

A RESIDENT'S GUIDE TO PEDIATRIC RHEUMATOLOGY

2011 Revised Edition



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This guide was prepared by the pediatric rheumatology fellows at The Hospital for Sick Children and is intended to provide a brief introduction to basic topics in pediatric rheumatology. Each topic is accompanied by at least one up-to-date reference that will allow you to explore the topic in greater depth. In addition, a list of several excellent textbooks for you to use to expand your knowledge is found in the Appendix.

We are interested in your feedback on the guide! If you have comments or questions, please feel free to contact us via email at pedrheum.guide@sickkids.ca.

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Notes:

Treatment regimens discussed in the guide are suggestions based on common practices by the Division of Rheumatology at The Hospital for Sick Children. Alternative treatment approaches may be used in other centres.

More detailed information on medications (class, action, dose, side effects, monitoring) may be found in the Medications section. Drugs are listed in alphabetical order by their generic names with the exception of Corticosteroids and NSAIDs, which are listed by their categories.

SECTION 1 – AN INTRODUCTION TO PEDIATRIC RHEUMATOLOGY

1A. Pediatric Rheumatologic History

An appropriate rheumatologic history for a new patient should cover the following areas:

History of presenting complaint

Onset, duration, pattern
Potential triggers, such as trauma, infection or immunizations
Severity and impact on function, including school
Associated symptoms
Factors that improve or worsen symptoms
Previous investigations
Previous treatment, including effectiveness and adverse reactions

Past medical history

Chronic medical conditions
Admissions to hospital, surgeries
Eye examinations

Development

Gross motor
Fine motor
Speech, language, hearing
Social

Immunizations

All childhood vaccinations
Varicella – Infection? Vaccination?

Medications

Prescribed medications – dose, route, frequency, adherence
Over-the-counter medications, vitamins, herbal supplements

Allergies

Travel history

Family history

Rheumatologic diseases: Juvenile idiopathic arthritis (JIA), rheumatoid arthritis (RA)
 Ankylosing spondylitis (AS)
 Premature osteoarthritis
 Inflammatory bowel disease (IBD)
 Psoriasis
 Systemic lupus erythematosus (SLE)
 Vasculitis
 Periodic fevers

Other autoimmune diseases: Diabetes mellitus type I, Celiac disease, Thyroid disease

Social history

Parents marital status, occupations, care providers, drug coverage, adolescent HEADSS

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Review of systems

- General:** Energy level, fatigue, poor sleep, non-restful sleep
Anorexia, weight loss
Fevers → frequency, duration, pattern, associated symptoms
Functioning → home, social, school, work
- HEENT:** Photophobia, blurred vision, redness, pain
Sicca symptoms (dry eyes, dry mouth)
Nasal and/or oral ulcers (painful or painless)
Epistaxis
Dysphagia
Otalgia, hearing difficulties
- CVS:** Chest pain, orthopnea, syncope
Peripheral acrocyanosis
Raynaud phenomenon
- Respiratory:** Difficulty breathing, shortness of breath
Pleuritic chest pain
Prolonged cough, productive cough, hemoptysis
- GI:** Recurrent abdominal pain, “heartburn”
Diarrhea, constipation, bloody stools, melena
Nausea, vomiting
- Skin:** Any type of skin rash on face, scalp, trunk, limbs
Petechiae, purpura
Nodules
Ulcers (includes genital/perineal)
Photosensitivity
Alopecia, hair changes
Nail changes (pits, onycholysis) and nail fold changes
- Joints:** Pain (day and/or night), swelling, redness, heat, decreased range of motion
Loss of function, reduced activities
Inflammatory → morning stiffness or gelling, improves with activity or exercise
Mechanical → improves with rest, “locking”, “giving away”
- Muscles:** Pain
Muscle weakness (proximal vs. distal)
Loss of function, reduced activities
- CNS:** Headaches
Psychosis, visual distortions
Cognitive dysfunction, drop in school grades
Seizures
- PNS:** Motor or sensory neuropathy
- GU:** Dysuria, change in urine volume or colour
Missed periods, prolonged periods

1B. Pediatric Rheumatologic Examination

Vital signs (including blood pressure percentiles)

Height and weight (percentiles, recent changes)

General appearance

- HEENT:** Conjunctival injection or hemorrhage, pupils (shape and reaction)
Complete ophthalmoscope examination from cornea to fundus
Nasal mucosa, nasal discharge, sinus pain
Oropharyngeal mucosa, tongue, tonsils
Thyroid
- CVS:** Heart sounds, murmurs, precordial examination
Vascular bruits
Peripheral pulses, peripheral perfusion, capillary refill
- Lungs:** Breath sounds, adventitious sounds, percussion, respiratory excursion
- Abdomen:** Tenderness, peritoneal signs, masses, bowel sounds, (bruits)
Hepatomegaly, splenomegaly
- LN:** Assess all palpable lymph node groups
- Skin:** Any type of skin rash
Petechiae, purpura
Nodules
Ulcers
Alopecia, hair abnormalities
- Nails:** Nail pits, clubbing
Nail fold capillaries – thickening, branching, drop-out, hemorrhages
Digital ulcers, loss of digital pulp
- CNS:** Mental status
Cranial nerves
Motor: muscle bulk, tone, power/strength, tenderness, deep tendon reflexes
Cerebellar
Gait (walking, running, heels, toes, and tandem)
Sensory (if indicated), allodynia borders (if indicated)
- Joints:** Assess all joints for heat, swelling, tenderness, stress pain, active and passive range of motion, deformity
Enthesitis sites
Localized bony tenderness
Leg length (functional and/or actual)
Thigh circumference difference (if indicated)
- Back:** Range of motion, tenderness, stress pain
Scoliosis
Modified Schober test (if indicated)
- Other:** Fibromyalgia tender points (if indicated)

1C. Laboratory Testing in Pediatric Rheumatology

Acute phase response

- Acute phase reactants are plasma proteins produced by the liver that change production during acute phase of inflammation
- Acute phase response mediated by cytokines, such as IL-1, IL-6 and TNF
- Substantial acute phase response may be seen in infection, trauma, burns, tissue infarction, advanced cancer and immune-mediated disease
- Moderate changes may occur following strenuous exercise or heatstroke
- Overall effect of acute phase response is to protect host from damage
- Excessive or prolonged acute phase response may be deleterious itself (e.g. septic shock, ARDS, macrophage activation syndrome, AIDS, amyloidosis, malignancy)
- **C-reactive protein (CRP)**
 - Protein recognizes pathogens and mediates action of complement and phagocytic cells
 - Level rises rapidly in response to inflammation and falls quickly with appropriate treatment
 - Reflects severe disease more closely than other acute phase reactants
- **Erythrocyte sedimentation rate (ESR)**
 - Measure of height of plasma layer vacated by red blood cells as the cells settle in a tube of anticoagulated blood in one hour
 - Depends on fibrinogen, gamma globulins
 - Indirect measure of acute phase reaction; changes more slowly than CRP

Increase in acute phase response	Decrease in acute phase response
CRP, ESR	Albumin
Complement proteins	Transferrin
Fibrinogen, coagulation proteins	IGF-1
Ferritin	
Ceruloplasmin	
Haptoglobin	
G-CSF	
IL-1 receptor antagonist	
Serum amyloid A	

Complete blood cell count

- Normocytic or microcytic anemia in chronic inflammatory disease
- Autoimmune hemolytic anemia in SLE
- Iron deficiency anemia if chronic blood loss (e.g. due to NSAIDs, IBD)
- High white cell count due to systemic inflammation or initiation of Corticosteroids
- Leukopenia with lymphopenia, neutropenia and/or thrombocytopenia in active SLE or medication-related
- Active inflammation may lead to abnormal platelet counts

Complement

- Increased levels of complement components frequently seen in inflammation
- Low complement levels present in systemic lupus erythematosus (SLE), acute post-infectious glomerulonephritis, membrano-proliferative glomerulonephritis, or liver disease
- Congenital complement deficiencies predispose either to recurrent infections or to unusual autoimmune disease ("lupus-like" disease)
- In SLE, serial measurements of C3 and C4 are useful to monitor disease activity
 - Complement levels tend to fall during a flare and return to normal concentration after appropriate therapy
 - Persistently low C3 associated with lupus nephritis

Autoantibodies

Antinuclear antibodies (ANA)

- Autoantibodies directed against nuclear, nucleolar or perinuclear antigens
- Low titres of ANA may be present in up to 30% of normal healthy population
- ANA may also be present in non-rheumatologic diseases (e.g. infection, malignancy, medications)
- Low titres of non-specific ANA in juvenile idiopathic arthritis (JIA) (e.g. ANA \leq 1:160)
 - Positive ANA in JIA associated with higher risk of uveitis, asymmetric arthritis and early disease onset
- Persistent high titres of ANA in connective tissue diseases, such as SLE
 - Negative ANA makes diagnosis of SLE unlikely
- Specific antibodies (e.g. anti-double stranded DNA) should only be requested if ANA is positive at higher titres (\geq 1:160) and disease other than JIA suspected

Specific antibodies	Characteristic disease associations
Anti-dsDNA	SLE
Anti-Ro/SSA	SLE, Neonatal lupus erythematosus, Sjögren
Anti-La/SSB	SLE, Neonatal lupus erythematosus, Sjögren
Anti-Sm	SLE
Anti-RNP	Mixed connective tissue disease, SLE, Systemic sclerosis
Anti-histone	Drug-induced lupus, SLE
Anti-Scl 70	Diffuse systemic sclerosis
Anti-centromere	Limited systemic sclerosis (CREST)
Anti-Jo1	Polymyositis with interstitial lung disease, juvenile dermatomyositis (JDM)
Anti-SRP	JDM with profound myositis & cardiac disease
Anti-Mi-2	JDM with good prognosis

Antiphospholipid antibodies

- Heterogeneous group of antibodies directed against cell membrane phospholipids
- May be produced due to primary antiphospholipid antibody syndrome (APS) or secondary to CTD, infection or drugs
- Include lupus anticoagulant, anticardiolipin, anti- β_2 -glycoprotein I
- Associated with increased risk of thrombosis (but paradoxically prolongs laboratory PTT)

Rheumatoid factor (RF)

- IgM autoantibody that reacts to Fc portion of IgG antibodies
- Present in 85% of adults with rheumatoid arthritis
- Present in only 5-10% of children with JIA
 - Helpful in classification and prognosis of JIA, but should not be used as a screening test since arthritis is a clinical diagnosis
 - Children with RF-positive polyarthritis are at higher risk of aggressive joint disease with erosions and functional disability
- RF may also be detected in chronic immune-complex mediated diseases, such as SLE, systemic sclerosis, Sjögren, cryoglobulinemia and chronic infection (subacute bacterial endocarditis, hepatitis B and C, TB)

Antineutrophil cytoplasmic antibodies (ANCA)

- Antibodies target antigens in cytoplasmic granules of neutrophils
- May be pathogenic by activating neutrophils, leading to perpetuation of chronic inflammation
- High sensitivity and specificity for primary small vessel systemic vasculitides

ANCA	Immunofluorescence pattern	Antigen specificity	Disease associations
c-ANCA	Cytoplasmic	Proteinase-3 (PR3)	Wegener granulomatosis
p-ANCA	Perinuclear	Myeloperoxidase (MPO)	Microscopic polyangiitis Churg-Strauss syndrome Ulcerative colitis Primary sclerosing cholangitis SLE

HLA B27

- Many genes of the major histocompatibility complex (especially Human Leukocyte Antigen (HLA) class I and II genes) have been associated with rheumatic disorders
- HLA B27 is an HLA class I gene that is present in only 7-10% of the general population (may be higher in some First Nations groups)
- HLA B27 is found in 90-95% of Caucasians with ankylosing spondylitis and many patients with JIA (particularly enthesitis related arthritis and psoriatic arthritis), inflammatory bowel disease, isolated acute anterior uveitis, and reactive arthritis
- HLA B27 may play a role in the pathogenesis of inflammatory disease

References:

1. Breda L, Nozzi M, De Sanctis S, et al. Laboratory tests in the diagnosis and follow-up of pediatric rheumatic diseases: An update. *Semin Arthritis Rheum*. 2009 Feb 24. [Epub ahead of print]
2. Gabay C, Kushner I. Acute phase proteins and other systemic responses to inflammation. *New Engl J Med*, 1999; 340:448-54.
3. McGhee JL, Kickingbird LM, Jarvis JN. Clinical utility of antinuclear antibody tests in children. *BMC Pediatr* 2004; 4:13.

SECTION 2 – JUVENILE IDIOPATHIC ARTHRITIS

2A. General Approach to Joint Pain in Children

Differential diagnosis for pain involving a single joint:

Trauma	Fracture, soft tissue injury (e.g. ligaments in older children) Foreign body synovitis
Infection-related	Septic arthritis Osteomyelitis Reactive arthritis Toxic synovitis Chronic infections, such as tuberculosis or Lyme disease
Inflammation	Juvenile idiopathic arthritis (JIA) Chronic non-bacterial osteomyelitis Familial Mediterranean Fever
Tumours	Bone tumours, such as osteoid osteoma or osteosarcoma
Haemarthrosis	Coagulopathy, such as haemophilia Pigmented villonodular synovitis
Mechanical	Overuse injury, apophysitis
Orthopedic	Avascular necrosis (AVN) Slipped capital femoral epiphysis (SCFE)
Pain syndrome	Complex regional pain syndromes (CRPS)

Differential diagnosis for pain involving multiple joints:

Inflammation	Juvenile idiopathic arthritis (JIA) Systemic lupus erythematosus (SLE) Juvenile dermatomyositis Systemic vasculitides, such as Henoch-Schönlein purpura Inflammatory bowel disease (IBD) Hereditary autoinflammatory syndromes Sarcoidosis Chronic recurrent multifocal osteomyelitis (CRMO) Serum sickness
Infection-related	Acute infections, such as parvovirus B19 and <i>Neisseria gonorrhoeae</i> Subacute bacterial endocarditis (SBE) Reactive arthritis, including acute rheumatic fever (ARF)
Malignancy	Leukemia, lymphoma Neuroblastoma Cancers with systemic involvement
Mechanical	Hypermobility, apophysitis Skeletal dysplasias
Pain syndrome	Fibromyalgia

What do the clinical features associated with joint pain/swelling tell you about the underlying diagnosis?

If sign/symptom present...	Consider these disorders
Severe joint pain	Infection-related, malignancy, trauma, AVN, chronic regional pain syndrome (CRPS)
Pinpoint tenderness	Osteomyelitis, trauma, AVN, malignancy, enthesitis, CRMO
Night pain	Malignancy, osteoid osteoma, "growing pains"
Redness	Septic arthritis, acute rheumatic fever, reactive arthritis
Migratory joint pain	Leukemia, acute rheumatic fever
Not walking	Infection, malignancy, discitis, myositis, CRPS
Hip pain	Infection-related, AVN, SCFE, malignancy, chondrolysis, toxic synovitis, JIA (particularly enthesitis related arthritis)
Back pain	Usually benign, but consider bone or spinal cord tumour, discitis, spondylolysis/spondylolisthesis, JIA (especially enthesitis related arthritis), myositis, osteoporosis, fibromyalgia
Periarticular pain	Malignancy, hypermobility, CRPS, fibromyalgia
Dactylitis	JIA (particularly enthesitis related arthritis and psoriatic arthritis), sickle cell, trauma
Clubbing	CF, IBD, malignancy (especially lung), familial
Weight loss	Malignancy, connective tissue diseases, IBD
Muscle weakness	Myositis, malignancy, pain-related weakness
Rash	Connective tissue disease, vasculitis, JIA (particularly systemic arthritis, enthesitis related arthritis and psoriatic arthritis), acute rheumatic fever, Lyme disease
Oral ulcers	Vasculitis
Nail or nail fold changes	Connective tissue diseases, psoriasis, subacute bacterial endocarditis
Raynaud phenomenon	Connective tissue diseases, vascular obstruction
School withdrawal	Fibromyalgia, chronic fatigue
Travel	Infection-related (e.g. tuberculosis, Lyme disease)
Consanguinity	Genetic or metabolic diseases

References:

1. Tse SM, Laxer RM. Approach to Acute Limb Pain in Childhood. *Pediatr Rev.* 2006; 27:170-80.
2. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet.* 2007; 369(9563):767-78.

