A RESIDENT’S GUIDE TO PEDIATRIC RHEUMATOLOGY

5th Revised Edition - 2023

McMaster University

SickKids®
A RESIDENT’S GUIDE TO PEDIATRIC RHEUMATOLOGY

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.

Supervising Editors:

- Dr. Ronald M. Laxer, SickKids Hospital, University of Toronto
- Dr. Tania Cellucci, McMaster Children’s Hospital, McMaster University
- Dr. Evelyn Rozenblyum, St. Michael’s Hospital, University of Toronto

Section Editors:

- Dr. Julie Barsalou, Centre Hospitalier Universitaire Sainte-Justine, University of Montréal
- Dr. Michelle Batthish, McMaster Children’s Hospital, McMaster University
- Dr. Roberta Berard, Children’s Hospital – London Health Sciences Centre, Western University
- Dr. Julie Couture, Centre Hospitalier Universitaire Sainte-Justine, University of Montréal
- Dr. Chelsea DeCoste, IWK Health Centre, Dalhousie University
- Dr. Liane Heale, McMaster Children’s Hospital, McMaster University
- Dr. Andrea Human, BC Children’s Hospital, University of British Columbia
- Dr. Clare Hutchinson, North York General Hospital, University of Toronto
- Dr. Mehul Jariwala, Royal University Hospital, University of Saskatchewan
- Dr. Lillian Lim, Stollery Children’s Hospital, University of Alberta
- Dr. Leeza Limenis, SickKids Hospital, University of Toronto
- Dr. Nadia Luca, Alberta Children’s Hospital, University of Calgary
- Dr. Dax Rumsey, Stollery Children’s Hospital, University of Alberta
- Dr. Gordon Soon, North York General Hospital and St. Joseph’s Health Centre, University of Toronto
- Dr. Rebeka Stevenson, Alberta Children’s Hospital, University of Calgary
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Topic</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pediatric Rheumatology Clinical Assessment</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Approaches and Differential Diagnoses for Common Complaints Referred to Pediatric Rheumatology</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Juvenile Idiopathic Arthritis</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>Systemic Lupus Erythematosus and Related Conditions</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>Systemic Vasculitis</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>Idiopathic Inflammatory Myopathies</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>Scleroderma and Related Syndromes</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>Autoinflammatory Diseases</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>Uveitis</td>
<td>86</td>
</tr>
<tr>
<td>10</td>
<td>Inflammatory Brain Diseases</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>Infection and Infection-Related Conditions</td>
<td>96</td>
</tr>
<tr>
<td>12</td>
<td>Pain Syndromes</td>
<td>104</td>
</tr>
<tr>
<td>13</td>
<td>Pediatric Rheumatology Emergencies</td>
<td>108</td>
</tr>
<tr>
<td>14</td>
<td>Medications</td>
<td>122</td>
</tr>
<tr>
<td>Appendix</td>
<td>Helpful Resources in Pediatric Rheumatology</td>
<td>131</td>
</tr>
</tbody>
</table>

Notes:

*Please consider that all treatment regimens discussed in the guide are suggestions 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. History

An appropriate rheumatologic history for a new patient should be tailored to the presenting complaint and may include the following:

**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
- Prior admissions to hospital and surgeries
- Brief review if all developmental milestones met appropriately

**Immunizations**
- All childhood vaccinations
  - Varicella and Coronavirus Disease of 2019 (COVID-19) – infection or vaccination?

**Medications**
- Prescribed medications – dose, route, frequency, adherence
- Over-the-counter medications, including vitamins
- Alternative, complementary, and natural therapies

**Allergies**
- Any relevant allergies, including allergies to medications

**Family history**
- Medical history in first degree relatives
  - Include age, medical conditions, ethnicity and consanguinity (if relevant)
- Rheumatologic diseases:
  - Juvenile idiopathic arthritis (JIA), rheumatoid arthritis (RA)
  - Ankylosing spondylitis (AS)
  - Premature osteoarthritis
  - Inflammatory bowel disease (IBD)
  - Psoriasis
  - Systemic lupus erythematosus (SLE)
  - Vasculitis
  - Recurrent fever episodes
  - Autoinflammatory diseases (if suspicious, include early hearing loss and early renal failure)

Other autoimmune diseases:
- Diabetes mellitus type I
- Celiac disease
- Thyroid disease
Social history
Functioning at home, social, school (including year of school, school issues and absences), extra-curricular activities, and/or work
Parents/care providers, including who the child lives with at home and custody arrangements (if relevant)
Parent/care provider occupations and drug coverage
Adolescent psychosocial assessment (e.g. HEEADSSS)
Travel history and risk factors for tuberculosis or Lyme infections, if relevant

Review of systems
Constitutional:
- Energy level, fatigue, quality of sleep
- Anorexia, weight loss
- Fevers

Head & Neck:
- Photophobia, blurred vision, redness, eye pain, most recent eye exam
- Sicca symptoms (dry eyes, dry mouth)
- Nasal and/or oral ulcers (painful or painless)
- Epistaxis
- Dysphagia
- Otolgia, hearing difficulties

Cardiovascular:
- Chest pain, orthopnea, activity tolerance, palpitations
- Syncope, pre-syncope
- Peripheral acrocyanosis or Raynaud phenomenon

Respiratory:
- Difficulty breathing, shortness of breath
- Pleuritic chest pain
- Cough (prolonged, productive, hemoptysis)

Gastrointestinal:
- Recurrent abdominal pain
- Reflux symptoms
- Dysphagia
- Diarrhea, constipation, bloody stools, melena
- Nausea, vomiting

Skin & Nails:
- Rash
- Petechiae, purpura
- Nodules
- Ulcers (includes genital/perineal)
- Photosensitivity
- Alopecia, hair changes
- Nail changes (pits, onycholysis)
- Nail fold capillary changes
Musculoskeletal:
- Joint pain (day and/or night), swelling, redness, warmth, decreased range of motion, inflammatory features (morning stiffness, gelling, improving with activity) and/or mechanical features (locking, giving away, improving with rest)
- Back pain, decreased range of motion and/or morning stiffness
- Muscle pain and/or weakness (specifying generalized, proximal and/or distal involvement)
- Loss of function, reduced activities, pain waking from sleep

