erythema–localized to the areas of the hands where the skin is stretched, over joints.
2. Gottron's papules usually occur in areas of injury—fingers, elbows, and knees.
3. Heliotrope rash on the upper eye lids
4. Calcinosis
5. The shawl sign rash on the upper chest

Muscular:

1. Bilateral symmetrical proximal muscle weakness.

- Expected Long term complications if undiagnosed and untreated:
  1. Interstitial lung disease
  2. Edema, either localized or general—secondary to capillary leak
  3. Hair loss—secondary to scalp inflammation/edema.
  4. Cardiovascular damage includes impaired cardiac conduction and subsequent cardiac systolic dysfunction.

Before referral to pediatric rheumatologist, request these investigations:

1. Do investigation to exclude other causes of myopathy as endocrinal disorders, thyroid dysfunction, electrolyte disturbance, vitamin D deficiency.
2. Muscle enzymes: (LDH, SGPT, CPK +- aldolase)
3. Other "routine initial" testing:
   - ***ANA (usually speckled)***
   - ***CBC with differential***
   - ***CRP (elevated in overlap syndrome but not usually in JDM)***
   - ***ESR (usually normal range)***
   - ***U/A, BUN, Creatinine***

Investigations that should be requested only by the pediatric rheumatologist

- Yositis-specific antibodies (antibody-TIF1-γ (transcriptional factor-1-γ), anti-NXP-2, anti-SRP, melanoma differentiation-associated gene 5(MDA-5),)
- Myositis-associated antibodies (anti-U1 RNP, anti -RO, anti-smith)
- Echo, ECG
- CT chest, PFT
- MRI of muscles or quantitative ultrasound
- EMG
- Assessment of muscle strength at diagnosis and follow up using childhood myositis assessment scale (CMAS) and Manual muscle test (MMT)
- Swallow function test
- Nailfold capillaroscopy for periungual capillary changes (CAT)

High risk patients that require urgent consultation of the pediatric rheumatologist without delay

Patients who have the following manifestations:

- ***Severe disability***
- ***Presence of aspiration or dysphagia***
- ***GIT vasculitis***
- ***Myocarditis***
- ***Parenchymal lung disease***
- ***CNS affection in form of seizures or LOC***
- ***Skin ulceration***
- ***Age <1 year***

Treatment

- Aim of treatment is:

  a. To control disease manifestations
  b. To prevent and stabilize organ damage and disease complications like calcinosis. Accordingly, treatment must be early and aggressive.
  c. To prevent relapses

- Assessment of the outcome is done with many tools including patient/parent report outcome measure at diagnosis and follow up.

Treatment includes:(prescribed by pediatric rheumatologist):

- Physiotherapy
- Initially high dose steroids along with DMD as MTX (15mg/m2), Cyclosporin and others
- Hydroxychloroquine (5mg/kg/day)
- Vitamin D supplements
- Sun blockers

For refractory cases:

- IVIG on 1-2gm/kg/every month
- MMF
- Cyclophosphamide
- Tacrolimus
- Rituximab
- Infliximab

For calcinosis:

- Bisphosphonates, infliximab, abatacept, diltiazem, probenecid, intralesional steroids or surgical debridement.

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Guidelines for the management of Bechet's Disease in pediatrics

Introduction

- Behçet's disease (BD) is a ***multisystem vasculitis***, that can involve vessels of all sizes and types.
- It was defined first as a disease with **triad** of **recurrent oral, genital ulcers** and **uveitis**, accompanied with **other** cutaneous, articular, vascular, neurological and gastrointestinal manifestation.
- ***Pediatric*** patients tend to have ***more*** **gastrointestinal, articular, neurologic** manifestations and more **positive family history** than the usual triad observed in the adult BD. However, better disease outcome with lower severity score and activity index has been reported in paediatrics.
- The **diagnosis** is based mainly on the **clinical** manifestation. It can be challenging to diagnose the disease due to the ***absence of a diagnostic test***, and the ***long interval from the first finding*** of the disease to the full-blown disease phenotype in pediatric patients.
- It usually causes ***recurrent, self-limited disease flares***.
- Due to the extensive distribution of the disease among various organs, the management should be made by multidisciplinary approach.

When to suspect Bechet's disease in pediatrics?

Mucocutaneous Lesions:

1. Recurrent painful oral ulcers (circular, non-scarring, with erythematous borders, on tongue, oropharyngeal and buccal mucosa).
2. Genital ulcers (on scrotum, labia major or minor).
3. Perianal aphthosis is specific feature for pediatrics.
4. Erythema nodosum, papulopustular lesions, and folliculitis.

Musculoskeletal involvement:

1. Oligoarticular or polyarticular pattern of arthritis.
2. Sacroiliac joint involvement and enthesopathy can be seen.

Ocular involvement:

1. It most often appears 2-3 years after oral ulcers.
2. It includes blurred vision, ocular pain, eye redness, bilateral posterior uveitis (most important), and non-granulomatous panuveitis.
3. Iridocyclitis, keratitis, episcleritis, vitreous hemorrhage, cataract, glaucoma, and retinal detachment can also be seen.

Neurologic involvement:

1. Central nervous system involvement is more common than peripheral nervous system, including recurrent aseptic meningitis, ataxia, epilepsy, meningoencephalitis, acute onset headache, papillary edema, and hemiparesis. Chronic neuropsychiatric conditions can be seen.

Vascular involvement:

1. Venous involvement is more common than arterial including deep vein thrombosis and dural venous sinuses thrombosis.
2. Pulmonary artery aneurysm is the most common cause of mortality in BD.

Gastrointestinal involvement:

1. Usually start 4-6 years after oral ulcers and the most common symptoms are abdominal pain, nausea, vomiting, dyspepsia, diarrhea, and gastrointestinal bleeding.

Pediatric Criteria for classification of Behçet's Disease

- ***Recurrent oral aphthosis:*** At least three attacks/year.
- ***Genital ulceration or aphthosis:*** Typically, with scar.
- ***Skin involvement:*** Necrotic folliculitis, acneiform lesions, erythema nodosum.
- ***Ocular involvement:*** Anterior uveitis, posterior uveitis, retinal vasculitis.
- ***Neurological signs:*** With the exception of isolated headaches.
- ***Vascular signs:*** Venous thrombosis, arterial thrombosis, arterial aneurysm.

At least 3 criteria are required for the diagnosis.

- The positive pathergy phenomenon (non-specific cutaneous hypersensitivity reaction to trauma) is not pathognomonic to BD.
- Oral ulceration is not a mandatory finding.

N.B:

"It should be kept in mind that *some of children* with BD *may not meet* the classification criteria in the early stages of the disease and such patients should be *followed-up carefully* in a pediatric rheumatology clinic for further clinical assessment"

Before referral to pediatric rheumatologist, request these investigations

- ***CBC with differential***
- ***ESR, CRP***
- ***Liver function test***
- ***Urine analysis***
- ***Ophthalmologic consultation***

Treatment of Bechet disease

The primary ***goal for the treatment*** is preventing the organ damages by suppressing the ongoing inflammation and forestalling the disease flares.

- ***Corticosteroids*** (topical, oral and intravenous route), have strong and rapid anti-inflammatory effects.
  - **a)** Topical corticosteroids for ocular manifestation and oral or genital ulcers.
  - **b)** Systemic steroids (in combination with other anti-inflammatory drugs) for cutaneous lesions unresponsive to topical steroid or colchicine, and for ocular, vascular, nervous and, gastrointestinal involvement.