2B. Introduction to Juvenile Idiopathic Arthritis (JIA)

- JIA refers to chronic, inflammatory arthritis in children. The current classification system by the International League of Associations for Rheumatology (ILAR) recognizes 7 distinct subtypes of JIA, based on their presentation within the first 6 months:
 1. **Oligoarthritis**
 2. **Polyarthritis (Rheumatoid Factor Negative)**
 3. **Polyarthritis (Rheumatoid Factor Positive)**
 4. **Systemic Arthritis**
 5. **Enthesitis Related Arthritis**
 6. **Psoriatic Arthritis**
 7. **Undifferentiated Arthritis**
- **General Definition of JIA**

Juvenile idiopathic arthritis is arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks; other known conditions are excluded:

References:

1. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: Second revision, Edmonton 2001. *J Rheumatol* 2004; 31(2):390-2.
2. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007; 369(9563):767-78.

2C. Oligoarthritis

ILAR Criteria for Oligoarthritis

Definition: Arthritis affecting 1 to 4 joints during the first 6 months of disease

Two subcategories are recognized:

1. Persistent oligoarthritis: Affects not more than 4 joints throughout disease course.
2. Extended oligoarthritis: Affects more than 4 joints after the first 6 months of disease.

Exclusions:

- Psoriasis or a history of psoriasis in the patient or first degree relative
- Arthritis in an HLA B27 positive male beginning after 6th birthday
- Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with IBD, or acute anterior uveitis, or history of one of these disorders in 1st degree relative
- Presence of IgM Rheumatoid Factor on at least 2 occasions at least 3 months apart
- Presence of systemic JIA

- Oligoarthritis is the most common subtype of JIA. The typical patient is a young girl with positive ANA who presents with a small number of swollen joints. The most frequent joints to be involved are knees, ankles, wrists, or elbows. Hip involvement is uncommon, especially early in disease. ANA is positive in 60-80% of patients (antigenic specificity is unknown for

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ANA in JIA). Oligoarticular JIA with positive ANA is associated with a higher risk of asymptomatic uveitis. (See Section 9A)

2D. Polyarthritis (Rheumatoid Factor Negative)

ILAR Criteria for Polyarthritis (Rheumatoid Factor Negative)

Definition:

- Arthritis affecting 5 or more joints during first 6 months of disease
- Negative testing for RF

Exclusions:

- Psoriasis or a history of psoriasis in the patient or first degree relative
- Arthritis in an HLA B27 positive male beginning after 6th birthday
- Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with IBD, or acute anterior uveitis, or history of one of these disorders in 1st degree relative
- Presence of IgM Rheumatoid Factor on at least 2 occasions at least 3 months apart
- Presence of systemic JIA

- Children with RF negative polyarthritis are frequently younger and have a better prognosis than those with RF positive disease. ANA is positive in 25% of patients. Affected joints are frequently symmetrical, affecting large and small joints alike. Less than 50% of patients go into remission, and long-term sequelae are frequent, especially with hip and shoulder involvement.

2E. Polyarthritis (Rheumatoid Factor Positive)

ILAR Criteria for Polyarthritis (Rheumatoid Factor Positive)

Definition:

- Arthritis affecting 5 or more joints during first 6 months of disease
- 2 or more positive tests for RF at least 3 months apart during first 6 months of disease

Exclusions:

- Psoriasis or a history of psoriasis in the patient or first degree relative
- Arthritis in an HLA B27 positive male beginning after 6th birthday
- Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with IBD, or acute anterior uveitis, or history of one of these disorders in 1st degree relative
- Presence of systemic JIA

- RF positive polyarthritis is essentially adult-type rheumatoid arthritis presenting in a child or adolescent. All patients, by definition, are RF positive and ANA is positive in 75%. This affects mostly adolescent girls. The clinical symptoms are similar to the adult disease with symmetrical polyarthritis especially involving the PIP joints and MCP joints.
- Children may develop rheumatoid nodules and similar complications to adult disease, including joint erosions and Felty syndrome (neutropenia and splenomegaly).

2F. Systemic Arthritis

ILAR Criteria for Systemic Arthritis

Definition:

- Arthritis affecting 1 or more joints
- Associated with or preceded by fever of at least 2 weeks' duration that is documented to be daily, or "quotidian" for at least 3 days
- Accompanied by 1 or more of:
 - Evanescent (non-fixed) erythematous rash
 - Generalized lymph node enlargement
 - Hepatomegaly and/or splenomegaly
 - Serositis

Exclusions:

- Psoriasis or a history of psoriasis in the patient or first degree relative
- Arthritis in an HLA B27 positive male beginning after 6th birthday
- Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with IBD, or acute anterior uveitis, or history of one of these disorders in 1st degree relative
- Presence of IgM Rheumatoid Factor on at least 2 occasions at least 3 months apart

- The typical symptoms of systemic JIA are as follows:
 - Once or twice daily fever spikes to temperatures >38.5 degrees Celsius, which return to baseline or below. Children are usually acutely unwell during fever episodes.
 - Salmon-colored, evanescent rash accompanying the fever, occasionally pruritic
 - Lymphadenopathy and hepatosplenomegaly
 - Arthritis may develop later (e.g. within one year of fever) and is usually oligoarticular, affecting knees, wrists and ankles, but cervical spine and hip involvement also occurs.
- The differential diagnosis for systemic JIA includes infection, Kawasaki disease, periodic fever syndromes, and malignancy, especially leukemia and lymphoma. An infectious work-up and bone marrow aspirate should be done before starting Corticosteroid treatment. Systemic JIA may be complicated by macrophage activation syndrome in 7% of patients. (See 8A)

2G. Enthesitis Related Arthritis

ILAR Criteria for Enthesitis Related Arthritis

Definition:

- Arthritis and enthesitis
- Or, arthritis or enthesitis with at least 2 of the following:
 - Presence or history of sacroiliac joint tenderness and/or inflammatory back pain
 - Presence of HLA B27 antigen
 - Onset of arthritis in a male over 6 years of age
 - Acute (symptomatic) anterior uveitis
 - History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, or acute anterior uveitis in a first-degree relative

Exclusions:

- Psoriasis or a history of psoriasis in the patient or first degree relative
- Presence of IgM Rheumatoid Factor on at least 2 occasions at least 3 months apart
- Presence of systemic JIA

- Enthesitis related arthritis (ERA) typically occurs in boys, usually over 6 years of age, with a familial predilection. The hallmark of this type of arthritis is enthesitis (inflammation of the insertion sites of tendons, ligaments and fascia). The most common sites are the insertion sites of the Achilles tendon, plantar fascia, patellar tendon, and quadriceps tendon. ERA commonly affects the lower extremities, including the hips. Axial involvement (involvement of the sacroiliac joints and/or spine) typically develops later.
- Other manifestations include tarsitis (diffuse inflammation of tarsal joints and surrounding tendon sheaths) and dactylitis (sausage-shaped swelling of entire digit). Symptomatic anterior uveitis may develop in children with ERA and this usually presents with significant eye pain and redness, which may be unilateral.

2H. Psoriatic Arthritis

ILAR Criteria for Psoriatic Arthritis

Definition:

- Arthritis and psoriasis
- Or, arthritis and at least 2 of the following:
 - Dactylitis
 - Nail-pitting or onycholysis
 - Psoriasis in a first-degree relative

Exclusions:

- Arthritis in an HLA B27 positive male beginning after 6th birthday
- Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with IBD, or acute anterior uveitis, or history of one of these disorders in 1st degree relative
- Presence of IgM Rheumatoid Factor on at least 2 occasions at least 3 months apart
- Presence of systemic JIA

- Psoriatic arthritis can occur before or after manifestation of psoriasis. In fact, children may be re-classified as having psoriatic arthritis if they develop psoriasis after their arthritis is diagnosed. Psoriatic arthritis is typically asymmetric, and involves both large and small joints. The clinical hallmark is dactylitis, which is caused by simultaneous inflammation of the flexor tendon and synovium, leading to the typical “sausage digit” appearance.

2I. Undifferentiated Arthritis

ILAR Criteria for Undifferentiated Arthritis

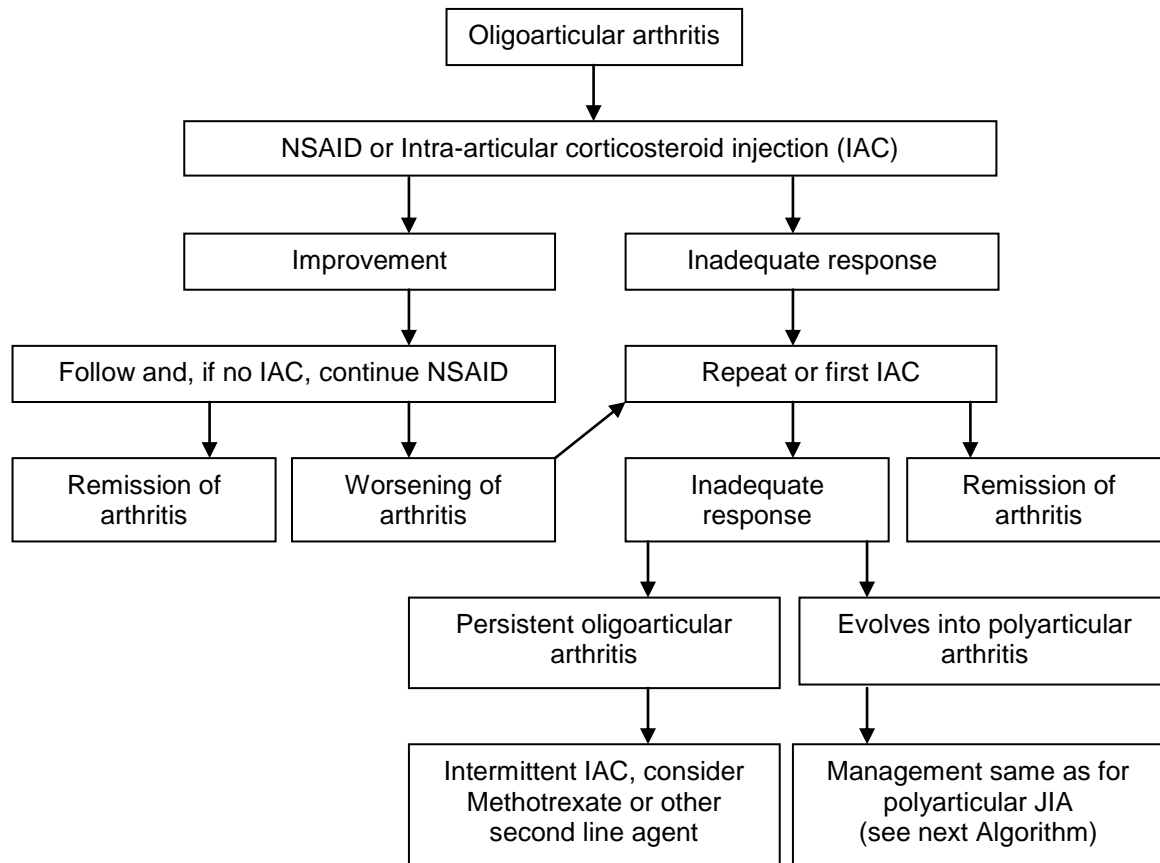
Definition:

- Arthritis that fulfils criteria in no category or in 2 or more of the above categories

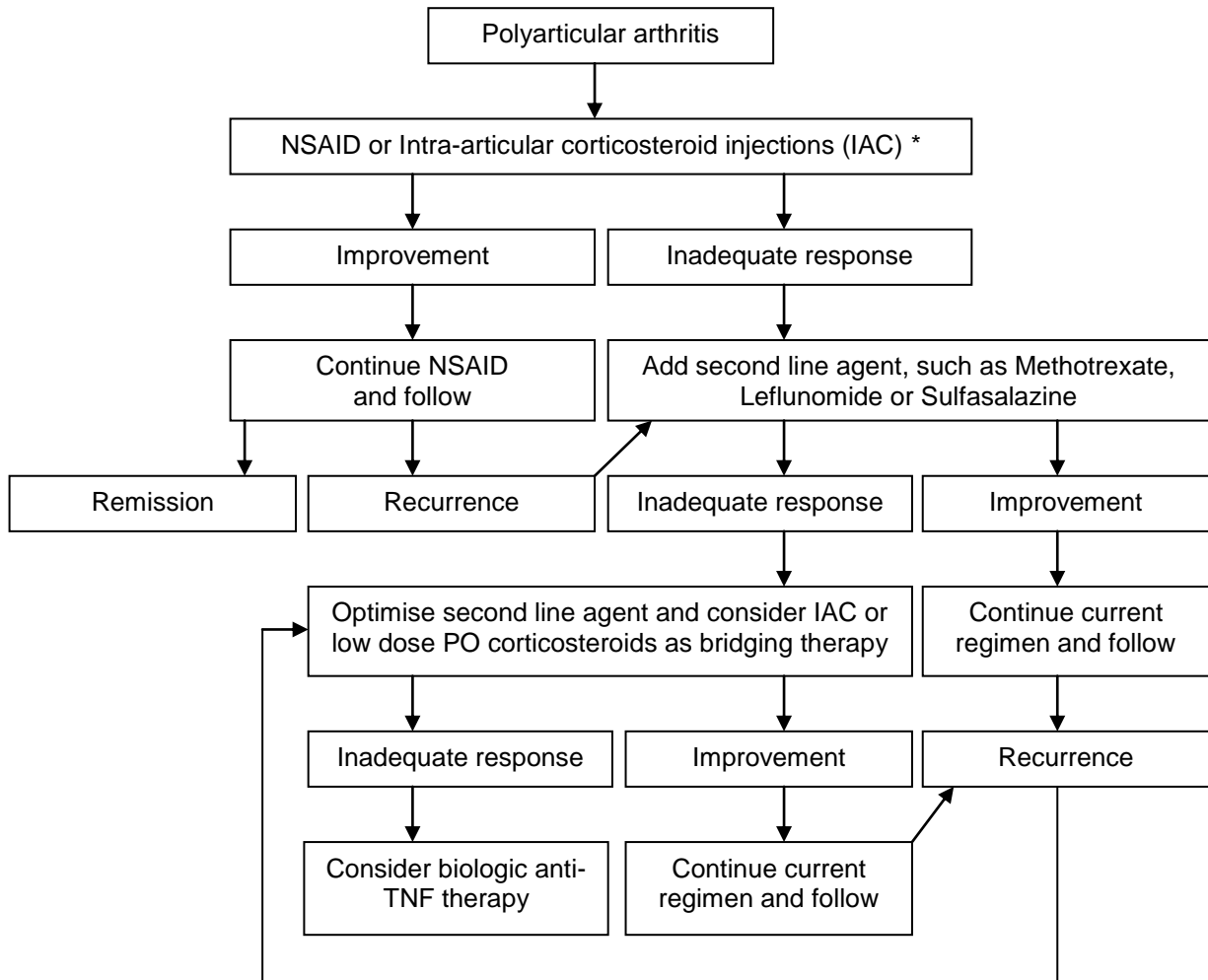
2J. Approach to Treatment of JIA

- **Goals of therapy:**
 1. Eliminate inflammation
 2. Prevent joint damage
 3. Promote normal growth and development as well as normal function
 4. Minimize medication toxicity
- Multidisciplinary approach is part of comprehensive JIA treatment
- Occupational and physical therapists may play an important role in treating JIA
- Initial therapy with an NSAID may be started by a patient's primary care physician; however, a referral should be made to a pediatric rheumatologist for all patients with JIA (especially for polyarthritis and systemic arthritis) in case rapid escalation of therapy is required.
- An eye examination should be requested for patients with JIA, especially those with oligoarthritis and positive ANA.