Neurologic:
- Headaches
- Psychosis, hallucinations, visual distortions
- Cognitive dysfunction, drop in school grades
- Seizures
- Chorea or other abnormal movements
- Dysarthria, change in spoken language or understanding
- Paralysis and/or weakness
- Motor or sensory neuropathy

Genito-urinary:
- Dysuria, change in urine volume or colour
- Age of menarche; irregular, missed or prolonged menstrual periods; heavy menses

1B. Physical Examination

An appropriate rheumatologic physical examination for a new patient should be tailored to the presenting complaint and may include the following:

Vital signs:
- Heart rate, blood pressure (including blood pressure percentiles, if relevant), respiratory rate, oxygen saturation and temperature
- Height and weight (including percentiles and significant recent changes), BMI, BSA
- General appearance

Head & Neck:
- Conjunctival changes and discharge
- Pupils (shape and reaction to light), cataracts
- Fundoscopy (papilledema, retinal hemorrhages)
- Nasal mucosa, nasal discharge, sinus tenderness
- Oropharyngeal mucosa, tongue, tonsils
- Cervical lymph nodes

Cardiovascular:
- Heart sounds, murmurs, rubs, precordial examination
- Vascular bruits (if indicated)
- Peripheral pulses, peripheral perfusion, capillary refill

Respiratory:
- Breath sounds (including adventitious)
- Work of breathing
- Excursion
- Percussion
A RESIDENT’S GUIDE TO PEDIATRIC RHEUMATOLOGY

Abdominal:
- Tenderness, masses
- Bowel sounds, bruits (if indicated)
- Peritoneal signs
- Hepatomegaly, splenomegaly

Lymph Nodes:
- Assess all accessible lymph node groups

Skin & Nails:
- Any type of skin rash, including petechiae, purpura, nodules, and ulcers
- Alopecia, hair abnormalities
- Nail pits, onychonychia, clubbing
- Nail fold capillaries – thickening, branching, drop-out, hemorrhages
- Digital ulcers, splinter hemorrhages, loss of digital pulp

Musculoskeletal:
- Begin with screening exam, such as Pediatric Gait Arms Legs Spine (pGALS)
- Joint examination (assess all joints for heat, swelling, tenderness, stress pain, active and passive range of motion, deformity and relevant special tests)
- Back examination (assess neck and back for range of motion, tenderness, stress pain, FABER, Modified Schober test)
- Muscle examination (assess for muscle bulk/atrophy, strength, tenderness)
- Additional musculoskeletal assessment
  - Dactylitis
  - Enthesitis sites
  - Tendinitis
  - Localized bony deformity and/or tenderness
  - Leg length (functional and/or actual)
  - Fibromyalgia tender points (if indicated)

Musculoskeletal examination videos:
- Gait: https://www.youtube.com/watch?v=AS1cQMR6oKs
- Arms: https://www.youtube.com/watch?v=UkRvXr9eBHM
- Legs: https://www.youtube.com/watch?v=A5BVOzU94-4
- Spine: https://www.youtube.com/watch?v=kToNTwHR3hs
- Enthesitis exam: https://www.youtube.com/watch?v=xtOLGlm1hhU

Neurologic:
- 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)

References:
1C. Laboratory Testing

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
- Trends in laboratory values may be more important than isolated abnormalities

Complete blood cell count and differential

- Hemoglobin, mean corpuscular volume, red blood cell count and distribution width
  - Normocytic or microcytic anemia in chronic inflammatory disease
  - Autoimmune hemolytic anemia in systemic lupus erythematosus (SLE) and macrophage activation syndrome (MAS)
  - Iron deficiency anemia if chronic blood loss (e.g. due to NSAIDs, inflammatory bowel disease, pulmonary hemorrhage)
- White blood cell count and differential
  - High white blood cell counts may be due to infection, inflammation, or corticosteroids
  - Leukopenia with lymphopenia and/or neutropenia may be due to systemic inflammation, infection, 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 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)

<table>
<thead>
<tr>
<th>Increase in acute phase response</th>
<th>Decrease in acute phase response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, ESR</td>
<td>Albumin</td>
</tr>
<tr>
<td>Complement proteins</td>
<td>Transferrin</td>
</tr>
<tr>
<td>Fibrinogen, coagulation proteins</td>
<td>IGF-1</td>
</tr>
<tr>
<td>Ferritin</td>
<td></td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td></td>
</tr>
<tr>
<td>Haptoglobin</td>
<td></td>
</tr>
<tr>
<td>G-CSF</td>
<td></td>
</tr>
<tr>
<td>IL-1 receptor antagonist</td>
<td></td>
</tr>
<tr>
<td>Serum amyloid A</td>
<td></td>
</tr>
</tbody>
</table>
• C-reactive protein (CRP)
  o Direct measure of inflammation (sensitive but not specific)
  o Level rises rapidly in response to inflammation and falls quickly with appropriate treatment
  o 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)
  o Indirect measure of acute phase reaction
  o Changes more slowly than CRP
  o Measures rate at which red blood cells settle in a tube of anticoagulated blood and may be altered by abnormal levels of fibrinogen and/or gamma globulins

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

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
  o Complement levels tend to fall during a flare and return to normal concentration after appropriate therapy
  o Persistently low C3 associated with lupus nephritis

Autoantibodies

Antinuclear antibodies (ANA)

• Autoantibodies directed against nuclear, nucleolar or perinuclear antigens
• ANA should not be used as a screening tool in patients without specific signs or symptoms of a rheumatic condition (from Choosing Wisely: Seven things clinicians and patients should question in Pediatric Rheumatology and Choosing Wisely Canada: Seven tests and treatments to question in Pediatric Rheumatology)
• Low titres of ANA (e.g. ANA ≤ 1:160) 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)
• Positive ANA titres ≥ 1:160 in patients with JIA 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 antigens (ENA)**

