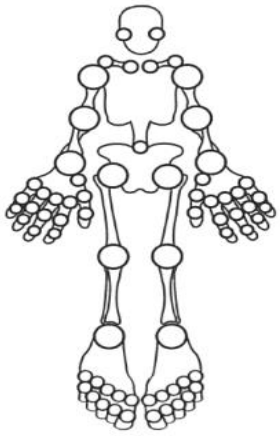

A RESIDENT'S GUIDE TO PEDIATRIC RHEUMATOLOGY

4th Revised Edition - 2019

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SickKids®

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CANADIAN RHEUMATOLOGY ASSOCIATION | SOCIÉTÉ CANADIENNE DE RHUMATOLOGIE

This guide 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 and other resources 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 pedrheumguide@gmail.com.

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Notes:

Please consider that all treatment regimens discussed in the guide are <u>suggestions</u> based on evidence-based guidelines and/or common practices by the pediatric rheumatologists who are Section Editors of the Guide. 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.

SECTION 1 – PEDIATRIC RHEUMATOLOGY CLINICAL ASSESSMENT

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 and activities of daily living
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

Brief review of all domains - gross motor, fine motor, speech, language, hearing, social

Immunizations

All childhood vaccinations
Varicella – Infection or vaccination?

Medications

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

Allergies

Travel history (especially risk factors for tuberculosis or Lyme infections)

Family history

Ethnicity and consanguinuity

Rheumatologic diseases: Juvenile idiopathic arthritis (JIA), rheumatoid arthritis (RA)
Ankylosing spondylitis (AS)
Premature osteoarthritis
Inflammatory bowel disease (IBD)
Psoriasis
Systemic lupus erythematosus (SLE)
Vasculitis
Autoinflammatory diseases, including early hearing loss and early renal failure

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

Social history

Parents marital status, occupations, care providers, drug coverage, adolescent psychosocial assessment (e.g. HEEADSSS)

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, extra-curricular activities, 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, pain waking from sleep 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 Irregular, missed or prolonged menstrual periods, heavy menses

1B. Pediatric Rheumatologic Examination

Vital signs (including blood pressure percentiles)

Height, weight, BMI (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 tenderness Oropharyngeal mucosa, tongue, tonsils Thyroid
CVS:	Heart sounds, murmurs, rubs, precordial examination Vascular bruits (if indicated) Peripheral pulses, peripheral perfusion, capillary refill
Lungs:	Respiratory excursion, percussion, breath sounds, adventitious sounds
Abdomen:	Tenderness, peritoneal signs, masses, bowel sounds, bruits (if indicated) Hepatomegaly, splenomegaly
LN:	Assess all accessible lymph node groups
Skin:	Any type of skin rash, including petechiae, purpura, nodules, and ulcers Alopecia, hair abnormalities
Nails:	Nail pits, clubbing, onychonychia Nail fold capillaries – thickening, branching, drop-out, hemorrhages Digital ulcers, splinter hemorrhages, 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:	Begin with a screening exam, such as the Pediatric Gait Arms Legs Spine (pGALS) Assess all joints for heat, swelling, tenderness, stress pain, active and passive range of motion, deformity Enthesitis sites Localized bony/joint tenderness Leg length (functional and/or actual) Thigh, calf circumference difference (if indicated)
Back:	Range of motion, tenderness, stress pain from repetitive motion Scoliosis Modified Schober test (if indicated)
Other:	Fibromyalgia tender points (if indicated)

References:

1. Foster HE, Jandial S. pGALS – paediatric Gait Arms Legs and Spine: a simple examination of the musculoskeletal system. *Pediatr Rheumatol Online J* 2013; 11(1):44.

1C. Laboratory Testing in Pediatric Rheumatology

General Principles

- Interpret all laboratory results in context of specific patient
- Consider the clinical rationale and potential impact of all laboratory tests that are ordered, especially for autoantibody testing
- Review all laboratory test results to guide interpretation of abnormalities
- Trends in laboratory values may be more important than isolated abnormalities

Complete blood cell count and differential

- Hemoglobin, red blood cell count and mean corpuscular volume
  - Normocytic or microcytic anemia in chronic inflammatory disease
  - Autoimmune hemolytic anemia in systemic lupus erythematosus (SLE)
  - Non-immune hemolytic anemia in macrophage activation syndrome (MAS)
  - Iron deficiency anemia if chronic blood loss (e.g. due to NSAIDs, inflammatory bowel disease)
- White blood cell count and differential
  - High white blood cell counts may be due to infection, systemic inflammation, or side-effect of corticosteroids
  - Leukopenia with lymphopenia and/or neutropenia may be due to systemic inflammation or medications
- Platelet count
  - Active inflammation may lead to increased platelet counts (e.g. subacute phase of Kawasaki disease, systemic juvenile idiopathic arthritis (JIA), or Takayasu arteritis)
  - Active disease may also lead to reduced platelet counts (e.g. SLE)

Acute phase response to systemic inflammation

- 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 (which are the target of many biologic agents used in childhood rheumatic diseases)
- Substantial acute phase response may be seen in infection, trauma, burns, tissue infarction, advanced cancer and immune-mediated disease
- Mild elevation may be seen in conditions such as obesity, pregnancy, and strenuous exercise
- 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, MAS, malignancy)

C-reactive protein (CRP)

- Direct measure of inflammation (sensitive but not specific)
- Level rises rapidly in response to inflammation and falls quickly with appropriate treatment
- May reflect severe disease more closely than other acute phase reactants, although this may be patient-specific and/or disease-dependent (e.g. CRP typically rises in patients with SLE when there is infection, serositis or MAS, but may be normal with active disease)

Erythrocyte sedimentation rate (ESR)
- Indirect measure of acute phase reaction
- Changes more slowly than CRP
- Measure rate at which red blood cells settle in a tube of anticoagulated blood in one hour
- Depends on fibrinogen, gamma globulins

Ferritin
- Protein central to iron homeostasis
- Serum ferritin levels increase in setting of inflammation
- Very high levels suggestive of macrophage activation syndrome
- May not function as a reliable measure of iron status in setting of inflammatory disease

Summary of laboratory changes in acute phase response to systemic inflammation:

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	

Complement

- Increased levels of complement components frequently seen in inflammation
- Low complement levels present in SLE, acute post-infectious glomerulonephritis, membrano-proliferative glomerulonephritis, or liver disease
- Congenital complement deficiencies predispose either to recurrent infections (mainly encapsulated organisms) 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
- ANA should <u>not</u> be used as a screening tool
    - Low titres of ANA (e.g. ANA ≤ 1:80) may be present in up to 30% of normal healthy population and may revert to negative over time
    - ANA may also be present in non-rheumatologic diseases (e.g. infection, malignancy, medications)
- No need to repeat ANA regularly once positive titre established (from *Choosing Wisely: Pediatric Rheumatology Top 5 by American College of Rheumatology*)

- Low titres of non-specific ANA may be seen in JIA patients, but positive ANA titres ≥ 1:160 in JIA patients are associated with younger age at onset, higher risk of uveitis, asymmetric arthritis and lower number of affected joints over time
- Persistent higher titres of ANA > 1:160 suggest 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 and there is evidence of rheumatic disease *(*highlighted in *Choosing Wisely: Pediatric Rheumatology Top 5 by American College of Rheumatology)*

Anti-double stranded DNA (Anti-dsDNA)

- Anti-dsDNA autoantibody targets DNA in nucleus of cell
- Highly specific for SLE
- Titres are affected by disease activity and may be used to monitor disease progression and response to therapy

Autoantibodies to extractable nuclear antigen (ENA)

Specific ENA antibodies	*Characteristic disease associations*
Anti-Ro/SSA	SLE, Neonatal lupus erythematosus, Sjögren
Anti-La/SSB	SLE, Neonatal lupus erythematosus, Sjögren
Anti-Sm (Anti-Smith)	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

Rheumatoid factor (RF)

- IgM autoantibody that reacts to Fc portion of IgG
- 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, mixed connective tissue disease, cryoglobulinemia and chronic infection (subacute bacterial endocarditis, hepatitis B and C, TB)

Anti-citrullinated peptide antibodies (ACCP)

- Antibodies to citrullinated peptides found in inflamed synovium
- Highly specific for rheumatoid arthritis, but often positive in older children with polyarticular Rheumatoid factor positive JIA
- Indicates increased risk of aggressive disease and progressive joint damage

Antiphospholipid antibodies

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

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 (ELISA)*	*Disease associations*
c-ANCA	Cytoplasmic	Proteinase-3 (PR3)	Granulomatosis with polyangiitis
p-ANCA	Perinuclear	Myeloperoxidase (MPO)	Microscopic polyangiitis Eosinophilic granulomatosis with polyangiitis Ulcerative colitis Primary sclerosing cholangitis SLE

Anti-Glomerular Basement Membrange (Anti-GBM) antibodies

- Antibodies target alpha-3 chain of type IV collagen, which is normally present in glomerular and alveolar basement membranes
- Antibody binding to basement membranes in lungs and kidneys activates classical complement pathway and neutrophil-dependent inflammation, leading to small vessel vasculitis with immune complex formation
- Production of antibodies may be triggered by environmental factors (e.g. infection, cigarette smoking)

Human Leukocyte Antigen (HLA) Genetics

- Many genes of the major histocompatibility complex (especially HLA class I and II genes) have been associated with rheumatic disorders

HLA-B27

- HLA class I gene that is present in only 7-10% of the general population (may be higher in some First Nations groups)
- 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

HLA-B51

- May be associated with Behçet disease

Additional tests:

Urinalysis
- Routinely used to assess for proteinuria and hematuria associated with renal involvement in autoimmune and autoinflammatory diseases

Fecal calprotectin
- May be measured as an indicator of underlying gastrointestinal inflammation

Genetic testing
- Often ordered to confirm diagnosis of genetic fever syndromes and other autoinflammatory disorders

Cytokine profiling
- May be used in research contexts to qualify the inflammatory response and guide therapy
- May become more widely available in upcoming years

References:

1. Mehta J. Laboratory testing in pediatric rheumatology. *Pediatr Clin N Am* 2012; 59:263-84.
2. Pilania RK, Singh S. Rheumatology panel in pediatric practice. *Indian J Pediatr* 2019; 56(5):407-14.

1D. Diagnostic Imaging in Pediatric Rheumatology

General Principles

- Interpret all imaging results in context of specific patient
- Consider the clinical rationale and potential impact of all imaging that is ordered, including risks of sedation, radiation and contrast administration
- Imaging alone is not sufficient to confirm any rheumatic disease
- Repeat imaging may be helpful to assess response to therapy, disease progression and development of damage or to screen for specific organ involvement in systemic conditions
- Review of questionable or unexpected imaging findings with a pediatric radiologist who has specific expertise (e.g. musculoskeletal or neuroradiology training) is recommended

X-ray

- Bone and joint X-rays
    - Often ordered as initial testing for pain and deformity
    - May be used to rule out bony abnormalities or injuries, such as fracture, that may explain symptoms
    - Helpful to image both affected and non-affected sides to assess for subtle changes
    - May be normal at disease onset
    - Most likely to be ordered in assessment of patients with possible JIA or other inflammatory arthritis, non-bacterial osteomyelitis, or systemic sclerosis
    - Findings in JIA may include effusion, soft tissue swelling, periarticular osteopenia, joint space narrowing, erosions, subchondral cysts, osteophytes, bone deformity, fusion, or accelerated bone development in young children

- Chest X-rays
    - May be used to assess for heart and lung involvement in systemic autoimmune or autoinflammatory diseases

Ultrasound

- May be used to assess for effusions and other findings of synovitis or to facilitate joint injections
- May also be used with Doppler to assess vasculature for obstruction of blood flow, which may be due to thrombosis or vasculitis in rheumatic diseases
- Highly operator dependent and requires specific skill and experience, especially with pediatric patients
- Many rheumatologists are currently performing point-of-care ultrasonography to aid clinical assessment of disease activity and joint injection

Computed tomography (CT)

- Chest CT may be useful to identify findings of interstial lung disease and pulmonary hemorrhage in connective tissue diseases
- CT angiograms may be used to assess for findings of vasculitis when magnetic resonance or conventional angiograms are not easily accessible
- While CT may identify findings for a number of rheumatic diseases, it is often not the first imaging of choice because of the associated radiation.
- If CT is deemed necessary, radiation may be reduced with high resolution techniques

Magnetic resonance imaging

- Ideal imaging modality for synovitis in specific joints (e.g. temporomandibular, sacroiliac and cervical spine) and may identify early signs of disease and/or damage in JIA
- Whole body MRI protocols have been developed to assess for enthesitis and chronic non-bacterial osteomyelitis
- Specialized protocols have been developed to identify findings in inflammatory myositis
- Ideal imaging modality to identify findings of brain inflammation (especially if 3T or higher strength magnet available) and may also be used to assess for inflammation in aorta, blood vessels and other organs (e.g. gastrointestinal tract); MR angiography should be requested for more accurate imaging of blood vessels
- Limitations are that MRI is expensive and less accessible and longer scan times often require sedation for younger children

Echocardiography

- Typically used to assess for coronary artery aneurysms in Kawasaki disease and for carditis or other cardiopulmonary involvement in systemic autoimmune or autoinflammatory diseases
- Antenatal use of echocardiography is important in babies at risk of neonatal lupus erythematosus to assess for myocarditis and endocardial fibroelastosis
- Some centres may require consultation with cardiologist in conjunction with imaging

Dual Energy X-ray Absorptiometry (DEXA) scan

- Measures bone mineral density
- Used most often in patients on chronic steroid therapy at baseline and at regular intervals to monitor for development of osteopenia/osteoporosis

References

1. Pilania RK, Singh S. Rheumatology panel in pediatric practice. *Indian J Pediatr* 2019; 56(5):407-14.

SECTION 2 – APPROACHES TO AND DIFFERENTIAL DIAGNOSES FOR COMMON COMPLAINTS REFERRED TO PEDIATRIC RHEUMATOLOGY

2A. Approach to Childhood Joint Pain

Differential diagnosis for pain involving a single joint:

Traumatic	Fracture Soft tissue injury (e.g. strains, sprains) Foreign body synovitis
Infection-related	Septic arthritis Osteomyelitis Chronic infections, such as tuberculosis or Lyme disease Reactive arthritis including post-Streptococcal reactive arthritis Acute rheumatic fever
Inflammatory	Juvenile idiopathic arthritis (JIA) Chronic non-bacterial osteomyelitis Inflammatory bowel disease Genetic autoinflammatory syndromes (e.g. familial Mediterranean fever, pyogenic arthritis pyoderma gangrenosum and acne) Behçet disease
Neoplastic	Musculoskeletal tumors (e.g. osteoid osteoma, osteosarcoma) Hematologic malignancy
Hemarthrotic	Traumatic Coagulopathy (e.g. hemophilia) Pigmented villonodular synovitis Arteriovenous malformation
Hematologic	Sickle cell disease (e.g. pain crisis, dactylitis)
Mechanical	Overuse or repetitive strain injury Tendon/ligament/meniscal injury Apophysitis Joint damage (e.g. prior trauma, infection, congenital anomaly)
Orthopedic	Avascular necrosis (AVN) Slipped capital femoral epiphysis (SCFE) Osteochonditis dissecans
Pain syndrome	Complex regional pain syndromes (CRPS)

Potential investigations for pain involving a single joint:

- X-rays
- Joint aspiration and synovial fluid analysis and/or culture
- Blood work: CBC and differential, ESR, CRP
- Consider, if indicated:
    - Further infectious testing (e.g. blood culture, Lyme serology, TB skin test)
    - Further imaging (e.g. ultrasound, MRI)
    - Autoimmune serology (e.g. ANA, HLA B27)

Differential diagnosis for pain involving multiple joints:

Inflammatory	Juvenile idiopathic arthritis (JIA) Systemic lupus erythematosus (SLE) Juvenile dermatomyositis Scleroderma/mixed connective tissue disease/overlap syndromes Systemic vasculitis (e.g. Henoch-Schönlein purpura / IgA vasculitis) Inflammatory bowel disease (IBD) Genetic autoinflammatory syndromes Sarcoidosis Chronic non-bacterial osteomyelitis / chronic recurrent multifocal osteomyelitis Serum sickness
Infection-related	Acute infections (e.g. parvovirus B19, EBV, *Neisseria gonorrheae)* Chronic infections (e.g. tuberculosis (Poncet arthritis), Lyme disease) Subacute bacterial endocarditis (SBE) Reactive arthritis, including acute rheumatic fever (ARF) Osteomyelitis and septic arthritis may rarely present with multifocal involvement
Immunological	Immunodeficiency associated with arthritis (e.g. Wiskott-Aldrich)
Neoplastic	Leukemia, lymphoma, neuroblastoma, cancers with systemic involvement
Mechanical	Overuse injuries, repetitive strain injuries Apophysitis Hypermobility – benign or due to connective tissue disease (e.g. Ehlers-Danlos) Skeletal dysplasias
Metabolic	Rickets Vitamin C deficiency (scurvy) Glycogen storage disease, mucopolysaccharidoses
Pain syndrome	Fibromyalgia

Potential investigations for pain involving multiple joints:

- Blood work: CBC and differential, blood film, ESR, CRP
- Infectious testing (e.g. Parvovirus B19 serology, EBV serology, throat culture, ASOT)
- Consider, if indicated:
    - Autoimmune serology (e.g. ANA, Rheumatoid factor, HLA B27)
    - Imaging (e.g. X-rays, ultrasound, MRI)
    - Urinalysis
    - Bone marrow aspirate and biopsy

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

Signs/symptoms	Associated conditions
Severe joint pain	Infection-related, malignancy, trauma, AVN, pain syndrome
Pinpoint tenderness	Osteomyelitis, trauma, AVN, malignancy, enthesitis, chronic non-bacterial osteomyelitis
Night pain	Malignancy, osteoid osteoma, benign nocturnal limb pain
Redness	Septic arthritis, acute rheumatic fever, reactive arthritis
Migratory joint pain	Leukemia, acute rheumatic fever
Non weight bearing	Infection, malignancy, discitis, myositis, pain syndrome
Hip pain	Infection-related, AVN, SCFE, malignancy, chondrolysis, transient synovitis, JIA (particularly enthesitis related arthritis)
Back pain	Usually benign, but consider bone or spinal cord tumour, discitis, spondylolysis/spondylolisthesis, JIA (enthesitis related arthritis), myositis, osteoporosis, CNO, pain syndrome
Periarticular pain	Malignancy, hypermobility, pain syndrome, CNO
Dactylitis	JIA (particularly enthesitis related arthritis and psoriatic arthritis), sickle cell, trauma
Clubbing	Cystic fibrosis, IBD, malignancy (especially lung), familial, hypertrophic osteoarthropathy
Weight loss	Malignancy, systemic autoimmune rheumatologic diseases, IBD
Muscle weakness	Myositis, overlap syndromes, malignancy, pain-related weakness
Rash	Systemic autoimmune rheumatologic diseases, vasculitis, JIA (particularly systemic arthritis and psoriatic arthritis), acute rheumatic fever, Lyme disease, serum sickness, autoinflammatory syndromes
Oral ulcers	Vasculitis, Behçet disease, SLE, IBD, autoinflammatory syndromes
Eye pain and redness	Reactive arthritis, enthesitis related arthritis. IBD, Behçet disease
Nail or nail fold changes	Systemic autoimmune rheumatologic diseases, psoriasis, subacute bacterial endocarditis
Raynaud phenomenon	Systemic autoimmune rheumatologic diseases
School withdrawal	Pain syndrome, chronic fatigue
Travel	Infection-related (e.g. tuberculosis, Lyme disease, viral)
Consanguinity	Genetic or metabolic diseases (e.g. autoinflammatory diseases)

References:

1. Nannery R, Heinz P. Approach to joint pain in children. *Paediatr and Child Health* 2018; 28(2):43-49.

2. Tse SM, Laxer RM. Approach to acute limb pain in childhood. *Pediatr Rev* 2006; 27:170-80.
3. Sen ES, et al. The child with joint pain in primary care. *Best Pract & Res Clin Rheumatol* 2014; 28:888-906.

2B. Approach to Childhood Back Pain

Differential diagnosis for back pain in children

Inflammatory	Juvenile idiopathic arthritis (JIA) Inflammatory bowel disease (IBD) Chronic non-bacterial osteomyelitis, chronic recurrent multifocal osteomyelitis Transverse myelitis (e.g. SLE)
Infection-related	Acute infections (e.g. osteomyelitis, septic arthritis, discitis, epidural abscess) Chronic infections (e.g. tuberculosis (Pott disease)) Reactive arthritis
Neoplastic	Musculoskeletal tumors (e.g. osteoblastoma, osteosarcoma, spinal cord tumors, metastases) Leukemia, lymphoma
Mechanical	Spondylolysis, spondylolisthesis Scoliosis Scheuermann disease Disc prolapse Degenerative disc disease
Trauma	Fracture
Hematologic	Sickle cell pain crisis
Pain syndrome	Fibromyalgia
Other	Neurofibromatosis

Potential investigations for back pain in children:

- Investigations may not be needed and depend on clinical assessment
- Consider, if indicated:
    - Imaging (e.g. X-rays, MRI)
    - Autoimmune serology (e.g. ANA, Rheumatoid factor, HLA B27)
    - Blood work (e.g. CBC and differential, ESR, CRP)

References:

1. Altaf F, et al. Back pain in children and adolescents. *Bone Joint J* 2014; 96B:717-23.
2. Nigrovic PA. Evaluation of the child with back pain. *UpToDate.* Updated December 2018. URL: https://www.uptodate.com/contents/evaluation-of-the-child-with-back-pain.

2C. Approach to Fevers

Definition of fever of unknown origin:

- Temperature > 38 degrees Celsius lasting ≥ 8 days with no clear source of fever

Differential diagnosis for fever of unknown origin in children

Infectious	Bacterial (e.g. abscess, mastoiditis, osteomyelitis, pyelonephritis, sinusitis, typhoid fever, tuberculosis) Viral (e.g. Adenovirus, CMV, EBV, Enterovirus, HIV) Other infections including parasitic and fungal (e.g. malaria, Lyme disease, Toxoplasma, Blastomycosis)
Inflammatory	Serum sickness Systemic vasculitis (e.g. Kawasaki disease) Systemic lupus erythematosus Juvenile dermatomyositis Systemic arthritis/JIA Behçet disease Inflammatory bowel disease Genetic autoinflammatory syndromes Castleman syndrome Hemophagocytic lymphohistiocytosis (primary or secondary HLH/MAS) Sarcoidosis
Drug-induced	Drug fevers or intoxication
Neoplastic	Leukemia, lymphoma Langerhans cell histiocytosis Neuroblastoma
Endocrinologic	Hyperthyroidism Thyroiditis Diabetes insipidus
Other	Pancreatitis Factitious fevers

Potential investigations for fever of unknown origin in children:

- Investigations will depend on clinical assessment and serial re-examination
- Initial blood work: CBC and differential, blood film, electrolytes, urea, creatinine, glucose, ESR, CRP, ferritin, liver enzymes, albumin, LDH
- Urinalysis
- Initial infectious work-up: blood culture, urine culture, nasopharyngeal swab for viruses
- Consider, if indicated:
    - Imaging (e.g. X-rays, abdominal ultrasound)
    - Further infectious testing (e.g. ASOT, Monospot, cerebrospinal fluid testing)
    - Testing for immunodeficiency (e.g. complement and immunoglobulin levels)

Definition of recurrent fevers:

- ≥ 3 episodes of unexplained fever within 6 months separated by ≥ 7 days of good health

Differential diagnosis for recurrent fevers

Infectious	Repeated viral or bacterial infections Viral (e.g. CMV, EBV, Parvovirus, hepatitis viruses, HIV) Bacterial (e.g. Typhoid fever, occult dental abscess, endocarditis, Mycobacteria) Parasitic or fungal (e.g. malaria, Borrelia, Brucellosis, Yersinia)
Inflammatory	Genetic autoinflammatory syndromes Periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA) Systemic lupus erythematosus Systemic arthritis/JIA Inflammatory bowel disease Behçet disease Polyarteritis nodosa Sarcoidosis Hemophagocytic lymphohistiocytosis (primary or secondary HLH/MAS) IgG4 disease
Hematologic	Cyclic neutropenia
Neoplastic	Leukemia, lymphoma
Immunologic	DiGeorge syndrome Chediak-Higashi Combined immunodeficiency syndrome
Drug-induced	Drug fevers or intoxication
Other	CNS abnormality (e.g. hypothalamic dysfunction) Castleman disease Factitious fevers

Potential investigations for recurrent fevers:

- Clinical assessment during episode of fever and when well
- Fever diary including pattern of fever and associated symptoms
- Blood work during episode and when well: CBC and differential, ESR, CRP, ferritin, liver enzymes, albumin, LDH, immunoglobulins (including IgD)
- Urinalysis
- Consider, if indicated:
    - Infectious testing (e.g. blood culture, viral serology)
    - Autoimmune serology (e.g. ANA)
    - Genetic testing

References:

1. Antoon JW, et al. Pediatric fever of unknown origin. *Pediatr Rev* 2015; 36(9):380-91.
2. Soon GS, Laxer RM. Approach to recurrent fever in childhood. *Can Fam Physician* 2017; 63(10):756-62.

2D. Approach to Recurrent Oral Ulcers

Differential diagnosis for recurrent oral ulcers in children

Inflammatory	Inflammatory bowel disease Celiac disease Behçet disease Systemic lupus erythematosus (SLE) Hyperimmunoglobulinemia D syndrome (HIDS) Periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA) A20 haploinsufficiency (HA20) Sarcoidosis
Infectious	Viral (e.g. Herpes simplex, Coxsackie) Reactive arthritis
Hematologic	Cyclic neutropenia
Drugs	Azathioprine, Methotrexate, Sulfasalazine
Other	Aphthous stomatitis

What are the characteristics of oral ulcers in different inflammatory conditions?

SLE	Painless shallow oral ulcers, typically located on roof of mouth where hard and soft palate meet
Inflammatory bowel disease	Painful aphthous ulcers anywhere in oropharynx, sometimes associated with cheilitis
Behçet disease	Painful aphthous ulcers or punched-out ulcers on tongue, lips, gingiva and/or buccal mucosa
Celiac disease	Painful recurrent aphthous ulcers
PFAPA	Painful aphthous ulcers with discrete margins, typically on buccal mucosa, associated with febrile episodes
HIDS	Painful aphthous ulcers with discrete margins, typically on buccal mucosa, associated with febrile episodes
Sarcoidosis	Painless well-circumscribed brownish red or violaceous lesions (sometimes nodular), erythematous gingival enlargement, submucosal swelling of palate

References:

1. Siu A, et al. Differential diagnosis and management of oral ulcers. *Semin Cutan Med Surg* 2015; 34(4):171-7.
2. Le Doare K, et al. Fifteen-minute consultation: a structured approach to the management of recurrent oral ulceration. *Arch Dis Child Educ Pract Ed* 2014; 99(3):82-6.
3. Stoopler ET, Al Zamel G. How to manage a pediatric patient with oral ulcers. *J Can Dent Assoc* 2014; 80:e9.