An Algorithm for Treatment of Oligoarticular JIA

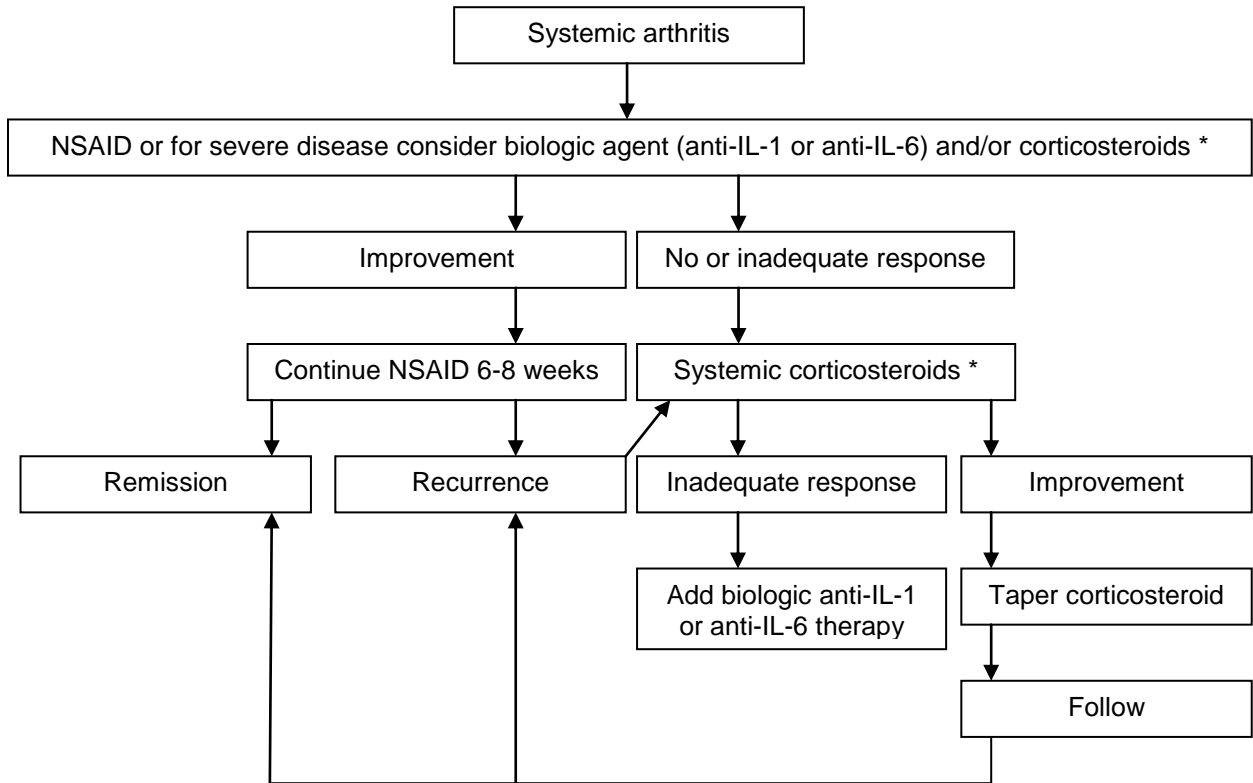


An Algorithm for Treatment of Polyarticular JIA



* May need to start a second line agent as part of initial therapy in children with severe polyarthritis.

An Algorithm for Treatment of Systemic JIA



* The recommendations to add a biologic agent (anti-IL-1 or anti-IL6) earlier during initial therapy are based on the new 2011 ACR recommendations for the treatment of JIA.

References

1. Zulian F, Martini G, Gobber D, et al. Comparison of intra-articular triamcinolone hexacetonide and triamcinolone acetonide in oligoarticular juvenile idiopathic arthritis. *Rheumatology* 2003;42(10):1254-9.
2. Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. *JAMA* 2005; 294(13):1671-84.
3. Kahn P. Juvenile idiopathic arthritis--current and future therapies. *Bull NYU Hosp Jt Dis* 2009;67:291-302.
4. Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res* 2011; 63(4):465-82. (Also Clinician's Guide with treatment algorithms at http://www.rheumatology.org/practice/clinical/guidelines/clinician's_guide2011.pdf.)

SECTION 3. SYSTEMIC LUPUS ERYTHEMATOSUS & RELATED CONDITIONS

3A. Systemic Lupus Erythematosus (SLE)

- Multi-system inflammatory disease characterized by autoantibody and immune-complex mediated inflammation of blood vessels and connective tissues
- 15-20% of cases of SLE are diagnosed before 16 years of age
- Female predominance, especially in adolescence and adulthood
- Ethnic predilection in blacks, Hispanics, and Asians
- Positive family history of SLE

1997 American College of Rheumatology (ACR) Classification Criteria for SLE

Need $\geq 4/11$ of following criteria:

- Malar rash (butterfly rash sparing nasolabial folds)
- Discoid lupus rash*
- Photosensitivity
- Oral or nasal mucocutaneous ulcerations (usually painless)
- Non-erosive arthritis
- Nephritis (characterized by proteinuria and/or cellular casts)
- Encephalopathy (characterized by seizures and/or psychosis)
- Pleuritis or pericarditis
- Cytopenia (thrombocytopenia, lymphopenia, leukopenia, Coombs-positive hemolytic anemia)
- Positive ANA
- Positive immunoserology (anti-dsDNA, anti-Sm, antiphospholipid antibodies)

*Uncommon in children

- 1997 ACR Classification criteria were designed to identify a homogeneous population of SLE patients for research studies; however, the presence of ≥ 4 criteria is highly sensitive and specific for SLE ($>95\%$) and so the criteria are widely used for diagnosis
- Other common clinical features of SLE not included in above classification criteria:
 - Constitutional symptoms – fevers, fatigue, weight loss, anorexia
 - Other rashes (e.g. maculopapular rashes secondary to vasculitis or perivasculitis on sun-exposed areas, fingers, toes, and earlobes)
 - Polyarthralgia
 - Raynaud phenomenon (see Section 5A)
 - Lymphadenopathy
 - Hepatomegaly, splenomegaly
 - Hypertension
- Other common laboratory features of SLE:
 - Elevated ESR with normal CRP
 - Low complement (C3, C4) levels
 - Elevated IgG levels
 - Other autoantibodies: anti-Ro, anti-La, anti-RNP, Rheumatoid factor

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- Presentation of SLE is not always “classic” → need to consider this diagnosis in adolescent females with polyarthritis; fever, rash and constitutional symptoms; ITP with positive ANA; unusual arterial or venous thrombosis; or chorea
- Childhood-onset SLE vs. adult-onset SLE
 - Children have more active disease at presentation and over time
 - Children more likely to have active renal disease
 - Children receive more intensive drug therapy and sustain more damage due to SLE
- Treatment:
 - Based on organ involvement
 - Use minimum required treatment to maintain clinical and laboratory quiescence
 - More aggressive treatment used for more severe organ involvement
 - Hydroxychloroquine
 - Considered standard therapy for SLE
 - Proven efficacy in decreasing frequency and severity of disease flares
 - Improves serum lipid profile
 - Corticosteroids
 - Often used in initial therapy for SLE with dose depending on severity and organ involvement
 - Pulse therapy for severe lupus nephritis, hematologic crisis, or CNS disease
 - Azathioprine
 - Typically used for hematologic and renal manifestations
 - Mycophenolate mofetil
 - Used for hematologic, renal and CNS manifestations
 - Cyclophosphamide
 - Used for severe renal and CNS manifestations
 - Rituximab
 - Used for resistant thrombocytopenia
- Course and Outcomes
 - Relapsing and remitting course of disease
 - 10 year survival >90%
 - Most deaths related to **infection**, renal, CNS, cardiac, and pulmonary disease
 - Additional morbidity related to disease and/or treatment:
 - Early onset coronary artery disease
 - Bone disease → osteopenia, avascular necrosis
 - Malignancy

References:

1. Benseler SM, Silverman ED. Systemic lupus erythematosus. *Rheum Dis Clin North Am* 2007; 33(3):471-98.
2. Hiraki LT, Benseler SM, Tyrrell PN, et al. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: A longitudinal study. *J Pediatr* 2008; 152:550-6.
3. Brunner HI, Gladman DD, Ibanez D, et al. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. *Arthritis Rheum* 2008; 58(2):556-62.

3B. Neonatal Lupus Erythematosus (NLE)

- Disease of developing fetus and newborn characterized by transplacental passage of maternal autoantibodies
- Pathogenesis linked to maternal anti-Ro and anti-La antibodies
- Presence of autoantibodies is necessary but not sufficient to cause NLE since many mothers with autoantibodies deliver healthy, unaffected infants
- Mothers of infants with NLE may have SLE, Sjögren syndrome, or other autoimmune diseases; however, many mothers may be healthy with no known autoimmune disease

- Incidence 1-2% of children in mothers with anti-Ro and/or anti-La antibodies
- Higher risk for subsequent children once one child has been affected (e.g. 16% of subsequent siblings of child with congenital heart block)

- Clinical features:
 - Cardiac
 - Most important and severe manifestation is complete congenital heart block
 - Complete heart block is associated with significant morbidity and mortality (congestive heart failure, fetal hydrops, intrauterine death)
 - Other manifestations include less severe conduction abnormalities, carditis
 - Skin
 - Classic NLE rash is annular, erythematous papulosquamous rash with fine scale and central clearing
 - Predilection for face and scalp (not malar distribution)
 - Typically photosensitive
 - Dermatitis may be present at birth but more commonly develops within first few weeks of life
 - New lesions appear for several months, but rarely develop after 6 months and typically heal without scarring
 - Telangiectasias may develop starting at 6-12 months of age, may not be in areas affected by previous rash
 - Hematologic
 - Thrombocytopenia is most common
 - Neutropenia and anemia less common
 - Usually resolve without sequelae and rarely requires treatment
 - Hepatic
 - Cholestatic hepatitis with mild to moderately elevated liver enzymes
 - Hepatomegaly
 - Typically resolve before 6 months without treatment
 - Neurologic
 - Reported CNS manifestations include macrocephaly, hydrocephalus, spastic paraparesis, asymptomatic neuroimaging abnormalities, and vasculopathy
 - Clinical significance still unclear

- Treatment:
 - If fetal bradycardia found during pregnancy, require fetal echocardiography to assess for heart block and may require treatment with Dexamethasone ± sympathomimetics
 - Pacemaker may be required soon after birth for neonates with complete heart block
 - Classic NLE rash does not require treatment since rash will completely resolve; Corticosteroids may hasten healing but may increase risk of telangiectasias

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- Future pregnancies require expectant management with fetal heart rate monitoring

References:

1. Izmirly PM, Rivera TL, Buyon JP. Neonatal lupus syndromes. *Rheum Dis Clin North Am* 2007; 33(2):267-85.
2. Cimaz R, Spence DL, Hornberger L, et al. Incidence and spectrum of neonatal lupus erythematosus: A prospective study of infants born to mothers with anti-Ro autoantibodies. *J Pediatr* 2003; 142(6):678-83.

3C. Antiphospholipid Syndrome (APS)

- Systemic autoimmune disorder characterized by recurrent arterial and/or venous thrombosis and elevated levels of antiphospholipid antibodies
- Primary APS if occurs without underlying disease
- Secondary APS due to SLE, other autoimmune diseases, drugs or viral infections (e.g. HIV)
- Venous thrombosis in ~60%, arterial thrombosis in ~30%, small vessel thrombosis in ~5%, mixed thrombosis in ~2%
- Thrombotic manifestations are most common, followed by hematologic, skin and non-thrombotic neurologic manifestations

Classification Criteria for Antiphospholipid Syndrome

Clinical criteria

- Vascular thrombosis
- Pregnancy morbidity
 - ≥ 3 consecutive unexplained spontaneous abortions before 10 wks gestation, *or*
 - ≥ 1 unexplained fetal loss beyond 10 wks gestation, *or*
 - ≥ 1 premature birth before 34 wks gestation due to severe pre-eclampsia, eclampsia, *or* placental insufficiency

Laboratory criteria

- Medium to high titre anticardiolipin (IgG or IgM) on ≥ 2 occasions at least 6 wks apart
- Moderate to high titre antibodies to β_2 -glycoprotein I on ≥ 2 occasions > 6 wks apart
- Lupus anticoagulant on ≥ 2 occasions > 6 wks apart

Definite APS requires 1 clinical criterion plus 1 laboratory criterion

- Additional clinical features of APS:
 - Livedo reticularis
 - Cardiac valve disease (Libman-Sachs endocarditis)
 - Chorea
 - Seizures
 - Transient cerebral ischemia
 - Transverse myelopathy

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- Additional laboratory features of APS:
 - Thrombocytopenia
 - Hemolytic anemia
 - Additional antibodies to prothrombin, annexin, or other phospholipids
 - False positive VDRL

- Treatment
 - If primary, treat as disorder of coagulation
 - If secondary, treat underlying disorder (often using Corticosteroids)
 - Anticoagulation using heparin (e.g. LMWH) required at least initially, may require lifelong LMWH or warfarin
 - Consider anti-platelet agents (e.g. ASA)
 - May consider Rituximab as direct therapy to target pathogenic autoantibodies in APS

References:

1. Ravelli A, Martini A. Antiphospholipid antibody syndrome in pediatric patients. *Rheum Dis Clin North Am* 1997; 23: 657-76
2. Avcin T, Cimaz R, Silverman ED, et al. Pediatric antiphospholipid syndrome: Clinical and immunologic features of 121 patients in an international registry. *Pediatrics* 2008; 122(5):e1100-7.