N.B:

"Pulse methyl prednisolone is recommended for acute sight threatening uveitis for 1–3 days"

- ***Colchicine*** is used for mucocutaneous lesions (oral ulcers- erythema nodosum) and for articular manifestations.
- ***Azathioprine*** is used in severe mucocutaneous manifestations, persistent arthritis, deep venous thrombosis, active posterior uveitis, or isolated anterior uveitis, gastrointestinal and neurologic involvement.
- ***Methotrexate*** is used for ocular and mucocutaneous lesions, as well as in neuro-Behçet's disease.
- ***Cyclosporine A*** is recommended for patients with severe ocular involvement and persistent mucocutaneous lesions.
- ***Cyclophosphamide*** is used for severe manifestations of the disease such as pulmonary artery involvement, Budd-Chiari syndrome, and parenchymal neurologic involvement.
- ***Mycophenolate mofetil*** can be uses in neuro beçhet disease.

- ***Antiaggregant and anticoagulant therapy*** used in children with vascular involvement (Aspirin is usually sufficient).
- ***IFN-alpha*** has an immunomodulatory property,with the best efficacy in uveitis.
- ***Anti-TNF agents*** (Etanercept, Adalimumab, and Infliximab) are recommended in patients who cannot be controlled by conventional immunosuppressive treatments or in cases with intolerance or allergic reactions to conventional agents. They are highly recommended in severe neuro Behçet disease, refractory deep venous thrombosis and arterial involvement, severe eye involvement, moderate and severe GI Behçet's disease.
- ***Anti-IL-1 agents*** (Anakinra) can be used in refractory uveitis, retinal vasculitis and mucocutanous manifestations.
- ***Anti-IL-6 agents*** (Tocilizumab) can be used in refractory BD with good results in uveitis and has promising results on CNS involvement.

N.B:

"The prognosis depends on the site and severity of involvement. The leading causes of BD-related morbidity and mortality are ocular, neurologic, and arterial involvements"

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Guidelines for diagnosis and management of Kawasaki disease

Introduction

- Kawasaki disease (KD) is a medium vessel vasculitis, with characteristic seasonality (1).
- It typically presents in children <5 years of age as an **acute, self-limited febrile disease** and is characterized by a combination of characteristic clinical signs, which include:

    a. ***Polymorphic rash***
    Non-purulent conjunctival injection
    Oropharyngeal and lip mucositis, tongue papillitis
    Erythema and edema of the hands and feet
    Unilateral cervical lymphadenopathy.

- The disease may affect the coronary arteries but can also affect medium-sized arteries (4).
- In the developed world, it is the most common cause of acquired cardiac disease in childhood, with 25% of untreated patients and 5% of treated patients developing coronary artery aneurysms (7).

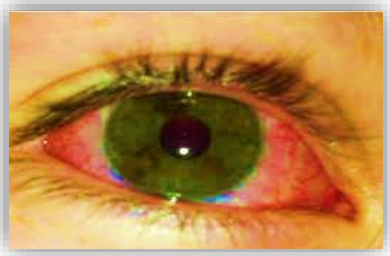
When to suspect Kawasaki disease?

- Diagnosis of KD is essentially based on a constellation of clinical signs and symptoms and supported by laboratory investigations.

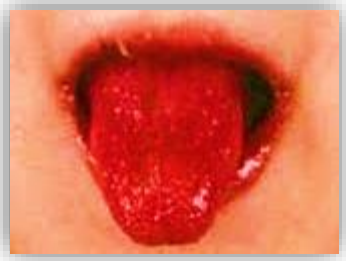
- Disease states:

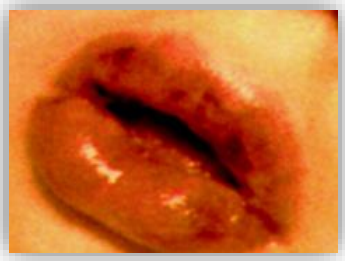
I. KD: Fever lasting at least 5 days without any other explanation with at least 4 of the 5 following principal clinical findings:

1. Bilateral bulbar conjunctival injection without exudate.



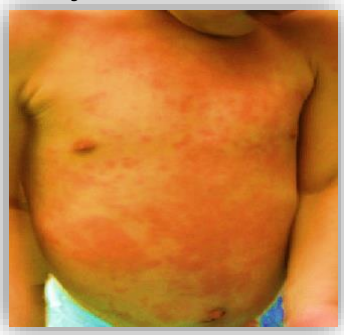
2. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa.





3. Erythema and edema of the hands or feet (acute phase), and/or periungual desquamation (subacute phase).

4. Maculopapular, diffuse erythroderma, or erythema multiforme–like rash.



5. Cervical lymphadenopathy (at least 1 lymph node >1.5 cm in diameter), usually unilaterally.

II. Incomplete KD: Prolonged (> 5 days) unexplained fever in an infant or child with compatible laboratory markers (elevated ESR/CRP level, elevated transaminase levels, UA with leukocyte esterase–negative WBCs) or echocardiographic findings (coronary artery dilatation)

III. Acute KD: Initial febrile phase of KD

- Children with < 5 days of fever, or those with incomplete Kawasaki disease may prove to be more of a diagnostic challenge.
- In patients presenting with Fever, consider the following differential diagnoses.

Infectious diseases	Rocky Mountain spotted fever
Measles	*Yersinia pseudotuberculosis* infection
Scarlet fever	**Allergic and rheumatic diseases**
Epstein–Barr virus infection	Drug reaction
Adenovirus infection	Steven–Johnson syndrome
Enterovirus infection	Juvenile rheumatoid arthritis
Human parvovirus B19 infection	Polyarteritis nodosa
Staphylococcal scalded skin syndrome	Reiter's syndrome
Toxic shock syndrome	**Toxic conditions**
Leptospirosis	Mercury poisoning

Consider Kawasaki disease in the differential diagnosis of any infant or child with prolonged fever (> 5 days) plus:

- *Irritability*
- *Unexplained aseptic meningitis*
- *Unexplained or culture-negative shock*
- *Cervical lymphadenitis unresponsive to antibiotic therapy*
- *Retropharyngeal or parapharyngeal inflammation unresponsive to antibiotic therapy.*
- *Pediatric rheumatologist should be consulted upon suspicion of a case of Kawasaki disease after exclusion of other causes of the child complaint.*

Before referral to pediatric rheumatologist, request these investigations (2)

a. *CBC with differential (leukocytosis, thrombocytosis), ESR ↑, CRP ↑ with titer*

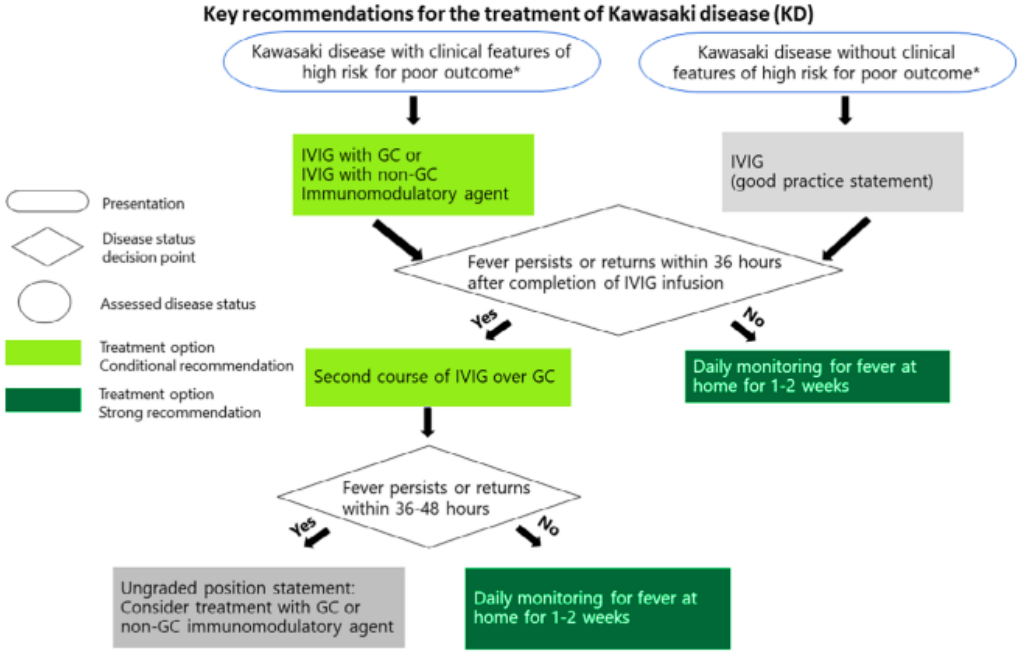
   Serum albumin ↓ Na level ↓

   BUN, creatinine, urine analysis (for evidence of sterile pyuria), microalbumin in urine