2E. Additional differential diagnoses

Differential diagnosis for lymphadenopathy in children

Inflammatory	Systemic lupus erythematosus Systemic arthritis/JIA Kawasaki disease Hemophagocytic lymphohistiocytosis (primary or secondary HLH) Kikuchi-Fujimoto disease Castleman disease Rosai-Dorfman disease Monogenic autoinflammatory diseases Periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA) Serum sickness Sarcoidosis
Infectious	Viral (e.g. EBV, CMV, HIV) Bacterial (e.g. Bartonella, tuberculosis) Bacterial spirochete/tick bourne (e.g. Lyme disease)
Neoplastic	Lymphoma, leukemia Langerhans cell histiocytosis Neuroblastoma
Other	Drug-induced

Differential diagnosis for erythema nodosum in children

Infectious	Viral (e.g. EBV, CMV, HIV) Bacterial (e.g. Group A Streptococcus, Mycoplasma, Bartonella, Yersinia, tuberculosis)
Inflammatory	Inflammatory bowel disease Systemic lupus erythematosus Behçet disease Systemic vasculitis (e.g. polyarteritis nodosa, granulomatosis with polyangiitis) Sarcoidosis
Neoplastic	Lymphoma, leukemia Hepatocellular carcinoma Renal cell carcinoma
Drug-related	Oral contraceptives Antibiotics (e.g. sulpha drugs, penicillins, macrolides)
Other	Idiopathic

Differential diagnosis for recurrent parotitis

Infectious	Viral: HIV (diffuse infiltrative lymphocytosis), Influenza B, mumps, EBV, CMV, Parvovirus, Paramyxovirus, Adenonvirus Bacterial: Streptococcal infections, Staphylococcus aureus, Bartonella, Haemophilus Tuberculosis
Inflammatory	Systemic lupus erythematosus Sjögren syndrome IgG4 related disease
Neoplastic	Parotid tumours Lymphoma
Other	Sialolithiasis Juvenile recurrent parotitis Pneumoparotid

Differential diagnosis for muscle weakness

Inflammatory	Juvenile dermatomyositis Juvenile polymyositis Systemic lupus erythematosus Mixed connective tissue disease Juvenile idiopathic arthritis Systemic sclerosis Overlap myositis Inclusion-body myositis Focal myositis Orbital myositis Granulomatous myositis Eosinophilic myositis Inflammatory bowel disease Autoinflammatory diseases (e.g. TNF-receptor associated periodic syndrome, Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, Familial Mediterranean fever)
Infectious	Viral (e.g. Enterovirus, Influenza, Coxsackievirus, Echovirus, Parvovirus, Hepatitis B, HTLV) Bacterial/Spirochetal (e.g. Staphylococcus, Streptococcus, Borrelia) Parasitic (e.g. Toxoplasmosis, Trichinosis)
Genetic	Muscular dystrophy (e.g. Duchenne, Becker) Congenital myopathies (e.g. Spinal muscular atrophy)
Metabolic	Metabolic diseases (e.g. mitochondrial, glycogen storage)
Other	Endocrinopathies (e.g. thyroid-associated myopathies) Trauma Toxins Neuromuscular transmission disorders (e.g. myasthenia gravis)

Differential diagnosis for chorea and abnormal movements in children

Inflammatory	Autoimmune encephalitis Systemic lupus erythematosus Antiphospholipid antibody syndrome Behçet disease Hashimoto encephalitis Polyarteritis nodosa Sjögren syndrome Celiac disease Sarcoidosis
Infectious	Acute rheumatic fever Lyme disease Malaria Neurosyphilis Tuberculosis Creutzfeld-Jacob disease
Neurologic	Benign hereditary chorea Huntington disease Idiopathic basal ganglia calcification Ataxia telengiectasia Tic disorder
Neoplastic	Paraneoplastic syndromes Tumors with basal ganglia involvement
Drug-related	Dopaminergic and other drugs
Other	Porphyria Wilson disease Liver failure

Differential diagnosis for stroke-like presentations in children

Inflammatory	CNS vasculitis (primary angiography-positive or secondary vasculitis) Systemic vasculitis (e.g. polyarteritis nodosa) Systemic lupus erythematosus Antiphospholipid antibody syndrome
Structural	Arterial dissection Fibromuscular dysplasia Moyamoya disease
Hematologic	Thromboembolic disease (e.g. prothrombotic condition, atherosclerosis) Hemoglobinopathies (e.g. sickle cell disease)
Vasospastic	Reversible vasoconstrictive syndromes Drug-induced (e.g. cocaine)
Genetic	Deficiency of adenosine deaminase 2 (DADA2) Channelopathies Connective tissue disorders (e.g. Ehlers-Danlos syndrome, Marfan syndrome) Neurofibromatosis
Metabolic	CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), MELAS (mitochondrial encephalopathy, lactic acidosis, stroke-like episodes)

References:

1. Hambleton L, et al. Lymphadenopathy in children and young people. *Paediatr and Child Health* 2016; 26(2):63-7.
2. Penn E, Goudy S. Pediatric inflammatory adenopathy. *Otolaryngol Clin North Am* 2015; 48(1):137-51.
3. Leung AKC, et al. Erythema nodosum. *World J Pediatr* 2018; 14(6):548-54.
4. Baszis K, et al. Recurrent parotitis as a presentation of primary pediatric Sjögren syndrome. *Pediatrics* 2012; 129:179-82.
5. Huber AM. Juvenile idiopathic inflammatory myopathies. *Pediatr Clin North Am* 2018; 65(4):739-56.
6. Gilbert DL. Acute and chronic chorea in childhood. *Semin Pediatr Neurol* 2009; 16(2):71-6.
7. Tsze DS, Valente JH. Pediatric stroke: a review. *Emerg Med Int* 2011; 734506.

SECTION 3 – JUVENILE IDIOPATHIC ARTHRITIS

3A. Introduction to Juvenile Idiopathic Arthritis (JIA)

- Arthritis is diagnosed in the presence of joint effusion OR two or more of the following: limited range of movement with joint line tenderness or painful range of movement
- Currently, the most widely-used classification criteria for JIA is by the International League of Associations for Rheumatology (ILAR) from the late 1990's
    - *Definition:* JIA is arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks and in which other causes of arthritis are excluded
    - *Classification:* 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**
- A recent re-classification of JIA was proposed by Pediatric Rheumatology International Trials Organization (PRINTO) in 2019, but has not been validated
    - Most prominent changes proposed in the new PRINTO criteria are that JIA is considered a group of distinct clinical phenotypes (rather than a single disease) that begin before the 18th birthday and are not classified by the number of joints involved

Oligoarthritis

ILAR Classification Criteria for Oligoarthritis *

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

Subcategories:

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

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

- Oligoarthritis is the most common subtype of JIA
- Typical patient is a young girl with positive ANA who presents with a small number of swollen joints
- Most frequent joints to be involved are knees, ankles, wrists, or elbows

- Hip involvement is distinctly uncommon, especially early in disease, unless the disease develops into extended oligoarthritis or is really part of enthesitis-related arthritis
- ANA is positive in 60-80% of patients (antigenic specificity is unknown for ANA in JIA)
- Oligoarticular JIA with positive ANA is associated with a higher risk of asymptomatic uveitis (see Section 9)

Polyarthritis (Rheumatoid Factor Negative)

ILAR Classification 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

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

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

Polyarthritis (Rheumatoid Factor Positive)

ILAR Classification 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

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

- All patients are RF positive, many are positive for anti-CCP antibodies, and ANA is positive in 40-50%

- RF positive polyarthritis mostly affects adolescent girls
- Patients with RF positive polyarthritis share many characteristics with adults with rheumatoid arthritis, including 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)
- RF positive polyarthritis is associated with more joint erosion and damage and with worse radiographic outcome
- Remission rates (off medications) are lowest among RF positive patients

Systemic Arthritis

ILAR Classification 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

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

- Typical symptoms of systemic arthritis include:
  - Once or twice daily fever spikes to >38.5°C, which then return to baseline or below
  - Salmon-coloured, evanescent rash accompanying the fever, occasionally pruritic, and lesions may be elicited by scratching the skin (Koebner phenomenon)
  - Lymphadenopathy (common), splenomegaly (10%) and hepatomegaly (less common)
  - Arthritis may develop later (usually within first year of fever) and is usually polyarticular, affecting knees, wrists and ankles, but cervical spine and hip involvement also occurs
- An infectious work-up should be done and bone marrow aspirate to exclude malignancy strongly considered before starting corticosteroid treatment
- Systemic JIA is associated with macrophage activation syndrome, a potentially life threatening inflammatory complication (see Section 13)

Enthesitis Related Arthritis (ERA)

ILAR Classification 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 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

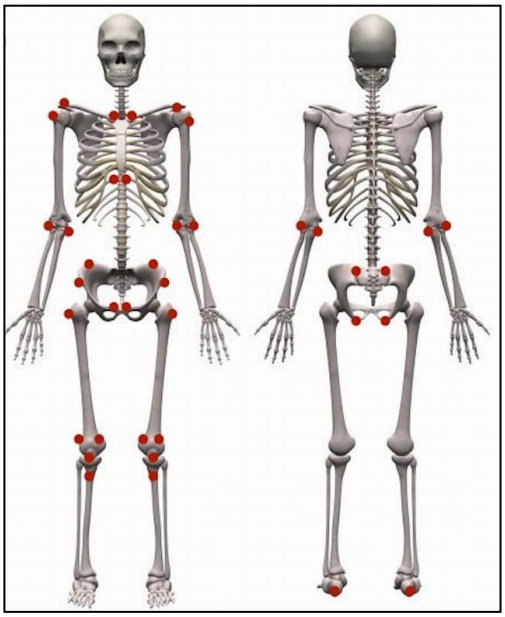
Exclusions:

- 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

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

- Hallmark of ERA is enthesitis (inflammation of the insertion sites of tendons, ligaments and fascia) and asymmetrical oligoarthritis, predominantly affecting the lower extremities

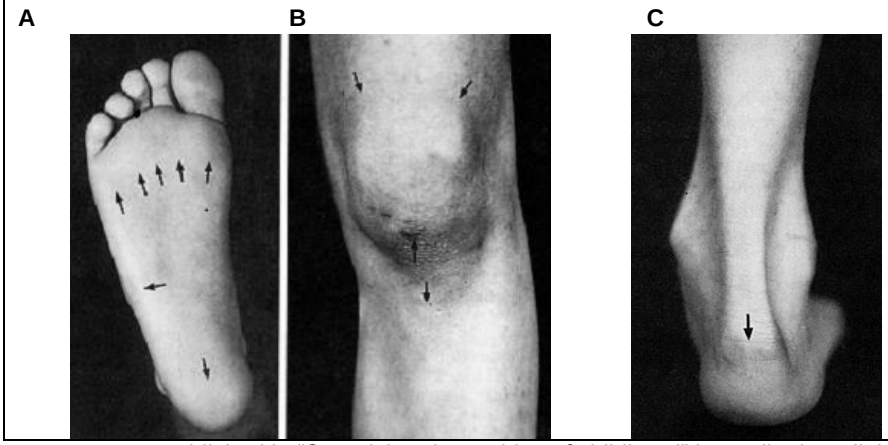
Entheses by anatomic region



Region	*Enthesitis exam*
Chest	Costernal junctions (1st and 7th)
Shoulder	Acromioclavicular junction Supraspinatus insertion into greater tubercle of humerus
Elbow	Common flexor insertion into medial epicondyle of humerus Common extensor insertion into lateral epicondyle of humerus
Pelvis	Abdominal muscle insertions into iliac crest Sartorius insertion into anterior superior iliac spine Posterior superior iliac spine Gracilis and adductor insertion into pubis symphysis Hamstring insertion into ischial tuberosity Hip extensor insertion into greater trochanter of femur
Knee	Quadriceps tendon insertion to patella Infrapatellar ligament insertion to patella and tibial tuberosity
Ankle	Achilles tendon insertion into calcaneus
Foot	Plantar fascia insertion into calcaneus, metatarsal heads and base of 5th metatarsal

Image adapted with permission from: Jariwala M, Burgos-Vargas R, "Juvenile Spondyloarthropathies" in *Pediatric Rheumatology: A Clinical Viewpoint,* 2017, Pages 229-46, Copyright Springer Singapore (2017).

Common sites of enthesitis in the lower body



A. Insertions of plantar fascia

B. Insertions of quadriceps and patellar tendons

C. Insertion of Achilles tendon

Images were published in "Spondyloarthropathies of childhood" in *Pediatrics Clinics of North America,* 1995, Volume 42, Pages 1051-1070, Copyright Elsevier (1995).

- ERA typically occurs in boys, usually over 6 years of age with familial predilection
- 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
- Gastrointestinal symptoms (e.g. chronic abdominal pain, diarrhea, hematochezia) should be carefully evaluated for possible inflammatory bowel disease

Psoriatic Arthritis

ILAR Classification 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

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

- Psoriasis may develop after arthritis and may lead to reclassification of JIA type as psoriatic
- Typically asymmetric, and involves both large and small joints

- Clinical hallmark is dactylitis, which is caused by simultaneous inflammation of the flexor tendon and synovium, leading to the typical "sausage digit" appearance

Undifferentiated Arthritis

ILAR Classification Criteria for Undifferentiated Arthritis *
Definition: Arthritis that fulfils criteria in no category or in 2 or more of above categories

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

References:

1. Crayne CB, Beukelman T. Juvenile idiopathic arthritis: Oligoarthritis and polyarthritis. *Ped Clin North Am* 2018; 65(4):657-74.
2. Weiss PF, Colbert RA. Juvenile spondyloarthritis: A distinct form of juvenile arthritis. *Ped Clin North Am* 2018; 65(4):675-90.
3. Lee JJY, Schneider R. Systemic juvenile idiopathic arthritis. *Ped Clin North Am* 2018; 65(4):691-709.
4. Petty RE, et al. ILAR classification of juvenile idiopathic arthritis: Second revision, Edmonton 2001. *J Rheumatol* 2004; 31(2):390-2.
5. Martini A, et al. Toward new classification critieria for juvenile idiopathic arthritis: First steps, Pediatric Rheumatology International Trials Organization International Consensus. *J Rheumatol* 2019; 46(2):190-7.

3B. Approach to Management of JIA

- **Goals of therapy**
    1. Eliminate inflammation with goal to achieve clinical remission
    2. Prevent joint damage
    3. Promote normal growth and development
    4. Maintain normal function and optimize quality of life
    5. Minimize medication toxicity

- Timing of assessments:
    - Children with suspected JIA should be reviewed by a pediatric rheumatologist in 4-6 weeks and those with possible systemic JIA within 7 days
    - Follow-up is recommended at intervals of 3-4 months in patients with controlled disease and more often in those with uncontrolled disease

- Disease monitoring:
    - Assessments of disease activity by a pediatric rheumatologist and multidisciplinary team are essential for disease monitoring
    - Laboratory monitoring is often an essential part of management, especially during disease flares and medication changes (escalation and weaning)
    - Surveillance joint X-rays should not be ordered routinely to monitor disease activity, but may be used as needed to assess for joint damage *(*highlighted in *Choosing Wisely: Pediatric Rheumatology Top 5 by American College of Rheumatology)*

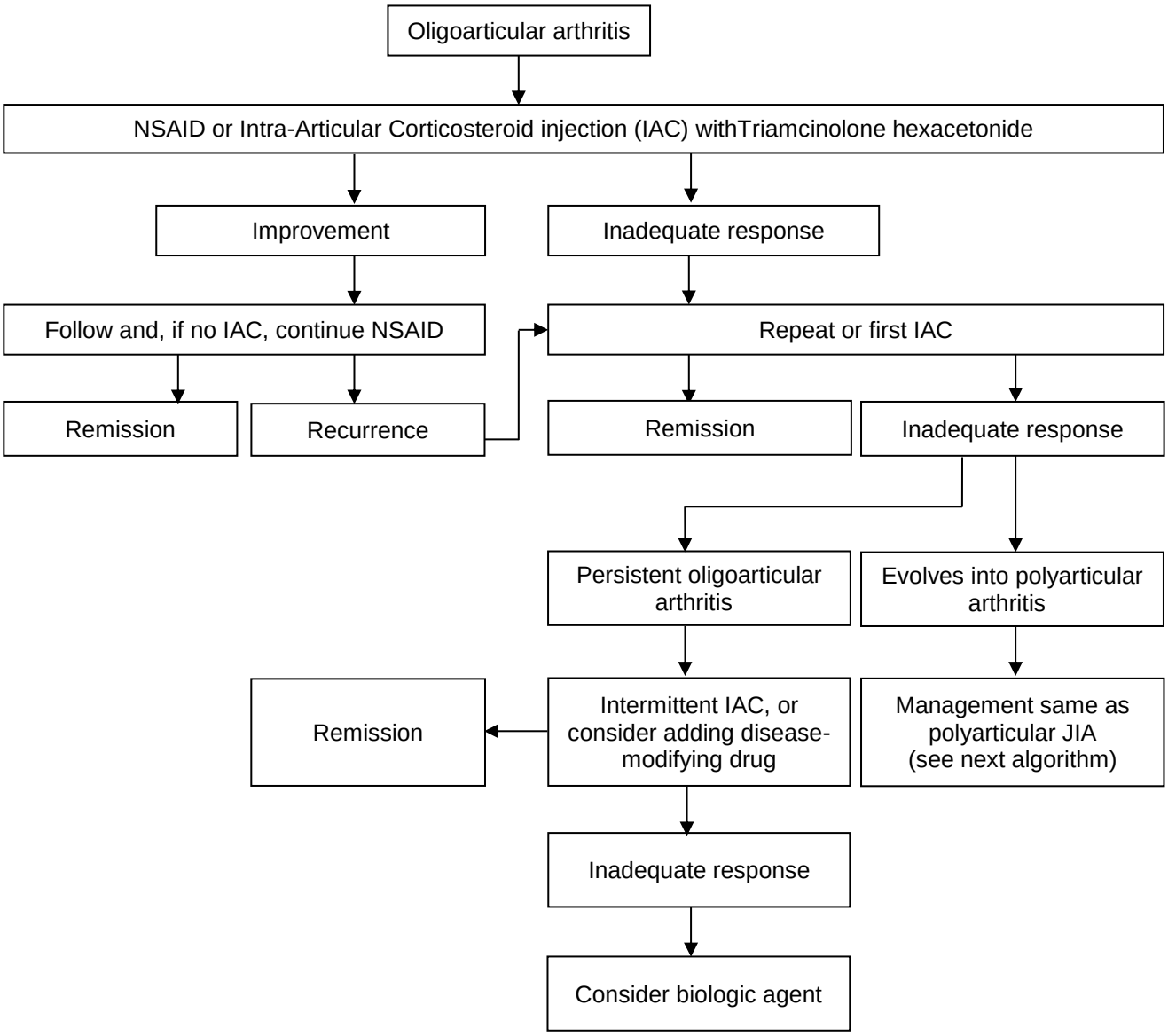
  - Ultrasound and/or MRI could be considered to detect early or subclinical disease activity or damage and MRI is usually indicated for monitoring of temporomandibular, sacroiliac, hip, and subtalar joints
  - Careful monitoring by an eye care provider is essential to assess for chronic anterior uveitis, especially in patients with oligoarthritis and positive ANA
  - Screening for asymptomatic uveitis should take place within 4 weeks of diagnosis

- Multidisciplinary approach:
  - Multidisciplinary team is part of comprehensive JIA management
  - Occupational and physical therapists play an important role in treating JIA
  - Psychosocial aspects of disease must be recognized and addressed

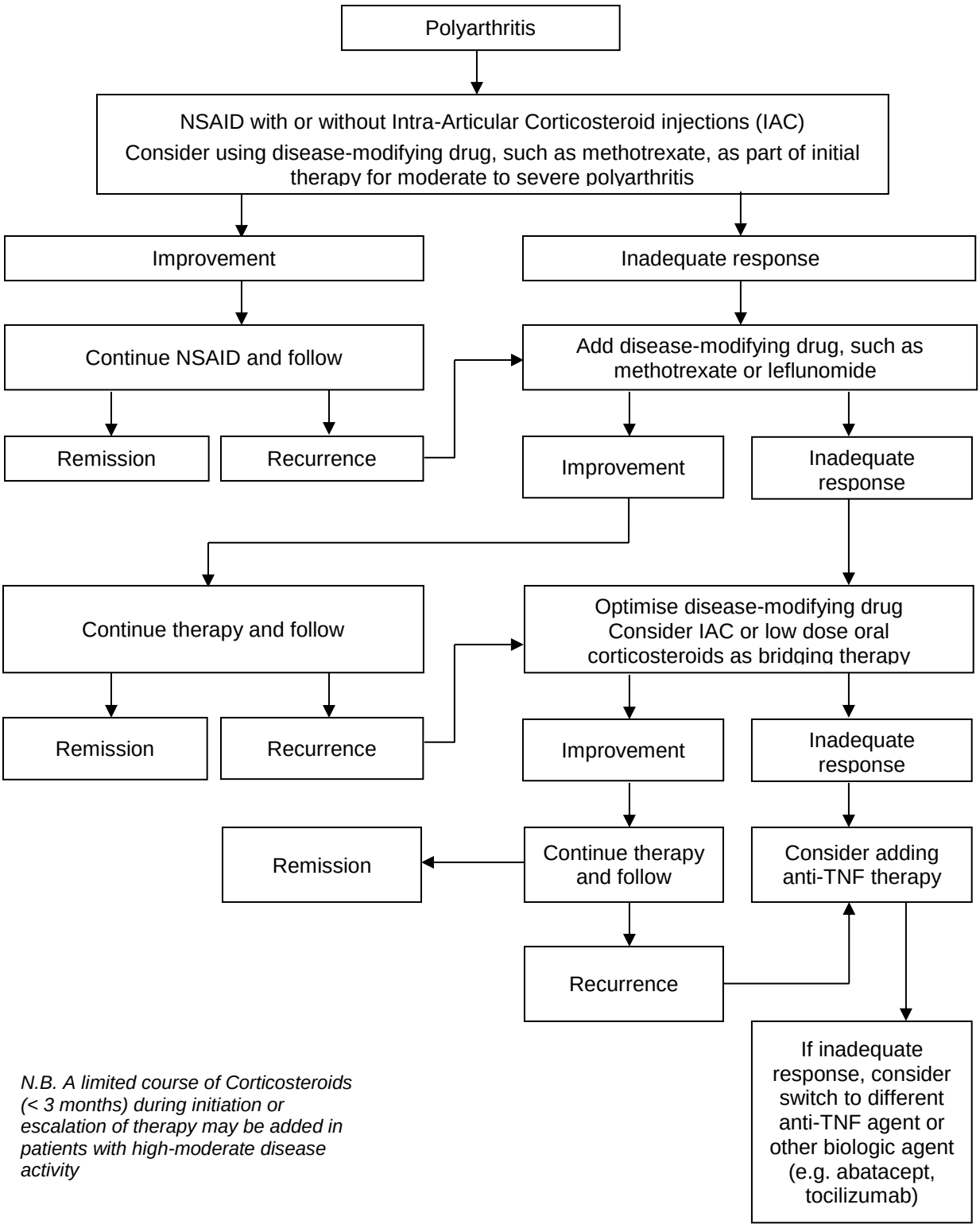
- Treat-to-Target Strategy for JIA:
  - Target of treatment is complete remission, which means absence of signs and symptoms of inflammatory disease activity, including extra-articular manifestations (e.g. uveitis)
  - Minimal or low disease activity may be an alternative target, particularly in patients with longstanding or difficult-to-treat disease
  - Setting the target and therapeutic decisions should be based on individual patient characteristics and agreed on with the patient/parents
  - Rapid escalation and changes in therapy may be required until target is achieved
  - In all patients, at least a 50% improvement in disease activity should be reached within 3 months and the target within 6 months; however, patients with systemic JIA should be fever-free within 1 week

- Medications:
  - Initial therapy with an NSAID may be started by a patient's primary care physician; however, further therapy should be directed by a pediatric rheumatologist
  - Intra-articular corticosteroids and methotrexate remain key medications for JIA
  - Potential algorithms for treatment of oligoarthritis, polyarthritis and systemic JIA are included in the following pages

An Algorithm for Treatment of Oligoarthritis

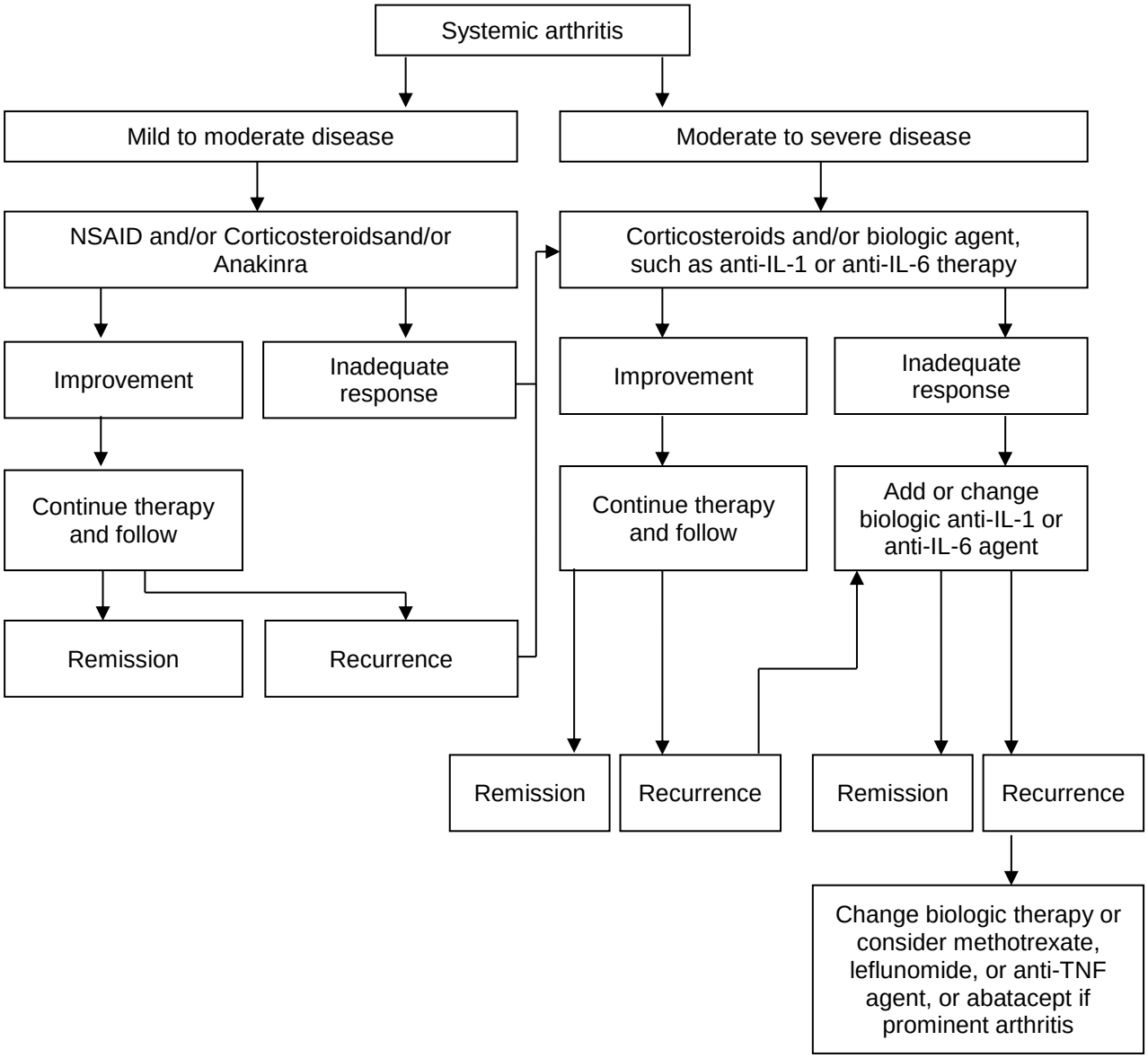


An Algorithm for Treatment of Polyarthritis



N.B. A limited course of Corticosteroids (< 3 months) during initiation or escalation of therapy may be added in patients with high-moderate disease activity

An Algorithm for Treatment of Systemic JIA



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1. Giancane G, et al. Recent therapeutic advances in juvenile idiopathic arthritis. *Best Pract Res Clin Rheumatol* 2017; 31(4):476-87.
2. Ravelli A, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2018; 77(6): 819-28.
3. Beukelman T, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis... *Arthritis Care Res* 2011; 63(4):465-82.
4. Ringold S, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline fot the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroilitis, and Enthesitis. *Arthritis Care Res* 2019; 71(6):717-34.
5. Cellucci T, et al. Management of Juvenile Idiopathic Arthritis 2015: A Position Statement from the Pediatric Committee of the Canadian Rheumatology Association. *J Rheumatol* 2016; 43(10):1773-6.