SECTION 4 – VASCULITIS

4A. Introduction to Vasculitis

- Group of multi-system inflammatory diseases characterized by inflammation and necrosis of blood vessels, resulting in vessel occlusion and tissue ischemia
- Consider vasculitis when:
 - Unexplained prolonged constitutional symptoms (fever, weight loss, fatigue)
 - Multisystem involvement (see below)
 - Unusual symptoms
 - Purpura, nodules, livedo
 - Unexplained glomerulonephritis, rapidly progressive renal failure
 - Mononeuritis
 - Pulmonary haemorrhage
- Multiple organ system involvement
 - CNS (headache, seizures, stroke); PNS (mononeuritis)
 - Cardiac (pericarditis, myocarditis, myocardial infarction)
 - Vascular (chronic vascular insufficiency, vascular bruits, claudication)
 - Pulmonary (hemorrhage, nodules, cavities, infiltrates)
 - Renal (nephritis, nephrotic syndrome, hypertension)
 - Ophthalmologic (episcleritis, iritis)
 - ENT (chronic sinusitis, epistaxis, chronic otitis, hearing loss, chondritis)
 - GI (ischemic abdominal pain)
 - MSK (arthritis, arthralgia, myalgias, calf pain)
 - Skin (palpable purpura, nodules, livedo, urticaria, ulcers)

Classification of vasculitis based on size of vessel involved	
Large vessel vasculitis	Takayasu arteritis Giant cell arteritis (older adults)
Medium vessel vasculitis	Kawasaki disease Polyarteritis nodosa (systemic, cutaneous)
Small vessel vasculitis	Wegener’s granulomatosis Churg-Strauss syndrome Microscopic polyangiitis Henoch-Schonlein purpura Cryoglobulinemia Hypocomplementemic urticarial vasculitis
Other vasculitis	Behçet disease Cogan syndrome Primary CNS vasculitis Vasculitis secondary to: <ul style="list-style-type: none"> • Drugs • Infection (e.g. hepatitis B virus, Parvovirus) • Malignancy

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- ANCA-associated vasculitides:
 - Wegener granulomatosis (classically c-ANCA (PR3))
 - Microscopic polyangiitis (p-ANCA (MPO))
 - Churg-Strauss syndrome (p-ANCA)
- Diagnostic investigations
 - Look for end-organ damage (eyes, skin, heart, lungs, kidneys, nervous system)
 - Look for triggers or underlying disease (drugs, malignancy, infection, CTD)
 - Immune serology (ANA, ANCA)
 - Tissue biopsy (histopathology & immunofluorescence)
 - Angiography (conventional; magnetic resonance; computed tomography)
- Treatment
 - Depends on specific disease, organ involvement, severity
 - Immunosuppressive agents plus supportive therapy
- Potential complications
 - Acute: organ failure (renal, pulmonary, cardiac), thrombus (renal, pulmonary, coronary, cerebral, GI vessels), hemorrhage (pulmonary, GI), **infection**
 - Chronic: hypertension, chronic renal failure, pulmonary insufficiency, hearing loss, saddle nose, subglottic stenosis

References:

1. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener's granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010; 69(5):798-806.
2. Dedeoglu F, Sundel R. Vasculitis in children. *Rheum Dis Clin North Am* 2007; 33:555–83.

4B. Takayasu arteritis

2008 EULAR/PRINTO/PRES Classification Criteria for Childhood Takayasu arteritis

Angiographic abnormalities of the aorta or its main branches and pulmonary arteries showing aneurysm/dilatation, narrowing, or thickened arterial wall (mandatory criterion)

Plus \geq 1/5 of the following:

- Peripheral pulse deficit or claudication (focal muscle pain induced by physical activity)
- Discrepancy of four limb systolic BP >10 mm Hg in any limb
- Bruits
- Hypertension ($>95^{\text{th}}$ percentile for height)
- Acute phase reactants (ESR >20 or increased CRP)

- Large vessel vasculitis involving the aorta and its branches (thoracic, abdominal, carotid)
- Chronic, relapsing disease
- Initially can present as non-specific inflammatory illness with fever

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- Then evolves into chronic, fibrotic phase with signs and symptoms of chronic vascular insufficiency (pulse deficit, claudication, BP discrepancy, bruits)
- Magnetic resonance angiography useful to show extension of disease and wall inflammation; often used to follow disease (less invasive than conventional)
- Rule out associated TB infection (PPD, Chest X-Ray)
- Treatment
 - Depends on degree of inflammation
 - If “active” disease (by acute phase reactants +/- wall enhancement on MRA):
 - Corticosteroids plus second line agent
 - Options for treatment include Cyclophosphamide, Methotrexate, Mycophenolate mofetil
 - Consider Infliximab if refractory disease
 - If “inactive” disease:
 - Control end-organ manifestations (medical therapy +/- vascular surgery)

References:

1. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener's granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010; 69(5):798-806.
2. Brunner J, Feldman BM, Tyrrell PN, et al. Takayasu arteritis in children and adolescents. *Rheumatology* 2010 Jun 18: [epub ahead of print].
3. Cakar N, et al. Takayasu arteritis in children. *J Rheumatol* 2008; 35:913–9.

4C. Kawasaki disease (KD)

Diagnostic Criteria for Kawasaki disease*

Fever persisting for ≥ 5 days

Plus $\geq 4/5$ of the following:

- Changes in peripheral extremities (edema/erythema) or perineal area
- Polymorphous exanthem
- Bilateral conjunctival injection, non-exudative
- Changes of lips and oral cavity (injection of oral and pharyngeal mucosa, fissured lips, strawberry tongue)
- Cervical lymphadenopathy (frequently unilateral, ≥ 1.5 cm)

* Other ways to make diagnosis of KD:

- a) In presence of fever and coronary artery involvement on echo, $<4/5$ criteria sufficient
 - b) Incomplete KD if ≥ 5 days of fever with 2 or 3 features (common in infants, who are at higher risk of coronary artery involvement)
 - c) Atypical KD if KD with unusual manifestation (e.g. renal failure)
- Small-medium vessel vasculitis, with predilection for coronary arteries
 - Most common between 3 months and 5 years of age
 - Most common cause of acquired heart disease in children in developed countries

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- Likely triggered by infectious agent (viral and/or bacterial super-antigen implicated)
- Other clinical manifestations:
 - Relatively common - irritability (aseptic meningitis), skin peeling in groin, arthritis, sterile pyuria (urethritis), gastroenteritis (abdo pain, vomiting, diarrhea), uveitis
 - Uncommon – gallbladder hydrops, GI ischemia, jaundice
 - Cardiac – myocarditis, pericarditis, cardiac failure, valvular regurgitation
 - Macrophage activation syndrome (MAS), DIC
 - Periungual desquamation in weeks 2 or 3
- Coronary artery disease in KD
 - Major concern is the development of coronary artery aneurysms, which most commonly occurs at 6-8 weeks after the acute illness
 - Risk factors: males, infants < 1 year or >9 yrs of age, prolonged fever, Asian or Hispanic ethnicity, thrombocytopenia, hyponatremia
- Laboratory features
 - Leukocytosis with left shift, normocytic anemia, elevated ESR/CRP, hypoalbuminemia, hyponatremia, may have elevated transaminases
 - Thrombocytosis in second week of illness, return to normal by 4-8 weeks
- Treatment
 - Target treatment within 7-10 days of fever onset
 - IVIG 2g/kg (unequivocally reduces the occurrence of coronary artery aneurysms)
 - *If still febrile 24-36 hrs after IVIG* → second dose of IVIG
 - High-dose ASA 80-100 mg/kg/day (anti-inflammatory) until afebrile x 24 hr, then switch to 3-5 mg/kg/day (anti-platelet)
 - *If IVIG-resistant* (10-15%) → pulse IV Methylprednisolone; consider TNF α blocker
 - *Myocarditis, MAS* → addition of Corticosteroids
 - *If large coronary aneurysm* → Abciximab (glycoprotein IIb/IIIa receptor inhibitor) in acute or subacute phase; long-term antiplatelet (+ Heparin or Warfarin if giant aneurysm)
- Prognosis
 - In-hospital mortality 0.17% (all cardiac-related)
 - ~ 2% risk of recurrent KD
 - Without treatment, coronary artery aneurysms occur in ~25% of patients → reduced to ~4% if IVIG treatment within 10 days
 - If coronary artery aneurysm → risk for thrombosis, obstruction and stenosis at inlet/outlet of aneurysm, ventricular dysfunction/arrhythmia, early atherosclerosis, myocardial infarction (highest risk if aneurysm \geq 8 mm)

References:

1. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A statement for health professionals by the committee on rheumatic diseases, endocarditis, and Kawasaki disease, Council on cardiovascular disease in the young, American Heart Association. *Pediatrics* 2004; 114: 1708-1733.
2. Son MBF, Gauvreau K, Ma L, et al. Treatment of Kawasaki disease: analysis of 27 US Pediatric Hospitals from 2001 to 2006. *Pediatrics* 2009; 124(1):1-8.

4D. Polyarteritis nodosa (PAN)

2008 EULAR/PRINTO/PRES Classification Criteria for Childhood PAN

Systemic illness characterized by:

- Histological findings of necrotizing vasculitis in medium or small sized arteries, *or*
- Angiography showing aneurysm, stenosis or occlusion of medium or small sized arteries

Plus $\geq 1/5$ of the following:

- Skin involvement (livedo reticularis, tender subcutaneous nodules, superficial skin infarctions, or deep skin infarctions)
- Myalgia or muscle tenderness
- Hypertension ($>95^{\text{th}}$ percentile for height)
- Peripheral neuropathy (motor mononeuritis multiplex, sensory peripheral neuropathy)
- Renal involvement (proteinuria >0.3 g in 24 hrs, hematuria, or red blood cell casts, impaired renal function)

Systemic PAN

- Very rare in childhood
- Additional clinical features:
 - Constitutional symptoms
 - Prolonged fever
 - Testicular pain or tenderness
 - Stroke or coronary artery disease
 - Bruits
 - Ischemic abdominal pain
- Treatment:
 - Prednisone plus second line agent (e.g. Cyclophosphamide, Azathioprine)

Cutaneous PAN

- Clinical syndrome characterized by absence of major organ involvement, but may involve skin, joints, muscles and peripheral nervous system
- Skin findings (tender subcutaneous nodules, livedo reticularis, superficial or deep ulcers)
- Additional clinical features
 - Constitutional features
 - Myalgia, arthralgia, non-erosive arthritis
 - Peripheral neuropathy
- Diagnosis requires deep skin biopsy showing necrotizing, non-granulomatous vasculitis
- Negative testing for ANCA
- May be associated with serological (ASOT) or culture evidence of Streptococcal infection
- Treatment
 - Corticosteroids with rapid wean +/- IVIG
 - Penicillin treatment (if proven associated Streptococcal infection) and prophylaxis

References:

1. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener's granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010; 69(5):798-806.
2. Ozen S, et al. Juvenile polyarteritis: Results of a multicenter survey of 110 Children. *J Pediatr* 2004; 145:517-22.
3. Fathalla BM, Miller L, Brady S, et al. Cutaneous polyarteritis nodosa in children. *J Am Acad Dermatol* 2005; 53:724-8.

4E. Wegener Granulomatosis (WG)

2008 EULAR/PRINTO/PRES Classification Criteria for Childhood WG

At least 3 of the six following criteria:

- Histopathology showing granulomatous inflammation within wall of artery or in perivascular or extravascular area
- Upper airway involvement (chronic purulent or bloody nasal discharge, recurrent epistaxis, nasal septum perforation, saddle nose deformity, chronic or recurrent sinus inflammation)
- Laryngo-tracheo-bronchial involvement (subglottic, tracheal or bronchial stenoses)
- Pulmonary involvement (nodules, cavities, or fixed pulmonary infiltrates)
- ANCA positive by immunofluorescence or ELISA
- Renal involvement (proteinuria >0.3 g in 24 hrs, hematuria, or red blood cell casts, impaired renal function)

- Predominantly small vessel vasculitis, characterized by granulomatous inflammation
- Common presenting features (in order of decreasing frequency)
 - Constitutional – fatigue, malaise, fever, weight loss
 - Pulmonary – SOB, chronic cough, hemoptysis/alveolar hemorrhage, lung nodules/cavitations/fixed infiltrates, abnormal PFTs (obstructive and restrictive)
 - ENT – nasal involvement (epistaxis, ulcers), sinusitis, otitis/mastoiditis, hearing loss, subglottic involvement
 - Renal – abnormal urinalysis, biopsy-proven GN, elevated creatinine
 - MSK – arthralgia/myalgia, arthritis
 - GI – nonspecific abdominal pain, chronic nausea
 - Eye – nonspecific red eye, conjunctivitis, scleritis
 - Cutaneous – palpable purpura/petechiae
 - CNS – severe headache, dizziness
- ANCA positive in ~90% of patients (~80% are C-ANCA positive with PR3 positivity)
- Treatment:
 - Initial therapy involves combination of Corticosteroids and Cyclophosphamide (or Methotrexate for mild disease).

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- Maintenance therapy with Methotrexate, Azathioprine, Mycophenolate mofetil, and low-dose Corticosteroids
- May use Rituximab (anti-CD20 [B cell] monoclonal antibody) for refractory or relapsing disease
- Prognosis
 - Significant morbidity associated with disease and medications
 - Severe pulmonary disease requiring mechanical ventilation in 11%
 - Dialysis required in 11%

References:

1. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener's granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010; 69(5):798-806.
2. Cabral DA, Uribe AG, Benseler S, et al. Classification, presentation, and initial treatment of Wegener's granulomatosis in childhood. *Arthritis Rheum* 2009; 60(11):3413-24.
3. Villa-Forte A. EULAR /European vasculitis study group recommendations for the management of vasculitis. *Curr Opin Rheumatol* 2010; 22:49-53.
4. Akikusa JD, Schneider R, Harvey EA, et al. Clinical features and outcome of pediatric Wegener's granulomatosis. *Arthritis Rheum* 2007; 57(5):837-44.

4F. Microscopic polyangiitis

- No 2008 EULAR/PRINTO/PRES classification criteria
- Pauci-immune, necrotizing, non-granulomatous small vessel vasculitis
- Rare in childhood
- Clinical features
 - Rapidly progressive, necrotizing, crescentic glomerulonephritis (90% of patients)
 - Pulmonary capillaritis leading to hemorrhage (57%)
 - Pulmonary-renal syndrome (30-50%)
 - Hypertension (57%)
 - Palpable purpura (common)
- Diagnosis
 - Serology: 50-75% p-ANCA positive with anti-MPO on ELISA
 - Renal biopsy with immunofluorescence: pauci-immune glomerulonephritis
- Treatment
 - Induction: corticosteroids + Cyclophosphamide or Methotrexate
 - Maintenance: Azathioprine, Mycophenolate mofetil, Methotrexate

References:

1. Peco-Antic A, Bonaci-Nikolic B, Basta-Jovanovic G, et al. Childhood microscopic polyangiitis associated with MPO-ANCA. *Pediatr Nephrol* 2006; 21:46-53.
2. Guillevin A, Durand-Gasselien B, Cevallos R, et al. Microscopic polyangiitis: Clinical and laboratory findings in 85 patients. *Arthritis Rheum* 1999; 42(3):421-30.