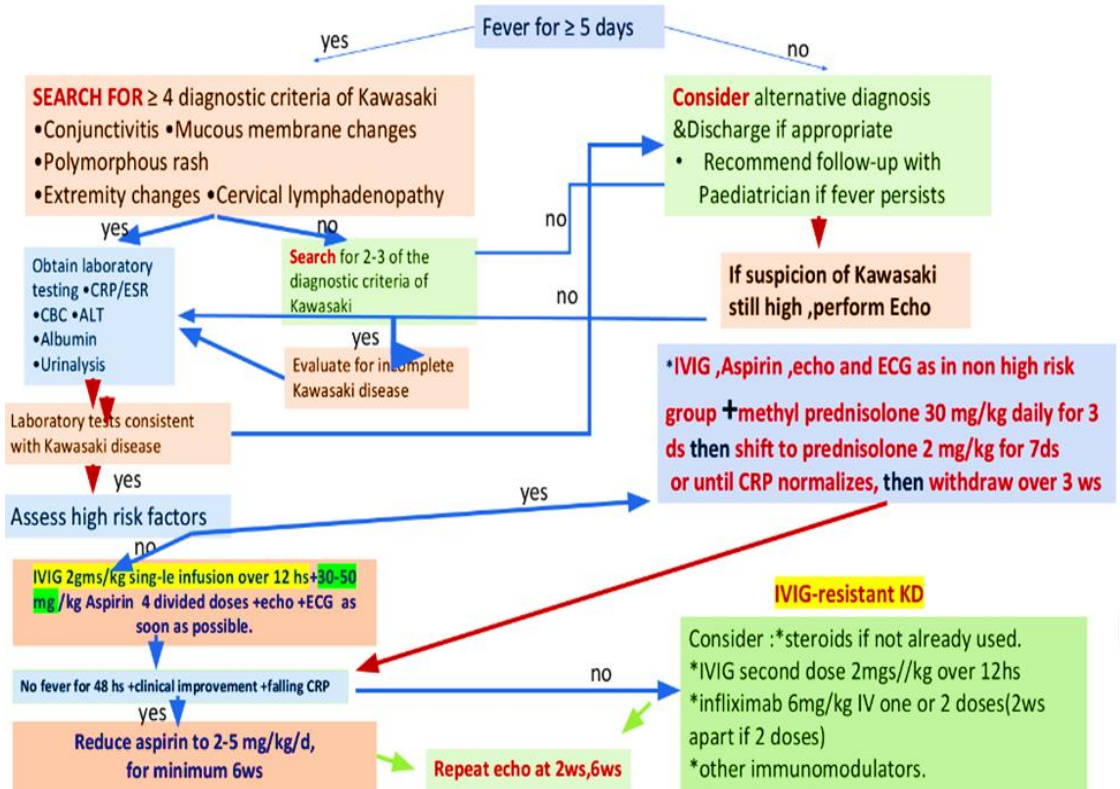
   Liver transaminases ↑

Treatment of Kawasaki disease

Under supervision of pediatric rheumatologist, pediatric cardiology



* Clinical features of high risk for poor outcome are any of the following: Z score of ≥2.5 for left anterior descending or right coronary artery at the time of initial echocardiogram, age < 6 months
IVIG = intravenous immunoglobulin; GC = glucocorticoid



Source:

- **2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Kawasaki Disease (1)**

References:

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Guidelines for diagnosis and management of IgA vasculitis

Introduction

- IgA vasculitis (IgAV), formerly known as Henoch Schoenlein purpura (HSP), is the ***commonest cause of vasculitis in childhood***, with a peak incidence in children between the ages of 4 and 6 years.
- Pathologically, it is an acute immunoglobulin A (IgA) immune-mediated disorder characterized ***by small vessel vasculitis*** of the ***skin, joints, kidney, gastrointestinal tract,*** and, rarely, the lungs and the central nervous system.
- ***Renal*** damage is considered the most common cause of morbidity and mortality in IgAV.
- Given its potential life-threatening systemic complications, ***early and accurate diagnosis*** represents a major challenge for health care professionals.

Classification criteria of IgAV according to the EULAR/PRINTO/Pediatric Rheumatology European Society (PRES) includes:

- ***Purpura*** or petechiae (mandatory) with lower limb predominance and at least ***one of the four*** following criteria:

    1. ***Abdominal pain***
    2. ***Histopathology (typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit)***
    3. ***Arthritis or arthralgia***
    4. ***Renal involvement***

When to suspect IgAV?

- Raised purpura with lower limb predominance.
- if symptoms do not resolve or improve within days to weeks, as would be expected in a "self-limited" infectious illness.
- Multisystem involvement should raise possibility of vasculitis.

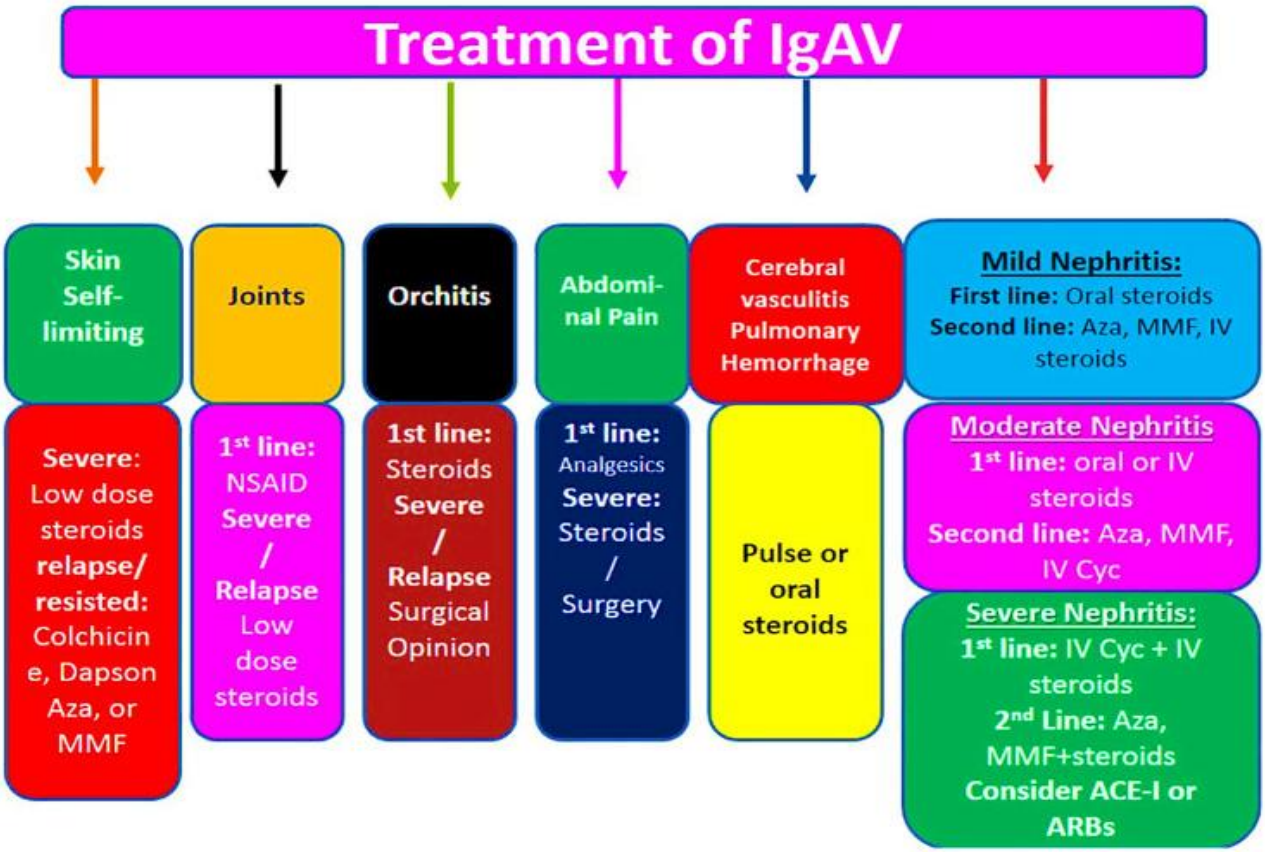
When to refer to pediatric rheumatologist?