<table>
<thead>
<tr>
<th>Specific ENA antibodies</th>
<th>Characteristic disease associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Ro/SSA</td>
<td>SLE, Neonatal lupus erythematosus, Sjögren</td>
</tr>
<tr>
<td>Anti-La/SSB</td>
<td>SLE, Neonatal lupus erythematosus, Sjögren</td>
</tr>
<tr>
<td>Anti-Sm (Anti-Smith)</td>
<td>SLE</td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>Mixed connective tissue disease, SLE, Systemic sclerosis</td>
</tr>
<tr>
<td>Anti-histone</td>
<td>Drug-induced lupus, SLE</td>
</tr>
<tr>
<td>Anti-Scl 70</td>
<td>Diffuse systemic sclerosis</td>
</tr>
<tr>
<td>Anti-centromere</td>
<td>Limited systemic sclerosis (CREST)</td>
</tr>
<tr>
<td>Anti-Jo1</td>
<td>Polymyositis with interstitial lung disease, juvenile dermatomyositis (JDM)</td>
</tr>
</tbody>
</table>

**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 rheumatic diseases, such as SLE, systemic sclerosis, Sjögren, mixed connective tissue disease, cryoglobulinemia and chronic infection (subacute bacterial endocarditis, hepatitis B and C, TB)
- Do not order RF in patients with arthralgia but no arthritis on exam (from Choosing Wisely: Seven Things Clinicians and Patients Should Question in Pediatric Rheumatology)

**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, antiphospholipid, anti-β2-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

<table>
<thead>
<tr>
<th>Disease associations</th>
<th>Type</th>
<th>Immunofluorescence pattern</th>
<th>Antigen specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomatosis with polyangiitis</td>
<td>c-ANCA</td>
<td>Cytoplasmic</td>
<td>Proteinase-3 (PR3)</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>p-ANCA</td>
<td>Perinuclear</td>
<td>Myeloperoxidase (MPO)</td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with polyangiitis</td>
<td>p-ANCA</td>
<td>Perinuclear</td>
<td>MPO</td>
</tr>
<tr>
<td>Ulcerative colitis and primary sclerosing cholangitis</td>
<td>a-ANCA</td>
<td>Perinuclear</td>
<td>Unknown target for atypical p-ANCA</td>
</tr>
<tr>
<td></td>
<td>p-ANCA (rare)</td>
<td>Cytoplasmic</td>
<td>MPO</td>
</tr>
<tr>
<td></td>
<td>c-ANCA (rare)</td>
<td></td>
<td>PR3</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>p-ANCA</td>
<td>Perinuclear</td>
<td>Atypical p-ANCA rarely targets MPO</td>
</tr>
</tbody>
</table>

**Anti-Glomerular Basement Membrane (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
- Do not order HLA-B27 unless spondyloarthritis is suspected based on clinical signs or symptoms (from Choosing Wisely: Seven Things Clinicians and Patients Should Question in Pediatric Rheumatology)

**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

**Liver and muscle enzymes**
- Elevation in liver enzymes (ALT, AST, GGT) may indicate hepatitis, which can be a manifestation of SLE, other systemic autoimmune rheumatic diseases, MAS, and drug toxicity
- Elevation in muscle enzymes (CK, ALT, AST, LDH, aldolase) may indicate myositis, which is present in juvenile dermatomyositis, and may also be present in other autoimmune conditions, such as SLE

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

**Genetic testing**
- Often ordered to confirm diagnosis of recurrent fever syndromes, other monogenic autoinflammatory disorders, and primary hemophagocytic lymphohistiocytosis

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

**References:**
3. https://choosingwiselycanada.org/rheumatology/

**1D. Diagnostic Imaging**

**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
A RESIDENT’S GUIDE TO PEDIATRIC RHEUMATOLOGY

- 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 interstitial 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 (MRI)

- 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
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

1E. Other Clinical Tests

ECG

- May be used to identify rhythm and conduction abnormalities in children with systemic autoimmune rheumatic diseases and Kawasaki disease
- Infants with neonatal lupus erythematosus may have heart block on ECG

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
- Often used to assess for pericarditis and myocarditis in systemic autoimmune rheumatic diseases, particularly SLE
- Used to assess valvular dysfunction from acute rheumatic fever
- Some centres may require consultation with cardiologist in conjunction with imaging

Pulmonary Function Tests

- May demonstrate decreased DLCO in children with early interstitial lung disease secondary to pulmonary renal syndromes and systemic autoimmune rheumatic diseases, especially systemic sclerosis, juvenile dermatomyositis, and mixed connective tissue disease
- DLCO may be elevated in the case of pulmonary hemorrhage
- Restrictive changes occur later in interstitial lung disease in children
- Children with ANCA-associated vasculitis may demonstrate airflow obstruction due to airway involvement

Lumbar Puncture & Cerebrospinal Fluid (CSF) Analysis

- May demonstrate leukocytosis and increased protein levels in patients with neuropsychiatric involvement of systemic autoimmune rheumatic diseases or MAS, inflammatory brain diseases, and infections
- Specialized tests (e.g. oligoclonal banding, testing for anti-neuronal autoantibodies) may be added if inflammatory brain disease is suspected
- May consider noting opening pressure, but accurate measurement is challenging
SECTION 2 – APPROACHES TO AND DIFFERENTIAL DIAGNOSES FOR COMMON COMPLAINTS REFERRED TO PEDIATRIC RHEUMATOLOGY

2A. Approach to Childhood Joint Pain

Differential diagnosis for pain affecting a single joint:

<table>
<thead>
<tr>
<th>Traumatic</th>
<th>Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Soft tissue injury (e.g. strains, sprains, meniscal injury)</td>
</tr>
<tr>
<td></td>
<td>Foreign body synovitis</td>
</tr>
<tr>
<td>Mechanical</td>
<td>Overuse or repetitive strain injury</td>
</tr>
<tr>
<td></td>
<td>Apophysitis (e.g. Osgoode Schlatter, Sever)</td>
</tr>
<tr>
<td></td>
<td>Joint damage (e.g. prior trauma, infection, congenital anomaly)</td>
</tr>
<tr>
<td></td>
<td>Avascular necrosis (AVN)</td>
</tr>
<tr>
<td></td>
<td>Slipped capital femoral epiphysis (SCFE)</td>
</tr>
<tr>
<td></td>
<td>Osteochondritis dissecans</td>
</tr>
<tr>
<td>Infection-related</td>
<td>Septic arthritis</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td></td>
<td>Infections, such as tuberculosis or Lyme disease</td>
</tr>
<tr>
<td></td>
<td>Reactive arthritis, including post-Streptococcal reactive arthritis</td>
</tr>
<tr>
<td></td>
<td>Acute rheumatic fever</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Juvenile idiopathic arthritis (JIA)</td>
</tr>
<tr>
<td></td>
<td>Chronic non-bacterial osteomyelitis (CNO)</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease (IBD)</td>
</tr>
<tr>
<td></td>
<td>Genetic autoinflammatory diseases (e.g. familial Mediterranean fever)</td>
</tr>
<tr>
<td></td>
<td>Behçet disease</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Musculoskeletal tumors (e.g. osteoid osteoma, osteosarcoma)</td>
</tr>
<tr>
<td></td>
<td>Hematologic malignancy</td>
</tr>
<tr>
<td>Hemarthrotic</td>
<td>Traumatic</td>
</tr>
<tr>
<td></td>
<td>Coagulopathy (e.g. hemophilia)</td>
</tr>
<tr>
<td></td>
<td>Pigmented villonodular synovitis</td>
</tr>
<tr>
<td></td>
<td>Arteriovenous malformation</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Sickle cell disease (e.g. pain crisis, dactylitis)</td>
</tr>
<tr>
<td>Pain syndrome</td>
<td>Complex regional pain syndrome (CRPS)</td>
</tr>
</tbody>
</table>

Potential investigations for pain involving a single joint:

- X-rays
- Joint aspiration and synovial fluid analysis with/without culture
- Blood work: CBC and differential, ESR, CRP
- Consider, if indicated:
  - Further infectious testing (e.g. blood culture, throat culture, Lyme serology, TB test)
  - Further imaging (e.g. ultrasound, MRI)
  - Autoimmune serology (e.g. ANA, HLA B27, rheumatoid factor)
Differential diagnosis for pain affecting multiple joints:

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical</td>
<td>Overuse injuries, repetitive strain injuries</td>
</tr>
<tr>
<td></td>
<td>Apophysitis (e.g. Osgoode Schlatter, Sever)</td>
</tr>
<tr>
<td></td>
<td>Hypermobility (e.g. benign, Ehlers-Danlos syndrome, Marfan syndrome)</td>
</tr>
<tr>
<td></td>
<td>Skeletal dysplasias</td>
</tr>
<tr>
<td>Infection-related</td>
<td>Acute infections (e.g. parvovirus B19, EBV, <em>Neisseria gonorrhoeae</em>)</td>
</tr>
<tr>
<td></td>
<td>Chronic infections (e.g. tuberculosis (Poncet arthritis), Lyme disease)</td>
</tr>
<tr>
<td></td>
<td>Subacute bacterial endocarditis</td>
</tr>
<tr>
<td></td>
<td>Reactive arthritis</td>
</tr>
<tr>
<td></td>
<td>Acute rheumatic fever (ARF)</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis and septic arthritis (rarely multifocal)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosus (SLE)</td>
</tr>
<tr>
<td></td>
<td>Juvenile dermatomyositis</td>
</tr>
<tr>
<td></td>
<td>Scleroderma/mixed connective tissue disease/overlap syndromes</td>
</tr>
<tr>
<td></td>
<td>Systemic vasculitis (e.g. Henoch-Schönlein purpura / IgA vasculitis)</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease (IBD)</td>
</tr>
<tr>
<td></td>
<td>Genetic autoinflammatory diseases</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Chronic non-bacterial osteomyelitis / chronic recurrent multifocal osteomyelitis (CNO/CRMO)</td>
</tr>
<tr>
<td></td>
<td>Serum sickness</td>
</tr>
<tr>
<td>Immunological</td>
<td>Immunodeficiency associated with arthritis (e.g. Wiskott-Aldrich)</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Leukemia, lymphoma, neuroblastoma, cancers with systemic involvement</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Rickets</td>
</tr>
<tr>
<td></td>
<td>Vitamin C deficiency (scurvy)</td>
</tr>
<tr>
<td></td>
<td>Glycogen storage disease, mucopolysaccharidases</td>
</tr>
<tr>
<td>Pain syndrome</td>
<td>Fibromyalgia</td>
</tr>
</tbody>
</table>

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?

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

References:
2B. Approach to Childhood Back Pain

Differential diagnosis for back pain in children

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical</td>
<td>Overuse injuries, repetitive strain injuries</td>
</tr>
<tr>
<td></td>
<td>Spondylolysis, spondylolisthesis</td>
</tr>
<tr>
<td></td>
<td>Scoliosis</td>
</tr>
<tr>
<td></td>
<td>Scheuermann disease</td>
</tr>
<tr>
<td></td>
<td>Disc prolapse</td>
</tr>
<tr>
<td></td>
<td>Degenerative disc disease</td>
</tr>
<tr>
<td>Infection-related</td>
<td>Acute infections (e.g. osteomyelitis, discitis, epidural abscess)</td>
</tr>
<tr>
<td></td>
<td>Chronic infections (e.g. tuberculosis – Pott disease)</td>
</tr>
<tr>
<td></td>
<td>Reactive arthritis</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Juvenile idiopathic arthritis (JIA), especially enthesitis related arthritis</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease (IBD)</td>
</tr>
<tr>
<td></td>
<td>Chronic non-bacterial osteomyelitis (CNO)</td>
</tr>
<tr>
<td></td>
<td>Transverse myelitis (e.g. SLE)</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Musculoskeletal tumors (e.g. osteoid osteoma, osteoblastoma, osteosarcoma,</td>
</tr>
<tr>
<td></td>
<td>spinal cord tumors, metastases)</td>
</tr>
<tr>
<td></td>
<td>Leukemia, lymphoma</td>
</tr>
<tr>
<td>Trauma</td>
<td>Fracture</td>
</tr>
<tr>
<td>Pain syndrome</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Other</td>
<td>Neurofibromatosis</td>
</tr>
</tbody>
</table>