4G. Henoch-Schonlein Purpura (HSP)

2008 EULAR/PRINTO/PRES Classification Criteria for Childhood HSP

Purpura (commonly palpable and in crops) or petechiae with lower limb predominance*

Plus \geq 1/4 of the following:

- Diffuse abdominal colicky pain with acute onset (may include intussusceptions and gastrointestinal bleeding)
- Skin biopsy showing leukocytoclastic vasculitis with predominant IgA deposits, or kidney biopsy showing proliferative glomerulonephritis with predominant IgA deposits
- Arthritis or arthralgias of acute onset
- Renal involvement (proteinuria >0.3 g in 24 hrs, hematuria, or red blood cell casts, impaired renal function)

* If purpura in atypical distribution, demonstration of IgA deposition is required

- **Most common** vasculitis in children
- Often follows a respiratory infection, most commonly Group A *Streptococcus*
- Predominantly small vessel vasculitis, characterized by IgA deposition and leukocytoclastic vasculitis
- Clinical features
 - Cutaneous purpura (100% of patients) with palpable lesions 2-10 mm in diameter, usually concentrated on lower extremities
 - Arthritis (75%) usually affecting knees and ankles, associated with painful oedema
 - GI involvement (50-75%), including abdominal pain and intussusception
 - Renal involvement (40-50%)
 - Most commonly microscopic hematuria
 - Proteinuria accompanies hematuria in 25%
 - Nephrotic syndrome in 5%
 - Urinary abnormalities may not manifest initially, thus must regularly monitor urinalysis x 3 mos after acute illness
 - Orchitis (10-20% of males) associated with pain and swelling
- No distinctive or diagnostic laboratory abnormalities
 - May have elevated WBC and ESR; platelet count/coagulation profile must be normal
 - Serum IgA increased in 50% of patients
- Treatment
 - Largely supportive
 - NSAIDS for joint pain
 - Prednisone in select patients
 - May decrease the severity and duration of GI symptoms
 - Unclear impact on risk of persistent renal disease (controversial)
 - No definite benefit for prevention of HSP recurrence
 - If severe nephritis (eg nephrotic syndrome, decreased renal function, crescentic nephritis): pulse IV Methylprednisolone \pm second line agent (e.g. Azathioprine, Mycophenolate mofetil, Cyclophosphamide)

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- Prognosis
 - Usually a self-limited condition that resolves within 4 weeks (average)
 - Recurrence occurs in about 1/3 of patients
 - Long-term prognosis depends on severity of nephritis (poorer prognosis with nephrotic syndrome or if >50% crescent formation on biopsy)
 - End-stage renal disease occurs in 1-3% of patients; in ~20% of those with nephritic or nephrotic syndrome (N.B. % varies among different studies)

References:

1. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener's granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010; 69(5):798-806.
2. Saulsbury FT. Clinical Update: Henoch-Schönlein Purpura. *Lancet* 2007; 369: 976-8.
3. Weiss PF, Feinstein JA, Luan X, et al. Effects of corticosteroid on Henoch-Schönlein Purpura: A systematic review. *Pediatrics* 2007; 120(5): 1079-87.
4. Chartapisak W, Opastirakul S, Hodson EM, et al. Interventions for preventing and treating kidney disease in Henoch-Schönlein Purpura (HSP). *Cochrane Database of Systematic Reviews* 2009; 3: Art. # CD005128.

4H. Churg- Strauss Syndrome

- No 2008 EULAR/PRINTO/PRES classification criteria
- Very rare in children
- Granulomatous small sized vessel vasculitis characterized by:
 - Preceding history of "difficult to control" chronic asthma
 - Paranasal sinus abnormalities
 - Peripheral eosinophilia ($\geq 10\%$) + eosinophilic infiltration on biopsy
 - Non-fixed pulmonary infiltrates
 - Peripheral neuropathy
- Additional clinical features
 - Cardiovascular (50%): Myocardial ischemia, pericarditis, cardiac failure
 - Ischemic abdominal pain
 - Cutaneous nodules
- Diagnosis
 - Biopsy (lung, skin) showing eosinophilic infiltrates and granulomas
 - Peripheral eosinophilia and increased IgE levels
- Treatment
 - Prednisone plus second line agent
 - Cyclophosphamide if cardiac, GI or neurologic involvement

References;

1. Pagnoux C, et al. Churg–Strauss syndrome. *Curr Opin Rheumatol* 2007, 19:25–32.
2. Boyer D, et al. Churg-Strauss syndrome in children: A clinical and pathologic review. *Pediatrics* 2006;118;e914-20.

4I. Childhood Primary Angiitis of the Central Nervous System (cPACNS)

- Inflammatory disease involving vessels of CNS
- Currently defined by Calabrese criteria:
 - Clinical evidence of a newly-acquired focal or diffuse neurologic deficit, *plus*
 - Angiographic or histologic evidence of CNS vasculitis, *plus*
 - Absence of a systemic condition associated with these findings
- 2 clinically and radiologically distinct types of cPACNS:
 1. **Angiography positive cPACNS** (Large-medium vessel CNS vasculitis)
 - Clinical features: headache, acute hemiparesis, hemisensory deficits, and/or fine motor deficits
 - MRI: focal areas of acute ischemia in a vascular distribution (T2 hyperintense lesions involving both grey and white matter)
 - Evidence of vasculitis on angiography (conventional or MRA)
 - Features associated with progressive cPACNS: neurocognitive dysfunction at presentation, multifocal T2 lesions on MRI, distal stenosis on angiography
 2. **Angiography negative cPACNS** (Small vessel CNS vasculitis)
 - Clinical features: systemic symptoms (fever, malaise), headache, intractable seizures, ataxia, cognitive decline and/or behaviour changes
 - MRI: multifocal T2 hyperintensities in both white and grey matter, with contrast enhancement, lesions do not conform to large-vessel vascular territory
 - By definition, angiography is negative
 - Brain biopsy (ideally lesional): segmental, non-granulomatous, intramural infiltration of predominantly T lymphocytes involving small arteries, arterioles, capillaries or venules
- Inflammatory markers may be elevated (not sensitive or specific)
- CSF pleocytosis and/or elevated protein, and/or elevated opening pressure may be seen
- Treatment
 - Based on subtype
 - Angiography positive cPACNS
 - Anti-coagulation with or without anti-platelet agent
 - Corticosteroids in non-progressive cPACNS may improve outcome
 - Progressive cPACNS also require treatment with Cyclophosphamide (induction x 6 mos) then Mycophenolate mofetil (maintenance x 18 mos) plus slowly tapering dose of corticosteroids
 - Angiography negative cPACNS
 - Treated with Cyclophosphamide (induction x 6 mos) then Mycophenolate mofetil (maintenance x 18 mos) plus slowly tapering dose of corticosteroids
- Prognosis
 - Limited long-term data, although early recognition and treatment has been associated with good recovery

References:

1. Cellucci T, Benseler SM. Diagnosing central nervous system vasculitis in children. *Curr Opin Pediatr* 2010; 22:731-8.
2. Benseler SM, Silverman ED, Aviv RI, et al. Primary central nervous system vasculitis in children. *Arthritis Rheum* 2006; 54:1291-1297.
3. Benseler SM, deVeber G, Hawkins C, et al. Angiography-negative primary central nervous system vasculitis in children. *Arthritis Rheum* 2005; 52(7):2159-2167.

4J. Behçet Disease

1990 International Study Group for Behçet Disease Criteria for Diagnosis

- Recurrent oral ulcers (major or minor aphthous ulcers, or herpetiform ulceration recurring at least 3 times in 12 months)

Plus ≥ 2 of the following criteria:

- Recurrent genital ulcers (aphthous ulceration or scarring)
- Eye lesions (including anterior or posterior uveitis, cells in vitreous on slit lamp examination, or retinal vasculitis, observed by an ophthalmologist)
- Skin lesions (including erythema nodosum, pseudo vasculitis, papulopustular lesions, or acneiform nodules consistent with Behçet)
- Pathergy (skin papule 2 mm or more in size developing 24 to 48 hours after oblique insertion of a 20-25 gauge needle 5 mm into the skin, generally of the forearm)

- Systemic vasculitis with characteristic oral and genital ulcers, vasculopathy and uveitis
- First described by a Turkish dermatologist in 1937 (Hulusi Behçet)
- Among the systemic vasculitides, Behçet disease is remarkable for its ability to involve blood vessels of all sizes - small, medium, and large - on both the arterial and venous sides of the circulation
- More common in certain ethnic groups along the "Silk Route" (Turks, Greeks)
- Uncommon in children
- Other clinical manifestations include:
 - CNS: aseptic meningitis, encephalitis, or pseudotumour cerebri
 - MSK: oligoarthritis or polyarthritis
 - Vascular: arterial and/or venous thrombosis
- Treatment
 - No controlled studies have been performed on children
 - Corticosteroids, colchicine, thalidomide, and anti-TNF agents (e.g. Infliximab) have been shown to be helpful

References:

1. Ozen S. Pediatric onset Behçet disease. *Curr Opin Rheumatol* 2010; 22(5):585-9.
2. Borlu M, Uksal U, Frahbas A, et al. Clinical features of Behçet's disease in children. *Int J Dermatol* 2006; 45: 713-6.
3. International Study Group for Behcet's Disease. Criteria for diagnosis of Behcet's Disease. *Lancet* 1990; 335: 1078-80.

SECTION 5 – INFLAMMATORY MYOPATHIES

5A. Juvenile Dermatomyositis (JDM)

- JDM is an autoimmune myopathy characterized on pathology by capillary vasculopathy primarily affecting skin and muscle

Bohan and Peter Criteria for Diagnostic of Juvenile Dermatomyositis

- Symmetrical proximal muscle weakness
- Characteristic skin changes, including Gottron papules on the dorsal surface of the knuckles and heliotrope rash over the eyelids
- Elevated muscle enzymes, including CK, AST, LDH, aldolase
- Abnormal EMG demonstrating denervation and myopathy
- Abnormal muscle biopsy demonstrating necrosis and inflammation

- Recently, MRI has become an important diagnostic tool to look at muscle inflammation and to direct a site for biopsy (if needed)
- Important clinical features:
 - Proximal muscle weakness (which is present in 95% of patients) may be described on history as difficulty getting up from sitting or lying, difficulty climbing stairs, and frequent falls. Children may demonstrate a Gower's sign on physical exam.
 - Nasal voice, difficulty swallowing and choking on foods (18-44%) may indicate weakness of the palate and cricopharyngeal muscles.
 - Characteristic skin rashes include Gottron papules (57-100%), heliotrope rash (66-100%), malar rash (42-73%) and photosensitive rashes. These may be confused with psoriasis, especially given the location of Gottron papules on extensor surfaces. In severe cases, there may be skin ulceration.
 - Capillary vasculopathy can be seen using capillaroscopy to look at changes in the nail fold capillaries (91%) such as tortuosity, dilatation, and dropout.
 - Other organ systems may also be involved:
 - Arthritis (23-58%)
 - GI tract symptoms (22-37%), including dysphagia, GI ulceration, perforation
 - Lungs (interstitial lung disease)
 - Heart (cardiomyopathy) – very rare
 - Constitutional features, such as fever and fatigue, are common.
- Important complications:
 - A long delay in diagnosis or insufficiently aggressive treatment may put patients at higher risk for complications and poor outcome.
 - Muscle weakness and pain can lead to joint contractures
 - Soft tissue calcification, or calcinosis, can develop within a few years of diagnosis or may be present at presentation of longstanding disease.
 - Lipoatrophy may occur with decreased subcutaneous fat accompanied by hyperinsulinism, hypertriglyceridemia, acanthosis nigricans, and type 2 diabetes.

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- Medication-related side effects from Corticosteroid toxicity can include infection, osteoporosis, growth delay, cataracts and glaucoma, type 2 diabetes, and hypertension.
- Treatment
 - Supportive: adequate nutrition, physiotherapy, sunscreen for photosensitive rash
 - Medications:
 - Corticosteroids starting from 1-2 mg/kg/day with slow taper
 - Methotrexate 15 mg/m² SC started at diagnosis
 - May be a role for IVIG, Cyclosporine, Rituximab in resistant or refractory disease
 - Topical therapies may also be considered for resistant skin disease
 - Cyclophosphamide may be used for interstitial lung disease and vasculitis
- Course and Outcomes
 - 40 – 60% of patients have a chronic course, 40 – 60% have a monophasic course, and <5% have a polyphasic course
 - Persistence of rash and nail fold abnormalities in first 6 months are best predictors of longer time to remission
 - Outcomes are favourable, since most children have no functional disability and <10% have moderate-to-severe disability

References:

1. Feldman BF, Rider LG, Reed AM, et al. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. *Lancet* 2008; 371:2201-12.
2. Stringer E, Singh-Grewal D, Feldman BF. Predicting the course of juvenile dermatomyositis: Significance of early clinical and laboratory features. *Arthritis Rheum* 2008; 58:3585-92.
3. Huber AM, Lang B, LeBlanc CM, et al. Medium- and long-term functional outcomes in a multicenter cohort of children with juvenile dermatomyositis. *Arthritis Rheum* 2000; 43(3):541-9.

5B. Juvenile Polymyositis

- Uncommon in children
- Characterized by proximal and distal muscle weakness
- No associated skin findings and normal nail fold capillaries
- Resistant to treatment

References:

1. Feldman BF, Rider LG, Reed AM, et al. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. *Lancet* 2008; 371:2201-12.

SECTION 6 – SYSTEMIC SCLEROSIS & RELATED SYNDROMES

6A. Classification of Scleroderma and Scleroderma-like Disorders

<p>Morphea/ Localized scleroderma (See Section 6C)</p>	<p>Circumscribed morphea Linear scleroderma Generalized morphea Pansclerotic morphea Mixed morphea</p>
<p>Systemic sclerosis (See Section 6D)</p>	<p>Diffuse * Limited + Overlap syndromes</p>
<p>Scleroderma-like Disorders</p>	<p>Graft versus host disease Drug or toxin induced Diabetic cheiroarthropathy Phenylketonuria Premature aging syndromes</p>

*Diffuse systemic sclerosis typically involves skin sclerosis extending proximal to wrists and ankles as well as involving the trunk, and is associated with internal organ involvement and earlier organ dysfunction.

+Limited systemic sclerosis (formerly known as CREST syndrome – calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) typically progresses more slowly, but has a higher risk for later development of pulmonary hypertension.

6B. Raynaud Phenomenon

- Vascular spasm leading to triphasic colour sequence → white (blanching due to ischemia), then blue (cyanosis related to desaturation), then red (erythema due to reperfusion)
- Well-demarcated areas of colour change
- Usually affects fingers and toes, but may also involve other acral areas (lips, tongue, tip of nose, earlobes)
- Precipitated by cold, physical or emotional stress, caffeine, or smoking

- Raynaud phenomenon may be primary or secondary
- Primary → no underlying etiology, often positive family history, no peripheral ulcerations
- Secondary → due to underlying autoimmune disease (scleroderma, mixed connective tissue disease, SLE, JDM, overlap syndromes), mechanical obstruction (thoracic outlet syndrome, cervical rib), hyperviscosity (polycythemia), cryoglobulinemia, or drugs/toxins

- If isolated Raynaud phenomenon, two best predictive factors for future development of autoimmune disease are:
 1. Positive ANA
 2. Abnormal nail fold vasculature

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- Treatment:
 - Preventative (avoid triggers; warm mittens, socks and boots in winter; etc...)
 - Low dose of peripheral vasodilator, such as Nifedipine, may be titrated to appropriate dose that alleviates episodes without causing hypotension, headaches, or light-headedness

References:

1. Duffy CM, Laxer RM, Lee P, et al. Raynaud syndrome in childhood. *J Pediatr* 1989; 114(1): 73-78.
2. Nigrovic PA, Fuhlbregge RC, Sundel RP. Raynaud's phenomenon in children: a retrospective review of 123 patients. *Pediatr* 2003; 111(4 pt 1): 715-721.