SECTION 4. SYSTEMIC LUPUS ERYTHEMATOSUS & RELATED CONDITIONS

4A. Systemic Lupus Erythematosus (SLE)

- Multi-system inflammatory disease characterized by autoantibody and immune-complex mediated inflammation of blood vessels and connective tissues
- Pediatric-onset SLE accounts for 10-20% of all cases of SLE
- Female predominance, especially in adolescence and adulthood
- Ethnic predilection in Blacks, Hispanics, and Asians
- Positive family history of SLE in 10%

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

Patients are classified as having SLE if they have ≥ 4/11 of following criteria:

- Malar rash (butterfly rash sparing nasolabial folds)
- Discoid lupus rash **
- Photosensitivity
- Oral or nasal mucocutaneous ulcerations (typically painless)
- Non-erosive arthritis involving two or more peripheral joints
- Nephritis (characterized by proteinuria and/or cellular casts)
- CNS involvement (characterized by seizures and/or psychosis)
- Serositis (pleuritis or pericarditis)
- Cytopenia (thrombocytopenia, lymphopenia, leukopenia, hemolytic anemia with reticulocytosis)
- Positive ANA
- Positive immunoserology (anti-dsDNA, anti-Sm (anti-Smith), antiphospholipid antibodies)

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

*** Uncommon in children*

- 1997 ACR classification criteria are not diagnostic criteria and were designed to identify a homogeneous population of SLE patients for research studies; however, the presence of ≥ 4 criteria is specific for SLE (>93%) and so the criteria have been widely used for diagnosis
- In 2012, newer Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE were developed that incorporated more immunologic criteria and were more sensitive (>95%) but less specific (83%) than the 1997 ACR criteria
- New EULAR/ACR classification criteria for SLE have been developed in 2019 and may be adopted in the future since they are both sensitive (>95%) and specific (>93%) for SLE

2019 Proposed European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) Classification Criteria for SLE *

Clinical domains	*Points***
Constitutional domain	
• Fever	2
Cutaneous domain	
• Non-scarring alopecia	2
• Oral ulcers	2
• Subacute cutaneous or discoid lupus	4
• Acute cutaneous lupus	6
Arthritis domain	
• Synovitis or tenderness in at least 2 joints	6
Neurologic domain	
• Delirium	2
• Psychosis	3
• Seizure	5
Serositis domain	
• Pleural or pericardial effusion	5
• Acute pericarditis	6
Hematologic domain	
• Leukopenia	3
• Thrombocytopenia	4
• Autoimmune hemolysis	4
Renal domain	
• Proteinuria >0.5 g/24 hours	4
• Class II or V lupus nephritis	8
• Class III or IV lupus nephritis	10

Immunological domains	*Points***
Antiphospholipid antibody domain	
• Anti-cardiolipin IgG >40 GPL Or anti-β_2-glycoprotein I IgG >40 units Or lupus anticoagulant	2
Complement proteins domain	
• Low C3 or low C4	3
• Low C3 and low C4	4
Highly specific antibodies domain	
• Anti-dsDNA antibody	6
• Anti-Sm (Anti-Smith) antibody	6

** In order to be classified as having SLE, patients must have all of the following: (a) ANA ≥1:80 (entry criterion); (b) ≥10 points in total; and (c) at least one clinical criterion*

N.B. Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice

*** Only the highest criterion in a given domain is counted toward total number of points*

- Other clinical features of SLE not included in any of the above classification criteria:
  - Additional constitutional symptoms (i.e. fatigue, weight loss, anorexia)
  - Other rashes (e.g. annular erythema, maculopapular or linear (nonspecific) rash, bullous lupus (rare), palmar/plantar/periungual erythema, livedo reticularis, or vasculitic rash)
  - Myalgia, and/ or myositis
  - Raynaud phenomenon (see Section 7E)
  - Lymphadenopathy
  - Hepatomegaly, splenomegaly
  - Decreased concentration and cognitive dysfunction, stroke, mood disorder, headache
  - Pneumonitis, pulmonary hemorrhage
  - Myocarditis, Libman-Sacks endocarditis
- Other common laboratory features of SLE:
  - Elevated ESR with normal CRP (except high CRP in infection and/or serositis)
  - Elevated IgG levels
  - Other autoantibodies: anti-Ro, anti-La, anti-RNP, Rheumatoid factor
- May be accompanied by macrophage activation syndrome (MAS) at onset or anytime during course

- Treatment
  - Use minimum required treatment to maintain clinical and laboratory quiescence
  - More aggressive treatment used for more severe organ involvement
  - Hydroxychloroquine (Plaquenil™)
    - Considered standard therapy for SLE
    - Proven efficacy in decreasing frequency and severity of disease flares
    - Improves serum lipid profile
    - May be helpful in lowering antiphospholipid antibody titres and preventing thrombotic recurrences in patients with SLE
  - Corticosteroids
    - Often used in initial therapy for SLE with dose depending on severity and organ involvement
    - Pulse (very high dose) therapy is used for severe lupus nephritis, hematologic crisis, CNS disease or other life or organ-threatening manifestations
  - 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 and in other specific scenarios, such as when a patient is unresponse to other therapies
  - Belimumab
    - Adjunctive therapy for mild/moderate SLE (trials excluded those with severe CNS and renal involvement)

- 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, osteoporosis, avascular necrosis
    - Malignancy
    - Infection

- 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 (~70% vs. 30-60% in adults)
  - Children receive more intensive drug therapy and sustain more long-term damage

References:

1. Harry O, et al. Childhood-onset systemic lupus erythematosus: a review and update. *J Pediatr* 2018; 196:22-30.
2. Tarvin SE, O'Neil KM. Systemic lupus erythematosus, Sjögren syndrome, and mixed connective tissue disease in children and adolescents. *Ped Clin North Am* 2018; 65(4):711-37.
3. Weiss JE. Pediatric systemic lupus erythematosus: More than a positive antinuclear antibody. *Pediatr Rev* 2012; 33(2):62-73.
4. Tedeschi SK, et al. Multicriteria decision analysis process to develop new classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* 2019; 78(5):634-40.

4B. 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 another autoimmune disease; however, many mothers are healthy with no known autoimmune disease

- Incidence of NLE is 1-2% in children of 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 atrioventricular (AV) 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 and risk of endocardial fibroelastosis
  - 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 commonly develops in first 6 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 are less common
        - Usually resolve without sequelae and rarely require treatment
        - Neutropenia is not typically associated with increased risk of infection
    - Hepatic
        - Asymptomatic cholestatic hepatitis with mildly to moderately elevated liver enzymes
        - Hepatomegaly and less commonly splenomegaly
        - May be the only manifestation(s) of NLE
        - Typically resolves before 6 months without treatment
    - Neurologic
        - Reported CNS manifestations include macrocephaly, hydrocephalus, spastic paraparesis, asymptomatic neuroimaging abnormalities, and vasculopathy
        - Clinical significance still unclear
        - Important to monitor head circumference

- Treatment
    - If fetal bradycardia found during pregnancy, require fetal echocardiography to assess for heart block and endocardial fibroelastosis (EFE) and may require treatment with Dexamethasone/Betamethasone ± sympathomimetics
    - Pacemaker may be required soon after birth for neonates with complete heart block
    - Classic NLE rash does not require treatment (although sun avoidance and sunscreen are recommended) since rash will completely resolve; Corticosteroids may hasten healing, but may increase risk of telengiectasias
    - Severe cytopenias may require treatment with IVIG
    - Future pregnancies require expectant management with fetal heart rate monitoring and mothers with autoantibodies may be treated with Hydroxychloroquine (Plaquenil)

References:

1. Vanoni F, et al. Neonatal systemic lupus erythematosus syndrome: a comprehensive review. *Clin Rev Allergy Immunol* 2017; 53(3):469-76.
2. Johnson B. Overview of neonatal lupus. *J Pediatr Health Care* 2014; 28(4):331-41.

4C. Drug-Induced Lupus

- Development of lupus-like symptoms that is temporally related to continuous drug exposure (>1 month) and that resolves with cessation of the offending drug
- Usually accompanied by serologic findings of positive ANA as well as anti-histone antibodies (in approximately 90% of patients)
- Variable time from drug exposure to onset of symptoms
- Onset generally insidious
- Patients commonly present with fever, arthralgias or arthritis, myalgias and serositis
- Usually mild, although life threatening disease has been reported
- Rarely involve classic malar or discoid rash, oral ulcers or major organ involvement

- Laboratory findings may include mild cytopenias, high ESR
- Drugs that have been implicated in drug-induced lupus include: Minocycline, anticonvulsants, Hydralazine, and biologic agents that target tumor necrosis factor (TNF)

- Treatment
  - Stop the offending drug
  - Corticosteroids and/or Hydroxychloroquine (Plaquenil™) may be used for moderate to severe manifestations (e.g. cardiac tamponade)

References:

1. Vaglio A, et al. Drug-induced lupus: Traditional and new concepts. *Autoimmun Rev* 2018; 17(9):912-8.

4D. Antiphospholipid Syndrome (APS)

- Systemic autoimmune disorder characterized by recurrent arterial and/or venous thrombosis and elevated levels of one or more antiphospholipid antibodies
- Primary APS if occurs without apparent 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%, and mixed thrombosis in ~2%
- Thrombotic manifestations are most common, followed by hematologic, skin and non-thrombotic neurologic manifestations

Adaptation of the Updated Sapporo Classification Criteria for Pediatric APS Patients *

Definite APS is considered to be present if the clinical criterion and at least 1 of the laboratory criteria are met

Clinical criterion:

- Vascular thrombosis: ≥1 clinical episode(s) of arterial, venous, or small vessel thrombosis in any tissue or organ confirmed objectively by validated criteria

Laboratory criteria:

- Lupus anticoagulant on ≥ 2 occasions at least 12 weeks apart
- Anticardiolipin antibody (IgG and/or IgM isotype) in medium or high titre (>40 GPL or MPL, or >99th percentile) on ≥ 2 occasions at least 12 weeks apart
- Antibodies to β_2-glycoprotein I (IgG and/or IgM isotype) in medium or high titre (>99th percentile) on ≥ 2 occasions at least 12 weeks apart

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

- Higher risk of thrombosis associated with higher antibody titres, IgG isotype and specific antibodies (e.g. anti-cardiolipin and lupus anticoagulant)
- Deep venous thrombosis is the most common type of venous thrombosis, while stroke is the most common type of arterial thrombosis (see Section 2: Differential Diagnosis of stroke-like presentations in children)

- Additional clinical features of APS:
  - Livedo reticularis, Raynaud phenomenon, and skin ulcers
  - Cardiac valve disease (Libman-Sachs endocarditis)
  - Chorea
  - Seizures
  - Transient cerebral ischemia
  - Transverse myelopathy
- Additional laboratory features of APS:
  - Thrombocytopenia
  - Hemolytic anemia
  - Additional antibodies to prothrombin, annexin, and/or other phospholipids
  - False positive VDRL

- Treatment
  - If primary, treat as a disorder of coagulation
  - If secondary (most commonly due to SLE), treat underlying disorder (often using Corticosteroids and/or Hydroxychloroquine)
  - Anticoagulation using heparin (e.g. low molecular weight heparin (LMWH)) is usually required at least initially, but patients could require LMWH or warfarin therapy lifelong
  - Consider anti-platelet agents (e.g. ASA)
  - May consider Rituximab as direct therapy to target pathogenic autoantibodies in APS

References:

1. Rumsey DG, et al. Diagnosis and treatment of antiphospholipid syndrome in childhood: A review. *Blood Cells Mol Dis* 2017; 67:34-40.
2. Aguiar C, et al. Pediatric antiphospholipid syndrome. *Curr Rheumatol Rep* 2015; 17(4):27.
3. Avcin T, et al. Pediatric antiphospholipid syndrome: Clinical and immunologic features of 121 patients in an international registry. *Pediatrics* 2008; 122(5):e1100-7.

SECTION 5 – SYSTEMIC VASCULITIS

5A. 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)
  - Multiple organ system involvement – see table below:

Organ System	Clinical features that suggest possible systemic vasculitis
Head and Neck	Chronic sinusitis Epistaxis Chronic otitis Hearing loss Chondritis
Ophthalmologic	Episcleritis Iritis Panuveitis Retinitis
Central nervous system	Headaches Seizures Strokes
Cardiac	Pericarditis Myocarditis Myocardial infarction
Pulmonary	Hemorrhage Nodules Cavities Infiltrates
Renal	Nephritis Nephrotic syndrome Hypertension Rapidly progressive renal failure
Gastrointestinal	Ischemic abdominal pain
Dermatologic	Palpable purpura Nodules Livedo reticularis Ulcers
Vascular	Chronic vascular insufficiency Vascular bruits Claudication
Peripheral nervous system	Mononeuritis
Musculoskeletal	Arthritis, arthralgia Myalgia, calf pain

Classification of vasculitis based on size of vessel (predominantly) involved	
Large vessel vasculitis	Takayasu arteritis Giant cell arteritis (older adults)
Medium vessel vasculitis	Kawasaki disease Polyarteritis nodosa (systemic, cutaneous)
Small vessel vasculitis	Immune complex vasculitis • IgA vasculitis (Henoch-Schönlein purpura) • Cryoglobulinemia • Hypocomplementemic urticarial vasculitis ANCA-associated vasculitis • Microscopic polyangiitis • Granulomatosis with polyangiitis (previously Wegener granulomatosis) • Eosinophilic granulomatosis with polyangiitis (previously Churg-Strauss Syndrome)
Variable vessel vasculitis	Behçet disease Cogan syndrome
Other vasculitis	Primary CNS vasculitis (see Section 10) Primary cutaneous vasculitis Vasculitis secondary to drugs, infection (e.g. hepatitis B virus, Parvovirus), or malignancy Monogenic disease causing vasculitis (e.g. Deficiency of Adenosine Deaminase 2)

- Investigations
  - Look for end-organ damage (eyes, skin, heart, lungs, kidneys, nervous system)
  - Look for triggers or underlying disease (drugs, malignancy, infection, CTD)
  - Inflammatory markers (CRP, ESR)
  - Immune serology (ANA, ANCA)
  - Tissue biopsy (histopathology & immunofluorescence)
  - Angiography (conventional; magnetic resonance; computed tomography); vessel wall itself may be assessed using magnetic resonance or computed tomography

- Treatment
  - Depends on specific disease, organ involvement, severity
  - Immunosuppressive agents plus supportive therapy

- Potential complications
  - Acute: organ failure (renal, pulmonary, cardiac), hemorrhage (pulmonary, GI), thrombus (renal, pulmonary, coronary, cerebral, GI vessels), infection (often treatment-related)
  - Chronic: hypertension, renal failure, pulmonary insufficiency, hearing loss, saddle nose deformity, subglottic stenosis, hemiplegia, neuropathy

References:

1. Barut K, et al. Pediatric Vasculitis. *Curr Opin Rheumatol* 2016; 28:29-38.

2. Jennette JC, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65(1):1-11.
3. Weiss P. Pediatric Vasculitis. *Pediatr Clin North Am* 2012; 59(2):407-23.

5B. 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 ≥ 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 or thrills over the aorta and/or its major branches
- Hypertension (>95th percentile for height)
- Acute phase reactants (ESR >20 or increased CRP)

* *Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

- 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
- Evolution to chronic, fibrotic phase with signs and symptoms of chronic vascular insufficiency (pulse deficit, claudication, BP discrepancy, bruits)

- Investigations
  - Magnetic resonance angiography useful to show extension of disease and vessel wall inflammation; often used to follow disease (less invasive than conventional angiography)
  - 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
    - Second line agents include Methotrexate, Mycophenolate mofetil, Infliximab or Adalimumab
    - May also use Tocilizumab, Cyclophosphamide, or Rituximab if refractory disease
  - If "inactive" disease:
    - Manage end-organ manifestations (medical therapy +/- vascular surgery)

References:

1. Ozen S, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener's granulomatosis and childhood Takayasu arteritis: Ankara 2008. *Ann Rheum Dis* 2010; 69(5):798-806.

2. Brunner J, et al. Takayasu arteritis in children and adolescents. *Rheumatology* 2010; 49:1806-14.
3. de Ranieri D. Great vessels of children: Takayasu's arteritis. *Pediatr Ann* 2015; 44(6):e148-52.

5C. Kawasaki disease (KD)

Diagnostic Criteria for Kawasaki disease *

Fever persisting for ≥5 days

Plus ≥4/5 of the following:

- Changes in peripheral extremities (edema/erythema) or perineal area (erythema/peeling)
- 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 diagnosed 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 diagnosed if KD with an unusual manifestation (e.g. renal failure)

- Medium vessel vasculitis, with predilection for coronary arteries
- Most common between 1 and 5 years of age
- Most common cause of acquired heart disease in children in developed countries
- May be triggered by infectious agent (viral and/or bacterial super-antigen implicated)
- Polygenic with genes identified that influence risk of KD and coronary artery involvement

- Clinical features
  - Common: irritability (aseptic meningitis), arthritis (at onset or delayed), sterile pyuria (urethritis), gastroenteritis (abdominal pain, vomiting, diarrhea), uveitis, periungual desquamantion in weeks 2 or 3 (subacute phase)
  - Uncommon: gallbladder hydrops, GI ischemia, jaundice
  - Cardiac involvement: myocarditis, pericarditis, cardiac failure, valvular regurgitation

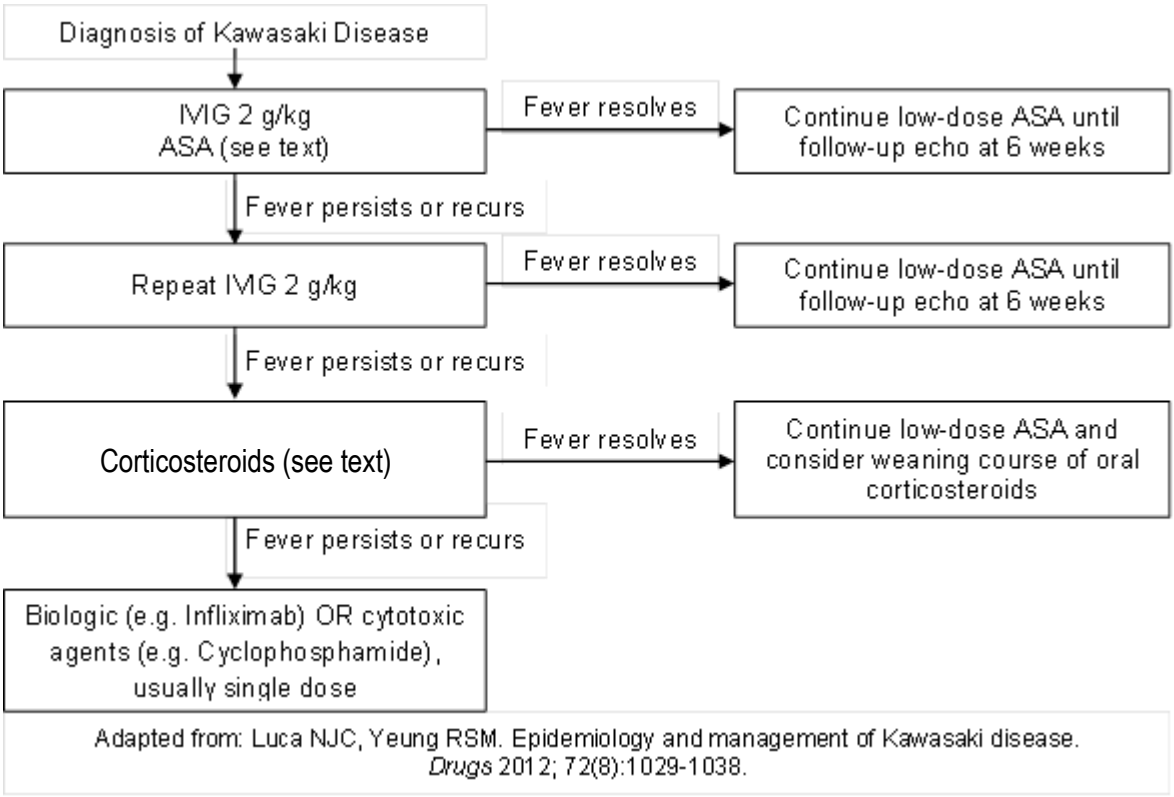
- Complications
  - Coronary artery disease
    - Major concern is the development of coronary artery aneurysms, which most commonly occurs at 4-6 weeks after the acute illness
    - Risk factors: males, infants <1 year or >9 years of age, prolonged fever, Asian or Hispanic ethnicity, thrombocytopenia, hyponatremia
  - KD shock syndrome (characterized by hypotension or poor perfusion)
  - Macrophage activation syndrome (MAS)
  - Dissemeniated intravascular coagulation

- Investigations
  - Leukocytosis with left shift, normocytic anemia, elevated ESR/CRP, hypoalbuminemia, hyponatremia, may have elevated transaminases
  - Thrombocytosis in second week of illness with return to normal by 4-8 weeks
  - Echoardiogram required at the time of diagnosis and 6 weeks later

- Treatment
  - See treatment algorithm on next page
  - Target treatment within 10 days of fever onset
  - IVIG
    - Unequivocally reduces the occurrence of coronary artery aneurysms
    - Recommended dose 2 g/kg
    - *If still febrile 24-36 hours after IVIG* → second dose of IVIG
    - Consider monitoring for IVIG-related hemolysis with CBC, blood film, reticulocytes and direct antiglobulin test initially at 24-92 hours and then at 5-7 days after IVIG
  - ASA
    - Historically, started with high-dose ASA 80-100 mg/kg/day (anti-inflammatory) until afebrile x 24 hours, then switched to low-dose 3-5 mg/kg/day (anti-platelet)
    - Many centres now start with low-dose ASA 3-5 mg/kg/day
    - Low-dose ASA (and/or other antiplatelet agents) may be continued longer than 6 weeks in patients with coronary artery aneurysms
  - Corticosteroids
    - May be used with first dose of IVIG in patients at high risk of coronary artery disease (see risk factors above) or may be reserved for patients with refractory fever after two doses of IVIG
    - Additional indications: myocarditis, MAS, Kawasaki shock-syndrome
    - Common treatment regimens include IV Methylprednisolone for 1-3 days or Prednisone PO 2 mg/kg/day for 3 days or for a longer course with slow wean in high-risk patients
  - *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, ventricular dysfunction/arrhythmia, early atherosclerosis, myocardial infarction (highest if ≥8 mm)

An algorithm for treatment of Kawasaki disease



Adapted from: Luca NJC, Yeung RSM. Epidemiology and management of Kawasaki disease. *Drugs* 2012; 72(8):1029-1038.

References:

1. McCrindle BW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. *Circulation* 2017; 135:e927-99.
2. Yellen ES, et al. Performance of 2004 American Heart Association recommendations for treatment of Kawasaki disease. *Pediatrics* 2010; 125(2): e234-e241.
3. Scuccimarri R. Kawasaki disease. *Ped Clin North Am* 2012; 59(2):425-445.