- Persistent symptoms, or atypical course
- Evidence of renal affection/ proteinuria
- When the diagnosis is doubtful
- If the rash distribution or characterization is atypical.

Before referral to pediatric rheumatologist, request these investigations

- **To exclude other diseases and to investigate any possible complications requiring immediate communication with a pediatric rheumatologist:**
    - ✓ CBC with blood film: to rule out thrombocytopenia/ leukemia.
    - ✓ CBC, CRP, and clotting: if concerned about sepsis.
    - ✓ Kidney function tests, serum electrolytes, albumin, calcium, phosphate, UP/ UC ratio: if urine dipstick has 2 + or more of proteinuria.
    - ✓ CBC and Clotting: if macroscopic hematuria.
    - ✓ Abdominal ultrasonography if there is abdominal pain
    - ✓ Fecal Occult blood if in doubt of bleeding

Treatment of IgA vasculitis



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2. **Ozen S, Marks SD, Brogan P, et al. European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis-the SHARE initiative. *Rheumatology* 2019; 58: 1607–1616.**

Guidelines for management of childhood polyarteritis nodosa (C-PAN)

Introduction

- PAN is a necrotizing vasculitis that primarily affects ***small*** and ***medium*** sized vessels.
- It manifests in a variety of ways from a ***benign cutaneous*** to a ***sever systemic*** type.
- The immunopathogenesis in PAN is heterogenous, *infectious triggers* have been implicated as *hepatitis B virus*, *cytomegalovirus*, *parvo B19* virus and *streptococcal infection. (*1)
- C-PAN can be associated with severe complications, therefore *early diagnosis* and *aggressive treatment* are important for improving prognosis without a sequel.

When to suspect polyarteritis nodosa (C-PAN)?

Systemic C-PAN is characterized by combination of the following:

- ***Constitutional manifestations.***
- ***Neurological manifestations.***
- ***Cutaneous manifestations.***
- ***Renal manifestations.***
- ***Gastrointestinal manifestations.***
- ***Diffuse myalgia, arthralgia, occasionally arthritis.***

EULAR/PRINTO/PRES Classification of C-PAN [2]	
Mandatory	• **Histopathological criteria:** Evidence of necrotizing vasculitis in medium or small arteries. **OR** • **Radiological criteria:** Angiographic abnormality of medium or small sized artery (aneurysm, stenosis, occlusion), not due to fibromuscular dysplasia or other non-inflammatory causes.
One out of five	• Skin involvement (livedo reticularis, skin nodules, superficial or deep skin infarcts). • Myalgia or muscle tenderness. • Hypertension. • Peripheral neuropathy (sensory, motor or mononeuritis multiplex). • Renal involvement (proteinuria, hematuria or impaired renal function).

Before referral to pediatric rheumatologist, order these investigations:

- *CBC.*
- *ESR, CRP.*
- *Kidney function tests.*
- *Liver function tests.*
- *Urine analysis.*
- *Echocardiogram, ECG.*

Treatment

Induction therapy:

- ***Corticosteroids: Methyl prednisolone or prednisolone.***
- ***Cyclophosphamide.***
- ***Plasmaphereses (in life threatening vasculitis).***
- ***IVIG.***
- ***Anti TNF.***
- ***Tocilizumab.***

Maintenance therapy:

- Maintenance therapy should be continued for 12-36 months after successful induction depending on clinical course, some patients may require longer treatment.

A- Immune modulatory agents:

- ***Azathioprine.***
- ***Methotrexate.***
- ***Mycophenolate mofetil.***
- ***Rituximab.***
- ***Anti TNF.***
- ***Tocilizumab.***
- ***IVIG.***

B- Anti platelets drugs.

C- Osteoporosis prophylaxis.

D- Antibiotics prophylaxis.

NB:

- C-PAN secondary to HBV infection is classified as secondary vasculitis and requires different therapeutic approach as conventional treatment with corticosteroids and cyclophosphamide, allows the virus to replicate, facilitating evolution to chronic hepatitis and liver cirrhosis
- The recommended approach is combined plasma exchange and antiviral medications with corticosteroids to control acute manifestation. (3)

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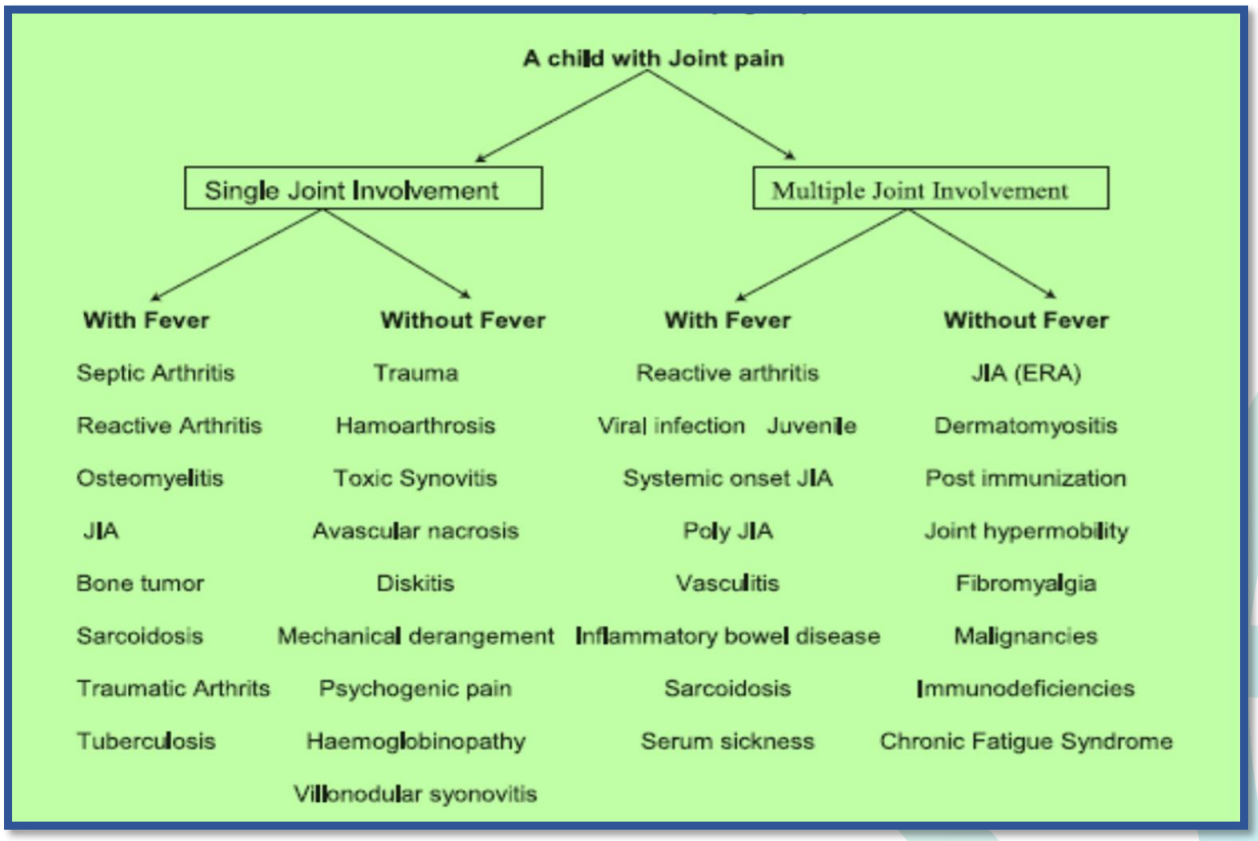
Guideline for management of child with arthritis

Introduction

- Joint pain is a common reason for children to present to primary care.
- The differential diagnosis is large including some diseases that do not primarily affect the musculoskeletal system.
- Arthritis and arthritis like symptoms can be the presentation of serious systemic diseases like leukemia, T.B.
- Identification of musculoskeletal emergencies (e.g. septic arthritis, systemic onset JIA) is very important for management purpose.