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:
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**

<table>
<thead>
<tr>
<th>Infection-related</th>
<th>Bacterial (e.g. abscess, bacteremia, mastoiditis, osteomyelitis, pyelonephritis, sinusitis, typhoid fever, tuberculosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Viral (e.g. Adenovirus, CMV, EBV, Enterovirus, HIV)</td>
</tr>
<tr>
<td></td>
<td>Other infections including parasitic and fungal (e.g. malaria, Lyme disease, Toxoplasma, Blastomycosis)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Serum sickness</td>
</tr>
<tr>
<td></td>
<td>Systemic vasculitis (e.g. Kawasaki disease)</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosis</td>
</tr>
<tr>
<td></td>
<td>Juvenile dermatomyositis</td>
</tr>
<tr>
<td></td>
<td>Systemic arthritis/JIA</td>
</tr>
<tr>
<td></td>
<td>Behçet disease</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>Recurrent fever and/or autoinflammatory diseases</td>
</tr>
<tr>
<td></td>
<td>Castleman disease</td>
</tr>
<tr>
<td></td>
<td>Hemophagocytic lymphohistiocytosis (primary or secondary HLH/MAS)</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Drug fevers or intoxication</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Leukemia, lymphoma</td>
</tr>
<tr>
<td></td>
<td>Langerhans cell histiocytosis</td>
</tr>
<tr>
<td></td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Endocrinologic</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>Thyroiditis</td>
</tr>
<tr>
<td></td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>Other</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Factitious fevers</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Infection-</th>
<th>Repeated viral or bacterial infections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Viral (e.g. CMV, EBV, Parvovirus, hepatitis viruses, HIV)</td>
</tr>
<tr>
<td></td>
<td>Bacterial (e.g. Typhoid fever, occult dental abscess, endocarditis, Mycobacteria)</td>
</tr>
<tr>
<td></td>
<td>Parasitic or fungal (e.g. malaria, Borrelia, Brucellosis, Yersinia)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Monogenic autoinflammatory diseases</td>
</tr>
<tr>
<td></td>
<td>Periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA)</td>
</tr>
<tr>
<td></td>
<td>Syndrome of undifferentiated recurrent fever (SURF)</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Systemic arthritis/JIA</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>Systemic vasculitis (e.g. Behçet disease, polyarteritis nodosa)</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Hemophagocytic lymphohistiocytosis (primary or secondary HLH/MAS)</td>
</tr>
<tr>
<td></td>
<td>IgG4-related disease</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Cyclic neutropenia</td>
</tr>
<tr>
<td></td>
<td>Castleman disease</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Leukemia, lymphoma</td>
</tr>
<tr>
<td>Immunologic</td>
<td>DiGeorge syndrome</td>
</tr>
<tr>
<td></td>
<td>Chediak-Higashi</td>
</tr>
<tr>
<td></td>
<td>Combined immunodeficiency syndrome and other immune deficiency</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Drug fevers or intoxication</td>
</tr>
<tr>
<td>Other</td>
<td>CNS abnormality (e.g. hypothalamic dysfunction)</td>
</tr>
<tr>
<td></td>
<td>Factitious fevers</td>
</tr>
</tbody>
</table>

**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 for autoinflammatory diseases

**References:**
# Approach to Recurrent Oral Ulcers

## Differential diagnosis for recurrent oral ulcers in children

<table>
<thead>
<tr>
<th>Infection-related</th>
<th>Viral (e.g. Herpes simplex, Coxsackie, HIV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reactive arthritis</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Inflammatory bowel disease (IBD)</td>
</tr>
<tr>
<td></td>
<td>Celiac disease</td>
</tr>
<tr>
<td></td>
<td>Behçet disease</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosus (SLE)</td>
</tr>
<tr>
<td></td>
<td>Hyperimmunoglobulinemia D syndrome (HIDS)</td>
</tr>
<tr>
<td></td>
<td>Periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA)</td>
</tr>
<tr>
<td></td>
<td>A20 haploinsufficiency (HA20), RELA (p65) haploinsufficiency</td>
</tr>
<tr>
<td></td>
<td>Erythema multiforme (EM)</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Cyclic neutropenia</td>
</tr>
<tr>
<td>Drugs</td>
<td>Azathioprine, methotrexate, sulfasalazine, tocilizumab</td>
</tr>
<tr>
<td>Other</td>
<td>Recurrent aphthous stomatitis</td>
</tr>
</tbody>
</table>

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

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

## References:

2E. Additional differential diagnoses

Differential diagnosis for lymphadenopathy in children

<table>
<thead>
<tr>
<th>Category</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection-related</td>
<td>Viral (e.g. EBV, CMV, HIV)</td>
</tr>
<tr>
<td></td>
<td>Bacterial (e.g. Bartonella, tuberculosis)</td>
</tr>
<tr>
<td></td>
<td>Spirochete/tick-bourne (e.g. Lyme disease)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Systemic lupus erythematosus (SLE)</td>
</tr>
<tr>
<td></td>
<td>Juvenile idiopathic arthritis, specifically systemic JIA</td>
</tr>
<tr>
<td></td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td></td>
<td>Hemophagocytic lymphohistiocytosis (primary or secondary HLH)</td>
</tr>
<tr>
<td></td>
<td>Kikuchi-Fujimoto disease/histiocytic necrotizing lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Castleman disease, Rosai-Dorfman disease</td>
</tr>
<tr>
<td></td>
<td>Genetic autoinflammatory diseases</td>
</tr>
<tr>
<td></td>
<td>Periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA)</td>
</tr>
<tr>
<td></td>
<td>Serum sickness</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Lymphoma, leukemia</td>
</tr>
<tr>
<td></td>
<td>Langerhans cell histiocytosis</td>
</tr>
<tr>
<td></td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Other</td>
<td>Drug-induced</td>
</tr>
</tbody>
</table>

References:

Differential diagnosis for erythema nodosum in children

<table>
<thead>
<tr>
<th>Category</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection-related</td>
<td>Viral (e.g. EBV, CMV, HIV)</td>
</tr>
<tr>
<td></td>
<td>Bacterial (e.g. Streptococcus, Mycoplasma, Bartonella, tuberculosis)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Behçet disease</td>
</tr>
<tr>
<td></td>
<td>Systemic vasculitis (e.g. polyarteritis nodosa)</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Lymphoma, leukemia</td>
</tr>
<tr>
<td></td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td></td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Drug-related</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td></td>
<td>Antibiotics (e.g. sulpha drugs, penicillins, macrolides)</td>
</tr>
<tr>
<td>Other</td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

Reference:
### Differential diagnosis for recurrent parotitis

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection-related</td>
<td>Viral: HIV (diffuse infiltrative lymphocytosis), Influenza B, mumps, EBV, CMV, Parvovirus, Paramyxovirus, Adenovirus</td>
</tr>
<tr>
<td></td>
<td>Bacterial: Streptococcal infections, Staphylococcus aureus, Bartonella, Haemophilus</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Sjögren syndrome</td>
</tr>
<tr>
<td></td>
<td>IgG4 related disease</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Parotid tumours</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Other</td>
<td>Sialolithiasis</td>
</tr>
<tr>
<td></td>
<td>Juvenile recurrent parotitis</td>
</tr>
<tr>
<td></td>
<td>Pneumoparotid</td>
</tr>
</tbody>
</table>

**Reference:**

### Differential diagnosis for muscle weakness

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

Differential diagnosis for chorea and abnormal movements in children

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

Reference:
### Differential diagnosis for stroke-like presentations in children

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

**Reference:**

3A. Diagnosis of 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 re-classification of JIA was proposed by Pediatric Rheumatology International Trials Organization (PRINTO) in 2019, but has not been validated
  - Most prominent changes 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

3B. JIA Subtypes

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)**

<table>
<thead>
<tr>
<th>ILAR Classification Criteria for Polyarthritis (Rheumatoid Factor Negative) *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition:</strong></td>
</tr>
<tr>
<td>• Arthritis affecting 5 or more joints during first 6 months of disease</td>
</tr>
<tr>
<td>• Negative testing for RF</td>
</tr>
<tr>
<td><strong>Exclusions:</strong></td>
</tr>
<tr>
<td>o Psoriasis or a history of psoriasis in the patient or first degree relative</td>
</tr>
<tr>
<td>o Arthritis in an HLA-B27 positive male beginning after 6th birthday</td>
</tr>
<tr>
<td>o Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with IBD, or acute anterior uveitis, or history of one of these disorders in 1st degree relative</td>
</tr>
<tr>
<td>o Presence of IgM Rheumatoid Factor on at least 2 occasions at least 3 months apart</td>
</tr>
<tr>
<td>o Presence of systemic JIA</td>
</tr>
</tbody>
</table>

* 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)**

<table>
<thead>
<tr>
<th>ILAR Classification Criteria for Polyarthritis (Rheumatoid Factor Positive) *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition:</strong></td>
</tr>
<tr>
<td>• Arthritis affecting 5 or more joints during first 6 months of disease</td>
</tr>
<tr>
<td>• 2 or more positive tests for RF at least 3 months apart during first 6 months of disease</td>
</tr>
<tr>
<td><strong>Exclusions:</strong></td>
</tr>
<tr>
<td>o Psoriasis or a history of psoriasis in the patient or first degree relative</td>
</tr>
<tr>
<td>o Arthritis in an HLA-B27 positive male beginning after 6th birthday</td>
</tr>
<tr>
<td>o Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with IBD, or acute anterior uveitis, or history of one of these disorders in 1st degree relative</td>
</tr>
<tr>
<td>o Presence of systemic JIA</td>
</tr>
</tbody>
</table>

* 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 (“quotidian”) 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:
  o Psoriasis or a history of psoriasis in the patient or first degree relative
  o Presence of IgM Rheumatoid Factor on at least 2 occasions at least 3 months apart
  o 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

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

Common sites of enthesitis in the lower body

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Insertions of plantar fascia</td>
<td>B. Insertions of quadriceps and patellar tendons</td>
<td>C. Insertion of Achilles tendon</td>
</tr>
</tbody>
</table>


- 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 *

*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:

3C. 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:
  o Children with suspected JIA should be reviewed by a pediatric rheumatologist in 4-6 weeks and those with possible systemic JIA within 7 days
  o 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:
  o Assessments of disease activity by a pediatric rheumatologist and multidisciplinary team are essential for disease monitoring
  o Laboratory monitoring is often an essential part of management, especially during disease flares and medication changes (escalation and weaning)
  o 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 (shared decision making)
  - 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

Oligoarticular arthritis

NSAID and/or Intra-Articular Corticosteroid injection (IAC) with Triamcinolone hexacetonide

Improvement

Inadequate response

Follow and, if no IAC, continue NSAID

Remission

Recurrence

Repeat or first IAC

Remission

Inadequate response

Persistent oligoarticular arthritis

Evolves into polyarticular arthritis

Remission

Intermittent IAC or add disease-modifying drug (e.g. methotrexate)

Management same as polyarticular JIA (see next algorithm)

Inadequate response

Consider biologic agent
An Algorithm for Treatment of Polyarthritis

Polyarthritis

NSAID may be tried for mild polyarthritis
However, initial disease-modifying drug (e.g. methotrexate) is recommended for treating moderate to severe polyarthritis

Improvement

Inadequate response

Continue initial therapy and follow

Add or optimize disease-modifying drug therapy (e.g. methotrexate)

Remission

Improvement

Inadequate response

Recurrence

Consider adding biologic anti-TNF agent; consider IAC or low dose oral corticosteroids as bridging therapy

Remission

Optimize dose or consider switch in biologic therapy (e.g. different anti-TNF agent, biologic anti-IL-6 agent)

Recurrence

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

Systemic arthritis

Mild to moderate disease

- NSAID and/or corticosteroids and/or biologic agent targeting IL-1 or IL-6
  - Improvement
  - Inadequate response
    - Continue therapy and follow, but taper steroids
    - Remission
    - Recurrence