5D. Polyarteritis nodosa (PAN)

- Necrotizing vasculitis in medium or small size muscular arteries
- Very rare in childhood

2008 EULAR/PRINTO/PRES Classification Criteria for Childhood PAN *

Systemic illness characterized by:

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

Plus ≥1/5 of the following:

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

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

Systemic PAN

- Additional clinical features
  - Constitutional symptoms, including prolonged fever
  - Testicular pain or tenderness
  - Stroke or coronary artery disease
  - Bruits
  - Ischemic abdominal pain

- Laboratory features
  - Leukocytosis, thrombocytosis, and elevation of ESR and CRP
  - Positive hepatitis B serology can occur although it is unusual

- Treatment
  - Prednisone plus second line agent (e.g. Methotrexate, Cyclophosphamide, Azathioprine, Mycophenolate mofetil)
  - Plasma exchange may be considered in acute life-threatening disease

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

- Investigations
  - Diagnosis requires deep skin biopsy to get small muscular arteries 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 or another second line agent (e.g. IVIG, Methotrexate)
  - Penicillin treatment (if proven associated *Streptococcal* infection) and prophylaxis

Deficiency of Adenosine Deaminase 2 (DADA2)

- Consider in differential diagnosis of polyarteritis nodosa
- Recently identified monogenic autoimmune recessive disease (mutations in *ADA2* gene) leading to vasculitis
- Clinical features are variable, depending on mutation type and number of affected alleles
- Common features:
  - Recurrent lacunar stroke (ischemic or hemorrhagic) with onset at young age
  - Fever
  - Vasculitis, including polyarteritis nodosa
  - Livedo reticularis
  - Hepatosplenomegaly
  - Various ophthalmologic manifestations

- Investigations
  - Elevated inflammatory markers
  - Diagnosis confirmed through genetic testing
  - MRI brain to assess for stroke

- Treatment
  - TNF-inhibitors have been successful in suppressing fever, vasculopathy and strokes
  - Hematopoetic stem cell transplantation may offer definitive treatment
  - Future therapies may include recombinant ADA2 protein or gene therapy

References:

1. Ozen S, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener's granulomatosis and childhood Takayasu arteritis: Ankara 2008. *Ann Rheum Dis* 2010; 69(5):798-806.
2. Beckum KM, et al. Polyarteritis nodosa in childhood: recognition of early dermatologic signs may prevent morbidity. *Pediatr Dermatol* 2014; 31(1):e6-9.
3. Falcini F, et al. Clinical overview and outcome in a cohort of children with polyarteritis nodosa. *Clin Exp Rheumatol* 2014; 32(3 Suppl 82):S134-7.
4. Ombrello AK, et al. Treatment strategies for deficiency of adenosine deaminase 2. *N Engl J Med.* 2019; 380(16):1582-84.

5E. IgA Vasculitis (also known as Henoch-Schönlein Purpura, or HSP)

- 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

2008 EULAR/PRINTO/PRES Classification Criteria for Childhood HSP *

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

Plus ≥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)

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

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

- 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%
    - Renal abnormalities may not manifest initially, thus must regularly monitor blood pressure and urinalysis x 6 mos after acute illness
  - Orchitis (10-20% of males) associated with pain and swelling

- Investigations
  - No distinctive or diagnostic laboratory abnormalities
  - May have elevated WBC, platelets, ESR and/or CRP
  - Coagulation profile must be normal and thrombocytopenia should be absent
  - Serum IgA increased in 50% of patients
  - Biopsy of skin or kidneys may be needed (see classification criteria above)

- Treatment
  - Largely supportive
  - NSAIDs may be used for joint pain (caution required due to potential renal involvement)
  - Prednisone in select patients
    - May decrease severity and duration of GI symptoms and may help bullous lesions
    - Unclear impact on risk of persistent renal disease (controversial)
    - No definite benefit for prevention of HSP recurrence

  - If severe nephritis (e.g. nephrotic syndrome, decreased renal function, crescentic nephritis): pulse IV Methylprednisolone ± second line agent (e.g. Azathioprine, Mycophenolate mofetil, Cyclophosphamide)

- 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. Gonzalez-Gay MA, et al. IgA vasculitis: Genetics and clinical and therapeutic management. *Curr Rheumatol Rep* 2018; 20(5):24.
2. Ozen S, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener's granulomatosis and childhood Takayasu arteritis: Ankara 2008. *Ann Rheum Dis* 2010; 69(5):798-806.
3. Hahn D, et al. Interventions for preventing and treating kidney disease in Henoch-Schönlein Pupura (HSP). *Cochrane Database of Systematic Reviews* 2015; 8:CD005128.
4. Weiss PK, et al. Corticosteroids may improve clinical outcomes during hospitalization for Henoch-Schönlein purpura. *Pediatrics* 2010; 126(4):674-81.

5F. Granulomatosis with Polyangiitis (GPA, formerly Wegener Granulomatosis)

- Predominantly small vessel vasculitis, characterized by granulomatous inflammation
- Generally occurs in the second decade of life, with a female preponderance
- Hallmark of GPA is triad of upper and lower respiratory tract inflammation and renal disease

2008 EULAR/PRINTO/PRES Classification Criteria for Childhood GPA *

At least 3 of the 6 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)

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

- Clinical features (in order of decreasing frequency)
  - Constitutional: fatigue, malaise, fever, weight loss
  - Pulmonary: dyspnea, chronic cough, hemoptysis/alveolar hemorrhage, lung nodules/cavitations/fixed infiltrates
  - Ear, nose and throat: nasal involvement (epistaxis, ulcers), sinusitis, otitis/mastoiditis, hearing loss, subglottic involvement
  - Renal: abnormal urinalysis, biopsy-proven glomerulonephritis, elevated creatinine, acute renal failure
  - Musculoskeletal: arthralgia/myalgia, arthritis
  - Gastrointestinal: nonspecific abdominal pain, chronic nausea
  - Eye: nonspecific red eye, conjunctivitis, scleritis
  - Cutaneous: palpable purpura/petechiae
  - Neurological: severe headache, dizziness

- Investigations
  - ANCA positive in ~90% of patients (~80% are c-ANCA positive with anti-PR3 positivity)

- Treatment
  - Initial therapy involves combination of Corticosteroids and a second-line agent, such as Cyclophosphamide, Rituximab or Methotrexate (choice depends on disease severity)
  - Plasma exchange may be used as part of induction therapy for children with life-threatening disease
  - Maintenance therapy with Methotrexate, Azathioprine, Rituximab, plus tapering doses of Corticosteroids
  - May consider endoscopic intervention for subglottic stenosis and endobronchial disease

- Prognosis
  - Significant morbidity associated with disease and medications
  - Rare complications include mechanical ventilation and dialysis in around 10% of patients

References:

1. Jariwala MP, Laxer RM. Primary vasculitis in childhood: GPA and MPA in childhood. *Front Pediatr* 2018; 16(6):226.
2. Ozen S, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener's granulomatosis and childhood Takayasu arteritis: Ankara 2008. *Ann Rheum Dis* 2010; 69(5):798-806.
3. Villa-Forte A. EULAR /European vasculitis study group recommendations for the management of vasculitis. *Curr Opin Rheumatol* 2010; 22:49-53.
4. McGeoch L, et al. CanVasc recommendations for the management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides. *Can J Kidney Health Dis* 2015; 2(43):1-6.

5G. Microscopic Polyangiitis (MPA)

- Pauci-immune, necrotizing, non-granulomatous small vessel vasculitis
- Rare in childhood
- No classification criteria have been developed

- Clinical features
  - Rapidly progressive, necrotizing, crescentic glomerulonephritis (90% of patients)
  - Pulmonary capillaritis leading to hemorrhage (30-60%)
  - Pulmonary-renal syndrome (30-50%)
  - Hypertension (50-60%)
  - Palpable purpura (common)
  - May have refractory anemia

- Diagnosis
  - Serology: 50-75% p-ANCA positive with anti-MPO on ELISA
  - Renal biopsy with immunofluorescence: pauci-immune glomerulonephritis

- Treatment
  - Induction: Corticosteroids + Cyclophosphamide, Methotrexate or Rituximab
  - Maintenance: Azathioprine, Methotrexate, or Rituximab

References:

1. Jariwala MP, Laxer RM. Primary vasculitis in childhood: GPA and MPA in childhood. *Front Pediatr* 2018; 16(6):226.
2. Cabral D, et al. Comparing presenting clinical features in 48 children with microscopic polyangiitis to 183 children who have granulomatosis with polyangiitis (Wegener's): An ARChiVe Cohort Study. *Arthritis Rheumatol* 2016; 68(10):2514-26.
3. Sun L, et al. Clinical and pathological features of microscopic polyangiitis in 20 children. *J Rheumatol* 2014; 41(8):1712-9.

5H. Eosinophilic Granulomatosis with Polyangiitis (formerly Churg-Strauss Syndrome)

- Granulomatous small vessel vasculitis
- No EULAR/PRINTO/PRES classification criteria – very rare in children
- Characterized by:
  - Preceding history of "difficult to control" chronic asthma
  - Paranasal sinus abnormalities
  - Peripheral eosinophilia (≥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
  - ANCA, usually anti-MPO, present in less than 50% patients

- Treatment
  - Prednisone plus second line agent
  - Cyclophosphamide or Rituximab if cardiac, GI or neurologic involvement

References;

1. Gendelman S, et al. Childhood-onset eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) : a contemporary single-center cohort. *J Rheumatol* 2013; 40(6):929-35.
2. Boyer D, et al. Churg-Strauss syndrome in children: A clinical and pathologic review. *Pediatrics* 2006; 118:e914-20.

5I. Behçet Disease

- Systemic vasculitis with characteristic oral and genital ulcers, vasculopathy and uveitis
- Among the systemic vasculitides, Behçet disease is remarkable for its ability to involve arteries and veins of all sizes (small, medium, large)
- More common in certain ethnic groups along the "Silk Road" (Turks, Greeks)
- Uncommon in children

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, pseudofolliculitis, 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)

2014 International Classification Criteria for Behçet Disease *

• Ocular lesions (anterior or posterior uveitis or retinal vasculitis)	2 points
• Genital aphthosis	2 points
• Oral aphthosis	2 points
• Skin lesions (erythema nodosus, pseudofolliculitis, skin aphthosis)	1 point
• Neurologic manifestations (peripheral and central)	1 point
• Vascular manifestations (arterial and/or venous thrombosis, phlebitis)	1 point
• Positive pathergy test	Bonus point

** Patients with total score ≥4 are classified as having Behçet disease*

N.B. Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice

- Other clinical features include:
  - CNS: aseptic meningitis, encephalitis, cerebral venous sinus thrombosis, or pseudotumour cerebri
  - MSK: oligoarthritis or polyarthritis
  - GI: abdominal pain, diarrhea, colitis
  - Vascular: arterial and/or venous thrombosis

- Diagnosis
  - Currently made clinically
  - Several sets of diagnostic criteria have been proposed (see above)
  - No pathognomonic clinical finding or laboratory test to provide definitive diagnosis
  - Genetics may be helpful – HLA-B51 (more prevalent in Mediterranean and Far East) and HLA-B51 (more prevalent in East Asian)

- 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
  - May treat isolated oral and/or genital ulcers with topical therapy, including analgesics and/or steroids
  - Apremilast (an oral phosphodiesterase 4 inhibitor) has recently been demonstrated to be effective for treatment of oral ulcers in Behçet disease

References:

1. Demir S, et al. Vasculitis in systemic autoinflammatory diseases. *Front Pediatr* 2018; 6:377.
2. Koné-Paut I. Behçet's disease in children, an overview. *Pediatr Rheumatol Online J* 2016; 14(1):10.
3. Ozen S, Eroglu FK. Pediatric-onset Behçet disease. *Curr Opin Rheumatol* 2013; 25(5):636-42.
4. Hatemi G, *et al*. EULAR recommendations for the management of Behçet disease. *Ann Rheum Dis* 2008; 67: 1656-1662.

SECTION 6 – IDIOPATHIC INFLAMMATORY MYOPATHIES

6A. Juvenile Dermatomyositis (JDM)

- JDM is an autoimmune myopathy characterized by capillary vasculopathy primarily affecting skin and muscle
- Not associated with cancer in children, unlike dermatomyositis in adults

Bohan and Peter Criteria for Diagnosis 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 for muscle inflammation and to direct a site for biopsy (if needed)
- Please see Section 2E for other diagnoses to consider when assessing a child with muscle weakness

- 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; also, children may demonstrate a Gower sign on physical exam (see https://www.youtube.com/watch?v=IpoT46EAuCU)
  - It is important to assess for 3D's – dysphagia, dysphonia and dyspnea – that indicate severe disease
  - 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%, but may be confused with psoriasis given location on extensor surfaces, see https://www.nejm.org/doi/full/10.1056/NEJMicm1002816)
    - Heliotrope rash (66-100%)
    - Malar rash (42-73%)
    - Photosensitive rashes
    - Skin ulceration in severe cases.
  - 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
  - Anasarca can be a rare initial manifestation and is associated with treatment resistance and poor prognosis

  - Amyopathic JDM (skin features without muscle involvement) is rare in children and may represent JDM with mild muscle involvement that has not yet been identified; however, treatment to prevent future complications (e.g. calcinosis) is recommended

- Investigations
  - Muscle enzymes (CK, AST, ALT, LDH, aldolase) and inflammatory markers (ESR, CRP) likely to be elevated
  - Positive ANA is common (up to 70% of patients) but not specific
  - Myositis-specific antibodies (MSA) are identified in up to 2/3 of children with JDM, but are not routinely available in all laboratories

MSA	Frequency	Associated Clinical Characteristics
Anti-p155/p140	60%	Rash (Gottron papules, malar rash, "shawl-sign" rash) Photosensitivity Low CK levels Chronic illness course Generalized lipodystrophy
Anti-MJ	20%	Muscles cramps Dysphonia High rate of hospitalization Monocyclic disease course
Anti-synthetase	5-10%	Interstitial lung disease "Mechanic's hands" Arthralgia Older age at diganosis
Anti-Mi2	5%	Hispanic ethnicity Rash (Gottron papules, heliotrope rash, malar rash) High CK Low mortality
Anti-SRP **In patients with polymyositis	25%	Black race Severe onset Distal weakness Raynaud phenomenon Cardiac involvement High CK levels Chronic disease course, may require wheelchair use
Anti-MDA5	7.4%	Japanese and East Asian patients Skin ulceration Milder muscle disease Arthritis May have progressive interstitial lung disease

- Complications
  - Long delays 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 seen at presentation of longstanding disease (see https://www.dermnetnz.org/topics/calcinosis-cutis/)
  - Lipoatrophy may occur accompanied by hyperinsulinism, hypertriglyceridemia, liver dysfunction, acanthosis nigricans, and type 2 diabetes
  - Medication-related side effects from Corticosteroid toxicity (see Section 14) can include infection, osteoporosis, growth delay, cataracts and glaucoma, type 2 diabetes, and hypertension

- Monitoring disease activity
  - Clinical: skin rash; periungual capillaroscopy; muscle strength and function as measured by the Childhood Myositis Activity Scale (CMAS)
  - Laboratory: muscle enzymes (CK, AST, ALT, LDH, aldolase), inflammatory markers (ESR), lipid abnormalities & organ involvement

- Treatment
  - Supportive: adequate nutrition, physiotherapy, exercise, sunscreen for photosensitive rash
  - Medications:
    - Induction therapy using Corticosteroids starting from 1-2 mg/kg/day with slow taper and subcutaneous Methotrexate
    - Cyclophosphamide may be used for interstitial lung disease, gastrointestinal disease and vasculitis
    - IVIG, Cyclosporine, Mycophenolate mofetil or Rituximab if resistant or refractory
    - Topical therapies may also be considered for resistant skin disease

- Course and Outcomes
  - 40-60% of patients have a chronic course, 40-60% have a monophasic course, and <5% have a polyphasic course
  - Ongoing rash and nail fold abnormalities in first 6 months are best predictors of longer time to remission
  - Persistent skin and nail fold changes may represent ongoing inflammatory disease and should be treated accordingly
  - Outcomes are favourable, since most children have no functional disability and <10% have moderate-to-severe disability

References:

1. Huber AM. Juvenile idiopathic inflammatory myopathies. *Pediatr Clin North Am* 2018; 65(4):739-56.
2. Huber A, Feldman BM. An update on inflammatory myositis in children. *Curr Opin Rheumatol* 2013; 25(5):630-5.
3. Rider LG, et al. Developments in the classification and treatment of the juvenile idiopathic inflammatory myopathies. *Rheum Dis Clin North Am* 2013; 39(4):10.
4. Rider LG, et al. The myositis autoantibody phenotypes of the juvenile idiopathic inflammatory myopathies. *Medicine (Baltimore)* 2013; 92(4):223.
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6B. Juvenile Polymyositis

- Uncommon in children
- Characterized by proximal and distal muscle weakness
- No associated skin findings and normal nail fold capillaries
- Myositis is typically more severe than in juvenile dermatomyositis or in other connective tissue diseases
- Resistant to treatment
- Anti-signal recognition particle (SRP) autoantibodies are seen in children with polymyositis and are associated with black race, severe onset, distal weakness, Raynaud phenomenon, cardiac involvement, high CK levels, chronic disease course and wheelchair use

References:

1. Huber AM. Juvenile idiopathic inflammatory myopathies. *Pediatr Clin North Am* 2018; 65(4):739-56.
2. Huber A, Feldman BM. An update on inflammatory myositis in children. *Curr Opin Rheumatol* 2013; 25(5):630-5.
3. Rider LG, et al. The myositis autoantibody phenotypes of the juvenile idiopathic inflammatory myopathies. *Medicine (Baltimore)* 2013; 92(4):223.

6C. Myositis in other connective tissue diseases

- Myositis may be present in other connective tissue diseases, such as systemic lupus erythematosus, systemic sclerosis, mixed connective tissue diseases and overlap syndromes
- Please see Section 2E for other diagnoses to consider when assessing a child with muscle weakness
- Typically accompanied by other features of the various connective tissue diseases, such as arthralgia, malar rash, Raynaud phenomenon, interstitial lung disease
- Laboratory findings include high titres of ANA and myositis-associated antibodies
    - Anti-PM-Scl and anti-Ku associated with scleroderma-myositis overlap syndrome
    - Anti-U1-RNP associated with mixed connective tissue disease and overlap syndromes
- Associated with higher mortality than other categories of myositis

References:

1. Huber AM. Juvenile idiopathic inflammatory myopathies. *Pediatr Clin North Am* 2018; 65(4):739-56.
2. Shah M, et al. The clinical phenotypes of the juvenile idiopathic inflammatory myopathies. *Medicine* 2013; 92(1):25-41.

SECTION 7 – SCLERODERMA & RELATED SYNDROMES

7A. Classification of Scleroderma and Scleroderma-like Disorders

Morphea/ Localized scleroderma (See Section 7B)	Circumscribed morphea Linear scleroderma Generalized morphea Pansclerotic morphea Mixed morphea
Systemic sclerosis (See Section 7C)	Diffuse cutaneous * Limited cutaneous ** Overlap syndromes
Scleroderma-like disorders	Graft versus host disease Drug or toxin induced (e.g. L-tryptophan, vinyl chloride, bleomycin) Diabetic cheiroarthropathy Phenylketonuria Eosinophilia-myalgia syndrome Eosinophilic fasciitis Nephrogenic systemic fibrosis Premature aging syndromes

*_Diffuse cutaneous systemic sclerosis_ characterized by skin sclerosis extending proximal to wrists and ankles and involving trunk and face; associated with internal organ involvement and earlier organ dysfunction

** _Limited cutaneous systemic sclerosis_ (formerly known as CREST syndrome – calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) progresses more slowly, but has higher risk for later development of pulmonary hypertension

7B. Localized Scleroderma or Morphea

- Morphea refers to a group of autoimmune disorders with sclerotic skin and subdermal connective tissue changes due to excessive accumulation of collagen
- 25% of children can have extracutaneous manifestations: arthritis, uveitis, neurologic findings (e.g. seizures, headache), Raynaud phenomenon

- **Circumscribed morphea**
  - Includes superficial lesions sometimes referred to as "plaque" morphea
  - May involve superficial and deep dermis as well as subcutaneous tissues
  - Early lesions are firm, ivory-coloured oval lesions surrounded by reddish-lilac coloured ring suggesting active inflammation
  - Later, there is atrophy, hyper- (or rarely hypo-) pigmentation and softening of lesions
  - More common on trunk than extremities

- **Generalized morphea**
  - When ≥4 individual circumscribed lesions become confluent and affect ≥2 anatomic sites
  - Often rapid onset over months

- **Linear scleroderma**
  - Most common form in children and adolescents
  - Characterized by ≥ 1 linear streaks (often following dermatomal distribution) extending over face, head, trunk and/or extremities
  - Unilateral in greater than 85% cases
  - Complications include joint flexion contractures, limb atrophy, leg length discrepancy
  - Facial Linear Variants: may be associated with intracranial lesions, seizures, uveitis, and dental abnormalities.
    - *En coup de sabre*: involves face or scalp, usually forehead; often with alopecia
    - *Parry-Romberg syndrome*: progressive hemi-facial atrophy; often involves face below the forehead; more disfiguring; no epidermal involvement

- **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

- Diagnosis
  - Clinical, although skin biopsy may be performed (to exclude other disorders or to assess if lesion actively inflamed or "burnt out")
  - MRI may be useful to determine extent of deep lesions

- Treatment
  - Topical: Corticosteroids, Calcipotriene (vitamin D), Imiquimod 5%, Tacrolimus
  - Systemic: Corticosteroids, Methotrexate, Mycophenolate mofetil, Cyclosporine, Biologic therapy may be considered in recalcitrant disease
  - Other: Phototherapy with Ultraviolet A rays
  - Supportive: physiotherapy, occupational therapy, psychosocial support
  - Surgery for facial lesions, tendo-achilles lengthening

References

1. Li SC. Scleroderma in children and adolescents. *Ped Clin North Am* 2018:757-781.
2. Zulian F. Scleroderma in children. *Best Pract Res Clin Rheumatol* 2017; 31:576-595.

7C. Systemic Sclerosis (SSc)

- Rare autoimmune disease in children, characterized by symmetrical skin thickening or hardening and fibrosis of internal organs
- Sexes equally affected until onset age of 8 years, followed by 3:1 ratio of females:males
- 90% of pediatric patients have diffuse cutaneous subtype and 10% have limited cutaneous subtype (formerly known as CREST syndrome – calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia)

2013 ACR/EULAR Classification Criteria for SSc *

Items	*Score*
Skin thickening **	
• Skin thickening of fingers of both hands extending proximal to metacarpophalangeal (MCP) joints	9
• Skin thickening of whole finger distal to MCP joints	4
• Puffy fingers	2
Finger tip lesions **	
• Digital tip ulcers	2
• Pitting scars in fingertips	3
Telengiectasia	2
Abnormal nailfold capillaries (enlarged capillaries and/or capillary loss with or without peri-capillary hemorrhages)	2
Pulmonary arterial hypertension and/or interstitial lung disease	2
Raynaud phenomenon	3
Scleroderma related antibodies (any of anti-centromere, anti-Scl70 (also known as anti-topoisomerase I), or anti-RNA polymerase III)	3

** Patients with total score of ≥ 9 are classified as having definite systemic sclerosis*

N.B. Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice

*** Only include highest score from these categories in calculation of total score*

2007 PRES/ACR/EULAR Provisional Classification Criteria for Juvenile SSc *

Major criterion (mandatory): Sclerosis/induration of skin proximal to MCP joints

Plus ≥ 2 of the following minor criteria:

- Cutaneous (sclerodactyly)
- Peripheral vascular (Raynaud phenomenon, nail fold capillary abnormalities, digital tip ulcers)
- Gastrointestinal (dysphagia, gastroesophageal reflux)
- Cardiac (arrhythmias, heart failure)
- Renal (renal crisis, new-onset arterial hypertension)
- Respiratory (pulmonary fibrosis, decreased DLCO, pulmonary arterial hypertension)
- Neurologic (neuropathy, carpal tunnel syndrome)
- Musculoskeletal (tendon friction rubs, arthritis, myositis)
- Serologic (antinuclear antibodies, SSc-selective autoantibodies including anti-centromere and anti-Scl70 (also known as anti-topoisomerase I))

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

Common clinical features of SSc:

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

- Investigations
  - Blood work to assess for evidence of systemic inflammation and organ involvement
  - Serology helpful for diagnosis and classification: ANA (common), Rheumatoid factor (rare), anti-Scl 70 (also known as anti-topoisomerase1, usually associated with diffuse cutaneous SSc), anti-centromere (usually associated with limited cutaneous SSc)
  - Blood pressure and urinalysis to evaluate renal involvement
  - ECG and echocardiogram to evaluate possible cardiac involvement and screen for pulmonary arterial hypertension; consider cardiac MRI
  - Chest X-ray, pulmonary function tests with DLCO and high resolution CT chest to assess for lung disease, especially alveolitis and interstitial pulmonary fibrosis
  - Upper GI series to look for dysmotility and GERD

- Treatment
  - Primarily supportive care
    - Avoid cold, stress, caffeine and nicotine (to prevent Raynaud phenomenon)
    - Eat small meals, avoid foods that exacerbate gastric acidity, remain upright after eating and elevate head of bed (for dysmotility and GERD)
    - Physiotherapy and occupational therapy
  - Symptomatic treatment
    - GERD: Proton pump inhibitors (e.g. Omeprazole)
    - Raynaud phenomenon: peripheral vasodilators (e.g. Nifedipine)
    - Hypertension, renal disease: ACE Inhibitors (e.g. Enalapril)
    - Pulmonary hypertension: endothelin-1 receptor antagonists (e.g. Bosentan), prostacyclin analogs (Epoprostenol)
  - Systemic therapy
    - Methotrexate or Mycophenolate mofetil (MMF) for active skin disease
    - Cyclophosphamide, MMF and Corticosteroids for alveolitis and interstitial lung disease
    - Other immunomodulatory agents have unclear efficacy in treatment of SSc
    - Autologous stem cell transplantation has been demonstrated to be efficacious and best cadidates appear to be patients with severe disease of short duration before irreversible damage has occurred

- Prognosis and outcome
  - 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 approximately 90%) compared to adults

References

1. Li SC. Scleroderma in children and adolescents. *Ped Clin North Am* 2018:757-781.
2. Zulian F. Scleroderma in children. *Best Pract Res Clin Rheumatol* 2017; 31:576-595.
3. Zulian F, 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.

7D. 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 over time GI manifestations (similar to SSc), interstitial lung and renal diseases
- Multiple different diagnostic criteria for MCTD exist (e.g. Sharp, Alarcon-Segovia, Kasukawa, Kahn), but no single set of criteria is 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. Berard RA, Laxer RM. Pediatric mixed connective tissue disease. *Curr Rheumatol Rep* 2016; 18(5):28.
2. Mier RJ, et al. Pediatric-onset mixed connective tissue disease. *Rheum Dis Clin North Am* 2005; 31(3):483-96.