  - ***Arthritis:*** Joint pain with signs of inflammation (limitation of range of movement, tenderness or pain on motion).
  - ***Arthralgia:*** Joint pain without any signs of inflammation.
  - ***Monoarthritis:*** only one joint involved.
  - ***Oligoarthritis:*** 1-4 joints during 1st 6 months of disease.
  - ***Polyarthritis:*** >5 joints during 1st 6 months of disease.



Approach to diagnosis

Take a good history including:

1. ***Child 'well' or 'sick'?***
2. ***History of trauma?***
3. ***whether there is involvement of single or multiple joints.***
4. ***Features suggestive of infection, either localized or systemic?***
5. ***Family history of bleeding diathesis?***
6. ***Nature of the onset?***
7. ***Night pains***

Examination

1. ***General Examination:***

   a. Pallor, rashes, palpable purpura

   b. peeling of the skin, thickening of the skin

   c. conjunctivitis, icterus

   d. Lymphadenopathy

   e. nail pitting, pigmentation

   f. psoriasis, oral ulcers, nodules

2. ***systemic examination:***

   a. Tachycardia / murmurs

   b. Presence of chest infection

   c. Hepatosplenomegaly

   d. Musculoskeletal system swelling, redness and soft tissue involvement

Investigations (guided by the clinical suspicion)

a. CBC, ESR, CRP
b. Urine analysis, Malta, Widal test if suspected reactive arthritis
c. Coagulation studies
d. Blood culture
e. ASO titre and Throat swab
f. Radiological evaluation, Ultrasound (if effusion and for diagnostic aspiration in septic arthritis)
g. Echo cardiography

Red flags, requiring urgent intervention or referral to a specialist

- ✓ Fever, malaise, systemic upset (reduced appetite, weight loss, sweating).
- ✓ Bone or joint pain with fever.
- ✓ Refractory or unremitting pain, persistent at night and or waking the patient from sleep.

N.B

" When *to suspect* juvenile idiopathic arthritis and *refer* to pediatric rheumatology "

- ✓ Morning stiffness.
- ✓ Duration more than 6 weeks.
- ✓ Restriction of activities.
- ✓ Red and painful eyes.
- ✓ Chronic skin disease such as psoriasis.
- ✓ Exclusion of other causes of arthritis.

Guidelines for management of oligoarticular JIA

Introduction

- According to 2019 ACR juvenile idiopathic arthritis JIA is an umbrella term for arthritis of unknown causes in children under the age of 16 years.
- Juvenile idiopathic arthritis (JIA) is one of the most common chronic conditions of childhood. JIA causes joint pain, swelling and stiffness in one or more joints, and decreased health-related quality of life and risk of permanent joint damage.
- Oligoarthritis JIA refers to JIA presenting with involvement equal to or less than 4 joints without systemic manifestations.
- It may include patients with different categories of JIA (10) who share a limited number of joints involved in guidance for patients with active uveitis, sacroilitis or enthesitis.

When to suspect?

- Patient presenting with arthritis in one or up to 4 joints with a duration of more than 6 weeks after exclusion of other causes of Arthritis

    a. *Joint swelling*
    Joint stiffens or limitation of movement
    Joint pain, hotness without redness
    In known cases of uveitis, sacroiliitis, or enthesitis

Before referral to pediatric rheumatologist Order these investigations:

a. *CBC with differential, ESR, CRP*
b. *Liver enzymes*
c. *Kidney functions*
d. *Urine analysis*
e. *ANA*
f. *Affected joint ultrasound*

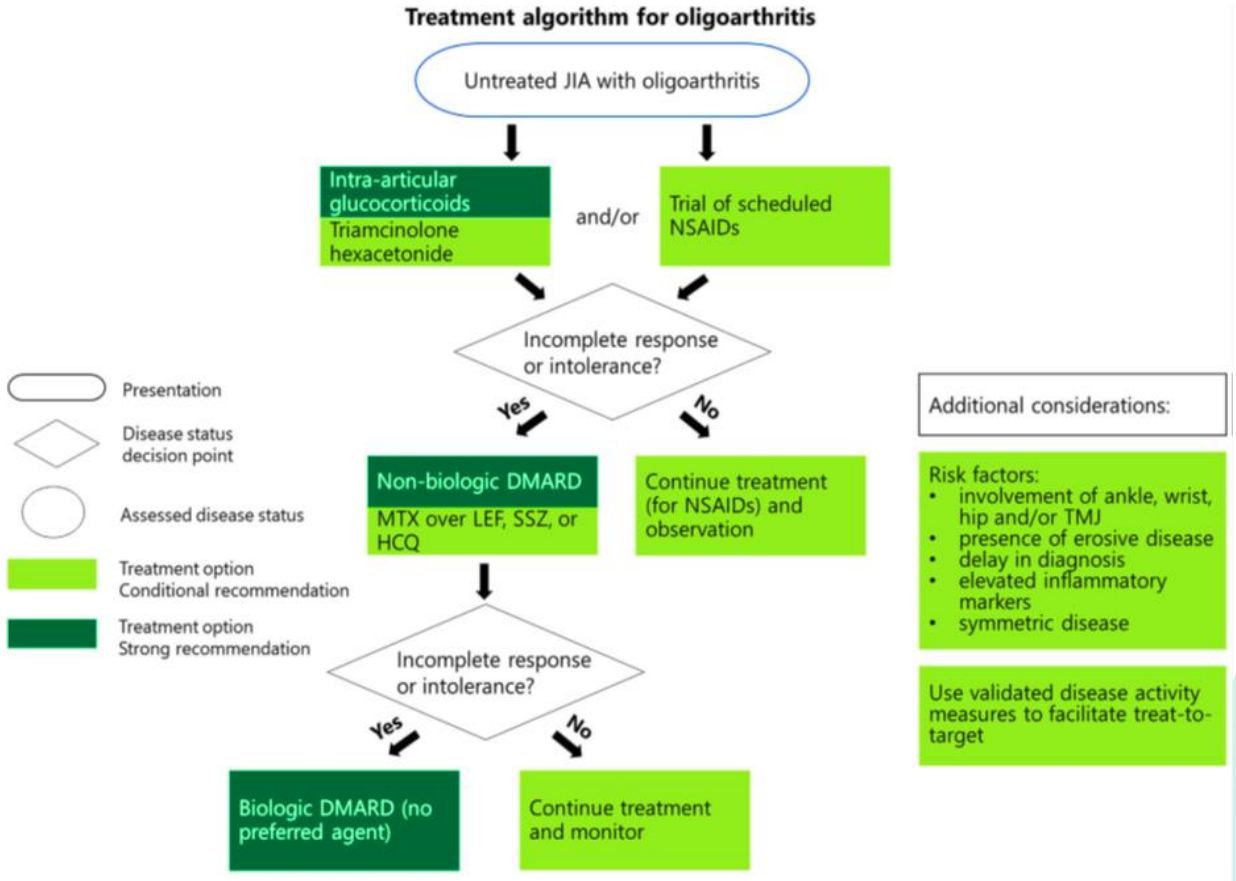
Classification criteria for oligoarticular JIA