6C. Morphea or Localized Scleroderma

- Morphea refers to a group of disorders with skin and subdermal connective tissue changes due to excessive accumulation of collagen
- Circumscribed morphea
 - Includes type of superficial lesions previously known as "plaque" morphea
 - May involve superficial and deep dermis as well as subcutaneous tissues
 - Typically firm, ivory-coloured oval lesions surrounded by reddish-lilac coloured ring suggesting active inflammation
 - Later, there is atrophy, hyperpigmentation and softening over time
- Generalized morphea
 - When individual circumscribed lesions become confluent or affect ≥ 3 anatomic sites
- Linear scleroderma
 - Most common form in children and adolescents
 - Characterized by ≥ 1 linear streaks (often following dermatomal distribution) extending over an upper or lower extremity
 - Unilateral in $> 85\%$ cases
 - May extend over joints, limiting range of motion
 - En coup de sabre \rightarrow linear lesion involving face or scalp, usually forehead
 - Parry-Romberg syndrome \rightarrow progressive hemi-facial atrophy, more disfiguring
 - Both forms of facial linear scleroderma may be associated with intracranial lesions, seizures, uveitis, and dental abnormalities
- Pansclerotic morphea
 - Least common subtype, but most disabling
 - Circumferential changes (often affecting a limb) that extend into tissues below dermis including muscle, tendon and bone
 - Frequently spares the fingers and toes
- Mixed morphea
 - Morphea of ≥ 2 subtypes in an individual patient
- Treatment options:
 - Topical: emollients, corticosteroids, Calcipotriene (vitamin D)
 - Systemic: corticosteroids, Methotrexate, Mycophenolate mofetil, Cyclosporine
 - Other: Psoralen with Ultraviolet A radiation therapy

References:

1. Zulian F. Systemic sclerosis and localized scleroderma in childhood. *Rheum Dis Clin North Am* 2008; 34(1):239-55.

6D. Systemic Sclerosis (SSc)

- Rare autoimmune disease in children
- Mean age of onset ~ 8 years
- 90% of pediatric patients who develop SSc have diffuse subtype
- Common clinical features of SSc are listed in the table below:

Raynaud Phenomenon	Common in children with SSc Associated with abnormal nail fold vasculature Can lead to digital pitting and gangrene
Sclerosis	Non-pitting edema and induration of skin resulting in restricted range of motion, usually fingers Later evolves to skin thickening causing joint contractures (sclerodactyly)
Calcinosis	Calcium deposits under the skin Often develop over bridge of nose and extensor surfaces
Vascular	Telangiectasias Abnormal nail fold capillaries
Musculoskeletal	Polyarthritis with minimal joint effusion Joint contractures often secondary to skin changes Subclinical myopathy with minimal weakness and mild elevation of muscle enzymes
Gastrointestinal	Major cause of morbidity Severe GERD due to dysfunction of lower esophageal sphincter Dysmotility leads to stasis, bacterial overgrowth, and malabsorption with diarrhea; may also result in severe constipation (megacolon)
Respiratory	Major cause of mortality Pulmonary hypertension (most severe) Interstitial lung disease (most common) Inflammatory alveolitis (precedes fibrosis)
Cardiac	Pericarditis with small pericardial effusions very common Micro-infarction of cardiac vasculature later leads to cardiomyopathy Bundle branch block and arrhythmias from fibrosis of conducting system
Renal	Major cause of morbidity prior to development of ACE inhibitors Renal vasculopathy leads to "scleroderma kidney" causing hypertension Proteinuria may precede hypertension Glomerular disease is unusual
Neurologic	Rare (e.g. trigeminal neuropathy)

- Investigations for SSc:
 - Bloodwork – evidence of systemic inflammation and organ involvement
 - Serology for diagnosis and classification → ANA (common), Rheumatoid factor (rare), anti-Scl 70 (usually associated with diffuse SSc), anti-centromere (usually associated with limited SSc)
 - Blood pressure and urinalysis for proteinuria
 - ECG and echo to assess for cardiac pathology, especially pulmonary hypertension
 - Chest X-Ray, pulmonary function tests with DLCO, and high resolution CT chest to assess for lung pathology, especially alveolitis and interstitial pulmonary fibrosis
 - Upper GI series to assess for dysmotility

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- Treatment for SSc:
 - Primarily supportive care
 - Avoid cold, stress, caffeine to prevent Raynaud phenomenon
 - Eat small meals, avoid foods that exacerbate gastric acids, and remain upright after eating for dysmotility and GERD
 - Proton pump inhibitors (e.g. Omeprazole) to treat GERD
 - Peripheral vasodilators (e.g. Nifedipine) for Raynaud phenomenon
 - ACE Inhibitors (e.g. Enalapril) for hypertension and renal disease
 - Cyclophosphamide and corticosteroids for alveolitis and interstitial lung disease
 - Endothelin receptor antagonist for pulmonary hypertension
 - Other immunomodulatory agents (e.g. Methotrexate, Mycophenolate mofetil, Anti-thymocyte globulin) have unclear efficacy in treatment of SSc
- Prognosis and outcome of SSc:
 - Prognosis depends on degree of organ dysfunction, which either later stabilizes or progresses to significant morbidity and mortality
 - Survival much better in children (5 year survival >90%) compared to adults
 - Largest reported survey of outcome in paediatric patients with SSc showed that 8 out of 135 patients died (5 from heart failure, 1 from renal failure, 1 from sepsis, and 1 from unknown causes)

References:

1. Zulian F, Woo P, Athreya BH, et al. The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. *Arthritis Rheum* 2007; 57(2):203-12.
2. Foeldvari I. Current developments in pediatric systemic sclerosis. *Curr Rheumatol Rep* 2009; 11(2):97-102.

6E. Mixed Connective Tissue Disease (MCTD)

- Autoimmune disorder characterized by several clinical and laboratory features:
 - High titre anti-U1 RNP antibodies
 - Swollen hands
 - Raynaud phenomenon
 - Arthritis
 - Myositis
 - Skin rashes (may include malar rash, Gottron-like papules, sclerosis)
- Children may also develop GI manifestations (similar to SSc), interstitial lung disease, and renal disease over time
- Multiple different diagnostic criteria for MCTD exist (e.g. Sharp, Alarcon-Segovia, Kasukawa, Kahn), but no single set of criteria validated in children
- Investigations should be directed to assess for multi-organ involvement
- Treatment depends on severity of clinical manifestations and organ involvement

Reference:

1. Mier RJ, Shishov M, Higgins GC, et al. Pediatric-onset mixed connective tissue disease. *Rheum Dis Clin North Am* 2005; 31(3):483-96.

SECTION 7 – FEVER & ASSOCIATED SYNDROMES

7A. Fever of Unknown Origin

- Definitions vary; consider in setting of fever duration > 2 weeks with standard investigations not resulting in a clear diagnosis.

Differential Diagnosis for Fever of Unknown Origin	
Infection	<ul style="list-style-type: none"> • Bacterial: <ul style="list-style-type: none"> ○ <i>Mycobacterium tuberculosis</i> ○ Consider localized infections, such as sinusitis, osteomyelitis, endocarditis, abscess (brain, abdominal, dental, hepatic, etc...) • Viral: CMV, EBV, HIV, Hepatitis • Lyme disease • Fungal • Parasitic
Inflammation	<ul style="list-style-type: none"> • Systemic JIA • SLE • Vasculitis • IBD • Autoinflammatory syndromes • Sarcoidosis
Malignancy	<ul style="list-style-type: none"> • Leukemia • Lymphoma • Neuroblastoma
Others	<ul style="list-style-type: none"> • Drug fever

Reference:

1. Miller LC, Sisson BA, Tucker LB, et al. Prolonged fevers of unknown origin in children: Patterns of presentation and outcome. *J Pediatr* 1996; 129(3):419-23.

7B. Macrophage Activation Syndrome

- Macrophage activation syndrome (MAS) is a multisystem inflammatory emergency
- MAS may complicate a number of autoimmune diseases (systemic JIA, SLE, Kawasaki disease most commonly)
- Classified as a form of secondary hemophagocytic lymphohistiocytosis (HLH)
 - Primary HLH is an inherited multi-system inflammatory disease caused by congenital abnormalities affecting natural killer cell, macrophage and T cell function
 - Similar abnormalities have recently been identified in patients with systemic JIA
 - Secondary HLH in children can also be triggered by infection, especially EBV
- **Diagnostic clinical and laboratory features of MAS**
 - Fever
 - Splenomegaly
 - Cytopenias (anemia, thrombocytopenia, neutropenia) or, in systemic JIA, may see decrease in previously elevated cell counts

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- Elevated triglycerides
- Decreased fibrinogen
- Elevated ferritin
- Hemophagocytosis on bone marrow, lymph node, liver or spleen biopsy
- Other important clinical and laboratory features
 - Bleeding, bruising, petechiae, due to DIC-like picture with prolonged INR/PTT, elevated D-dimers
 - Hepatic dysfunction with hepatomegaly, elevated bilirubin and liver enzymes
 - Elevated LDH
 - Persistently raised CRP, but decreasing ESR (due to consumption of fibrinogen)
 - CNS dysfunction, including confusion, seizures, and coma
 - Respiratory distress including ARDS, pulmonary dysfunction
 - MAS may be life-threatening and can result in death
- Treatment
 - Supportive
 - Fluids for hypotension
 - Blood products (platelets, red blood cells)
 - Respiratory support
 - Medications
 - IVIG often used to treat clinical features during diagnostic work-up
 - Currently treating MAS using HLH protocol, which involves a step-wise progression starting with Corticosteroids IV (Dexamethasone or pulse Methylprednisolone) to Cyclosporine and Etoposide
 - Case reports suggest biologic agents, such as Anakinra (anti-IL-1), may be effective

References:

1. Grom AA, Mellins ED. Macrophage activation syndrome: Advances towards understanding pathogenesis. *Curr Opin Rheumatol* 2010; 22(5):561-6.
2. Ravelli A, Magni-Manzoni S, Pistorio A, et al. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *J Pediatr* 2005; 146:598-604.
3. Hemophagocytic Lymphohistiocytosis Study Group. HLH-2004: Treatment protocol of the second international HLH study 2004. (Available online or through the Histiocytosis Association of America.)

7C. Autoinflammatory Syndromes

- Group of inflammatory conditions caused by dysregulation of innate immune system
- Often present diagnostic challenge to clinicians
- Better understanding of disease pathogenesis has provided improved diagnostic tests and therapeutic options
- Key to diagnosis is careful history and physical examination

Familial Mediterranean Fever (FMF)

- Most common hereditary autoinflammatory disease
- Autosomal recessive inheritance; linked to genetic mutation in MEFV gene encoding pyrin
- Ethnic predilection in Arabic, Turkish, Armenian and Mediterranean populations
- Usually presents in childhood with 60% of patients presenting prior to 10 years of age
- Clinical features
 - Fever episodes last for 1-3 days and occur every 4-8 weeks
 - Clinical hallmark is serositis (peritonitis, pleuritis, synovitis)
 - Skin: Erysipelas-like rash on shins and dorsum of feet
 - MSK: Monoarthritis, myalgia
- Morbidity is associated with amyloidosis, especially renal amyloidosis
- Treatment
 - Colchicine is highly effective therapy for 75% of patients with FMF
 - Anakinra therapy effective in Colchicine-resistant FMF

TNF-Receptor Associated Periodic Syndrome (TRAPS)

- Originally known as Familial Hibernian Fever
- Autosomal dominant inheritance
- TRAPS is linked to genetic mutation in TNFRSF1A gene that encodes TNF receptor
- Age of onset ranges from early childhood to several decades
- Clinical features
 - Distinguishing feature is relatively long duration of most attacks, which can last 3-4 weeks and occur at irregular intervals
 - Skin: Migrating erythematous, maculopapular rash that spreads from trunk to extremities
 - MSK: Severe migratory myalgias associated with rash, arthralgias
 - Ocular: Conjunctivitis, periorbital edema
 - GI: Severe abdominal pain
- Treatment
 - Standard therapy is unproven
 - Corticosteroids provide symptomatic relief but do not diminish frequency
 - Anti-TNF agents (e.g. Etanercept) thought to be promising, but results of studies disappointing

Hyperimmunoglobulinemia D Syndrome (HIDS)

- Rare recurrent fever syndrome
- Caused by genetic mutations in mevalonate kinase gene
- More than 90% of patients show symptoms within first year of life
- Clinical features
 - Fever episodes lasting 4 to 7 days that recur every 4 to 8 weeks
 - Fever typically associated with abdominal pain, vomiting and diarrhea
 - Other common features include tender cervical lymphadenopathy, oral ulcers, arthralgias, and large joint symmetric arthritis
 - Elevated inflammatory markers and WBC
 - Striking elevation of serum IgD and IgA during fever episodes

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- Treatment
 - NSAIDs and corticosteroids often limit symptoms
 - Biologic agents (anti-TNF and anti-IL-1) may be more effective

Cryopyrin Associated Periodic Syndrome (CAPS)

- Group of autoinflammatory syndromes that are associated with genetic mutations involving NLRP3 gene encoding cryopyrin
- All syndromes characterized by disease onset in infancy, although may develop later
- Spectrum of 3 diseases on a continuum of increasing disease severity

1. Familial Cold Autoinflammatory Syndrome (FCAS)

- Children develop fever, chills and generalized, non-pruritic urticarial skin lesions within 30 minutes to 6 hours of exposure to cold
- Symptoms persist up to 24 hours
- Associated symptoms during attacks include conjunctivitis and arthralgias
- Risk of developing amyloidosis in adulthood

2. Muckle Wells Syndrome (MWS)

- Frequent episodes of fever lasting 24 to 48 hours
- Characterized by generalized urticarial rash, arthralgias, myalgias, arthritis, and conjunctivitis
- Progressive neurosensory hearing loss emerges in adolescence
- Higher risk of amyloidosis (25%)

3. Neonatal Onset Multisystem Inflammatory Disease (NOMID)

- Nearly continuous clinical features that develop shortly after birth
- Frequent fever episodes lasting 24 to 48 hours several times per week
- Distinguishing feature from other autoinflammatory syndromes is poor growth, or failure to thrive
- Skin: Nearly-constant generalized urticarial rash
- CNS: Aseptic meningitis, intellectual disability, neurosensory hearing loss, optic nerve atrophy
- MSK: Deforming arthropathy
- Ocular: Conjunctivitis, episcleritis, uveitis, papilloedema
- Lymphadenopathy, hepatomegaly, splenomegaly
- Poor long-term prognosis with high morbidity and mortality

- Treatment of CAPS
 - Anti-IL-1 therapy (e.g. Anakinra, Canakinumab, Rilonacept) highly effective treatment for CAPS
 - Early treatment may reduce risk of developing amyloidosis and improve functional outcome

Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis (PFAPA)

- Most common recurrent fever syndrome in children in North America
- No known genetic association or inheritance pattern
- Typically starts in early childhood before 5 years and is self-limited (resolves within 5 years)
- Clinical features
 - Episodes of high fever that occur with regular periodicity every 4-6 weeks
 - Fever episodes generally last up to 5 days
 - Characteristic findings of small non-scarring aphthous ulcers, non-exudative pharyngitis, and cervical adenitis
 - May be associated nausea, vomiting, abdominal pain and headache
 - Throat cultures are consistently negative
- Treatment:
 - No consensus regarding treatment
 - Single dose of corticosteroid effectively stops symptoms during episode
 - Other options include tonsillectomy and cimetidine

References:

1. Goldsmith DP. Periodic fever syndromes. *Pediatr Rev* 2009; 30(5):e34-41.
2. Hoffman HM, Simon A. Recurrent febrile syndromes – What a rheumatologist needs to know. *Nat Rev Rheumatol* 2009; 5:249-56.