7E. Raynaud Phenomenon

- Vascular spasm in extremities leading to triphasic colour sequence: white (blanching due to ischemia), 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 areas (lips, tongue, tip of nose, earlobes)
- Precipitated by cold, physical or emotional stress, caffeine, medications or smoking
- Raynaud phenomenon may be primary or secondary
  - *Primary*
    - No underlying etiology, but often positive family history
    - No peripheral ulcerations
  - *Secondary*
    - Due to underlying autoimmune disease (scleroderma, overlap syndromes, MCTD, SLE, JDM), mechanical obstruction (thoracic outlet syndrome, cervical rib), hyperviscosity (polycythemia), cryoglobulinemia, drugs/toxins, or vibration-induced phenomenon
- In isolated Raynaud phenomenon, two best predictive factors for future development of autoimmune diseases are:
  1. Positive ANA
  2. Abnormal nail fold capillaries

- Investigations
  - Blood work – complete blood count and differential, inflammatory markers, complement levels, serology (ANA, specific autoantibodies, RF)
  - Urinalysis

- Treatment
  - Preventive (avoid triggers; warm mittens, socks and boots in winter etc)
  - Systemic therapy may be used to prevent ischemic tissue injury
    - Peripheral vasodilator, such as Nifedipine, may be titrated to alleviate the Raynaud episodes; avoid medication-related hypotension, headaches or dizziness
    - If severe, may require IV prostaglandins
  - Topical therapy (e.g. nitroglycerin 2% ointment) may be used for digital ulcers

References

1. Nigrovic PA, et al. Raynaud's phenomenon in children: a retrospective review of 123 patients. *Pediatrics* 2003; 111(4):715-721.
2. Gargh K, et al. A retrospective clinical analysis of pharmacological modalities used for symptomatic relief of Raynaud's phenomenon in children treated in a UK paediatric rheumatology centre. *Rheumatology* 2010; 49(1):193-4.
3. Wigley FM, Flavahan NA. Raynaud's phenomenon. *N Engl J Med* 2016; 375(6):556-65.

7F. Sjögren Syndrome

- Multisystem autoimmune disease characterized by decreased secretion of lacrimal and salivary glands leading to dry eyes (keratoconjunctivitis sicca) and xerostomia (dry mouth)
- Most common presentation in children is parotid swelling or parotitis
- Clinical diagnosis, given lack of validated pediatric criteria
- Diagnosis in adults based on weighted scoring system, including the following:
  - Presence of focal lymphocytic sialadenitis in labial salivary gland biopsy (higher weight)
  - Positivity for anti-SSA/Ro (higher weight)
  - Ocular staining score (see below)
  - Schirmer's test (see below)
  - Unstimulated whole saliva flow

- Sjögren syndrome may be primary or secondary
  - *Primary* (idiopathic) has no underlying etiology
  - *Secondary* occurs in the context of an autoimmune disease, such as systemic lupus erythematosus

- Investigations
  - Ocular: Schirmer's test (tear production ≤ 5 mm in 5 minutes is abnormal), tear break-up time, Rose Bengal staining of devitalized areas
  - Salivary glands: scintigraphy, biopsy
  - Blood work: complete blood count and differential, inflammatory markers, immunoglobulin levels, serology (ANA, anti-Ro/SSA, anti-La/SSB, specific autoantibodies, RF)

- Treatment
  - Supportive (artificial tears for dry eyes; increase fluid intake, chewing gum for dry mouth)
  - Hydroxychloroquine (Plaquenil) may be helpful

- Complications
  - Increased risk of eye irritation and conjunctivitis
  - Oral problems (dental caries, gingivitis, and infections such as Candida)
  - Increased risk of non-Hodgkin lymphoma

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SECTION 8 – AUTOINFLAMMATORY DISEASES

8A. Periodic Fever/Autoinflammatory Syndromes

- The *recurrent* or *periodic fever syndromes* are defined by ≥3 episodes of unexplained fever in a 6-month period, occurring at least 7 days apart, separated by at least one week of good health
- Fevers are typically associated with a constellation of symptoms, including ocular, oropharyngeal, gastrointestinal, dermatologic, musculoskeletal, and neurologic manifestations
- Interval between attacks of fever may be irregular or regular
- Patients typically feel well between episodes

Characteristic Features of the Periodic Fever Syndromes

Features	FMF	TRAPS	HIDS	CAPS			PFAPA
				FCAS	MWS	NOMID	
Age of onset	< 20 yrs	< 20 yrs	< 1 yr	< 1 yr	Often < 1yr	At birth or within first months	< 5 yrs
Duration of attack	1-3 days	1-4 weeks	3-7 days	1-3 days	1-3 days to continuous	Hours or continuous	3-6 days
Interval of attacks	Weeks to months	Weeks to months	Weeks to months	Variable; cold-induced	Variable	Days	3-6 weeks
Skin rash	Erysipelas-like in ~40%	Migratory rash; may be painful	Maculopapular in 90%	Cold-induced; urticarial	Urticarial	Urticarial	No
Adenopathy	No	Not typical	Common; may be generalized	Not typical	Not typical	Not typical	Yes
Oral ulcers	No	No	May occur	No	No	No	Yes
Abdominal pain	In ~95%; pain, peritonitis, constipation	Common; colicky	Often present; can be severe with diarrhea	May occur	May occur	May occur	May occur
MSK	Arthralgia; oligoarthritis; myalgia	Localized myalgia; arthralgia; arthritis	Symmetric oligoarthritis of large joints; arthralgia	Arthralgia	Arthralgia; arthritis; clubbing	Arthralgia; osseous overgrowth; clubbing	Arthralgia
Serositis	Peritonitis; pleuritis; pericarditis	Pleuritis; peritonitis	No	No	Pericarditis (uncommon)	Not typical	No
Amyloidosis	Occurs in 60% if untreated	Occurs in ~25% if untreated	Uncommon, <5-10%	May occur	Occurs in ~30% if untreated	May occur	No
Other	Scrotal swelling and pain	Periorbital edema; conjunctivitis; headache; testicular pain	Headache	Conjunctivitis	Conjunctivitis; episcleritis; sensorineural hearing loss	Conjunctivitis; episcleritis; papilledema; chronic meningitis; sensorineural hearing loss	
Inheritance	AR	AD	AR	AD	AD	AD / *de novo*	None
Mutation **Chromosome** **Gene** **Protein**	16p13 *MEFV* Pyrin	12p13 *TNFRSF1A* TNF receptor P55	12q24 *MVK* Mevalonate kinase	1q44 *NLRP3* Cryopyrin	1q44 *NLRP3* Cryopyrin	1q44 *NLRP3* Cryopyrin	No gene identified

AD: autosomal dominant, AR: autosomal recessive

Familial Mediterranean fever (FMF)

- Most common hereditary autoinflammatory disease
- Typically autosomal recessive inheritance but occasionally autosomal dominant transmission; linked to genetic mutation in *MEFV* gene encoding pyrin
- Ethnic predilection among Sephardi and Ashkenazi Jewish, Arab, Armenian, and Turkish populations with carrier rates as high as 1:3 to 1:5
- 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 at irregular intervals
  - Clinical hallmark is serositis (e.g. peritonitis, pleuritis, pericarditis)
  - Skin: Erysipelas-like rash on shins and dorsum of feet
  - MSK: Monoarthritis or oligoarthritis, arthralgia, myalgia
- Morbidity is associated with amyloidosis, especially renal amyloidosis
- Treatment
  - Colchicine is highly effective therapy for most patients with FMF
  - Anti-IL-1 therapy with Anakinra, Canakinumab or Rilonacept is effective in Colchicine-resistant or intolerant FMF

TNF-Receptor Associated Periodic Syndrome (TRAPS)

- Rare recurrent fever syndrome
- Originally known as Familial Hibernian Fever
- Autosomal dominant inheritance; linked to genetic mutation in *TNFRSF1A* gene that encodes TNF receptor
- Age of onset ranges from early childhood to later adulthood
- 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, arthritis
  - Ocular: Conjunctivitis, periorbital edema
  - GI: Severe abdominal pain
  - Other: oral ulcers, lymphadenopathy
- Treatment
  - Corticosteroids provide symptomatic relief but do not diminish frequency of attacks
  - Anti-TNF agents (e.g. Etanercept) thought to be promising, but results of studies disappointing
  - Anti-IL-1 therapy may be beneficial

Mevalonate kinase deficiency- Hyperimmunoglobulinemia D Syndrome (HIDS)

- Rare recurrent fever syndrome
- Autosomal recessive inheritance; linked to genetic mutations in *MVK* gene encoding mevalonate kinase
- More than 90% of patients show symptoms within first year of life
- Clinical features
  - Fever episodes lasting 3-7 days that recur every 4-8 weeks

- Fever typically associated with abdominal pain, vomiting, diarrhea and a diffuse maculopapular or urticarial rash
- Other common features include tender cervical lymphadenopathy, oral ulcers, headaches, arthralgias, and large joint symmetric arthritis
- May have a striking elevation of serum IgD and IgA during fever episodes
- Elevation of urinary mevalonic acid during episodes
- Often triggers are identified, especially immunizations

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

Cryopyrin Associated Periodic Syndrome (CAPS)

- Group of autoinflammatory syndromes that are associated with genetic mutations involving *NLRP3* gene encoding cryopyrin
- FCAS and NOMID characterized by disease onset in infancy; MWS may develop later
- Spectrum of 3 diseases on a continuum of increasing disease severity

1. **Familial Cold Autoinflammatory Syndrome (FCAS)**
   - Autosomal dominant inheritance of *NLRP3* mutations
   - 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
   - Amyloidosis extremely rare

2. **Muckle Wells Syndrome (MWS)**
   - Autosomal dominant inheritance of *NLRP3* mutations
   - Frequent episodes of fever lasting 24-48 hours
   - Characterized by generalized urticarial-like rash, arthralgias, myalgias, arthritis, and conjunctivitis
   - Progressive sensorineural hearing loss emerges in adolescence
   - Higher risk of amyloidosis (25%)

3. **Neonatal Onset Multisystem Inflammatory Disease (NOMID)**
   - Spontaneous *NLRP3* mutations
   - Nearly continuous clinical features that develop shortly after birth
   - Frequent fever episodes lasting 24-48 hours several times per week
   - Distinguishing features from other autoinflammatory syndromes are poor growth or failure to thrive, severe neuroinflammation and deforming arthropathy
   - Skin: Nearly-constant generalized urticarial-like rash
   - CNS: Aseptic meningitis, intellectual disability, neurosensory hearing loss, optic nerve atrophy
   - MSK: Deforming arthropathy with epiphyseal overgrowth, clubbing
   - Ocular: Conjunctivitis, episcleritis, uveitis, papilledema, visual loss

    - Hepatomegaly, splenomegaly
    - Poor long-term prognosis with high morbidity and mortality

- Treatment
    - Anti-IL-1 therapy with Anakinra, Canakinumab, or Rilonacept are highly effective
    - Early treatment may reduce risk of 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 before 5 years and is self-limited (usually resolves within 5 years)
- Clinical features
    - Episodes of high fever that occur with regular periodicity every 3-6 weeks
    - Fever episodes generally last up to 3-6 days
    - Characteristic findings of small non-scarring aphthous ulcers, non-exudative pharyngitis, and cervical adenitis
    - May have associated nausea, vomiting, abdominal pain and headache
    - Throat cultures are consistently negative
- Treatment
    - No consensus regarding treatment
    - Single dose of prednisone at onset of symptoms and, if necessary, the following day can abort the attack; however, interval between fever attacks may shorten
    - Other options include cimetidine and tonsillectomy +/- adenoidectomy

References:

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2. Soon GS, Laxer RM. Approach to recurrent fever in childhood. *Can Fam Physician* 2017; 63(10):756-62
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4. Federici S, Gattorno M. A practical approach to the diagnosis of autoinflammatory diseases in childhood. *Best Pract Res Clin Rheumatol* 2014; 28(2):263-76.
5. Goldsmith DP. Periodic fever syndromes. *Pediatr Rev* 2009; 30(5):e34-41.

8B. Other Inherited Autoinflammatory Diseases

- The term ***'autoinflammatory'*** has been used to distinguish disorders of innate immune system characterized by recurrent, seemingly unprovoked episodes of inflammation from more common ***'autoimmune'*** diseases characterized by dysregulation of the adaptive immune system (with high-titre autoantibodies and proliferation of antigen-specific T cells)
- Hereditary periodic fever syndromes (described above) were first group of monogenic disorders to be classified as autoinflammatory
- New monogenic autoinflammatory diseases continue to be discovered (described below)
- Spectrum of autoinflammatory diseases is now thought to include disease, such as systemic juvenile idiopathic arthritis, Behçet disease, and chronic non-bacterial osteomyelitis (CNO), which may prove to be polygenic in origin

Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome

- Rare autosomal dominant autoinflammatory syndrome
- Clinical features
  - Recurrent episodes of sterile, erosive arthritis in early childhood
  - As patients progress to puberty, skin involvement may predominate
  - Characterized by cystic acne, recurrent and often debilitating aggressive ulcerative skin lesions of the lower extremities indistinguishable from pyoderma gangrenosum
- Treatment
  - Arthritis may respond to corticosteroids, but adverse effects often limit their use
  - Reports of successful treatment with Anti-IL-1 and Anti-TNF therapy

Deficiency of the Interleukin-1 Receptor Antagonist (DIRA)

- Rare autosomal recessive autoinflammatory syndrome
- Clinical features
  - Systemic inflammation in the perinatal period
  - Bone pain with characteristic radiographic findings of multifocal sterile osteolytic bone lesions, widening of multiple anterior ribs, and periostitis
  - Pustular skin lesions
- Treatment
  - Patients treated with Anakinra have shown rapid clinical and immunological responses

Deficiency of the Interleukin-36 Receptor Antagonist (DITRA)

- Rare life-threatening multisystem disease with repeated flares of sudden onset
- Clinical features
  - High-grade fever, malaise
  - Generalized pustular psoriasis
- Treatment
  - Treatment with anakinra has been described

Deficiency of Adenosine Deaminase 2 (DADA2) (also see Section 5D)

- Newly recognized autosomal recessive syndrome with presentation very early in life
- Clinical features
  - Recurrent fevers, livedoid skin rash and vascular involvement
  - Vascular involvement may include recurrent lacunar strokes, cerebral haemorrhage, polyarteritis nodosa
  - May have hypertension, hepatosplenomegaly and cutaneous vasculitis
- Treatment
  - Reports of successful treatment with Anti-TNF therapy
  - Hematopoeitic stem cell transplantation considered for severe phenotypes

Type 1 Interferonopathies

- Rare diseases characterized by mutations in interferons, which are molecules that represent the cell's first lines of defence again pathogens, mainly viruses
- Type I interferon (INFαß) signalling defects can phenotypically manifest as a group of heterogeneous autoinflammatory diseases

- Common clinical features in type 1 Interferonopathies
  - Lupus-like symptoms during infancy or prepubertal age
  - Signs of vasculopathy such as chilblains or strokes
- Specific conditions
  - Aicardi-Goutières syndrome
    - Prototypic type 1 interferonopathy
    - Characterized by neonatal onset
    - Clinical features include progressive congenital encephalopathy, intracranial calcification, white matter disease, chilblain-like skin lesions, glaucoma, hypothyroidism, cardiomyopathy, demyelinating peripheral neuropathy
  - Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, also known as Nakajo-Nishimura syndrome (NNS)
- Diagnosis
  - Gene studies are the most accurate diagnostic test
  - Interferon gene signature test
- Treatment
  - Unlike other fever syndromes, general immunosuppression with Corticosteroids, Methotrexate, or anti-IL1 (e.g. Anakinra or Canakinumab which are effective in other periodic fever syndromes) are not effective
  - Anti-IL6 and Jak inhibitors have been effective in these conditions

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2. Hashkes PJ, Toker O. Autoinflammatory syndromes. *Pediatr Clin North Am* 2012; 59(2):447-70.
3. Davidson S, et al. An Update on Autoinflammatory Diseases: Interferonopathies. *Curr Rheumatol Rep* 2018; 20(7):38

8C. Role of Genetic Testing in Suspected Autoinflammatory DIsease

- Genetic testing may be used to confirm a diagnosis when the clinical pattern fits with one of the autoinflammatory diseases
- A genetic diagnosis should be pursued in a logical manner recognizing the cost and limitations of testing, although panels of genetic mutations associated with these conditions are now more accessible and cost-effective
- While genetic testing may help to confirm a diagnosis, it is important to consider the differential diagnosis and potential investigations for recurrent fevers outlined in Section 2C
- A simple interactive tool is available online (https://www.printo.it/eurofever/scoreCriteria.asp) to guide ordering of genetic tests for recurrent fever syndromes

References:

1. Gattorno M, et al. A diagnostic score for molecular analysis of hereditary autoinflammatory syndromes with periodic fever in children. *Arthritis Rheum* 2008; 58(6):1823-32.

8D. Chronic Non-Bacterial Osteomyelitis (CNO)

- A non-infectious, autoinflammatory disease involving bone
- Pathophysiology poorly understood, neutrophil mediated
- CNO affects females > males and is more common in children and adolescents
- Known as chronic recurrent multifocal osteomyelitis (CRMO) if multiple bony sites
- Some cases (20-30%) are unifocal at diagnosis and many have non-recurrent disease
- 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
- Must consider bone malignancy, infection, and histiocytosis in work-up as CNO is a diagnosis of exclusion
- There are no validated diagnostic criteria for CNO/CRMO, but Jansson et al proposed a clinical score (see table below) that may aid in differentiating non-bacterial osteitis from other bone lesions and may guide the diagnostic approach

Proposed clinical score for nonbacterial osteitis (Jansson et al)

Risk factor	*Score*
Normal blood count	13
Symmetrical bone lesions	10
Lesions with marginal sclerosis	10
Normal body temperature	9
Vertebral, clavicular or sternal lesions	8
Radiographically proven lesions ≥ 2	7
CRP ≥ 1 mg/dL (10 mg/L)	6
*Total clinical score **	*63*

**** Total clinical score***	***Recommended diagnostic approach***	
	1 lesion on whole body imaging	*>1 lesion on whole body imaging*
≤ 28	Bone biopsy with culture	Clinical monitoring
28-38	Clinical monitoring	Clinical monitoring
≥ 39	Consistent with CNO diagnosis	Consistent with CNO diagnosis

Adapted from Jansson et al, Arthritis Rheum 2009.

- Clinical features
  - Presents with acute or insidious onset of bone pain often associated with localized swelling, tenderness and warmth; some patients also have fever and malaise
  - Typical sites of involvement include the clavicles, pelvis, vertebral bodies and metaphyses of long bones
  - CNO is associated with inflammatory disorders of skin (e.g. palmoplantar pustulosis, psoriasis, generalized pustulosis, severe acne, pyoderma gangrenosum), disorders of the gastrointestinal tract (e.g. inflammatory bowel disease), and arthritis adjacent to active bone lesions and (less commonly) distant to the osteitis

  - The term SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome is often used in adults -- SAPHO may represent a later presentation of childhood CNO or may be a distinct disorder within the same disease spectrum
  - Clinical course characterized by periods of exacerbation with symptom-free intervals

- Imaging
  - X-Rays:
    - Mixed osteolytic and sclerotic bone lesions localized in the metaphyses close to the growth plate
    - Periosteal reaction may be present
    - Cortical thickening may occur later in disease course
  - MRI (whole body, if available): sensitive to assess extent and activity of lesions, as well as asymptomatic lesions
  - Bone scan: may be helpful to assess the extent of lesions, but is associated with significant radiation exposure and may not distinguish inflammatory lesions from metabolically active growth plates

- Treatment
  - Most lesions resolve without significant sequelae and spontaneous remission can occur; however severe pain, recurrences, and functional limitations may necessitate therapy
  - First-line therapy: NSAIDs provide symptomatic relief in up to 80% of patients
  - Corticosteroids may sometimes be used for brief periods of time to provide symptomatic relief or as a bridge to second-line therapy
  - Second-line agents include Bisphosphonates (e.g. Pamidronate, Zolendronate), Sulfasalazine, Methotrexate, anti-TNF agent (e.g. Infliximab)

References:

1. Zhao Y, Ferguson PJ. Chronic nonbacterial osteomyelitis and chronic recurrent multifocal osteomyelitis in children. *Pediatr Clin North Am* 2018; 65(4):783-800.
2. Twilt M, Laxer RM. Clinical care of children with sterile bone inflammation. *Curr Opin Rheumatol* 2012; 23(5):424-31.
3. Jansson AF, et al. Clinical score for nonbacterial osteitis in children and adults. *Arthritis Rheum* 2009; 60(4):1152-9.
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8E. Relapsing Polychondritis

- A rare immune-mediated condition associated with inflammation in cartilage and other tissues (particularly ears, nose, eyes, joints, respiratory tract, and heart valves)
- Children have similar clinical features to adults, but are more likely to have family history of autoimmunity and less likely to have associated inflammatory diseases
- Early manifestations often remain unrecognized until emergence of classic features, such as auricular inflammation and saddle-nose deformity
- Associated with high morbidity and mortality
- Screening for complications (e.g. aortic dilatation, cardiac lesions) is mandatory
- Diagnosis based on clinical criteria – all 3 sets of criteria were established based on single-centre cohort studies and none have been validated in an independent cohort

1976 McAdam et al Criteria for Relapsing Polychondritis

≥ 3 of the following clinical features:

- Bilateral auricular chondritis
- Non-erosive, seronegative inflammatory polyarthritis
- Nasal chondritis
- Ocular inflammation (conjunctivitis, keratitis, scleritis/episcleritis, uveitis)
- Respiratory tract chondritis (laryngeal and/or tracheal cartilages)
- Cochlear and/or vestibular dysfunction (neurosensory hearing loss, tinnitus, vertigo)

1979 Damiani and Levine Criteria for Relapsing Polychondritis

≥ 1 of the clinical features proposed by McAdam *plus* positive histologic confirmation

or

≥ 2 of the clinical criteria proposed by McAdam *plus* response to Corticosteroids or Dapsone

1989 Modified Michet et al Criteria for Relapsing Polychondritis

Proven chondtritis in at least 2/3 cartilage sites of:

- Auricular cartilage
- Nasal cartilage
- Laryngotracheal cartilage

or

Proven inflammation in at least 1/3 of the above cartilage sites (auricular, nasal, laryngotracheal) *plus* 2 other minor criteria:

- Occular inflammation
- Vestibular dysfunction
- Seronegative inflammatory arthritis
- Hearing loss

- Treatment
  - No evidence-based guidelines for treatment
  - In adults, largely empiric and based on disease severity
  - Options include NSAIDs, corticosteroids, Methotrexate, Dapsone, Azathioprine and anti-TNF therapy

References:

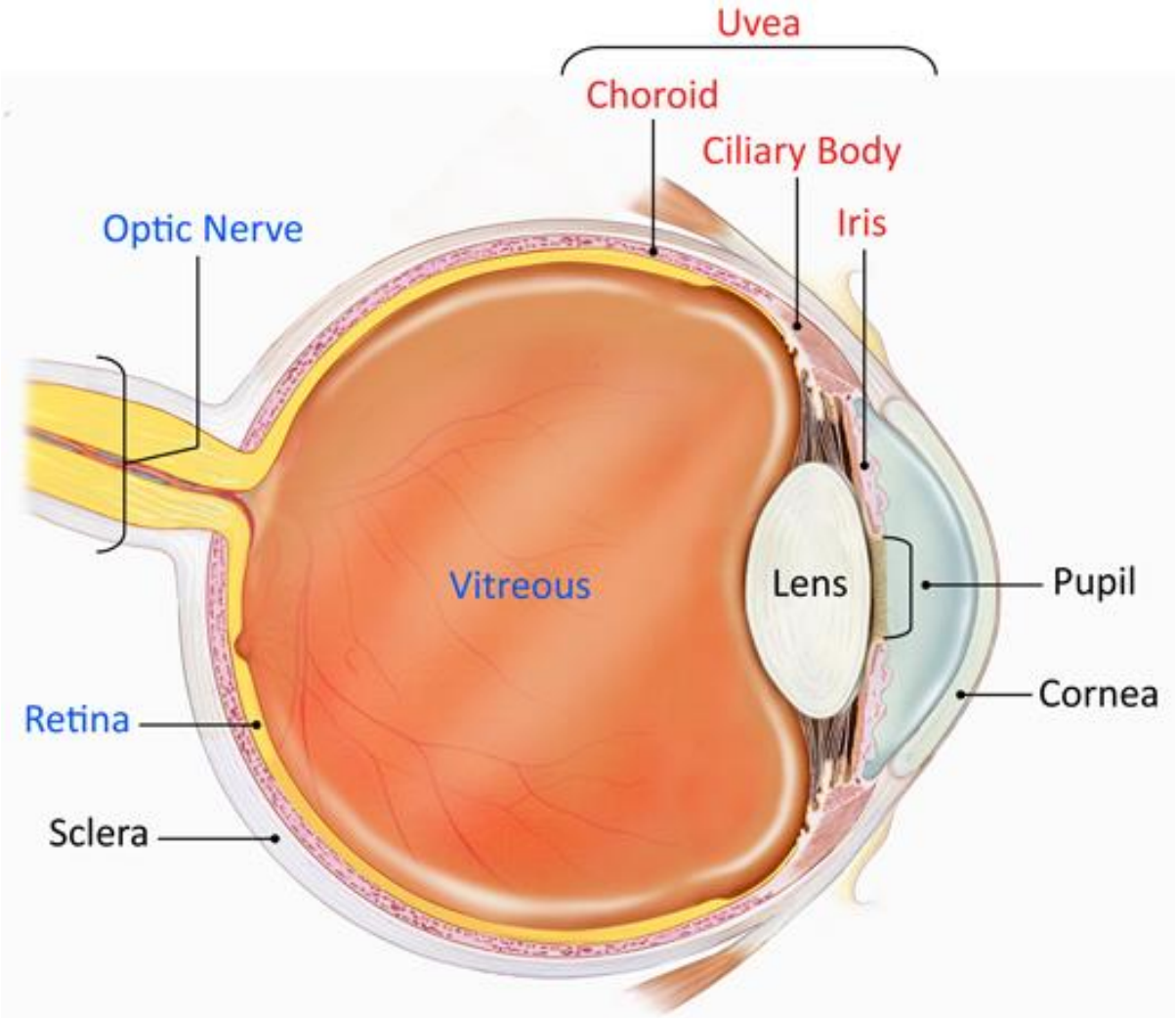
1. Belot A, et al. Pediatric-onset relapsing polychondritis: case series and systematic review. *J Pediatr* 2010;156(3):484-9.
2. Kemta LF, Chevalier X. Refractory relapsing polychondritis: Challenges and solutions. *Open Access Rheumatology: Research and Reviews* 2018; 1-11.
3. Borgia F, et al. Relapsing polychondritis: An updated review. *Biomedicines* 2018; 6(3):E84.