Diagnosis of oligoarticular JIA mainly depends on clinical diagnosis:

- Arthritis affecting from one to four joints.
- Affected joints: large, weight bearing joints such as the knees and the ankles are typically affected.
- Oligoarthritis JIA child appears to be well despite ambulating with a limp.
- In cases of asymmetric arthritis there is a subsequent leg length discrepancy.
- Muscle atrophy may be present above the affected joint :

  - ✓ ***Presence of a few small joints in the hand is atypical***
  - ✓ ***Presence of redness in the joint is also atypical***
  - ✓ ***Uveitis is present in 20% or less of those screened by slit lamb examination, especially with positive ANA.***

Treatment



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

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Polyarticular JIA

Introduction

- Polyarticular JIA is defined as arthritis affecting 5 or more joints for the last 6 months with or without positive rheumatoid factor.
- Joint Damage is defined as limited mobility, loss of cartilage thickness, erosion, loss of joint space that may lead to the need of surgical intervention.

Role of general practitioner

- Suspect the case depending on the previous definition
- Exclude other diseases in the DD of this condition (other causes of arthritis) including:

    a. ***Malignancy***
    Infections
    Other autoimmune diseases as Juvenile SLE, dermatomyositis.

- Start NSAIDs to relieve pain till finalizing your diagnosis. You can add PPI for the patient.
- If diagnosis of polyarticular JIA is suggestive, refer to pediatric rheumatologist.

Before referral to pediatric rheumatologist, request these investigations:

a. ***CBC with diff, ESR, CRP.***
ANA, RF.
Lfts, kidney function tests.
Musculoskeletal U/S on the affected joints better done by an experienced Healthcare Professional.

Treatment of polyarticular JIA

Done by an experienced pediatric rheumatologist by:

1. Monitoring of the patient can be done by Patient & Physician global assessment, JADAS-27 score, ESR &CRP and Functional ability (CHAQ, PROMIS).
2. Risk factors assessment before planning the treatment ,these include one or more of the following:

    a. ***Positive rheumatoid factor***
    Positive anti–cyclic citrullinated peptide antibodies,
    Joint damage

3. Moderate/high disease; score based on the cJADAS-10 >2.5. Low disease activity Clinical JADAS-10 ≤2.5 and ≥1 active joint.
4. Initial treatment includes DMARDS as initial monotherapy (MTX, Leflunomide) and/or short course of NSAIDS.
5. If there is incomplete response, shift to the other biological (anti-TNF)
6. Immunizations inactivated vaccines can be given unconditionally, live activated vaccines are given with special conditions.
7. Nonpharmacologic therapies as Physical therapy; dietary changes; herbal supplements should be advised.

Systemic juvenile idiopathic arthritis

Introduction

- Systemic juvenile idiopathic arthritis (SJIA) is distinct from all other categories of JIA due to fever, rash, and visceral involvement and is considered by some to be an autoinflammatory disorder.
- Disease pathogenesis and cytokine involvement in sJIA are different than in other JIA categories.
- SJIA is suspected in child less than 16 years of age if he starts to experience arthritis in1 or more joints with, or preceded by, fever of at least 2 weeks' duration.
- Signs or symptoms must have been documented daily for at least 3 days and accompanied by 1or more of the following:

    b. ***Evanescent rash.***
    Generalized lymphadenopathy.
    Hepato/splenomegaly and serositis.

Role of general practitioner

1. Suspect the case depending on the previous definition
2. Exclude other diseases in the DD of this condition including:

    a. ***Malignancy as leukemia/lymphoma/neuroblastoma***
    b. ***Infections***
    c. ***other autoimmune diseases as Juvenile SLE***

3. The following investigations may be done guided by clinical presentation and before referral to paediatric rheumatologist.

    a. ***CBC with diff, ESR, CRP***
    b. ***Serum Ferritin***
    c. ***ANA, RF***
    d. ***peripheral smear.***
    e. ***Bone marrow aspirate, pet scan and body imaging are highly considered to exclude malignancy when there is clinical suspicion.***
    f. ***Joint US and doppler to the affected joints may be needed***

4. A short course of NSAIDs 1-3 mg/kg/day can be started
5. If diagnosis of sJIA is still possible after exclusion of infection and malignancy, refer to pediatric rheumatologist.

Treatment of systemic JIA

Done by an experienced pediatric rheumatologist through:

1. Monitoring of the patient can by Patient & Physician global assessment, JADAS-27 score, ESR & CRP and Functional ability (CHAQ, PROMIS).

2. Systemic steroids can't be a single agent in treatment, it can be used any time during disease activity with the smallest dose and shortest duration possible to avoid side effect.

3. Start with IL-1 or IL-6 as initial monotherapy (according to availability) and/or short course of NSAIDS.

4. If there is residual arthritis, start c DMARD.

5. If there is incomplete response, shift to the other biological (IL-1 or IL-6).

6. If inactivity is achieved, withdraw steroids gradually to stop then taper biological agent gradually.

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Guidelines for management of macrophage activation syndrome (MAS) in pediatrics

Introduction

- Macrophage activation syndrome (MAS) is a serious, potentially life threatening hyperinflammatory condition, which can complicate several immunologic and rheumatic disorders (1).
- Among pediatric rheumatic diseases, MAS is observed most commonly in patients with systemic juvenile idiopathic arthritis (sJIA), MAS can also be encountered in juvenile systemic lupus erythematosus, Kawasaki disease, juvenile dermatomyositis (2) and multi system inflammatory syndrome in children (MIS-C) (3).
- If untreated, MAS may progress to multi-organ failure and have fatal outcome. So, early diagnosis and treatment of MAS is critical to improve survival.

When to suspect macrophage activation syndrome?

- A high degree of ***suspicion*** is warranted, and it should be considered in any ***febrile child*** with ***underlying rheumatic disease***, although fever may be absent in patients on biological medications (4).

- Clinically, MAS is characterized by:

1. ***The acute onset of unremitting high fever.***
2. ***Drop in the three blood cell lines.***
3. ***Hyperferritinemia.***
4. ***Hepatosplenomegaly, lymphadenopathy.***
5. ***Liver dysfunction, clotting abnormalities with Hemorrhagic manifestations.***
6. ***Central neurological affection.***

N.B

" Pediatric rheumatologist should be consulted upon suspicion of a case of MAS "

Before referral to pediatric rheumatologist, order these investigations:

1. *CBC with differential.*
2. *ESR.*
3. *CRP.*
4. *Serum ferritin.*
5. *Liver transaminases.*
6. *Serum albumin.*
7. *LDH.*
8. *Fibrinogen.*
9. *Triglycerides.*

Early diagnostic tools with special considerations

1. *Progressive increase in serum ferritin.*
2. *Relative decrease in platelet count followed by decrease in total leukocytic count.*
3. *Relative decrease in fibrinogen level.*

Classification criteria of MAS in patient with sJIA according to Pediatric Rheumatology International Trails Organization (PRINTO) (4)

- A febrile child with known or suspected sJIA is classified as having MAS if the ***serum ferritin > 684 ng/mL*** ***and ≥ 2 of the*** following:
    - *Platelets ≤181×109 /L*
    - *Aspartate aminotransferase (AST) >48 U/L*
    - *Triglycerides >156 mg/dL*
    - *Fibrinogen ≤360 mg/dL*
- These classification criteria are used also to classify MAS associated with MIS-C (4).
- MAS may be the first presentation of juvenile SLE
- Bone marrow aspiration is used for evidence of macrophage hemophagocytosis in doubtful cases only.