7D. Chronic Recurrent Multifocal Osteomyelitis (CRMO)

- Also known as chronic non-bacterial osteomyelitis
- CRMO is a diagnosis of exclusion
- Presents with acute or insidious onset of bone pain associated with fever and malaise
- Clinical and radiographic findings initially mimic septic osteomyelitis
- However, no abscess formation is noted, cultures are negative, and there is a poor response to antibiotic therapy

Diagnostic Criteria for Non-Bacterial Osteitis (Jansson 2006)

Major criteria

- Osteolytic or sclerotic bone lesion on X-ray
- Multifocal bone lesions
- Pustulosis palmoplantaris or psoriasis
- Sterile bone biopsy with signs of inflammation and sclerosis

Minor criteria

- Normal complete blood cell count and good health
- CRP/ESR mildly to moderately elevated
- Course > 6 months
- Hyperostosis
- Association with other autoimmune diseases
- First or second degree relative with autoimmune disease

* Diagnosis requires 2 major criteria *or* 1 major plus 3 minor criteria

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- Pathophysiology of CRMO is poorly understood
- CRMO affects females > males and is more common in children and adolescents
- Clinical course characterized by periods of exacerbation with symptom-free intervals
- Typical sites of involvement include clavicles, tibia, femur, metaphyses of tubular bones
- Associated inflammatory disorders include IBD, psoriasis, acne, palmoplantar pustulosis
- Imaging
 - Plays central role in diagnosis
 - X-Rays:
 - Osteolytic bone lesions localized in the metaphyses close to the growth plate
 - Sclerosis and periosteal reaction
 - Bone scan: Helpful to assess the extent of lesions and detect asymptomatic lesions
 - MRI: Sensitive when looking at the extent and activity of the lesions
- Treatment
 - Empiric with lack of controlled studies
 - First line therapy: NSAIDS
 - Other options include corticosteroids, bisphosphonates and anti-TNF agents (e.g. Infliximab)

References:

1. Tloutan BE, Podjasek JO, O'Haver J, et al. Chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome with associated neutrophilic dermatoses: a report of seven cases and review of the literature. *Pediatr Dermatol* 2009; 26(5):497-505.
2. Simm PJ, Allen RC, Zacharin MR. Bisphosphonate treatment in chronic recurrent multifocal osteomyelitis. *J Pediatr* 2008; 152(4):571-5.
3. Catalano-Pons C, Comte A, Wipff J, et al. Clinical outcome in children with chronic recurrent multifocal osteomyelitis. *Rheumatol (Oxford)* 2008; 47(9):1397-9.

SECTION 8 – INFECTION & INFECTION-RELATED CONDITIONS

8A. Bone and Joint Infections

Osteomyelitis

- Intraosseous infection with bacteria or rarely, fungi
- Classified as acute, subacute, or chronic.
 - Acute osteomyelitis is of recent onset and short duration
 - Most often hematogenous in origin but may result from trauma such as a compound fracture or puncture wound
 - Can be metaphyseal, epiphyseal, or diaphyseal in location
 - Subacute osteomyelitis is of longer duration and is usually caused by less virulent organisms
 - Chronic osteomyelitis results from ineffective treatment of acute osteomyelitis and is characterized by necrosis and sequestration of bone
- Source may be (1) hematogenous (2) local invasion from contiguous source (3) direct invasion of bone
- Usually blood-borne to metaphysis, slow blood flow allows organisms to pass through fenestrations in vessel wall, migrate through haversian canal to sub-periosteal space
- Unique features:
 - Neonates may present with pseudoparalysis or sepsis; fever is common; organisms frequently cross the physis and cause growth arrest
 - Patients with hemoglobinopathy frequently have salmonella and other gram-negative organisms
- Key symptoms:
 - Fever, severe bone pain, and tenderness with or without local swelling should suggest the possibility of acute osteomyelitis
- Bones involved:
 - Femur, tibia, humerus, fibula, radius, calcaneus, ilium
- Organisms:
 - *Staphylococcus* most common
 - Group A *Streptococcus*, MRSA, atypical Gram negative bacteria and *Salmonella*
- Labs:
 - Elevated WBC, ESR, CRP are non-specific
- Cultures:
 - Blood (sensitivity 60%), bone (sensitivity 80%)
- Imaging:
 - X-Ray important for exclusion of other diagnoses; signs include soft-tissue swelling, muscle edema, subperiosteal changes and bone destruction (diagnostic findings may not be clear until days 10 to 21)
 - Bone scan has positive predictive value of 83% (MRI 85%) and allows detection of other sites
- Treatment:
 - Antibiotics for at least 4-6 weeks (starting with IV for minimum 7 days)

Septic Arthritis

- Intra-articular infection with bacteria or rarely, fungi
- Medical emergency (surgical emergency if hip or shoulder involved)
- Unique features:
 - Infection with *Mycobacterium tuberculosis* is an unusual cause of septic monarthrititis in childhood
 - *Kingella kingae* is emerging as an important pathogen in children with septic arthritis and may also account for a significant portion of culture negative cases
- Key symptoms:
 - Usually accompanied by systemic signs of illness (e.g., fever, vomiting, headache)
 - May be a component of a more generalized infection that may include meningitis, cellulitis, osteomyelitis, or pharyngitis
 - Joint pain is usually severe, and the infected joint and periarticular tissues are swollen, hot, and sometimes erythematous
- Joints involved:
 - The joints of the lower extremity are most commonly the sites of infection.
 - Knees, hips, ankles, and elbows account for 90% of infected joints in children.
- Organisms:
 - *Staphylococcus aureus* and non-Group A β *Streptococcus* are most common overall
 - *Streptococcus pneumoniae* is common in children younger than 2 years
 - *Neisseria gonorrhoeae* in sexually active adolescents
- Labs:
 - Must aspirate prior to antibiotics
 - Characteristics of synovial fluid:
 - Cloudy, very high WBC count (50,000-300,000, > 75% neutrophils)
 - GRAM STAIN POSITIVE
 - Elevated WBC with neutrophilia, CRP and ESR are non-specific
- Cultures:
 - Synovial fluid (sensitivity 80%), blood (sensitivity 10%)
 - Cultures require special handling if suspect *Neisseria* or Tuberculosis
- Imaging:
 - Plain radiographs are not diagnostic, but may be helpful in excluding other disorders, and may show an underlying osteomyelitis as the etiology of the septic arthritis .
 - May demonstrate only increased soft tissue and capsular swelling.
 - Delineation of soft tissue structures by MRI is superior to that provided by CT.
 - Changes may be seen as soon as 24 hours following infection.
 - Synovial enhancement is detected in virtually all patients.
- Treatment:
 - Antibiotics for a minimum of 21 days (starting with IV for a minimum of 7 days)

References:

1. Copley LA. Pediatric musculoskeletal infection: trends and antibiotic recommendations. *J Am Acad Orthop Surg* 2009;17(10):618-26.
2. Sonnen GM, Henry NK. Pediatric bone and joint infections. Diagnosis and antimicrobial management. *Pediatr Clin North Am* 1996; 43: 933-47
3. Kang SN, Sanghera T, et al. The management of septic arthritis in children: systematic review of the English language literature. *J Bone Joint Surg Br* 2009; 91(9):1127-33.

8B. Reactive Arthritis

- A form of non-septic arthritis developing after an extra-articular infection
- Arthritogenic bacteria:
 - **GI:** *Salmonella, Shigella, Yersinia, Campylobacter*
 - **GU:** *Chlamydia, Ureaplasma*
- Clinical manifestations:
 - Several stages involved:
 1. Clinical infection precedes the appearance of arthritis and/or enthesitis by 1 to 4 weeks
 2. Active period of weeks to months
 3. Sustained remission or recurrent episodes which may evolve to ERA, especially in patients that are positive for HLA B27
 - Acute arthritis and/or enthesitis usually seen (may see tenosynovitis, bursitis, dactylitis)
 - Patients may continue to have fever, weight loss, fatigue and muscle weakness
 - Painless, shallow mucosal ulcers are common
 - Urethritis and cervicitis are rare
 - Conjunctivitis occurs in about two thirds of children at onset
- Laboratory examination:
 - Mild decrease in haemoglobin and leukocytosis with neutrophilia
 - Elevated inflammatory markers (platelets, immunoglobulins, ESR and CRP)
 - Autoantibodies (RF and ANA) are usually absent but reactive arthritis most frequently occurs in HLA-B27 positive individuals
 - Synovial fluid is sterile
 - Cultures (blood, urine, stool) obtained at the time of infection may be positive
- Treatment:
 - NSAIDs
 - No clear evidence that antibiotics during the inflammatory phase alter the course of the disease
 - Rarely, corticosteroids (oral or intra-articular) may be required

References:

1. Carter JD, Hudson AP. Reactive arthritis: clinical aspects and medical management. *Rheum Dis Clin North Am* 2009; 35(1):21-44.
2. Rihl M, Klos A, Köhler L, et al. Infection and musculoskeletal conditions: Reactive arthritis. *Best Pract Res Clin Rheumatol* 2006; 20(6):1119-37.

8B. Acute Rheumatic Fever (ARF)

- The arthritis in ARF has characteristics that help in its differentiation from other causes:
 - Characteristically migratory and additive
 - Usually initially a monoarthritis involving large joints
 - Short duration of arthritis (hours to days)
 - Dramatic response to ASA/NSAIDs

• **Modified Jones Criteria for diagnosis of initial attack of ARF**

MAJOR Manifestations*	MINOR Manifestations*	Supporting evidence of antecedent GAS infection*
Polyarthritis Carditis Sydenham’s chorea Erythema marginatum Subcutaneous nodules	Clinical: <ul style="list-style-type: none"> ○ Fever ○ Arthralgia Laboratory: <ul style="list-style-type: none"> ○ Elevated ESR, CRP ○ Prolonged PR interval 	Elevated or rising streptococcal antibody titers Positive throat culture

*The presence of 2 major manifestations or 1 major plus 2 minor manifestations indicates a high probability of acute rheumatic fever if supported by evidence of preceding GAS infection.

- Treatment:
 - 10 days oral antibiotics (usually Penicillin)
 - ASA 100 mg/kg/day divided QID PO for 3–5 days, then 75 mg/kg/day divided QID PO for 4 weeks (or may consider Naproxen instead)
 - Prednisone for carditis/cardiomegaly and heart failure +/- Digoxin
 - Carbamazepine, Phenobarbital, Haloperidol, or Chlorpromazine for chorea
 - Prophylaxis for recurrence: up to age 21 or 5 years post initial attack, whichever is later.

References:

1. Dajani AS, et al. Guidelines for the diagnosis of rheumatic fever: Jones criteria, Updated 1992. *Circulation* 1993; 87: 302-307.
2. Hilario MO, Terreri MT. Rheumatic fever and post-streptococcal arthritis. *Best Pract Res Clin Rheumatol* 2002; 16(3):481-94.
3. da Silva N and de Faria Pereira B. Acute rheumatic fever: still a challenge. *Rheum Dis Clin N Am* 1997; 23: 545-568.

8D. Post-Streptococcal Reactive Arthritis (PSRA)

- Characteristics that help distinguish PSRA from ARF include:
 - Non-migratory arthritis
 - Typically asymmetric oligoarthritis of lower extremities
 - Axial involvement in 25%
 - Shorter latency in PSRA (<10 days) compared to ARF (14-21 days)
 - Protracted course
 - Less dramatic response to ASA/NSAIDs than ARF
 - Carditis develops in 5% of children with PSRA (compared to 50% with ARF)
- Treatment
 - 10 days oral antibiotics (usually Penicillin)
 - ASA or NSAID
 - Antibiotic prophylaxis recommended

Reference:

1. Van der Helm-van Mil AH. Acute rheumatic fever and poststreptococcal reactive arthritis reconsidered. *Curr Opin Rheumatol* 2010; 22(4):437-42.

8E. Lyme Disease

- Most common vector-borne infection in North America and Europe
- *Borrelia burgdorferi* spirochete transmitted by hard-bodied ticks of the genus *Ixodes*
- Found in the temperate zones of the northern hemisphere
- Symptoms of Lyme disease can be divided into early and late manifestations
- Early manifestations of Lyme disease develop within weeks or few months of tick bite
- Late manifestations of Lyme disease begin several months or even years later

Organ system	Early Lyme disease	Late Lyme disease
Skin	Erythema migrans	Acrodermatitis chronic atrophicans*
Nervous system	Cranial nerve palsy Lymphocytic meningitis	Chronic encephalomyelitis
Musculoskeletal system	Arthralgia or arthritis	Arthritis
Cardiovascular system	Carditis*	

*Rare in childhood

- Erythema migrans:
 - Usually begins as a round, erythematous macule or papule that rapidly expands, often with central clearing, to a diameter of at least 5 cm
 - Resolves within four weeks if untreated
- Laboratory examination:
 - Elevated ESR, CSF lymphocytic pleocytosis
 - Serologic confirmation (initially with ELISA, then confirm with Western blot)
- Treatment:
 - Varies according to disease manifestations
 - Erythema migrans only:
 - Amoxicillin or Doxycycline (only if >10 years of age) PO x 14-21 days
 - Early Lyme disease (except isolated rash) or Late Lyme disease:
 - Ceftriaxone or Cefotaxime IV x 2-4 weeks, or
 - Amoxicillin or Doxycycline (only if >10 years of age) PO x 4 weeks

References:

1. Ogden NH, Lindsay LR, Morshed M, et al. The emergence of Lyme disease in Canada. *CMAJ* 2009;180(12):1221-4.
2. Feder HM Jr. Lyme disease in children. *Infect Dis Clin North Am* 2008; 22(2):315-26.
3. Steere AC. Lyme disease. *New Engl J Med* 2001; 345: 115-125.

SECTION 9 – UVEITIS

9A. Uveitis

- Inflammation of the structures of the uvea, which is the middle layer of the eye
- May be asymptomatic or symptomatic

- Classification based on involved eye structures:
 - Anterior uveitis involves the irises and ciliary body
 - Intermediate uveitis involves the pars plana between the ciliary body and retina
 - Posterior uveitis involves the choroids and retina
 - Panuveitis involves the entire uvea

- Complications of uncontrolled uveitis include:
 - Cataracts
 - Glaucoma
 - Band keratopathy
 - Synechiae (adhesion of iris to lens)
 - Cystoid macular edema
 - Vision loss

9B. Systemic Inflammatory Diseases Associated with Uveitis

Disease	Acute/Chronic	Location	Clinical Features	Investigations
JIA – Oligoarthritis, Polyarthritis	Chronic, recurrent, asymptomatic	Anterior > Posterior	Oligoarthritis >> Polyarthritis	ANA
JIA - ERA	Acute, symptomatic	Anterior	Enthesitis, sacroiliitis; also with reactive arthritis, IBD	HLA B27
Infantile sarcoidosis	Chronic	Posterior, Anterior, Panuveitis	Skin, Resp, MSK	Calcium, ACE, Chest X-ray
Behcet disease	Acute or chronic	Posterior	Ulcers, arthritis, skin rash	Pathergy
Kawasaki disease	Acute, asymptomatic	Anterior	Coincides with conjunctivitis	Echocardiogram
Tubulo-interstitial nephritis and uveitis (TINU)	Acute	Anterior	Constitutional symptoms; nephritis	U/A, renal function

9C. Infectious Causes of Uveitis

Disease	Acute/Chronic	Location	Clinical Features	Investigations
Toxoplasmosis	Chronic, acute recurrences	Posterior	Congenital; Immune compromise; Cat exposure	Serology
Tuberculosis	Chronic	Anterior	Chest, skin; Travel/exposure history	PPD, Chest X-ray
Lyme disease	Chronic	Anterior, Posterior	Erythema migrans, arthritis, CNS symptoms; Tick bites in endemic areas	Serology
Cat scratch	Chronic	Anterior, Posterior	Optic nerve edema, "macular star"	Serology
Cytomegalovirus	Chronic	Posterior	Congenital; immunocompromised;	Serology, Buffy coat

References:

1. Kump LI, Cervantes-Castañeda RA, Androudi SN, Forster CS. Analysis of pediatric uveitis cases at a tertiary referral center. *Ophthalmology* 2005; 112(7):1287-92.