SECTION 9 – UVEITIS

9A. Uveitis

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

- Classification based on anatomic location of inflammation:
  - **Anterior uveitis** involves the iris and/or ciliary body
  - **Intermediate uveitis** involves the pars plana between the ciliary body and retina
  - **Posterior uveitis** involves the choroid and/or retina
  - **Panuveitis** describes the presence of inflammation in all three anatomic locations in which there is no predominant site of inflammation



* Image published in "Facts About Uveitis" by the National Eye Institute: https://nei.nih.gov/health/uveitis/uveitis

- Complications of uncontrolled uveitis include:
  - Cataracts
  - Glaucoma
  - Band keratopathy

  - Synechiae (adhesion of iris to lens)
  - Cystoid macular edema
  - Vision loss

- Treatment
  - Prompt and aggressive treatment to prevent or minimize visual complications
  - Minimize chronic use of topical corticosteroids (due to side effects such as cataract formation and glaucoma)
  - Close collaboration between rheumatologists and ophthalmologists is essential
  - Options include topical (corticosteroids, cycloplegics, mydriatics, anti-glaucoma agents) and systemic (Methotrexate, Infliximab, Adalimumab, other) therapies

9B. Systemic Inflammatory Diseases Associated with Uveitis

Disease	Acute/Chronic	Location	Associated clinical features	Investigations
Juvenile idiopathic arthritis (except enthesitis related arthritis)	Chronic, recurrent, asymptomatic	Anterior > Posterior	Oligoarthritis >> Polyarthritis	ANA
Enthesitis related arthritis	Acute symptomatic, often recurrent	Anterior	Enthesitis, sacroiliitis; often associated with reactive arthritis, IBD, or a family history of these conditions	HLA-B27
Behçet disease	Acute or chronic	Posterior	Recurrent oral and/or genital ulcers, arthritis, skin rash	Pathergy
Blau syndrome (Infantile sarcoidosis)	Chronic	Posterior, Anterior, Panuveitis	Skin rash, arthritis	Consider genetic testing (*NOD2/ CARD15* mutations)
Kawasaki disease	Acute, asymptomatic	Anterior	Consider if patient presents with severe conjunctivitis and photophobia	Echocardiogram
Sarcoidosis	Chronic	Posterior, Anterior, Panuveitis	Skin rash, arthritis, lung involvement, lymphadenopathy	Biopsy, consider genetic testing (*NOD2/CARD15* mutations)
Tubulo-interstitial nephritis and uveitis (TINU)	Acute	Anterior	Fever, arthralgias, fatigue, abdominal pain, and nephritis; uveitis may present before or after renal disease	U/A, renal function

9C. Infectious Causes of Uveitis

Disease	Acute/Chronic	Location	Associated clinical features	Investigations
Cat scratch (Bartonella henselae)	Chronic	Anterior, Posterior	Fever of unknown origin, regional lymphadenopathy, abdominal pain, weight loss, hepatosplenomegaly Cat exposure	Serology
Cytomegalovirus	Chronic	Posterior	Congenital; fever, malaise Immunocompromised host	Serology, viral PCR
Herpes virus	Acute or chronic	Anterior, posterior	Keratouveitis, fever, gingivostomatitis	Serology, viral culture and/or PCR
Lyme disease	Chronic	Anterior, Posterior	Erythema migrans, arthritis, CNS symptoms Tick bites in endemic areas	Serology
Toxoplasmosis	Chronic, acute recurrences	Posterior	Congenital exposure (chorioretinitis, hydrocephalus, intracranial calcifications); bilateral symmetric non-tender cervical lymphadenopathy, constitutional symptoms, headaches, myalgias and hepatosplenomegaly Immunocompromised host; cat exposure	Serology
Tuberculosis	Chronic	Anterior	Chronic cough, fever, weight loss, multi-organ manifestations Travel/exposure history	PPD, Chest X-ray

References:

1. Krishna U, et al. Uveitis: a sight-threatening disease which can impact all systems. *Postgrad Med J* 2017; 93(1106);766-73.
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SECTION 10 – INFLAMMATORY BRAIN DISEASES

10A. Introduction to Inflammatory Brain Diseases

- Inflammatory brain disease encompasses a wide range of disorders
- Clinical and diagnostic features vary depending on the underlying disease
- A broad differential diagnosis should be considered when a child presents with newly acquired neurological or psychiatric deficits

Types of inflammatory brain diseases in children:

Vasculitis	Primary Angiitis of the Central Nervous System in childhood (cPACNS) • Angiography-positive cPACNS: progressive and non-progressive • Angiography-negative cPACNS Secondary CNS vasculitis
Non-vasocentric neuroinflammatory disorders	Demyelinating disorders • Multiple sclerosis, acute demyelinating encephalomyelitis (ADEM), optic neuritis, transverse myelitis Antibody mediated inflammatory brain disease • Autoimmune encephalitis, neuromyelitis optica, Hashimoto encephalopathy Systemic inflammatory diseases with CNS involvement • Systemic lupus erythematosus, antiphospholipid syndrome, celiac disease, Beçhet disease, sarcoidosis Post-infectious or infection-associated inflammatory encephalopathy • Post-Streptococcal neuropsychiatric disorders (including acute rheumatic fever, Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS)), post-Mycoplasma basal ganglia encephalitis, post-Herpes Simplex Virus encephalitis, Febrile infection-related epilepsy syndrome (FIRES) Other neuroinflammatory disorders • Rasmussen encephalitis

10B. Childhood Primary Angiitis of the Central Nervous System (cPACNS)

- Currently defined by modified Calabrese criteria:
  - Clinical evidence of a newly-acquired focal or diffuse neurologic and/or psychiatric deficit in child <18 years of age, *plus*
  - Angiographic or histologic evidence of CNS vasculitis, *plus*
  - Absence of an underlying systemic condition

- 2 clinically and radiologically distinct types of cPACNS

1. **Angiography positive cPACNS** (Large-medium vessel CNS vasculitis)

    - Clinical features: stroke presentation with headache, acute hemiparesis, hemisensory deficits, and/or fine motor deficits
    - Inflammatory markers: often normal
    - CSF: often normal
    - MRI: unilateral focal areas of acute ischemia in a vascular distribution
    - Evidence of vasculitis on angiography (conventional angiography or MRA)
    - Brain biopsy not required
    - Further divided into progressive and non-progressive subtypes
    - Non-progressive cPACNS
        - Defined by absence of progression on imaging 3 months after initial angiography (i.e. monophasic disease)
        - More common than progressive cPACNS
    - Progressive cPACNS
        - Defined by progression on neuroimaging 3 months after initial angiography
        - Presents with both focal and diffuse neurologic deficits
        - Multifocal T2 lesions on MRI, proximal and distal stenosis on angiography

2. **Angiography negative cPACNS** (Small vessel CNS vasculitis)

    - Clinical features: systemic symptoms (fever, malaise), headache, seizures, ataxia, cognitive decline and/or behaviour changes
    - Inflammatory markers: may be elevated
    - CSF: more likely to have pleocytosis, elevated protein and/or elevated opening pressure compared to angiography-positive disease; oligoclonal bands may also be present
    - MRI: multifocal T2 hyperintensities in both white and grey matter, lesions do not conform to large-vessel vascular territory
    - By definition, angiography is negative
    - Brain biopsy (ideally lesional): non-granulomatous, intramural and perivascular T lymphocytes in small arteries, arterioles, capillaries or venules

- Treatment
    - Based on type of cPACNS
    - Angiography positive cPACNS
        - Anti-coagulation with or without anti-platelet agent
        - Corticosteroids in non-progressive cPACNS may improve outcome
        - Progressive cPACNS treated with same protocol as for angiography negative cPACNS
    - Angiography negative cPACNS
        - Induction (first 6 months) using Cyclophosphamide and Corticosteroids
        - Maintenance (up to 24 months) using Mycophenolate mofetil and Corticosteroids
    - Rehabilitation addressing cognitive, behavioural, physical and psychological deficits
    - Adjunctive therapy: PJP prophylaxis while on Cyclophosphamide; Vitamin D supplementation and ensure adequate calcium intake while on steroids

- Prognosis
    - Complications: persistent neurological deficits, seizures, cognitive disability

References:

1. Gowdie P, et al. Primary and secondary CNS vasculitis. *J Child Neurol*. 2012; 27(11):1448-59.
2. Van Mater H. Pediatric inflammatory brain disease: a diagnostic approach. *Curr Opin Rheumatol* 2014; 26(5):553-61.

10C. Secondary Central Nervous System Vasculitis

- Occurs in context of an underlying systemic illness
- Can occur in context of infections, as well as other systemic inflammatory and autoimmune diseases
- Treatment may involve Corticosteroids as well as medications directed to underlying cause

Causes of secondary CNS vasculitis:

Infections	Bacteria: *Mycobacterium tuberculosis, Mycoplasma pneumonia, Streptococcus pneumonia* Virus: Epstein-Barr virus, Cytomegalovirus, Enterovirus, Varicella zoster virus, Hepatitis C virus, Parvovirus B19, West Nile virus Fungus: *Candida albicans, Actinomycosis*, *Aspergillus* Spirochete: *Borrelia burgdorferi, Treponema pallidum*
Inflammatory diseases	Systemic vasculitis: granulomatosis with polyangiitis, microscopic polyangiitis, Kawasaki disease, polyarteritis nodosa, Behçet disease Systemic lupus erythematosus Juvenile dermatomyositis Morphea Autoinflammatory syndromes Inflammatory bowel disease Hemophagocytic lymphohistiocytosis
Other	Drug-induced vasculitis Malignancy-associated vasculitis

References:

1. Gowdie P, et al. Primary and secondary CNS vasculitis. *J Child Neurol*. 2012; 27(11):1448-59.

10D. Pediatric autoimmune encephalitis (AE)

- Brain inflammation caused by antibodies directed against intracellular neuronal antigens, synaptic receptors, ion channels and other neuronal proteins
- Most common autoantibodies in children target the N-methyl-D-aspartate (NMDA) receptor, myelin oligodendrocyte glycoprotein (MOG) and glutamic acid decarboxylase 65 (GAD65)
- Addional antibody targets identified in children include aquaporin 4, dopamine-2 receptor, gamma-aminobutyric acid (GABA) (A) receptor, GABA(B) receptor, and glycine receptor
- Better prognosis if antibody target is extracellular or synaptic protein

- Clinical features of pediatric AE include seizures, memory deficits, behaviour changes, psychiatric symptoms, altered mental state, and focal neurological deficits
- Investigations
  - MRI may be normal or abnormal (findings often depend on antibody)
  - Serum testing may show inflammatory changes or may be normal
  - CSF may show increased white blood cell counts
  - EEG is often abnormal with seizures, epileptiform discharges and/or slowing
  - Psychoeducational testing often shows cognitive dysfunction, including impaired memory and slow cognitive processing speeds
- Diagnosis confirmed by identification of anti-neuronal antibodies in CSF or serum
- Management in collaboration with pediatric neurologist is recommended
- Treatment typically involves Corticosteroids, IVIG and other immunosuppressants, such as Rituximab

Anti-NMDA receptor encephalitis

- Most common neuronal antibody mediated encephalitis syndrome in children
- Clinical features
  - Typically evolves in stages
  - Prodrome of fever and headache
  - Subsequent development of psychiatric or behavioral manifestations, speech changes, decreased consciousness, seizures, choreoathetoid movements and autonomic instability (tachycardia, fever, hypertension, hypoventilation)

- Investigations
  - Diagnosed by presence of anti-NMDA receptor antibodies in CSF or serum (testing more sensitive in CSF)
  - MRI: frequently normal
  - CSF: usually abnormal (lymphocytic pleocytosis, increased protein, or oligoclonal bands)
  - EEG: often abnormal with diffuse slowing in children and more focal findings in teenagers and adults
  - Consider imaging for ovarian or testicular teratoma (association between anti-NMDA receptor encephalitis and tumor in adults)

- Treatment
  - First line therapy includes Corticosteroids, IVIG and/or plasma exchange
  - Rituximab may also be considered

- Outcome
  - Over 80% of patients have full recovery
  - Recovery may be slow with continued improvement seen up to 2 years after onset of symptoms

Autoimmune encephalitis associated antibodies to MOG

- Most common antibody associated with autoimmune demyelination
- Antibodies more common in children than adults
- Clinical features
  - Typically patients have symptoms consistent with ADEM, including encephalopathy, weakness, ataxia, sensory changes and/or seizures

  - Also associated with optic neuritis (especially bilateral) and transverse myelitis

- Investigations
  - Diagnosed by presence of anti-MOG antibodies in CSF or serum (testing more sensitive in serum)
  - MRI: focal or multifocal white matter lesions, longitudinally extensive myelitis and/or optic neuritis
  - CSF: neutrophilic pleocytosis may be present
  - EEG: non-specific slowing

- Treatment
  - First line therapy with Corticosteroids
  - IVIG and/or plasma exchange added for severe disease
  - Chronic immunotherapy, including IVIG, Azathioprine and//or Mycophenolate mofetil, may be considered for relapsing disease

- Outcome
  - Significant improvement expected within three months of initiating therapy
  - Disappearance of antibodies associated with monophasic course, whereas persistent antibodies are associated with relapsing course

Neuromyelitis Optica (NMO)

- Neuroinflammation due to antibodies to aquaporin-4
- Inflammation and demyelination mostly affecting the spinal cord and optic nerves

- Clinical features
  - Commonly present with acute optic neuritis and transverse myelitis
  - Other reported clinical features: encephalopathy, ophthalmoparesis, vertigo, nausea and vomiting, hyponatremia, inappropriate diuresis, intractable hiccups
  - Reported in association with Sjögren syndrome

- Investigations
  - Diagnosis requires identification of antibodies to aquaporin-4 in serum or CSF
  - CSF: pleocytosis and elevated protein
  - MRI: lesions in the periventricular regions of the third and fourth ventricles and in the periaqueductal grey matter

- Treatment
  - Initial therapy: Corticosteroids, IVIG and/or plasma exchange
  - Maintenance with second line agent should be considered (e.g. Azathioprine, Rituximab)

- Outcome
  - Frequent relapsing course with accumulation of neurological deficits

References:

1. Dalmau J, Graus F. Antibody-mediated encephalitis. *N Eng J Med* 2018; 378:840-51.
2. Armangue T, et al. Autoimmune encephalitis in children. *J Child Neurol* 2012; 27(11): 1460-9.

3. Van Mater H. Pediatric inflammatory brain disease: a diagnostic approach. *Curr Opin Rheumatol* 2014; 26(5):553-61.
4. Co DO, et al. Immune-mediated diseases of the central nervous system. *Pediatr Clin North Am* 2017; 64(1):57-90.

SECTION 11 – INFECTION & INFECTION-RELATED CONDITIONS

11A. 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, calcaneus, pelvis
- Organisms:
  - *Staphylococcus* most common
  - Group A *Streptococcus*, MRSA, atypical Gram negative bacteria and *Salmonella*

- Investigations
  - Blood work: Elevated WBC, ESR, CRP are non-specific
  - Blood cultures (sensitivity 60%), bone biopsy culture (sensitivity 80%)
  - Imaging:
    - X-rays important for exclusion of other diagnoses
    - X-ray signs include soft-tissue swelling, soft tissue 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
  - For the treatment of uncomplicated osteomyelitis, in which fever and symptoms resolve rapidly, 2 to 4 days of intravenous antibiotics can be followed by high dose oral antibiotics, for a total antibiotic course of 3 weeks.

Septic Arthritis

- Intra-articular infection with bacteria or rarely, fungi
- Medical emergency (surgical emergency if hip or shoulder involved)
- 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; often difficulty weight bearing if lower extremities are involved
- Joints involved:
  - Joints of 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 gonorrheae* in sexually active adolescents
  - *Salmonella* is commonly associated with sickle cell disease
  - *Mycobacterium tuberculosis* is an unusual cause of septic monarthritis 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

- Investigations
  - Joint aspiration - need to **aspirate** joint prior to antibiotics
    - Synovial fluid usually appears cloudy
    - Very high WBC count (50,000-300,000, > 75% neutrophils)
    - Gram stain positive
  - Blood work
    - Elevated WBC with neutrophilia, CRP and ESR are non-specific
  - Cultures
    - Synovial fluid culture (sensitivity 80%), blood culture (sensitivity 10%)
    - Require special handling if suspect *Neisseria* or *Mycobacterium tuberculosis*
    - *Kingella kingae* may require cultures for 7 days to isolate the organism
  - Imaging
    - Plain X-rays are not diagnostic, but may be helpful in excluding other disorders; may show an underlying osteomyelitis as the etiology of the septic arthritis; may demonstrate only increased soft tissue and capsular swelling
    - Ultrasound may be helpful in identifying/quantifying joint effusions and in joint aspiration for diagnostic purposes
    - MRI superior to CT in delineation of soft tissue structures and MRI changes may be seen as soon as 24 hours following infection; synovial enhancement detected in virtually all patients
    - Bone scans are not used for diagnositic evaluation

- Treatment
  - Antibiotics
    - Choice of antibiotics depends on presence of predisposing factors, age of child and suspected organism
    - Cefazolin often first line antibiotic or Clindamycin for penicillin allergic patients

        - Course of antibiotics typically 2 to 7 days of intravenous therapy (depending on organism) followed by high dose oral antibiotics for a total duration of 2 weeks
    - Surgical
        - May require surgical debridement, joint irrigation, drainage or recurrent aspiration for infections in deep joints (e.g. hips)

References:

1. Paakkonen M, Peltola H. Bone and Joint Infections. *Ped Clinic North Am* 2013; 60(2);425-436.
2. Castellazzi L, et al. Update on the management of pediatric acute osteomyelitis and septic arthritis. *Int J Mol Sci* 2016; 17(6):855-63.
3. Montgomery NI, Rosenfeld S. Pediatric osteoarticular infection update*. J Pediatr Orthop 2015;* 35(1):74-81.
4. Kocher MS, et al. A clinical practice guideline for treatment of septic arthritis in children: efficacy in improving process of care and effect on outcome of septic arthritis of the hip. *J bone Joint Surg Am* 2003; 85(6):994-9.

11B. 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 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 (marked pain, sometimes erythema over affected joint) and/or enthesitis
    - 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
    - Conjuctivitis occurs in about two thirds of children at onset
    - Skin lesions include erythema nodosum, circinate balanitis and keratoderma blennorrhagicum

- Investigations
    - Mild decrease in hemoglobin, mild leukocytosis with neutrophilia
    - Elevated inflammatory markers (platelets, immunoglobulins, ESR and CRP)
    - Autoantibodies (RF and ANA) are usually absent, but reactive arthritis is more common 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 inflammatory phase alter course of disease
- Rarely, Corticosteroids (oral or intra-articular) may be required
- Sulfasalazine is recommended in the management of resistant arthritis and enthesitis

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, et al. Infection and musculoskeletal conditions: Reactive arthritis. *Best Pract Res Clin Rheumatol* 2006; 20(6):1119-37.

11C. Acute Rheumatic Fever (ARF)

- Inflammatory illness following Group A Streptococcus (GAS) infection
- Diagnosis of ARF using Jones Criteria
  - Most recent revision of Jones Criteria in 2015 developed distinct criteria for low and moderate-high risk populations to increase sensitivity for patients at higher risk

2015 Revised Jones Criteria for Diagnosis of Acute Rheumatic Fever *For all patient populations with evidence of preceding GAS infection, diagnosis of initial ARF requires 2 major criteria or 1 major plus 2 minor criteria*		
Population risk	*Low risk populations* Cases of ARF ≤ 2/100,000 in school-aged children *or* rheumatic heart disease in ≤ 1/1000 at any age	*Moderate- and high-risk populations* Cases of ARF > 2/100,000 in school-aged children *or* rheumatic heart disease in > 1/1000 at any age
Major criteria	1. Carditis (clinical and/or subclinical) 2. Polyarthritis 3. Chorea 4. Erythema marginatum 5. Subcutaneous nodules	1. Carditis (clinical and/or subclinical) 2. Monoarthritis, polyarthritis or polyarthralgia 3. Chorea 4. Erythema marginatum 5. Subcutaneous nodules
Minor criteria	1. Polyarthralgia 2. Fever ≥ 38.5 degrees Celsius 3. ESR ≥ 60 and/or CRP ≥ 3.0 mg/dL (30 mg/L) 4. Prolonged PR interval (unless carditis is a major criterion)	1. Monoarthralgia 2. Fever ≥ 38 degrees Celsius 3. ESR ≥ 30 and/or CRP ≥ 3.0 mg/dL (30 mg/L) 4. Prolonged PR interval (unless carditis is a major criterion)

Adapted from Gewitz et al, Revision of Jones Criteria for the diagnosis of ARF, *Circulation 2015.*

- Clinical features
  - Arthritis in ARF has characteristics that help differentiate it from other causes
    - Characteristically migratory and additive starting with monoarthritis of large joints
    - Short duration of arthritis (hours to days)
    - Dramatic response to ASA/NSAIDs

  - Chorea often occurs as a late manifestation; may be diagnosed as being due to ARF without accompanying evidence of GAS infection if other causes (e.g. tic disorder, encephalitis, familial chorea, etc…) have been excluded
  - Subcutaneous nodules not often present as sole major manifestation

- Investigations
  - Infectious testing
    - Diagnosis of ARF requires supporting evidence of antecedent GAS infection with positive throat culture or elevated/rising streptococcal antibody titres
  - Echocardiography
    - Echo should be performed in all suspected cases of ARF
    - Common cardiac findings of ARF include pathological mitral valve regurgitation, pathologic aortic regurgitation, acute/chronic mitral or aortic valve changes

- Treatment
  - Antibiotic therapy: 10 days oral antibiotics, usually Penicillin
  - Anti-inflammatory therapy:
    - 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 may be used for carditis/cardiomegaly and heart failure +/- Digoxin
  - Carbamazepine, Phenobarbital, Haloperidol, or Chlorpromazine for chorea
  - Prophylaxis for recurrence:
    - Without carditis: Up to age 21 or 5 years post initial attack, whichever is later
    - With carditis, but without residual heart disease: Up to age 21 or 10 years post initial attack, whichever is later
    - With carditis and residual heart disease: Up to age 40 or 10 years post initial attack, whichever is later

References:

1. Karthikeyan G, Guilherme L. Acute rheumatic fever. *Lancet* 2018; 392(10142):161-74.
2. Gewitz MH, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of doppler echocardiography: a scientific statement from the American Heart Association. *Circulation* 2015;131(20):1806-18.
3. Gerber MA, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. *Circulation* 2009;119:1541-51.

11D. Post-Streptococcal Reactive Arthritis (PSRA)

- PSRA defined as inflammatory arthritis of ≥1 joint (with poor response to NSAID) associated with a recent Group A Streptococcus (GAS) infection, but not meeting the Jones criteria to diagnose acute rheumatic fever (ARF) (see Section 12C)
- Characteristics that help distinguish PSRA from ARF include the following:

	PSRA	ARF
Age distribution	Bimodal: 8-14 years and 21-37 years	5-15 years with peak around 12 years
Timing of disease onset following GAS infection	7-10 days	10-28 days

Pattern of joint involvement	Additive and persistent, non-migratory arthritis involving large, small and axial joints	Migratory, transient arthritis involving mainly large joints
Response to ASA/NSAID	Poor to moderate	Dramatic improvement
Carditis	Uncommon	Occurs in 60-70% of ARF patients

- Treatment
  - Antibiotic therapy: 10 days oral antibiotics, usually Penicillin
  - Anti-inflammatory therapy:
    - ASA or NSAID
    - Corticosteroids may be used in refractory cases
  - Prophylaxis for recurrence:
    - Controversial
    - Antibiotic prophylaxis may be given for up to 1 year after onset of symptoms with close monitoring for development of carditis; if clinically well after one year and echocardiogram remains normal, then may discontinue prophylaxis

- Prognosis
  - Most cases resolve spontaneously within a few weeks, but some recurrent or prolonged

Reference:

1. Bawazir Y, et al. Post-streptococcal reactive arthritis (PSRA). *Curr Rheumatol Rev* 2019 [Epub ahead of print].
2. Van der Helm-van Mil AH. Acute rheumatic fever and poststreptococcal reactive arthritis reconsidered. *Curr Opin Rheumatol* 2010; 22(4):437-42.

11E. Lyme Disease

- Complex tic-borne disease with multiple organ involvement (skin, joint, neurologic)
- 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
- Incidence continues to rise
- Clinical manifestations divided into early and late manifestations
  - Early manifestations develop within weeks or few months of tick bite
  - Late manifestations 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	Chronic encephalomyelitis
	Lymphocytic meningitis	
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 and resolves within four weeks if untreated
  - Arthritis is typically monoarthritis, but may sometimes be polyarthritis

- Investigations
  - Elevated ESR
  - CSF lymphocytic pleocytosis
  - Serologic confirmation (initial screening performed with ELISA, then positive or equivocal tests confirmed with Western blot)
  - Do not test for Lyme disease as a cause of musculoskeletal symptoms without an exposure history and appropriate examination findings *(*highlighted in *Choosing Wisely: Pediatric Rheumatology Top 5 by American College of Rheumatology)*

- 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
  - Post-exposure prophylaxis:
    - If tick removed (while in endemic area) and was engorged, may benefit from Doxycycline 200 mg (or 4.4 mg/kg) PO as a single dose within 72 hours of removing tick (however, not enough data to recommend amoxicillin prophylaxis)

- Prevention
  - Appropriate clothing (e.g. long pants and sleeves)
  - Tick repellents (e.g. DEET, permethrim) applied to clothing
  - Search for and remove ticks promptly with tweezers

References:

1. Shapiro ED. Lyme disease. *New Engl J Med* 2014; 370(18):1724-31.
2. Sood SK. Lyme disease in children. *Infect Dis Clin North Am* 2015: 29(2);281-94.
3. Eldin C, et al. Review of European and American guidelines for the diagnosis of Lyme borreliosis. *Med Mal Infect* 2019;49(2):121-32.
4. Onyett H, et al. Lyme disease in Canada: Focus on children. Canadian Pediatric Society position statement. *Paediatr Child Health* 2019. [Epub ahead of print]

SECTION 12 – PAIN SYNDROMES

12A. Chronic Pain Syndromes

- Primary pain syndromes may have a greater impact on patients' and families' quality of life than inflammatory disease
- Many children with chronic musculoskeletal (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 and 10 years of age
- Typical history is deep aching cramping pain in bilateral thighs or calves, usually at night and intermittently waking the patient from sleep
- Improve with gentle massage, heat and/or analgesia
- Symptoms disappear by morning
- Normal physical examination
- Investigations not necessary for diagnosis

Fibromyalgia (aka Generalized Amplified Musculoskeletal Pain)

- Chronic generalized pain syndrome
- May be triggered by change in physical activity due to injury or chronic illness

- Clinical features
  - Widespread pain with gradual onset and chronic course lasting at least 3 months
  - Associated with fatigue, poor sleep and waking feeling unrefreshed
  - Pain may be affected by anxiety, stress, activities and weather
  - Symptoms may wax and wane over time
  - Absence of physical findings that indicate another condition (*caveat – fibromyalgia may occur in context of another medical condition (e.g. JIA) but would be disproportionate for that condition and would involve pain at sites that are not affected by the disease)*

- Diagnosis
  - No confirmatory blood or imaging investigations, as these are typically normal
  - Tender points are no longer included in most recent diagnostic criteria due to inconsistencies in examination
  - Most recent criteria for juvenile fibromyalgia were adapted from adult 2010 ACR criteria for fibromyalgia (sensitivity 83.8%, specificity 89.4%) and published in 2016

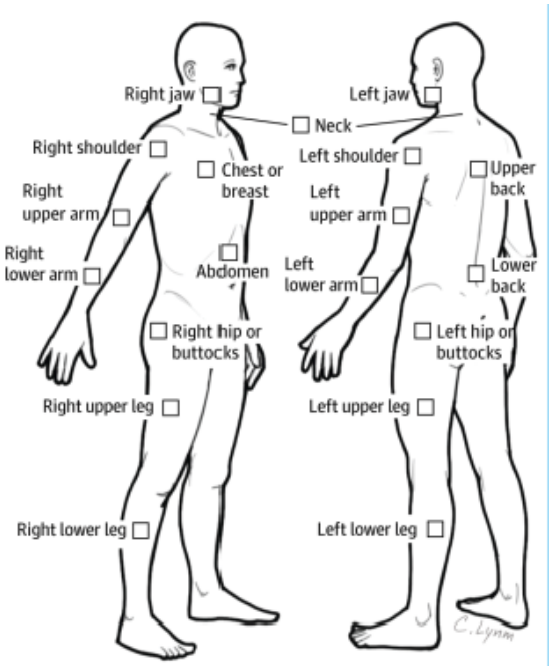
Adapted Juvenile Fibromyalgia Diagnostic Criteria

Diagnosis requires all 3 of the following criteria:

1. Widespread pain index (WPI) ≥7 points and symptom severity (SS) scale ≥5 points or WPI 3-6 points and SS scale ≥9 points *(see next page for WPI and SS scale)*
2. Symptoms have been present at a similar level for at least 3 months
3. Patient does not have a disorder that would otherwise explain the pain

Widespread Pain Index
(1 point per check box; score range 0-19 points)

Patient instructed to indicate if they have had pain or tenderness during the past 7 days in the areas shown below and to check the boxes in the diagram for each area in which they have had pain or tenderness.