Diagnostic guidelines for macrophage activation syndrome as acomplication of juvenile SLE (5)

- Simultaneous presence of at least 1 clinical criterion and at least 2 laboratory criteria.

Clinical criteria:

a. *Fever (>38°C)*
b. *Hepatomegaly (≥3 cm below the costal arch)*
c. *Splenomegaly (≥3 cm below the costal arch)*
d. *Hemorrhagic manifestations (purpura, easy bruising, or mucosal bleeding)*
e. *Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, or coma)*

Laboratory criteria:

a. *Cytopenia affecting 2 or more cell lineages (white blood Cell count ≤4.0 × 109/liter, hemoglobin ≤90 gm/liter, or platelet count ≤150 × 109/liter) - Increased aspartate aminotransferase (>40 units/liter)*
b. *Increased lactate dehydrogenase (>567 units/liter)*
c. *Hypofibrinogenemia (fibrinogen ≤1.5 gm/liter)*
d. *Hypertriglyceridemia (triglycerides >178 mg/dl)*
e. *Hyperferritinemia (ferritin >500 µg/liter)*

Histopathologic criterion:

a. *Evidence of macrophage hemophagocytosis in the bone marrow aspirate.*

Treatment

- The aim of treatment is to control the underlying cytokine activation by using immunosuppression and controlling the triggering factors.

1. ***Empirical antibiotics and/or antifungals*** to cover the probable infectious trigger.
2. ***Intravenous immunoglobulin (IVIG),*** especially in the settings where underlying infection is a possibility (4).
3. ***Intravenous methylprednisolone*** pulse therapy for 3 to 5 days, followed by oral prednisolone until normalization of haematological abnormalities.
4. ***dexamethasone palmitate*** in refractory cases or CNS involvement in MAS.
5. ***Anti-IL-1 (anakinra)*** in high dose is recommended in early stage if there is no response to Intravenous methylprednisolone pulse therapy (6).
6. ***Rituximab,*** a monoclonal antibody to CD20, may be considered in EBV triggered MAS (3).
7. ***Calcineurin inhibitor cyclosporine*** should be ***used with caution*** in the acute setting of patients with multiorgan dysfunction due to its neurotoxic and nephrotoxic side effects
8. ***Etoposides*** in refractory cases.

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Guidelines for management of Familial Mediterranean Fever (FMF) in pediatrics

Introduction

- Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease. It is a mainly diagnosed on clinical basis, supported by Mediterranean Fever (MEFV) gene mutation analysis (1).
- FMF increases the risk of other inflammatory disorders, such as ankylosing spondylitis, immunoglobulin A–associated (IgA) vasculitis (formerly Henoch-Schoenlein purpura), juvenile idiopathic arthritis, polyarteritis nodosa, multiple sclerosis and Bechet disease.
- The most significant long-term complication of FMF is chronic renal failure caused by deposition of amyloid protein in the kidneys. Amyloid may also be deposited in the gastrointestinal tract, liver, spleen, heart, testes and thyroid (2).

When to suspect FMF?

- Patient presents with:

    1. ***History of recurrent attacks of Fever as high as 40° C.***
    2. ***Abdominal pain, abdominal distention.***
    3. ***Chest pain.***
    4. ***Arthralgia or arthritis.***
    5. ***Myalgia.***
    6. ***Erysipelas-like rash of the lower leg.***
    7. ***Scrotal swelling and pain.***
    8. ***Rarely pericarditis (3).***

- FMF has a broad differential diagnosis, so proper history taking, documentation of symptoms, accurate clinical examination are required to exclude other causes with similar presentations.

Before referral to pediatric rheumatologist, request these investigations:

1. *CBC with differential count, ESR and CRP (During attack and attack free period).*
2. *Liver enzymes.*
3. *Kidney functions.*
4. *Urine analysis.*
5. *Stool analysis.*
6. *Serum amyloid A.*
7. *Pelviabdominal ultrasound.*

Diagnostic criteria for FMF

Eurofever/PRINTO clinical+ genetic criteria (4)

- Presence of confirmatory MEFV genotype and at least ONE among the following:

1. *Duration of episodes 1-3 days*
2. *Arthritis*
3. *Chest pain*
4. *Abdominal pain*

OR

- Presence of non-confirmatory MEFV genotype and at least TWO among the following:

1. *Duration of episodes 1-3 days*
2. *Arthritis*
3. *Chest pain*
4. *Abdominal pain*

- Clinical classification criteria are used as an indication tool for molecular analysis or as classification criteria in case genetic testing is not available (5).

Eurofever/PRINTO clinical only criteria (> 6 criteria) (4)

- **Presence of:**

1. *Eastern Mediterranean ethnicity*
2. *Duration of episodes 1 - 3 days*
3. *Arthritis*
4. *4- Chest pain*
5. *Abdominal pain*

- **Absence of:**

1. *Aphthous stomatitis*
2. *Urticarial rash*
3. *Maculopapular rash*
4. *Painful lymph node*

Treatment

- **The aim of treatment is:**

1. *To prevent the recurrence of attacks.*
2. *To normalize inflammatory markers.*
3. *To minimize subclinical inflammation in attacks-free intervals.*
4. *To prevent the medium and long-term complications (4).*

Colchicine:

a. *Should be started as soon as a clinical diagnosis is made.*
b. *Colchicine is a life-long treatment.*
c. *Symptoms should be evaluated 3-6 months after initiation of colchicine treatment.*
d. *Monitoring of colchicine intolerance and colchicine resistance.*

NSAID:

In cases of arthritis and myalgia.

Corticosteroids:

In some colchicine resistant patients.

Anti-IL1 (Anakinra):

Indicated in patients who are unresponsive or intolerant of colchicine (6).

Tumor necrosis factor (TNF)-inhibitors:

Indicated in colchicine resistant patients, especially with articular involvement (7).

Treatment of any accompanying inflammatory condition as stated by guidelines.

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Guidelines for management of multisystem inflammatory syndrome of children post-COVID (MIS-C)

Introduction

- Multisystem inflammatory syndrome in children (MIS-C) is a newly identified and serious health condition ***associated with SARS-CoV-2*** infection.
- Also known as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)
- MIS-C was first described in Europe in April, 2020, and can affect multiple organ systems.[1]

MIS-C has different clinical presentations which include:

- ***Kawasaki like features*** (conjunctivitis, red or swollen hands and feet, rash; red cracked lips, lymphadenopathy.
- ***Gastrointestinal*** symptoms (abdominal pain, diarrhea, nausea, vomiting, colitis, hepatitis and questionable appendicitis).
- ***Toxic shock syndrome-like*** features with hemodynamic instability and poor heart function.
- ***Cytokine storm/ macrophage activation*** or hyperinflammatory features.
- ***Thrombosis.***
- ***Acute kidney injury***
- ***Congestive heart failure.***
- ***Pulmonary embolism.***

When to suspect MIS-C?

- MIS-C should be considered as a differential diagnosis in any ***child with persistent fever*** **without** a clear clinical source.
- Also, any child presents with ***fever*** that is accompanied by ***multi-system*** involvement and ***history*** of exposure to a person with recent COVID-19 infection.

The CDC case definition for MIS-C [2]

- Age <21 years presenting with fever. **AND**
- Clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological). **AND**
- Laboratory evidence of inflammation. **AND**
- No alternative possible diagnoses. **AND**
- Positive for current or recent SARS-CoV-2 (COVID-19) infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

Initial evaluation:

- ***History, clinical examination.***
- ***Vital signs.***
- ***Assessment of perfusion.***
- ***Oxygen saturation.***

Important Notes:

- ***Early consultation*** and coordination with the nearest pediatric infectious disease and rheumatologist and pediatric referral center for optimal testing and management is mandatory.
- Patients under investigations of MIS-C, should be ***admitted to the hospital*** for further observation while completing the diagnostic evaluation, especially ***if they display*** the following:
    - Abnormal vital signs.
    - Respiratory distress of any severity.
    - Neurologic deficits or altered mental status.
    - Evidence of renal or hepatic injury (including mild injury).
    - Markedly elevated inflammatory markers.
    - Abnormal ECG, Echo, troponin T or B-type natriuretic peptide (BNP).
- A child under investigations for MIS-C should be ***also evaluated*** for other ***infectious and noninfectious etiologies*** that may explain the clinical presentation.