SECTION 10 – PAIN SYNDROMES

10A. Chronic Pain Syndromes

- Pain symptoms may be worse than inflammatory disease
- Many children with chronic MSK pain do not have an identified cause
- Potential role of psychosocial stress in development of chronic pain syndromes

Growing Pains

- Onset usually between 4 to 10 years old
- Deep aching cramping pain in bilateral thighs or calves, usually at night and often awoken from sleep
- Improve with gentle massage, heat and/or analgesia with acetaminophen
- Symptoms disappear by morning
- Normal physical examination

Fibromyalgia

- Generalized MSK aches at ≥ 3 sites for ≥ 3 months
- Absence of underlying condition or cause and normal laboratory tests
- ≥ 5 tender points
- Associated with fatigue, poor sleep, chronic anxiety, chronic headaches, irritable bowel syndrome
- May be triggered by change in physical activity due to injury or chronic illness
- Family history may be present
- Treatment involves education, sleep hygiene, exercise therapy to reverse immobility and increase function, and cognitive behavioural therapy
- Medications less effective
- Better outcomes in children compared to adults

Complex Regional Pain Syndrome Type I (Reflex Sympathetic Dystrophy)

- Chronic pain often involving peripheral extremity
- Initiating injury or cause of immobilization
- Continuing pain, allodynia, or hyperalgesia in which pain is disproportionate to inciting event
- Associated swelling, changes in skin blood flow leading to discolouration, and/or abnormal sweating in the region of pain
- No other condition that would account for the degree of pain and dysfunction
- Treatment involves intense physiotherapy with manipulation of extremity with goal to restore function; another potential treatment option is desensitization

Complex Regional Pain Syndrome Type II

- Pain caused by nerve injury, but not limited to distribution of injured nerve
- Similar to type I in symptoms and treatment

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References:

1. Anthony KK, Schanberg LE. Pediatric pain syndromes and management of pain in children and adolescents with rheumatic disease. *Pediatr Clin North Am* 2005; 52(2):611-39.
2. Sherry DD, Malleson PN. The idiopathic musculoskeletal pain syndromes in childhood. *Rheum Dis Clin North Am* 2002; 28:669-85.

10B. Hypermobile joint syndrome

- Joint pain caused by idiopathic increased flexibility – may be generalized or local
- Pain typically occurs after activity
- Need to consider and exclude syndromes associated with generalized joint hypermobility (Ehlers-Danlos, Marfan, Down, Turner, osteogenesis imperfecta, Stickler's syndrome)
- Several different sets of criteria for diagnosis

Beighton Criteria for Hypermobile joint syndrome*

- Able to touch thumb to volar surface of forearm (1 point each for left and right)
- Able to hyperextend 5th finger MCP joint to 90 degrees (1 point each for left and right)
- Able to hyperextend elbows > 10 degrees (1 point each for left and right)
- Able to hyperextend knees > 10 degrees (1 point each for left and right)
- Able to touch palms to floor with knees extended (1 point)

* Diagnosis requires $\geq 6/9$ points

- Additional features consistent with hypermobility include:
 - Flat feet
 - Able to sit in "W" position
 - Able to touch elbows behind back
 - Able to put heel behind head
- Treatment may involve:
 - Education
 - Activity modification (avoid exacerbating activity)
 - Physiotherapy to strengthen muscles around affected joints
 - Orthotics

Reference:

1. Murray KJ. Hypermobility disorders in children and adolescents. *Best Pract Res Clin Rheumatol* 2006; 20(2):329-51.

SECTION 11 – MEDICATIONS

Medications are listed in alphabetical order by their generic names with the exception of Corticosteroids and NSAIDs, which are listed by their categories.

- **Abatacept**
 - Biologic agent
 - Fusion protein consisting of extracellular portion of CTLA4 (protein on T cells) and constant region of human immunoglobulin
 - Action: blocks activation of T cells
 - Dose: 10 mg/kg/dose (maximum 1000 mg) IV every 4 weeks
 - Side effects: infusion reactions, anaphylaxis, GI upset, bronchospasm, infections, future malignancy

- **Adalimumab**
 - Biologic agent
 - Monoclonal antibody directed against TNF
 - Action: binds to TNF to block pro-inflammatory signalling
 - Dose: 24 mg/m²/dose (maximum 40 mg) SC every 2 weeks
 - Side effects: injection site reactions, headaches, infections, cytopenias, future malignancy, demyelinating disease, new or worsening heart failure

- **Anakinra**
 - Biologic agent
 - Antagonist to IL-1 receptor
 - Action: blocks IL-1 receptor to prevent pro-inflammatory signalling
 - Dose: 1-2 mg/kg/day (maximum 100 mg) SC daily
 - Side effects: injection site reactions, infections, GI upset

- **Azathioprine**
 - Disease-modifying anti-rheumatic drug (DMARD)
 - Action: interferes with enzymes involved in DNA synthesis, inhibits T cells and monocytes
 - Dose: 0.5-2.5 mg/kg/day (maximum 150 mg) as single daily dose PO
 - Side effects: GI upset, oral ulcers, rash, cytopenias, and hepatotoxicity
 - Monitoring: CBC, differential and liver enzymes weekly until achieve stable dose then monthly

- **Canakinumab**
 - Biologic agent
 - Monoclonal antibody directed against IL-1
 - Action: binds to IL-1 to prevent pro-inflammatory signalling
 - Dose: 2 mg/kg/dose SC or IV every 8 weeks
 - Side effects: injection site reactions, headache, vertigo, GI upset, infections

- **Colchicine**
 - Used in Familial Mediterranean Fever and Behçet disease
 - Action: binds to microtubules to prevent activation, proliferation and functioning of inflammatory cells
 - Dose: 0.3-1.8 mg/day divided once or twice daily

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- Side effects: GI upset, cytopenias, rhabdomyolysis, renal failure
- Monitoring: CBC, differential, renal function
- **Corticosteroids**
 - Potent anti-inflammatory agents
 - Action: multiple anti-inflammatory actions including binding to transcription factors (such as NF- κ B) to block production of pro-inflammatory proteins, binding to enzymes to block function of inflammatory cells and direct inhibition of cytokines
 - Commonly used corticosteroids
 - Prednisone, prednisolone (PO)
 - Methylprednisolone (IV)
 - Dexamethasone (PO or IV)
 - Triamcinolone hexacetonide (intra-articular)
 - Dose: depends on severity of inflammation
 - Side effects of systemic therapy
 - Early: increased appetite, GI upset, gastritis, mood and behaviour changes
 - Late: infections, Cushing syndrome (truncal obesity, moon facies, cutaneous striae), acne, growth suppression, osteoporosis, AVN, psychosis, hypertension, dyslipidemia, hyperglycemia, myopathy, cataracts, glaucoma
 - Monitoring: clinical
- **Cyclophosphamide**
 - DMARD
 - Action: alkylating agent prevents cell division leading to B and T cell lymphopenia
 - Dose: 500 – 1000 mg/m²/dose IV monthly up to 6 months
 - Side effects
 - Short-term: GI upset, alopecia, cytopenias, opportunistic infections, hemorrhagic cystitis, SIADH, teratogenicity, gonadal dysfunction
 - Long-term: bladder fibrosis, bladder carcinoma, fertility issues, malignancy
 - Prophylaxis:
 - Mesna administered with infusion to prevent hemorrhagic cystitis
 - Cotrimazole given 3 times weekly to prevent opportunistic infection by *Pneumocystis jirovecii*
 - Monitoring: CBC, differential on day of infusion and then days 7, 10 and 14 after infusion to monitor cytopenias
- **Cyclosporine**
 - DMARD
 - Action: inhibits calcineurin leading to inhibition of nuclear factor of activated T cells (NF-AT) resulting in profound inhibition of T cell proliferation and cytokine production
 - Dose: 3-5 mg/kg/day PO divided twice daily
 - Side effects: renal toxicity, hypertension, hepatotoxicity, GI upset, tremor, paresthesias, gingival hyperplasia
 - Monitoring: renal function, urinalysis, CBC, differential, and liver enzymes monthly
- **Etanercept**
 - Biologic agent
 - Fusion protein consisting of extracellular portion of TNF receptor and constant region of human immunoglobulin
 - Action: binds to TNF to block pro-inflammatory signalling

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- Dose: 0.4 mg/kg/dose (maximum 25 mg) SC twice weekly or 0.8 mg/kg/dose weekly
- Side effects: injection site reactions, headaches, infections, cytopenias, future malignancy, demyelinating disease, new or worsening heart failure
- **Hydroxychloroquine**
 - DMARD
 - Action: interferes with antigen processing and antigen-antibody interactions, inhibits nucleic acid and protein synthesis
 - Dose: 4-6 mg/kg/day (maximum 400 mg) PO daily
 - Side effects: retinal toxicity (limits dose), GI upset, headache, tinnitus, neuropathy, myopathy
 - Monitoring: eye examinations every 6 months to assess for retinal deposits
- **Infliximab**
 - Biologic agent
 - Monoclonal antibody directed against TNF
 - Action: binds to TNF to block pro-inflammatory signalling
 - Dose: 3-6 mg/kg/dose every 4 to 8 weeks
 - Side effects: injection site reactions, headaches, infections, cytopenias, future malignancy, demyelinating disease, new or worsening heart failure
- **IVIG**
 - Action: multiple anti-inflammatory mechanisms including inhibition of antibody-mediated cytotoxicity, attenuation of complement-mediated damage, modulation of cytokine production, and neutralization of superantigens
 - Dose: 2 g/kg/dose IV
 - Side effects: infusion reactions, anaphylaxis or allergic reactions, acute aseptic meningitis, acute renal failure
 - Need to delay future immunizations by 11 months
- **Leflunomide**
 - DMARD
 - Action: inhibits enzyme involved in DNA synthesis and interferes with lymphocyte proliferation
 - Dose: 10-20 mg PO daily
 - Side effects: GI upset, allergic rash, hepatotoxicity, teratogenicity, future malignancy
 - Need to discuss alcohol avoidance and birth control
 - Monitoring: CBC, differential, liver enzymes every 4-6 weeks
- **Methotrexate**
 - DMARD
 - Action: inhibits enzymes in DNA synthesis
 - Dose: 10-15 mg/m²/dose (maximum 25 mg) PO or SC weekly
 - Often better response with SC injection
 - Side effects: GI upset, oral ulcers, hepatotoxicity, bone marrow suppression, teratogenicity, future malignancy
 - Need to discuss alcohol avoidance and birth control
 - Prophylaxis against oral ulcers with folic acid 1 mg PO daily
 - Monitoring: CBC, differential, liver enzymes every 4-6 weeks

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- **Mycophenolate mofetil**

- DMARD
- Action: inhibits enzyme in DNA synthesis leading to inhibition of B and T cell proliferation, suppresses antibody response
- Dose: 800-1200 mg/m²/day (maximum 3000 mg/day) PO twice daily
 - Typical starting dose is 250 mg daily
 - Use drug levels (MMF kinetics) to optimize dose
- Side effects: GI upset, headaches, cytopenias, infections, teratogenicity, future malignancy, progressive multifocal leukoencephalopathy
- Monitoring: CBC and differential every 4-6 weeks

- **Non-steroidal anti-inflammatory drugs (NSAIDs)**

- First-line anti-inflammatory agents for arthritis
- Action: inhibit cyclo-oxygenase to block production of pro-inflammatory prostaglandins
- Commonly used NSAIDs
 - ASA (high dose 50-100 mg/kg/day PO divided 4 times daily and low dose 3-5 mg/kg/day PO daily)
 - Naproxen (dose: 10 mg/kg/dose (maximum 500 mg) PO twice daily)
 - Indomethacin (dose: 2-3 mg/kg/day (maximum 150 mg /day) PO three times daily)
- Side effects: GI upset, gastritis, GI bleeding, renal toxicity, hepatotoxicity, ototoxicity
- Monitoring: hemoglobin, renal function and liver enzymes with clinic visits

- **Rilonacept**

- Biologic agent
- Fusion protein consisting of extracellular portion of IL-1 receptor and constant region of human immunoglobulin
- Action: binds to IL-1 to prevent pro-inflammatory signalling
- Dose: 2.2-4.4 mg/kg/dose SC weekly
- Side effects: injection reactions, infections, dyslipidemia

- **Rituximab**

- Biologic agent
- Monoclonal antibody directed against CD20 on B cells
- Action: selectively depletes B cells
- Dose: 750 mg/m²/dose IV x 2 infusions separated by 2 weeks
- Side effects: infusion reactions, allergic reaction, hypogammaglobulinemia, infection, progressive multifocal leukoencephalopathy

- **Sulfasalazine**

- DMARD
- Analogue of 5-aminosalicylic acid linked to sulfa group
- Action: inhibits enzymes and transcription factors involved in production of pro-inflammatory cytokines
- Dose: 50 mg/kg/day (maximum 3 g daily) PO divided twice daily
- Side effects: GI upset, Stevens-Johnson, rash, oral ulcers, cytopenias, hypogammaglobulinemia, hepatotoxicity, allergy
- Monitoring: CBC, differential and liver enzymes every 2 months, immunoglobulin levels every 6 months

- **Tocilizumab**

- Biologic agent
- Monoclonal antibody directed against IL-6 receptor
- Action: binds to IL-6 receptor to block IL-6 mediated pro-inflammatory signalling
- Dose: 8-12 mg/kg/dose IV every 2 weeks
- Side effects: infusion reactions, headaches, GI upset, gastritis, infections, hepatotoxicity, dyslipidemia, cytopenias

APPENDIX – HELPFUL RESOURCES IN PEDIATRIC RHEUMATOLOGY

Textbooks

Cassidy JT, Petty RE, Laxer RM, Lindsley CB. *Textbook of Pediatric Rheumatology, Sixth Edition*. 2010: Saunders Elsevier Publishing.

Firestein GS, Budd RC, Harris ED, McInnes IB, Ruddy S, Sergent JS. *Kelley's Textbook of Rheumatology, Eighth Edition*. 2009: Saunders Elsevier Publishing.

Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, Eds. *Rheumatology, Fourth Edition*. 2010: Mosby Elsevier Publishing.

Szer I, Kimura Y, Malleson P, Southwood T. *Arthritis in Children and Adolescents: Juvenile Idiopathic Arthritis*. 2006: Oxford University Press.

Woo P, Laxer RM, Sherry DD. *Pediatric Rheumatology in Clinical Practice*. 2007: Springer-Verlag.

Websites

Rheumatlas website: <http://rheumatlas.org>.

We are interested in your feedback on the guide! If you have comments or questions, please feel free to contact us via email at pedrheum.guide@sickkids.ca.