Moderate to severe disease

- Corticosteroids and/or biologic agent, such as anti-IL-1 or anti-IL-6 therapy
  - Improvement
  - Inadequate response
    - Continue therapy and follow
    - Add or change biologic anti-IL-1 or anti-IL-6 agent
    - Remission
    - Recurrence

Remission
Recurrence

N.B. Corticosteroid therapy should be limited by initiating taper as soon as possible to avoid significant side effects

References

SECTION 4. SYSTEMIC LUPUS ERYTHEMATOSUS & RELATED CONDITIONS

4A. Systemic Lupus Erythematosus (SLE)

- Diagnosis of 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, Indigenous, Hispanics, and Asians
  - Positive family history of SLE in 10%
  - Monogenic SLE (1-4% of pediatric SLE patients) should be considered in patients with very young onset (≤5 years of age), strong family history, refractory or progressive disease, and severe and/or resistant skin disease

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 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 they 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 (84%) than the 1997 ACR criteria, especially in early disease
- 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%)
### 2019 Proposed European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) Classification Criteria for SLE *

**Clinical domains**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Points **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional domain</td>
<td></td>
</tr>
<tr>
<td>• Fever</td>
<td>2</td>
</tr>
<tr>
<td>Mucocutaneous domain</td>
<td></td>
</tr>
<tr>
<td>• Non-scarring alopecia</td>
<td>2</td>
</tr>
<tr>
<td>• <strong>Oral ulcers</strong></td>
<td>2</td>
</tr>
<tr>
<td>• <strong>Subacute cutaneous</strong> or <strong>discoid</strong> lupus</td>
<td>4</td>
</tr>
<tr>
<td>• <strong>Acute cutaneous lupus</strong></td>
<td>6</td>
</tr>
<tr>
<td>Arthritis domain</td>
<td></td>
</tr>
<tr>
<td>• Synovitis or tenderness in at least 2 joints</td>
<td>6</td>
</tr>
<tr>
<td>Neurologic domain</td>
<td></td>
</tr>
<tr>
<td>• Delirium</td>
<td>2</td>
</tr>
<tr>
<td>• Psychosis</td>
<td>3</td>
</tr>
<tr>
<td>• Seizure</td>
<td>5</td>
</tr>
<tr>
<td>Serositis domain</td>
<td></td>
</tr>
<tr>
<td>• Pleural or pericardial effusion</td>
<td>5</td>
</tr>
<tr>
<td>• <strong>Acute pericarditis</strong></td>
<td>6</td>
</tr>
<tr>
<td>Hematologic domain</td>
<td></td>
</tr>
<tr>
<td>• Leukopenia</td>
<td>3</td>
</tr>
<tr>
<td>• Thrombocytopenia</td>
<td>4</td>
</tr>
<tr>
<td>• Autoimmune hemolysis</td>
<td>4</td>
</tr>
<tr>
<td>Renal domain</td>
<td></td>
</tr>
<tr>
<td>• Proteinuria &gt;0.5 g/24 hours</td>
<td>4</td>
</tr>
<tr>
<td>• Class II or V lupus nephritis</td>
<td>8</td>
</tr>
<tr>
<td>• Class III or IV lupus nephritis</td>
<td>10</td>
</tr>
</tbody>
</table>

**Immunological domains**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Points **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiphospholipid antibody domain</td>
<td></td>
</tr>
<tr>
<td>• <strong>Anti-cardiolipin antibodies</strong></td>
<td>2</td>
</tr>
<tr>
<td>Or anti-β2-glycoprotein I antibodies</td>
<td></td>
</tr>
<tr>
<td>Or lupus anticoagulant</td>
<td></td>
</tr>
<tr>
<td>Complement proteins domain</td>
<td></td>
</tr>
<tr>
<td>• Low C3 or low C4</td>
<td>3</td>
</tr>
<tr>
<td>• Low C3 and low C4</td>
<td>4</td>
</tr>
<tr>
<td>Highly specific antibodies domain</td>
<td></td>
</tr>
<tr>
<td>• Anti-dsDNA antibody</td>
<td>6</td>
</tr>
<tr>
<td>• Anti-Sm (Anti-Smith) antibody</td>
<td>6</td>
</tr>
</tbody>
</table>

*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**
Comparing SLE Classification Criteria

<table>
<thead>
<tr>
<th>1987 ACR</th>
<th>2012 SLICC</th>
<th>2019 EULAR/ACR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any 4 of 11 criteria</td>
<td>Histology compatible with</td>
<td>Positive ANA</td>
</tr>
<tr>
<td></td>
<td>lupus nephritis and ANA</td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>or anti-dsDNA</td>
<td>≥ 10 points in total (only</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>highest in each domain</td>
</tr>
<tr>
<td></td>
<td>Any 4 of 17 criteria with</td>
<td>counts)</td>
</tr>
<tr>
<td></td>
<td>at least 1 immunological</td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At least 1 clinical criterion</td>
</tr>
</tbody>
</table>


- Other clinical features of SLE not included in any of the classification criteria:
  - Additional constitutional symptoms (i.e., fatigue, weight loss, anorexia)
  - Other rashes (e.g., annular erythema, 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 macrophage activation syndrome (MAS), infection and/or serositis)
  - Elevated IgG levels
  - Other autoantibodies: anti-Ro, anti-La, anti-RNP, Rheumatoid factor

- May be accompanied by 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™, HCQ)
    - Considered standard therapy for all SLE patients
    - Proven efficacy in decreasing frequency and severity of disease flares and in reducing damage, infections, and mortality
    - Improves serum lipid profile, musculoskeletal symptoms, rash, and alopecia; may also lower autoantibody titres, particularly antiphospholipid antibodies
  - 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 (AZA)
    - Typically used for hematologic and renal manifestations
  - Mycophenolate mofetil (MMF)
    - Used for hematologic, renal and CNS manifestations
  - Cyclophosphamide (CYC)
▪ Used for severe renal and CNS manifestations
  o Methotrexate
    ▪ May be used in mild to moderate SLE, especially for joint and mucocutaneous involvement
  o B-cell-therapy
    ▪ Rituximab may be used for resistant cytopenias and in other specific scenarios, such as when a patient is unresponsive to other therapies
    ▪ Belimumab may be used as adjunctive therapy for mild/moderate SLE (previous trials excluded those with severe CNS and renal involvement) and recent adult trial showed efficacy when added to standard therapy in lupus nephritis