Symptom Severity Scale
(Score range 0-12 points)

Patient instructed to indicate the severity of the following symptoms during the past 7 days using the scale below:

Severity	*Description*
0	*No problem*
1	*Slight or mild problem: generally mild or intermittent*
2	*Moderate problem: often present and/or at moderate level of intensity*
3	*Severe problem: continuous, life-disturbing symptoms*

Symptoms	*Severity*			
	0	1	2	3
Fatigue				
Trouble thinking or remembering				
Waking up tired (unrefreshed)				
Somatic symptoms* in general				

* Somatic symptoms include: muscle pain, irritable bowel syndrome, fatigue, thinking or remembering problem, weakness, headache, abdominal pain or cramps, nausea, loss of appetite, numbness or tingling, dizziness, insomnia, depression, constipation, chest pain, shortness of breath, blurred vision, dry mouth, dry eyes, itching, wheezing, ringing in ears, heartburn, hair loss, easy bruising, frequent or painful urination, bladder spasms.

Final SS score is sum of severity of first 3 symptoms (fatigue, waking unrefreshed and cognitive symptoms each on a scale of 0-3 points) plus the score of severity of somatic symptoms in general (0-3 points).

Criteria and scales adapted from:
1. Zemel L, Blier PR. Juvenile fibromyalgia: A primary pain or pain processing disorder. Semin Pediatr Neurol 2016; 23:231-41.
2. Clauw, DJ. Fibromyalgia: A clinical review. JAMA 2014. 311(15):1547-55.

- Treatment strategies for chronic pain in children and adolescents that are supported by research evidence include:
  - Education about chronic pain
  - Progressively increasing aerobic physical activity over time to a target of 60 minutes daily
  - Improving sleep hygiene, including consistent bed and waking times, and eliminating long naps during the day
  - Learning coping strategies for chronic pain
  - Counselling, cognitive behavioural therapy (CBT), other psychotherapy and/or biopsychosocial approaches to manage anxiety, low mood, and other consequences and contributors to pain
  - Intensive interdisciplinary pain treatment, including physiotherapy, recommended for more severe pain-related disability
- Medications less effective in childhood fibromyalgia
- Better outcomes in children compared to adults

Complex Regional Pain Syndrome (CRPS) Type I (previously known as Reflex Sympathetic Dystrophy)

- Chronic pain often involving peripheral extremity (lower extremities more common in kids)
- Initiating mild injury or cause of immobilization can lead to CRPS Type I
- Continuing pain, allodynia, and/or hyperalgesia in which pain is disproportionate to inciting event
- Associated autonomic signs, including swelling, changes in skin blood flow leading to discolouration, and/or abnormal sweating in the region of pain
- Diagnosis using Budapest clinical criteria (see below) involves exclusion, therefore no other condition should 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

Budapest Clinical Criteria for Complex Regional Pain Syndrome

Diagnosis requires all 4 of the following critieria:

1. Continuing pain, disproportionate to inciting event
2. At least 1 symptom (reported) in 3 or more categories*
3. At least 1 sign (at evaluation) in 2 or more categories*
4. No other diagnosis can better explain the patient's signs and symptoms

* *Categories*

- Sensory: hyperesthesia, hyperalgesia or allodynia
- Vasomotor: temperature or skin colour asymmetry
- Sudomotor/Edema: edema or sweating asymmetry
- Motor/Trophic: decreased range of motion, motor dysfunction, trophic changes in skin, hair and nails

References:

1. Weiss JE, Stinson JN. Pediatric pain syndromes and non-inflammatory musculoskeletal pain. *Pediatr Clin North Am* 2018; 65(4):801-26.
2. Zemel L, Blier PR. Juvenile fibromyalgia: A primary pain or pain processing disorder. *Semin Pediatr Neurol* 2016; 23:231-41.
3. Sherry DD, et al. The treatment of juvenile fibromyalgia with an intensive physical and psychosocial program. *J Pediatr* 2015; 167(3):731-7.
4. Hechler TH, et al. Systematic review on intensive interdisciplinary pain treatment of children with chronic pain. *Pediatrics* 2015; 136(1):115-27.
5. Kashikar-Zuck S, et al. Longitudinal evaluation of patient-reported outcomes measurement information systems measures in pediatric chronic pain. *Pain* 2016; 157(2):339-47.
6. Weissmann R, Uziel Y. Pediatric complex regional pain syndrome: a review. *Pediatr Rheumatol* 2016; 14(29):1-10.

12B. Hypermobile Joint Syndrome

- Joint pain caused by idiopathic increased flexibility – may be generalized or local
- Pain typically occurs after activity
- More common in females
- Need to consider and exclude syndromes associated with generalized joint hypermobility (e.g. Ehlers-Danlos, Marfan, Down, Turner, Stickler and osteogenesis imperfecta syndromes)
- 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 ≥6/9 points prior to puberty and ≥5/9 points after puberty

- 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
  - Education and reassurance
  - Activity modification (avoid exacerbating activity)
  - Physiotherapy to strengthen muscles around affected joints
  - Orthotics and supportive footwear
  - Cognitive behavioural therapy for more severely affected individuals

- Course
  - Can predispose to injuries in sports
  - Does not seem to increase prevalence of joint dislocations in early teens
  - In general, quality of life may be lower due to frequent joint pain

References:

1. Weiss JE, Stinson JN. Pediatric pain syndromes and non-inflammatory musculoskeletal pain. *Pediatr Clin North Am* 2018; 65(4):801-26.
2. Cattalini M, et al. When flexibility is not necessarily a virtue: a review of hypermobility syndromes and chronic or recurrent musculoskeletal pain in children. *Pediatr Rheumatol Online* J 2015; 13(1):40.
3. Pacey V, et al. Joint hypermobility syndrome: A review for clinicians. *J Paediatr Child Health* 2015; 51(4):373-80.

SECTION 13 – PEDIATRIC RHEUMATOLOGY EMERGENCIES

13A. Introduction to Pediatric Rheumatologic Emergencies

- Can present with a wide spectrum of clinical illness, affecting virtually any organ
- Prompt recognition and treatment may be organ and even life saving
- May occur in the context of a pre-existing rheumatic disease or may be the initial presentation

13B. Neonatal Lupus Erythematosus with Complete Heart Block (CHB)

- 85% of neonates with CHB have transplacentally acquired maternal antibodies to Ro/SSA or La/SSB
- Prevalence of CHB is 0.65-2% in infants of anti-Ro/SSA women; in affected mother, likelihood of recurrence is 19%
- 1 year mortality up to 54% if untreated
- Rheumatology consultation may be requested urgently for complete heart block with signs of active inflammation (such as pericardial effusion or carditis), congestive heart failure or antenatal fetal hydrops

- Clinical Presentation
  - Bradycardia with potential congestive heart failure (CHF)
  - May already have been diagnosed antenatally
  - May manifest other findings typical of NLE such as rash, hepatitis and cytopenias

- Diagnostic Investigations
  - Confirm CHB with electrocardiogram
  - Cardiology assessment with echocardiogram to assess for active inflammation or endocardial fibroelastosis (EFE)
  - Presence of antinuclear antibodies, specifically those against Ro/SSA and La/SSB in maternal and neonatal serum
  - Elevated troponin levels may indicate secondary myocardial ischemia

- Treatment
  - Infants with complete heart block may need pacemaker soon after birth
  - If active inflammation is seen on echocardiogram, may consider steroids +/- IVIG (treatment will depend on presence of CHF/myocarditis and EFE)

References:

1. Izmirly PM, et al. Progress in the pathogenesis and treatment of cardiac manifestations of neonatal lupus. *Curr Opin Rheumatol* 2017: 29(5):467-72.
2. Hornberger LK, Al Rajaa N. Spectrum of cardiac involvement in neonatal lupus. *Scan J Immunol* 2010;72(3):189-97.

13C. Macrophage Activation Syndrome

- Macrophage activation syndrome (MAS) is a potentially life-threatening multisystem inflammatory condition
- Consider in the broad differential of an unexplained persistently febrile child, especially in the presence of pancytopenia – a high index of suspicion is required
- MAS may complicate a number of autoimmune diseases (e.g. systemic arthritis/JIA, SLE, Kawasaki disease most commonly)
- May occur at any time during the disease course (especially following a change in therapy) or may be part of the initial presentation
- Classified as a form of secondary hemophagocytic lymphohistiocytosis (HLH)
    - Primary HLH is an inherited multi-system inflammatory disease caused by genetic 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 associated with malignancy or infection, especially EBV
    - Primary and secondary HLH share similar clinical and biochemical features
    - Recent development of an MAS/HLH score to discriminate between primary HLH and MAS includes age, splenomegaly, neutrophil count, platelet count, hemoglobin and fibrinogen

- Diagnostic clinical and laboratory features of MAS
    - Fever (continuous/persistent)
    - Splenomegaly
    - Cytopenias (anemia, thrombocytopenia, neutropenia) or, in systemic JIA, may see decrease in previously elevated cell counts
    - 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 headache, confusion, seizures, and coma
    - Respiratory distress including ARDS, pulmonary dysfunction
    - Lymphadenopathy
    - Changes in blood pressure and heart rate
    - MAS may be life-threatening and can result in death
    - Critically important to monitor clinical features and trends in laboratory investigations

- Diagnostic criteria
    - No single universally-accepted diagnostic criteria for MAS
    - Different criteria using a range of abnormal laboratory values have been proposed for various diseases
    - Most criteria involve a combination of the features listed above
    - A high index of suspicion is needed to make the diagnosis

- Additional urgent investigations prior to starting treatment (especially prior to IVIG)
  - Cultures of blood, urine and throat should be ordered to rule out an underlying bacterial infection since it will take time to receive results
  - Infectious serology and PCR (e.g. EBV, CMV, Parvovirus B19, Herpes viruses) may be helpful to diagnose an underlying viral infection in primary or secondary HLH
  - If the child does not have an established diagnosis and a systemic rheumatologic condition is suspected, autoantibodies (e.g. ANA, ENA panel, rheumatoid factor, ANCA) and direct antiglobulin test should be ordered
  - Soluble CD163, soluble IL-2 receptor, NK cell function and lymphocyte typing may be helpful to identify underlying immune dysfunction and/or monitor inflammation

- Treatment
  - Very close monitoring of labs, vital signs, and fluid input/output
  - All patients require supportive management
    - Fluids for hypotension
    - Blood products (platelets, red blood cells)
    - Respiratory support
  - Consider informing and/or involving the pediatric intensive care unit early – if site does not have ability to provide critical care, consider transfer to a different institution
  - If patient is critically ill and complete evaluation is not possible, additional treatment should be commenced without delay
  - If infection suspected, concurrent treatment with appropriate antimicrobial therapy should be started
  - Immunosuppressive therapy
    - IVIG often used initially during diagnostic work-up, but is rarely sufficient
    - Current HLH protocol involves a step-wise algorithm starting with high-dose or pulse IV Corticosteroids (may use Dexamethasone or Methylprednisolone) and followed by addition of Cyclosporine and then Etoposide if there is no improvement
    - Plasmapheresis has been used in life-threatening disease
    - Case series suggest that biologic agents, in particular Anakinra (anti-IL-1), may be effective treatments for MAS
    - In children with primary HLH or refractory HLH, bone marrow transplant is definitive treatment

References:

1. Sen ES, et al. Macrophage activation syndrome. *Indian J Pediatr* 2016; 83(3):248-53.
2. Minoia F, et al. Development and initial validation of the macrophage activation syndrome/primary hemophagocytic lymphohistiocytosis score, a diagnostic tool that differentiates primary hemophagocytic lymphohistiocytosis from macrophage activation syndrome. *J Pediatr* 2017;187:72-8.
3. Borgia RE, et al. Features, treatment, and outcomes of macrophage activation syndrome in childhood-onset systemic lupus erythematosus. *Arthritis Rheumatol* 2018;70(4):616-624.
4. Ravelli A, et al. 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European league against rheumatism/American College of rheumatology/paediatric rheumatology international trials organization collaborative initiative. *Ann Rheum Dis* 2016;75(3):481-9.
5. Wang W, et al. Macrophage activation syndrome in Kawasaki disease: more common than we thought? *Semin Arthritis Rheum* 2015; 44(4):405-10.

13D. Pulmonary Renal Syndrome

- Should be considered in any child presenting with respiratory distress and renal involvement
- Clinical presentation of diffuse alveolar hemorrhage in combination with rapidly progressive glomerulonephritis
- May be rapidly fatal from devastating pulmonary hemorrhage or progressive renal failure

Causes of pulmonary renal syndrome

Specific	Systemic lupus erythematosus (SLE) Granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis) Microscopic polyangiitis (MPA) Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss) Henoch-Schönlein purpura (HSP, now also known as IgA vasculitis) Goodpasture syndrome
Non-specific	Pulmonary edema Pulmonary embolism } in a child with renal disease Pulmonary infection Renal disease in a child with pulmonary disease, usually infection Hemolytic uremic syndrome IgA nephropathy

- Clinical Presentation
  - Dyspnea and cough associated with hypoxemia in room air
  - Frank hemoptysis may not be present in all cases
  - Renal involvement/failure: oliguria, hypertension, nephritic syndrome, nephrotic syndrome

- Diagnostic Investigations
  - Tests to assess presence of pulmonary hemorrhage or vasculitis
    - Complete blood count showing anemia (often microcytic) or decreasing hemoglobin, elevated reticulocyte count
    - Chest X-ray may show diffuse alveolar infiltrates
    - Chest CT may show patchy ground glass opacities or nodules
    - Pulmonary function tests may show an increase in DLCO consistent with intra-alveolar bleeding
    - Bronchoscopy may demonstrate fresh blood and bronchalveolar lavage (BAL) demonstrates presence of red blood cells and hemosiderin-laden macrophages; fluid should also be sent for culture to exclude infection
  - Tests to assess presence of renal involvement
    - Urinalysis demonstrating proteinuria, hematuria, cellular casts and/or elevated urine protein:creatinine ratio
    - Increases in creatinine and/or urea

- Tests to determine underlying cause of pulmonary renal syndrome
  - Autoantibodies and immune markers:
    - Positive ANCA in GPA, MPA, EGPA (see Section 5)
    - ANA, anti-dsDNA, antibodies to extractable nuclear antigens, and antiphospholipid antibodies may be positive in SLE
    - Anti-glomerular basement membrane (GBM) antibodies seen in Goodpasture syndrome
    - Complement levels decreased in SLE
  - Renal biopsy:
    - ANCA-associated vasculitis: pauci-immune necrotizing crescentic glomerulonephritis
    - SLE: glomerular immune deposits with histologic changes of lupus nephritis
    - Goodpasture syndrome: IgG deposition along glomerular basement membrane with crescentric changes
    - HSP: deposition of IgA-containing immune complexes in glomeruli with mesangial cell proliferation, glomerular sclerosis and crescent formation
  - Skin biopsy:
    - HSP: leukocytoclastic vasculitis with IgA deposits
    - SLE: immunofluorescence demonstrates immunoglobulins and complement at the dermal-epidermal junction; may see damage of keratinocytes, follicular plugging, basal layer vacuolation, perivascular infiltrates and dermal mucin deposition

- Treatment
  - Early recognition and management of pulmonary renal syndrome is critical
  - Initial therapy is identical for any underlying cause of pulmonary renal syndrome and should be started promptly
  - Supportive therapy may include oxygen, intubation, ventilation and/or dialysis
  - Initial immunomodulatory therapy with pulse IV methylprednisolone followed by high dose prednisone (1-2 mg/kg/day)
  - Cyclophosphamide or Rituximab may be used depending on the underlying disease
  - Addition of plasmapheresis may be considered; commonly done for anti-GBM disease but benefits less clear for ANCA-associated vasculitis (PEXIVAS trial)
  - If concurrent infection cannot be excluded, appropriate anti-microbial coverage should be considered

References:

1. West SC, et al. Pulmonary Renal Syndrome: a life threatening but treatable condition. *Postgrad Med J* 2013: 89(1051):274-83.

13E. Catastrophic Antiphospholipid Syndrome (APS)

- A severe variant of the classic APS, characterized by:
  - Multiple organ dysfunction and failure developing over short period of time
  - Histopathological evidence of multiple small vessel occlusions, although the patient may not have obvious thrombosis
  - Laboratory confirmation of the presence of antiphospholipid antibodies (aPL), usually in high titre

- Multisystem microvascular thrombosis with a secondary systemic inflammatory response syndrome (SIRS) due to tissue damage
- 2/3 of patients have an underlying trigger (infection, surgery, trauma, malignancy, and flares of SLE) and children are more likely to have infectious trigger compared to adults
- Catastrophic APS more likely to be first manifestation of APS in children compared to adults
- Majority of catastrophic APS patients do not have underlying rheumatic disease
- Occurs in <1% of patients with APS; mortality rate of 33-50%

- Clinical Presentation
  - May be mistaken for overwhelming sepsis
  - Cardiopulmonary manifestations are the most frequent at presentation
    - May look like acute respiratory distress syndrome
    - Pulmonary embolus or alveolar hemorrhage may occur
  - CNS features are next most common
    - Cerebral infarction, seizures, and encephalopathy
    - Cerebral venous sinus thrombosis
  - Renal and abdominal involvement is common
    - Renal failure, proteinuria, significant abdominal pain
    - 80% of patients experience an intra-abdominal thrombotic event over the course of an episode
  - Clinical signs of systemic inflammation and lab features of DIC

Diagnostic Criteria for Catastrophic Antiphospholipid syndrome

Definite diagnosis requires all of the following criteria:

- Evidence of vessel occlusion, or effect of vessel occlusion, in ≥3 organs or tissues
- Occurrence of diagnostic features simultaneously or in <1 week
- Histopathologic evidence of small vessel occlusion in at least one affected organ or tissue
- Presence of antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin) persistent over at least 6 weeks

Probable diagnosis if:

- Only 2 organ systems affected, or
- Occurrence of two diagnostic features in <1 week and another within 4 weeks, or
- Histopathologic demonstration of small vessel occlusion not possible
- Unable to demonstrate persistence of antibodies due to death

- Diagnostic Investigations
  - Tests to confirm presence of thrombotic disorder
    - Look for organ infarction (kidney, spleen, or bowel) on imaging or organ failure (cardiac or renal) with markers of DIC, coagulation dysfunction, and/or peripheral destruction of blood elements
    - May require tissue sample
  - Tests to confirm presence of aPL antibodies
    - Lupus anticoagulant, anti-cardiolipin, anti-β2-glycoprotein I

        - Novel aPL antibodies (e.g. anti-phosphatidylserine-prothrombin antibodies) also reported in catastrophic APS cases but testing not widely available
    - Investigate underlying triggers for the episode
        - Cultures and infectious serology to assess for infection (respiratory, skin, urinary tract)
        - Bone marrow biopsy or imaging may be needed to assess for an underlying malignancy
        - Investigations for a systemic inflammatory condition, such as SLE, may be indicated if the child does not have a previous diagnosis

- Treatment
    - Patients are often critically ill
    - ICU support should be available and anticipated
    - May need acute measures such as mechanical ventilation or dialysis
    - Treatment aimed at removing triggering factor, if known, eliminating existing thrombus, and controlling SIRS
    - Empiric antibiotics until infection ruled out
    - Targeting two main pathologic processes may reduce mortality
        - Thrombosis: treated acutely with Heparin; may also need vasodilators, fibrinolytics, and embolectomy; long-term anticoagulation with either Low Molecular Weight Heparin or Warfarin
        - SIRS: treated with systemic corticosteroids, therapeutic plasma exchange (TPE) and IVIG (should be given after TPE)
    - Other agents for severe or refractory cases include Rituximab and Eculizumab (anti-C5 agent)

References:

1. Go EJL, O'Neil KM. The catastrophic antiphospholipid syndrome in children. *Curr Opin Rheumatol* 2017; 29(5):516-22.
2. Rodríguez-Pintó I, et al. CAPS Registry Project Group (European Forum on Antiphospholipid Antibodies). Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the International CAPS Registry. *Autoimmun Rev* 2016; 15:1120-24.
3. Asherson RA, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus* 2003; 12(7):530-4.
4. Litvinova E, et al. Prevalence and signification of non-conventional antiphospholipid antibodies in patients with clinical APS criteria. *Front immunol* 2018;9:2971

13F. Cardiac Tamponade

- Uncommon but life-threatening complication of pericarditis with effusion
- Autoimmune cause identified in 13-30% of children with tamponade
- May occur in children with known rheumatologic disease or as part of initial presentation

- Clinical Presentation
    - Typically presents with dyspnea, tachypnea and chest pain
    - May have elevated jugular venous pressure, facial edema or plethora, tachycardia, pulsus paradoxus, muffled heart sounds, and if advanced, hypotension
    - Fever is common

  - May see clinical features suggestive of associated rheumatic disease (e.g. SLE, systemic JIA)

- Diagnostic Investigations
  - ECG typically shows sinus tachycardia and may also show low voltage QRS complexes, ST elevation/PR segment depression, and electrical alternans
  - Chest X-ray may show a large cardiac silhouette
  - Echocardiography may demonstrate a moderate to large pericardial effusion, findings of chamber collapse, respiratory variation in volumes and flows, IVC dilatation due to increased central venous pressure

- Treatment
  - Initial priority is to stabilize cardiorespiratory status and to restore adequate cardiac output by removal of pericardial fluid (pericardiocentesis)
  - Temporizing measures can be used such as IV fluids or sympathomimetics
  - Corticosteroids are the mainstay of acute treatment for life-threatening conditions
  - Other immunosuppressive agents may be added if there is insufficient improvement or if required to treat an underlying rheumatic disease and may include NSAIDs, Colchicine, and Anti-IL-1 agents

References:

1. Imazio M, et al. Contemporary management of pericardial effusion: practical aspects for clinical practice. *Postgrad Med* 2017; 129(2):178-186.
2. Mok GC, Menahem S. Large pericardial effusions of inflammatory origin in childhood. *Cardiol Young* 2003; 13(2):131-6.
3. Maharaj SS, Chang SM. Cardiac tamponade as the initial presentation of systemic lupus erythematosus: a case report and review of the literature. *Pediatr Rheumatol Online J* 2015; 13:9.

13G. Kawasaki Disease (KD) Shock Syndrome (KDSS)

- Uncommon but life-threatening complication of KD
- Occurs in <10% of children diagnosed with KD; older age of onset
- Children often present with shock before the KD diagnosis is made and more likely to have incomplete presentation
- May have more prominent inflammatory markers in early phase and higher risk of coronary artery dilatation

- Clinical Presentation
  - Hemodynamic instability with tachycardia, hypotension and poor peripheral perfusion
  - May have muffled heart sounds or gallop rhythm
  - Typically associated with more severe manifestations of KD, although not necessarily longer duration of fever
  - KDSS is a multisystem disease with impaired cardiac function, gastrointestinal symptoms (e.g. vomiting), respiratory failure, encephalopathy, and acute renal injury
  - More likely to demonstrate IVIG resistance

- Diagnostic Investigations
  - Compared to children with KD who are hemodynamically stable, children with KDSS are more likely to have:
    - Higher CRP and ESR
    - Higher white blood cell and neutrophil counts with bands
    - Lower hemoglobin and platelet counts
    - Lower sodium and albumin levels
    - Consumptive coagulopathy with low platelet counts, increased D-dimers and prolonged PTT
    - Emerging data shows higher levels of IL-6, IL-10 and IFN-ɣ (if testing available at center) may be useful to distinguish KDSS from KD
  - ECG typically shows sinus tachycardia
  - Echocardiography:
    - Impaired left ventricular systolic function with a lower ejection fraction and mitral regurgitation
    - More likely to develop coronary artery abnormalities

- Treatment
  - Initial priority is to stabilize cardiorespiratory status
  - Require careful fluid resuscitation – large fluid boluses not recommended as these may precipitate congestive heart failure
  - May require inotropic and/or vasopressor support
  - IVIG and ASA remain mainstay of therapy; however, IVIG resistance is more common and may need to progress to further therapies, such as corticosteroids (see Section 5C)
  - If treated early and aggressively, most children survive without sequelae

References:

1. Ma L, et al. Clinical Manifestations of Kawasaki Disease Shock Syndrome. *Clin Pediatr (Phila)* 2018; 57(4):428-35.
2. Kanegaye JY, et al. Recognition of a Kawasaki Shock Syndrome. *Pediatrics* 2009; 123(5):e783-9.
3. Li Y, et al. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN-γ as biomarkers for early recognition. *Pediatr Rheumatol Online J* 2019; 17(1):1.