Screening Evaluation

- CBC with differential, CRP, ESR
- ALT, AST
- BUN, creatinine
- Glucose, calcium, Na, k
- Albumin, urine analysis.
- SARS-Cov2-PCR or COVID IgG.

Complete Diagnostic Evaluation

If labs showed:

a. CRP>3 mg/dl or ESR> 40 mm/hour.
b. At least 1 suggestive laboratory feature (ALC<1000/uL, platelets count <15000/uL, Na<135 mmoles/l, neutrophilia, hypoalbunemia).

1) BNP, troponin T
2) Ferritin, LDH, fibrinogen, triglycerides
3) D dimer, PT, PTT
4) Blood culture
5) Cytokine panel
6) SARA-COVID 19 serology.
7) Cardiac assessment by ECG, Echo.

Important Notes:

- If the patient is stable and do not meet criteria for diagnosis of MIS-C, **continue close observation** and complete diagnostic evaluation as per standard of care.
- Management of MIS-C is a ***multi-disciplinary*** approach involving many pediatric specialties.
- Infection control policies should be followed.

Treatment

Management of MIS-C includes:[3]

A. **Treatment of correctable conditions:** as hypotension or sepsis by intravenous fluids, antibiotics, inotropes, if necessary, until bacterial infection has been ruled out (use sepsis guidelines).

B. **IVIG:** 2 grams /Kg over 24-36 hours with close observation of hemodynamics and cardiac functions.

C. **Corticosteroids therapy:** Dose ranging from 2-30 mg/kg/day depending on severity of illness.

D. **Biologics:** Indicated for treatment of MIS-C cases that are refractory to IVIG and corticosteroids.

1) **Anakinra:** 4-10 mg/Kg/day subcutaneous.
2) **Infliximab:** 5-10 mg/kg/day intravenous once (should not be used in treatment of cases of MIS-C with features of macrophage activation syndrome).

E. **Thromboprophylaxis:**

1) Aspirin (3-5 mg/kg/day) should be continued until normalization of platelets count and confirmed normal coronary arteries 4 weeks after diagnosis (Aspirin is contraindicated if platelets count< 80000/ɯL).
2) Consult hematologist for LMWH anticoagulation treatment recommendations.
3) Consult cardiologist and hematologist in cases of MIS-C with features of Kawasaki disease and coronary arteries affection that needs anticoagulation.

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Guidelines for the management of Sarcoidosis in pediatrics

Introduction

- Pediatric sarcoidosis is a rare non-necrotizing ***granulomatous inflammatory syndrome*** with multisystemic manifestations, affecting preferentially lungs, lymph nodes and liver.
- Children are less frequently affected when compared to adults, with a phenotypic spectrum ranging from a sub-clinical form with only two organs involved to a severe multi-organic disease.
- Pediatric sarcoidosis remains a "***diagnosis of exclusion***" that is suggested by clinical manifestations and needs to be confirmed by the observation of a typical granuloma at the histologic examination of a biopsied tissue
- Comprehensive investigations for excluding ***alternative causes*** of granuloma as **infectious** granulomatous conditions (e.g., fungal or mycobacterial tuberculosis), **granulomatous** inflammatory disorders (e.g., Crohn's disease, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and lymphomatoid granulomatosis), **immune deficiency** such as combined immunodeficiency, **tumors** as lymphoma, and rarely **drug induced** granulomatosis.
- The diagnostic considerations of pediatric sarcoidosis need to be supported with a ***compatible clinic-radiographic*** presentation and the pathologic findings of non-necrotizing granulomas. There is no reliable diagnostic test for sarcoidosis.

When to suspect Sarcoidosis in pediatric age group?

- Pediatric sarcoidosis appears to have ***two distinct clinical courses*** depending on the age of onset. ***Blau Syndrome*** and early onset sarcoidosis/BS-EOS in children under 5 years of age is characterized by a triad of rash, uveitis, and arthritis.
- In contrast, ***sarcoidosis in older*** children presents with lymphadenopathy (mainly hilar), pulmonary involvement, and non-specific signs and symptoms (i.e., fever and malaise), as in adults.
- Hilar lymphadenopathy, pulmonary infiltration, cutaneous and ophthalmic manifestation are the most common presentation.
- **Pulmonary manifestations** as dry hacking cough, with or without mild to moderate dyspnea, and occasionally chest pain. Bilateral symmetrical hilar lymphadenopathy with or without parenchymal interstitial involvement is the most common radiographic finding.
- Peripheral lymphadenopathy and hepatosplenomegaly could be seen.
- **Ocular manifestations** as uveitis, iritis and conjunctival granuloma.
- **Cutaneous manifestations** as nodules, hyper or hypopigmented lesions, ulcers, erythema nodosum and subcutaneous tumors.
- **Musculosketetal involvement** as peripheral arthritis with boggy tenosynovitis and painless effusion with good range of motion.
- **Renal involvement** is rare in children as proteinuria, leucocyturia, hematuria, concentration defect, hypertension, membranous nephropathy, interstitial nephritis, and renal failure.
- Moreover, it may involve central nervous system, parotid glands, pancreas and heart.

Before referral to pediatric rheumatologist, order these investigations:

1. *CBC with differential, ESR, CRP*
2. *Liver function test*
3. *kidney function test*
4. *Urine analysis*
5. *Serum calcium*
6. *Chest X-ray*
7. *Abdominal Sonar*
8. *Opthalmologic examination*

Together with appropriate radiographic and clinical findings, histopathologic demonstration of typical non-caseating granulomas on biopsy specimen is necessary to confirm the diagnosis.

Treatment

The goal of therapy in sarcoidosis is ***to prevent*** or minimize inflammation and granuloma formation (ie, disease activity) leading to organ system dysfunction, which may ultimately cause end-stage organ destruction.

- **Corticosteroids:** are usually the first line treatment for sarcoidosis. (Dose and duration should be individualized).
- In some cases, corticosteroids can be applied directly to an affected area — via a cream to a skin lesion or eye drops in cases with uveitis.
- **Low-dose Methotrexate** has been used to treat a subset of patients with persistent active or progressive disease that is unresponsive to corticosteroids or those with joint problems.
- Other immunosuppressive medication as azathioprine, mycophenolate mofetil, cyclosporin A, and cyclophosphamide can be used according to severity of disease and response to methotrexate.
- **Hydroxychloroquine** is helpful for skin lesions and elevated blood-calcium levels.
- **Tumor necrosis factor-alpha (TNF-alpha) inhibitors** as infliximab and adalimumab. They can also be helpful in treating sarcoidosis that hasn't responded to other treatments.
- **Other new biological treatments may be used in refractory cases according to consensus guidelines**

Systemic steroids (oral prednisolone) and methotrexate are cornerstone of the therapy of sarcoidosis

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Pediatric Rheumatology Centers in Egypt:

- Cairo university Pediatric Rheumatology Unit, Specialized Children's Hospital, Faculty of Medicine, Cairo University (Abu El reesh hospital)
- Allergy, Immunology and Rheumatology unit, Children's Hospital. Faculty of Medicine, Ain Shams University.
- Alexandria pediatric rheumatology unit, Alexandria university hospital
- Pediatric Allergy, Immunology and Rheumatology Unit, Children's Hospital, Faculty of Medicine, Assiut
- Pediatric Rheumatology unit, Children's Hospital, Faculty of Medicine, Minia University

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