13H. Renal Crisis in Systemic Sclerosis (SSc)

- Rare and potentially life-threatening complication of SSc
- High rate of mortality and progression into end-stage renal disease (ESRD)
- Incidence of 4-6% in SSc patients, primarily in diffuse SSc
- Usually develops within the first 4 years of onset of the disease
- Risk factors: presence of anti-RNA polymerase antibodies, rapid progression of skin thickening, congestive heart failure, high dose glucocorticoids,

- Clinical Presentation
  - Reflects thrombotic microangiopathy of kidney similar to thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
  - Acute renal failure without warning signs

  - Sudden onset of moderate to severe hypertension (normal blood pressure in 10% of renal crisis cases)
  - May be accompanied by hypertensive encephalopathy, congestive heart failure, arrhythmia, or acute cerebrovascular event

- Diagnostic Investigations
  - Elevated creatinine, proteinuria and hematuria
  - Thrombotic microangiopathy: hemolytic anemia and thrombocytopenia
  - Renal biopsy findings include proliferation and thickening of arcuate and interlobar arteriole intima, leading to narrowing or full obliteration of vessels
  - CXR may demonstrate pulmonary edema
  - Eye exam may identify retinal hemorrhages or exudates
  - MRI/CT head may show signs of stroke

- Treatment
  - Rapid (within 72 hr) control of blood pressure
    - Provides stabilization of renal function in 70% of patients
  - ACE inhibitors (Captopril most widely studied)
  - Plasma exchange to be considered if intolerant to ACE inhibitor or concomitant hemolytic microangiopathy
  - Adjunctive treatment with endothelin receptor antagonist (e.g. Bosentan) or Eculizumab (anti-C5a) if refractory
  - If ESRD: dialysis and possibly transplantation

References:

1. Gordon SM, et al. Risk Factors for Future Scleroderma Renal Crisis at Systemic Sclerosis Diagnosis. *J Rheumatol* 2019;46(1):85-92.
2. Zanatta E, et al. Therapy of Scleroderma Renal Crisis: State of the Art. *Autoimmun Rev* 2018;17(9):882-9.
3. Guillevin L and Mouthon L. Scleroderma Renal Crisis. *Rheum Dis Clin N Am* 2015; 41:475-88.

13I. Acute Adrenal Crisis

- Many children with rheumatic diseases are treated with systermic glucocorticosteroids in high doses to achieve disease control or lower doses for prolonged periods of time to maintain remission
- Adrenal crisis may occur during withdrawal of therapy or at times of stress (e.g. illness, disease flare) requiring additional steroids
- Patients at risk of adrenal suppression include those who have used corticosteroids for more than a 2 week period at >2mg/kg or multiple courses totalling >3 weeks in the previous 6 months
- Associated with higher mortality in the pediatric population

- Clinical Presentation
  - May be variable
  - Many signs and symptoms are non-specific and can be mistaken for symptoms of an intercurrent illness or the underlying condition being treated
  - Signs and symptoms include:

  - Arthralgias, myalgias, generalized weakness
  - Headache
  - Abdominal pain, nausea, vomiting, diarrhea
  - Fever
  - Hypotension
  - Decreased level of consciousness, lethargy
  - Unexplained hypoglycemia
  - Hyponatremia
  - Seizures, coma

- Treatment
  - Hydrocortisone injection 100 mg/m2 (maximum 100 mg) IV/IM stat with IV normal saline volume expansion, followed by hydrocortisone 25 mg/m2 every 6 hours (maximum 25 mg every 6 hours)
  - Consult endocrinologist on call for further advice

- Prevention
  - Stress dosing with hydrocortisone during illness, fever or surgery
  - Education of patient and family

References:

1. Levy-Shraga Y, Pinhas-Hamiel O. Novel insights into adrenal insufficiency in childhood. *Minerva Pediatr* 2014; 66(6):517-32.
2. Shulman DI, et al. Adrenal insufficiency: still a cause of morbidity and death in childhood. *Pediatr* 2007; 119(2):e484-94.
3. Huber BM, et al. Adrenal insufficiency after glucocorticoid withdrawal in children with rheumatic diseases. *Acta Paediatr* 2010; 99(12):1889-93.

SECTION 14 – MEDICATIONS

Medications are listed in alphabetical order by their generic names with the exception of Corticosteroids and NSAIDs, which are listed by their categories. A table summarizes the mechanisms of action of the monoclonal antibody (mAb) and fusion protein biologic agents.

- **Abatacept**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: Selectively inhibits co-stimulatory signal for T-cell activation
  - Dose: 10 mg/kg/dose if <75 kg; 750 mg if 75-100 kg; or 1000 mg if >100 kg via IV every 2 weeks for 3 doses then every 4 weeks thereafter
  - Side effects: infusion reactions, anaphylaxis, GI upset, bronchospasm, infections, potential risk of future malignancy (very rarely)

- **Adalimumab**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: recombinant mAb that binds to circulating and cell surface TNFα
  - Dose: 24 mg/m^2/dose if <15 kg; 20 mg if 15-30 kg; or 40 mg if >30 kg via SC injection every 2 weeks (can be given weekly when clinically indicated)
  - Side effects: injection site reactions, headaches, infections, cytopenias, potential risk of future malignancy, demyelinating disease, new or worsening heart failure (adult patients)
  - Monitoring: CBC, differential, AST, ALT, creatinine every 3-6 months

- **Anakinra**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: human recombinant form of IL-1 receptor antagonist (IL-1Ra)
  - Dose: 1-2 mg/kg/dose (max 100 mg) SC daily; in sJIA, may titrate up to 4 mg/kg/dose (max 200 mg) SC daily
  - Side effects: injection site reactions, flu-like symptoms, infections
  - Monitoring: Neutrophil count prior to initiating; monthly for 3 months; then quarterly

- **Azathioprine**
  - Class: antimetabolic agent; purine analogue
  - Mechanism of action: interferes with DNA synthesis; inhibits T cells and monocytes
  - Dose: 2-3 mg/kg/day (max 150 mg) PO daily
  - Side effects: nausea, diarrhea, oral ulcers, rash, cytopenias, pancreatitis, hepatotoxicity
  - Monitoring: CBC, differential and liver enzymes every 2 weeks until achieve stable dose then every 2 months; consider thiopurine methyltransferase (TPMT) genetic testing if abnormally low CBC (e.g., neutropenia) unresponsive to dose reduction

- **Belimumab**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: human IgG1 neutralizing monoclonal antibody against B-lymphocyte stimulating factor (also known as B-lymphocyte simulator [BLyS])
  - Dose: 10 mg/kg via IV every 2 weeks for 3 doses then every 4 weeks
  - Side effects: infusion reactions, nausea, diarrhea, headaches, infections, potential risk of future malignancy (very rarely)
  - Monitoring: CBC (e.g., leukopenia) and liver enzymes with each infusion

- **Biologic agents**

Biologic Class	Medication	Mechanism of Action	Approved in pediatrics (Health Canada)
B cell depletion	Belimumab	• Human monoclonal antibody directed against BLyS • Inhibits BLyS-induced proliferation of B cells and decreases survival of autoreactive B cells	Yes
	Rituximab	• Chimeric mouse-human monoclonal antibody directed against CD20 on pre-B and mature B cells • Selectively depletes B cells	No
IL-1 inhibitors	Anakinra	• IL-1 receptor antagonist • Blocks IL-1 receptor to prevent pro-inflammatory signaling (both IL-1α and IL-1β)	Yes
	Canakinumab	• Human monoclonal antibody directed against IL-1β • Binds to IL-1β to prevent pro-inflammatory signaling	Yes
	Rilonacept	• Fully human dimeric fusion protein consisting of extracellular portion of IL-1 receptor and constant region of human immunoglobulin • Binds to IL-1 to prevent pro-inflammatory signaling	No
IL-6 inhibitor	Tocilizumab	• Humanized monoclonal antibody against IL-6 receptor • Blocks IL-6 mediated pro-inflammatory signaling	Yes
IL-12/IL-23 inhibitor	Ustekinumab	• Humanized monocloncal antibody against IL-12 and IL-23 • Blocks IL-12/23 to prevent pro-inflammatory signaling	No
IL-17A inhibitor	Secukinumab	• Humanized monocloncal antibody against IL-17A • Blocks IL-17A mediated pro-inflammatory signaling, which is mainly produced by T helper 17 cells	No
T cell co-stimulatory modulator	Abatacept	• Fusion protein consisting of extracellular portion of CTLA-4 and constant region of human immunoglobulin • Blocks co-stimulation and activation of T cells	Yes
TNF inhibitors	Adalimumab	• Human monoclonal antibody directed against circulating and membrane-bound TNFα • Binds to TNFα to block pro-inflammatory signaling • May result in cell lysis in presence of complement	Yes
	Certolizumab	• PEGylated Fab fragment of humanized monoclonal antibody directed against TNFα • Binds to TNFα to block pro-inflammatory signaling	No
	Etanercept	• Soluble fusion protein consisting of extracellular portion of TNFα receptor and the constant region of human immunoglobulin • Binds to circulating (but not membrane-bound) TNFα to block pro-inflammatory signaling	Yes
	Golimumab	• Human monoclonal antibody directed against TNFα • Binds to TNFα to block pro-inflammatory signaling	No
	Infliximab	• Monoclonal human-mouse antibody directed against circulating and membrane-bound TNFα • Binds to TNFα to block pro-inflammatory signaling • Enables antibody-dependent and complement-dependent cytotoxicity	Yes

TNF: tumor necrosis factor; IL: interleukin; BLyS: B-lymphocyte stimulator; CTLA-4: cytotoxic T lymphocyte-associated antigen-4; Note: suffix of monoclonal antibody (mAb) = -mab

- **Biosimilars**
  - A biosimilar is a newer type of biologic medication that is designed to be identical to an existing biologic medication, but is created using a different process
  - Uncertain whether biosimilars will have identical effects to reference biologic product since even minor modifications may alter pharmacokinetic, immunogenetic, glycosylation, sialylation, stability, safety, and efficacy
  - Biosimilars often more cost-effective than the biologic agents that they replicated
  - Rare events and long-term safety will be assessed in postmarketing surveillance studies
  - Currently approved Anti-TNF biosimilars
    - Infliximab biosimilars: Remsina, Inflectra and Renflexis are approved for adults in Canada, but not yet mandated for use in children
    - Adalimumab biosimilar: Hadlima approved for adults in Canada
    - Etanercept biosimilars: Brezys and Erelzi are approved for adults in Canada, while Erelzi is mandated for use by certain Canadian provinces for children over 62 kg (dose 50 mg SC weekly)

- **Canakinumab**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: fully human mAb targeting IL-1β
  - Dose: sJIA → 4 mg/kg/dose SC every 4 weeks; CAPS → 2-4 mg/kg if 15-40 kg; or 150 mg (may consider 300 mg) if >40 kg via SC injection every 8 weeks
  - Side effects: injection site reactions, headache, flu-like symptoms, GI upset, infections

- **Colchicine**
  - Class: alkaloid
  - Mechanism of action: binds to microtubules to prevent activation, proliferation and functioning of inflammatory cells
  - Dose: 0.6-1.8 mg/day; may divide into twice daily doses if side effects
  - Side effects: nausea, vomiting, diarrhea, cytopenias, rhabdomyolysis, renal failure
  - Monitoring: CBC, differential, renal function

- **Corticosteroids**
  - Potent anti-inflammatory agents
  - Mechanism of action: multiple anti-inflammatory actions including binding to transcription factors (such as NF-κB) 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 (PO tablets), prednisolone (PO liquid) – equivalent
    - Methylprednisolone (IV) – very similar to prednisone/prednisolone
    - Dexamethasone (PO or IV) – superior blood-brain barrier penetration, more potent
    - Triamcinolone hexacetonide (intra-articular)
  - Dose: depends on indication and severity of inflammation
  - Side effects:
    - 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 (including blood pressure); consider monitoring bone health carefully if long-term corticosteroids are used

- **Cyclophosphamide**
  - Class: cytotoxic alkalating agent
  - Mechanism of action: alkylating metabolites prevent cell division by crosslinking DNA and RNA strands, particularly affecting lymphocytes (B and T cells)
  - Dose: 500-1000 mg/m^2/dose IV every 2 to 4 weeks up to 6 months
  - Side effects:
    - Short-term: nausea, vomiting, anorexia, alopecia, oral ulcers, cytopenias, opportunistic infections, hemorrhagic cystitis, SIADH, teratogenicity, gonadal dysfunction
    - Long-term: bladder fibrosis, bladder carcinoma, fertility issues, malignancy
  - Monitoring: CBC, differential on day of infusion and then days 7, 10 and 14 after infusion to monitor cytopenias
  - Special consideration: prophylaxis
    - Mesna administered with infusion to prevent hemorrhagic cystitis
    - Cotrimazole (trimethoprim-sulfamethoxazole) given 3 times weekly to prevent opportunistic infection by *Pneumocystis jirovecii*

- **Cyclosporine**
  - Class: immunomodulatory agent
  - Mechanism of 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; may be given by IV in MAS
  - Side effects: hypertension, headache, nausea, vomiting, myalgias, renal toxicity, hepatotoxicity, GI upset, tremor, paresthesias, gingival hyperplasia, hirsutism
  - Monitoring: BP, renal function, urinalysis, CBC, differential, and liver enzymes monthly

- **Etanercept**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: fully human dimeric fusion protein that binds to circulating TNFα
  - Dose: 0.4 mg/kg/dose (max 25 mg) twice weekly or 0.8 mg/kg/dose (max 50 mg) weekly via SC injection
  - Side effects: injection site reactions, headaches, flu-like symptoms, infections, cytopenias, potential risk of future malignancy, demyelinating disease, new or worsening heart failure (adult patients)
  - Monitoring: CBC, differential, AST, ALT, creatinine every 3-6 months

- **Hydroxychloroquine**
  - Class: disease-modifying antirheumatic drug (DMARD); antimalarial agent
  - Mechanism of action: interferes with antigen processing and antigen-antibody interactions, inhibits nucleic acid and protein synthesis
  - Dose: up to 6.5 mg/kg/day (max 400 mg) PO daily
  - Side effects: nausea, anorexia, skin rash, headache, dizziness, photosensitivity, retinal toxicity
  - Monitoring: eye examinations every 12 months to assess for retinal deposits

- **Infliximab**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: monoclonal chimeric human-mouse antibody that binds to circulating and cell surface anti-TNFα

  - Dose: 6-10 mg/kg/dose on week 0, 2, 6 then every 4 to 8 weeks (may occasionally require higher doses)
  - Side effects: injection site reactions, headaches, infections, cytopenias, potential risk of future malignancy, demyelinating disease, new or worsening heart failure
  - Monitoring: CBC, differential, AST, ALT, creatinine every 3-6 months
  - Special consideration: human anti-chimeric antibodies (HACAs) can develop and decrease efficacy and increase risk of infusion reactions; incidence is lower in patients receiving continuous (rather than intermittent) therapy and concomitant immunosuppressive therapy (e.g., methotrexate)

- **IVIG**
  - Class: biologic agent; plasma-derived protein
  - Mechanism of 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, haemolysis, aseptic meningitis 18-36 hours post infusion (headache and vomiting), cough, acute renal failure
  - Special consideration: need to delay future immunizations with live-virus vaccines by 11 months due to possible inefficacy of subsequent vaccines for this time period

- **Leflunomide**
  - Class: disease-modifying antirheumatic drug (DMARD)
  - Mechanism of action: inhibits enzyme involved in DNA synthesis and interferes with lymphocyte proliferation
  - Dose: 10 mg PO every other day for patients <20 kg, 10 mg PO daily for patients 20-40 kg, 20 mg PO daily for patients >40 kg
  - Side effects: oral ulcers, nausea, vomiting, allergic rash, alopecia, leukopenia, hepatotoxicity, teratogenicity
  - Monitoring: CBC, differential, liver enzymes, creatinine at baseline, in 2-4 weeks after starting and then every 8-12 weeks
  - Special consideration: need to discuss alcohol avoidance and birth control

- **Methotrexate**
  - Class: disease-modifying antirheumatic drug (DMARD)
  - Mechanism of action: inhibitor of dihydrofolate reductase enzyme (folate pathway) and DNA synthesis
  - Dose: 10-15 mg/m^2/dose (max 25 mg) PO or SC weekly (note: often better response and fewer side effects with SC route)
  - Side effects: GI upset, oral ulcers, hepatotoxicity, bone marrow suppression, teratogenicity
  - Monitoring: CBC, differential, liver enzymes, creatinine at baseline, in 2-4 weeks and then every 8-12 weeks
  - Special considerations: need to discuss alcohol avoidance and birth control; administer with folic or folinic acid to minimize side effects

- **Mycophenolate mofetil**
  - Class: antimetabolic agent
  - Mechanism of action: inhibits enzyme in DNA synthesis leading to inhibition of B and T cell proliferation

- Dose: 800-1200 mg/m^2/day (max 3000 mg/day) PO divided twice daily
  - Typical starting dose is 250 mg daily
  - May use drug levels (MMF kinetics) to optimize dose where available
- Side effects: GI upset, headaches, cytopenias, infections, teratogenicity
- Monitoring: CBC, differential, liver enzymes, creatinine at baseline, in 2-4 weeks and then every 8-12 weeks

- **Non-steroidal anti-inflammatory drugs (NSAIDs)**
  - First-line anti-inflammatory agents for arthritis
  - Mechanism of action: inhibit cyclooxygenase (COX) to block production of pro-inflammatory prostaglandins
  - Dose: see table below for doses of commonly used NSAIDs
  - Side effects: abdominal pain, nausea, vomiting, diarrhea, constipation, pseudoporphyria (Naprosyn), gastritis, GI bleeding, rare renal toxicity, rare hepatotoxicity, rare ototoxicity
  - Monitoring: no routine monitoring necessary if NSAIDs used as monotherapy, but hemoglobin, renal function and liver enzymes with clinic visits

NSAID	Dose	Comments
Aspirin/ASA	High dose (anti-inflammatory): 50-100 mg/kg/day PO div QID Low dose (anti-platelet): 3-5 mg/kg/day PO OD	Used mostly in the setting of Kawasaki disease and acute rheumatic fever
Celecoxib	50 mg PO BID if 10-25 kg 100 mg PO BID if >25 kg	Selective COX-2 inhibitor; expensive
Ibuprofen	20-40 mg/kg/day PO div TID or QID	Commonly used in childhood JIA
Indomethacin	2-3 mg/kg/day (max 150 mg/day) PO div TID	Commonly used in ERA and sJIA, can be compounded into liquid
Meloxicam	0.125 mg/kg (max 15 mg/day) PO daily	Used in JIA, can be compounded into liquid
Naproxen	20 mg/kg/day (max 500 mg/dose) PO div BID	Frequently used in childhood JIA
Piroxicam	0.4 mg/kg (max 20 g/day) PO daily	Used in JIA, capsule may be opened and sprinkled on food

ERA: enthesitis related arthritis; sJIA: systemic juvenile idiopathic arthritis; COX = cyclooxygenase

- **Pamidronate**
  - Class: bisphosphonate
  - Mechanism of action: inhibits bone resorption, decreases mineralization by inhibiting osteoclast activity
  - Dose: 1 mg/kg/day if >3 yrs (max 60 mg/day) monthly for 3 months (note: first dose to be given over 2 days)
  - Side effects: bone pain, fever, headaches, lethargy, fetal toxicity, unclear risk of osteonecrosis of the jaw
  - Monitoring: calcium, phosphate, creatinine, ALP and PTH prior to each infusion

- **Rilonacept**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: fully human dimeric fusion protein that blocks IL-1 by acting as a soluble decoy receptor; also known as "IL-1 Trap"
  - Dose: loading dose 4.4 mg/kg/dose (max 320 mg) then 2.2 mg/kg/dose SC weekly (max 160mg)
  - Side effects: injection reactions, infections, dyslipidemia, potential risk of future malignancy
  - Monitoring: CBC and liver transaminases after 4 weeks and then every 3 months; serum lipid monitoring added 8-12 weeks after initiation

- **Rituximab**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: chimeric mouse-human monoclonal antibody that binds to the B cell CD20 receptor (on pre-B and mature B cells but not on stem cells or plasma cells)
  - Dose: dosing may depend on indication; 375 mg/m^2 once weekly for 2-4 doses or 750 mg/m^2 on days 1 and 15; for polyarticular RF-positive JIA patients 500 mg/m^2 (max 1000 mg) every 2 weeks for 2 doses or 375 mg/m^2 once weekly for 4 doses
  - Side effects: infusion reactions, allergic reaction, hypogammaglobulinemia, infection, potential risk of future malignancy, progressive multifocal leukoencephalopathy (PML)
  - Monitoring: screen for hepatitis B; check B cell numbers before and 1 month after infusion; quantitative immunoglobulins every 3 months; follow liver transaminases
  - Special considerations:
    - Prophylaxis with cotrimazole (trimethoprim-sulfamethoxazole) given 3 times weekly to prevent opportunistic infection by *Pneumocystis jirovecii*
    - Human anti-chimeric antibodies (HACAs) can develop and decrease efficacy and increase risk of infusion reactions
    - Recommend screening for hepatitis status
    - Recommend pre-medication with Hydrocortisone

- **Sulfasalazine**
  - Class: disease-modifying antirheumatic drug (DMARD); analogue of 5-ASA linked to a sulfonamide
  - Mechanism of action: inhibits enzymes and transcription factors involved in production of pro-inflammatory cytokines
  - Dose: 50 mg/kg/day (max 3 g daily) PO divided twice daily; typically start at 10 mg/kg/day and increase weekly over 4 weeks to target dose
  - Side effects: nausea, vomiting, rash, oral ulcers, photosensitivity, cytopenias, hypogammaglobulinemia, hepatotoxicity, allergy (Stevens-Johnson syndrome)
  - Monitoring: CBC, differential and liver enzymes every 2 months, immunoglobulin levels every 6 months
  - Special consideration: contraindicated if history of allergy to sulfonamide antibiotics

- **Tocilizumab**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: humanized monoclonal antibody that binds both soluble and membrane-bound IL-6 receptor
  - Dose:
    - Systemic JIA: 12 mg/kg/dose if <30 kg; or 8 mg/kg/dose (max 800 mg) if ≥ 30 kg via IV *every 2 weeks*

        - Polyarticular JIA: 10 mg/kg/dose if <30 kg; or 8 mg/kg/dose (max 800 mg) if ≥ 30 kg via IV *every 4 weeks*
    - Side effects: infusion reactions, headaches, GI upset, hepatotoxicity, dyslipidemia, neutropenia, thrombocytopenia, GI perforation, infection, potential risk of future malignancy
    - Monitoring: AST, ALT, absolute neutrophil count at baseline, at second infusion and then every 2-4 weeks; lipid panel 4-8 weeks after start of treatment then every 6 months

- **Tofacitinib**
    - Class: Janus Kinase inhibitor
    - Mechanism of action: interferes with Jak-stat system (Jak 3 and Jak 1) and subsequent production of selective interleukins and interferons
    - Dose: dosing in adult rheumatoid arthritis 5 mg PO twice daily
    - Side effects: infections, viral reactivation, anemia, thrombocytopenia, neutropenia, lymphopenia, hypercholesterolemia, increased liver transaminases, GI perforation, potential risk of future malignancy

- **Secukinumab**
    - Class: biologic agent (see Biologic agents for summary table)
    - Mechanism of action: humanized monoclonal antibody that binds soluble and membrane bound IL-17A
    - Dose: for ankylosing spondylitis and psoriatic arthritis 150 mg SC every week for 4 weeks and then every 4 weeks
    - Side effects: infections, flu-like symptoms, injection site reactions, potential risk of future malignancy, may un-mask or lead to flares of inflammatory bowel disease

- **Ustekinumab**
    - Class: biologic agents (see Biologic agents for summary table)
    - Mechanism of action: humanized monoclonal antibody that binds soluble and membrane bound IL-12 and IL-23
    - Dose: for psoriasis 0.75 mg/kg if <60 kg, 45 mg if 60-100 kg or 90 mg for >100 kg; given by SC injection at baseline, in 4 weeks and then every 12 weeks
    - Side effects: infections, injection site reactions, potential risk of future malignancy, rare reports of posterior reversible encephalopathy syndrome

APPENDIX – HELPFUL RESOURCES IN PEDIATRIC RHEUMATOLOGY

Textbooks

Petty RE, Laxer RM, Lindsley CB, Wedderburn L. *Textbook of Pediatric Rheumatology, Seventh Edition.* 2015: Saunders Elsevier Publishing.

Foster HE, Brogan P. Paediatric Rheumatology. 2018: Oxford University Press.

Laxer RM, Sherry DD, Hashkes PN *Pediatric Rheumatology in Clinical Practice*. 2nd edition. 2016: Springer-Verlag.

Hashkes PJ, Laxer RM, Simon A. *Textbook of Autoinflammation*. 2019: Springer Nature Switzerland.

Monographs

Li SC, Higgins GC, Eds. Pediatric Rheumatology. *Pediatr Clin North Am* 2018; 65(4).

Laxer RM, Sherry DD, Eds. Pediatric Rheumatology. *Pediatr Clin North Am* 2012; 59(2).

Rouster-Stevens KA, et al. Choosing Wisely: The American College of Rheumatology's Top 5 for Pediatric Rheumatology. *Arthritis Care Res* 2014; 66(5):649-57.

Internet Resources for Images in Rheumatology

American College of Rheumatology Image Bank: http://images.rheumatology.org/

Rheumatlas website: http://rheumexamatlas.com/atlas/

Internet Resources for Patients

Paediatric Rheumatology InterNational Trials Organisation (PRINTO) – provides information on all childhood rheumatic diseases in many languages:
https://www.printo.it/pediatric-rheumatology/IE/info/IE

RheumInfo – provides easy-to-read pictopamphlets on medications
https://rheuminfo.com/

About Kids Health – provides information on multiple childhood rheumatic diseases from a general pediatric perspective
https://www.aboutkidshealth.ca/

Teens Taking Charge (Managing JIA Online) – provides resources for adolescent JIA patients
https://www.aboutkidshealth.ca/Article?contentid=1087&language=English

Arthritis Australia - provides information on JIA and chronic pain in children
https://arthritisaustralia.com.au/managing-arthritis/arthritis-and-children/

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