### Treatment options by SLE manifestation

<table>
<thead>
<tr>
<th></th>
<th>NSAIDs</th>
<th>Steroids</th>
<th>HCQ</th>
<th>AZA</th>
<th>MMF</th>
<th>CYC</th>
<th>B-cell therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Renal</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>CNS</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Hematologic</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td></td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
</tbody>
</table>

- Prognosis
  o Relapsing and remitting course of disease
  o 10-year survival >90%
  o Most deaths related to infection, renal, CNS, cardiac, and pulmonary disease
  o 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:

4B. Neonatal Lupus Erythematosus (NLE)

- Overview
  - Disease of developing fetus and newborn characterized by transplacental passage of maternal autoantibodies
  - Pathogenesis linked to maternal anti-Ro, anti-La, anti-RNP 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 congenital heart block is 1-5% in children of mothers with anti-Ro and/or anti-La antibodies
  - Higher risk of congenital heart block for subsequent children once one child has been affected (e.g. 18-25% 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, endocardial fibroelastosis, and dilated cardiomyopathy
  - Skin
    - Classic NLE rash is annular, erythematous papulosquamous rash with fine scale and central clearing
    - Predilection for face and scalp (not malar distribution)
    - Sometimes photosensitive
    - Dermatitis may be present at birth, but commonly develops in first few months of life (peak onset at 6 weeks)
    - 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 and occurs during the neonatal period
    - Neutropenia is the next most common and occurs at 2 to 4 months of age
    - Anemia is less common
    - Usually resolve without sequelae and rarely require treatment
    - Neutropenia is not typically associated with increased risk of infection
  - Hepatic
    - Asymptomatic hepatitis with mildly to moderately elevated liver enzymes ± cholestasis
    - 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
    - Important to monitor head circumference
Treatment
- Women with higher titres of anti-Ro autoantibodies during pregnancy require routine fetal echocardiography to assess for heart block and endocardial fibroelastosis (EFE) and may require treatment with dexamethasone, IVIG ± sympathomimetics (if fetal bradycardia present)
- 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; topical corticosteroids may hasten healing, but may increase risk of telangiectasias
- Severe cytopenias may require treatment with IVIG ± corticosteroids
- For future pregnancies, mothers with higher titres of anti-Ro may be treated with hydroxychloroquine to lower the risk of recurrent cardiac NLE

References:

4C. Drug-Induced Lupus

Overview
- Development of lupus-like symptoms that is temporally related to continuous drug exposure (>2-3 month) and that resolves with cessation of the offending drug
- Usually accompanied by serologic findings of positive ANA as well as anti-histone antibodies (>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 and (rarely) low complement levels
- Drugs that have been implicated in drug-induced lupus include: minocycline, anticonvulsants, hydralazine, procainamide and biologic agents that target tumor necrosis factor (TNF)

Treatment
- Stop the offending drug
- Rarely, hydroxychloroquine (Plaquenil™), NSAIDs, corticosteroids and/or other immunosuppressants may be needed

References:
4D. **Antiphospholipid Syndrome (APS)**

- **Overview**
  - 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, infections, or malignancies
  - Venous thrombosis in ~60%, arterial thrombosis in ~30%, small vessel thrombosis in <10%, and mixed thrombosis in ~2%
  - Thrombotic manifestations are most common, followed by hematologic, skin and non-thrombotic neurologic manifestations
  - Catastrophic APS (small vessel thrombosis in ≥3 organs occurring in <1 week) is rare, but associated with a high risk of mortality

---

### 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 β2-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.*

---

- **Clinical features**
  - Higher risk of thrombosis associated with multiple antibody positivity, higher antibody titres, persistent antibody positivity, IgG isotype and specific antibodies (e.g. 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:
    - Skin: livedo reticularis, Raynaud phenomenon, skin ulcers
    - Cardiac: Libman-Sacks endocarditis, cardiomyopathy
    - Renal: thrombotic microangiopathy
    - Neurological: chorea, seizures, transverse myelitis
  - Additional laboratory features of APS:
    - Hematologic: thrombocytopenia, hemolytic anemia, leukopenia
    - 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 (including use of hydroxychloroquine in SLE)
- 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) for primary prevention of thrombosis
- May consider rituximab, IVIG, corticosteroids, and plasmapheresis as direct therapy, depending on clinical presentation and disease severity

References:
SECTION 5 – SYSTEMIC VASCULITIS

5A. Introduction to Vasculitis

- Overview
  - 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 Clinical Manifestations of Systemic Vasculitis

<table>
<thead>
<tr>
<th>Clinical Manifestations of Systemic Vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polychondritis</td>
</tr>
<tr>
<td>Nasal crusting</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Persistent rhinorrhea</td>
</tr>
<tr>
<td>Purulent/bloody discharge</td>
</tr>
<tr>
<td>Nasal ulcers</td>
</tr>
<tr>
<td>Oral ulcers</td>
</tr>
<tr>
<td>Hoarseness</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Stridor</td>
</tr>
<tr>
<td>Wheezing</td>
</tr>
<tr>
<td>Large airway inflammation*</td>
</tr>
<tr>
<td>Alveolar opacities*</td>
</tr>
<tr>
<td>Haematuria</td>
</tr>
<tr>
<td>Red cell casts</td>
</tr>
<tr>
<td>Other casts</td>
</tr>
<tr>
<td>Proteinuria</td>
</tr>
<tr>
<td>Tender nodules</td>
</tr>
<tr>
<td>Polyarthritis</td>
</tr>
<tr>
<td>Polymyalgia</td>
</tr>
</tbody>
</table>

Flu-like symptoms:
- Fever
- Polymyalgia
- Polyarthritis
- Headache
- Neck ache
- Malaise
- Fatigue
- Anorexia
- Weight loss

Reproduced from “Diagnosis and management of ANCA associated vasculitis” in BMJ 2012;344:e26, 2012 with permission from BMJ Publishing Group Ltd.
### Classification of vasculitis based on size of vessel (predominantly) involved

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

- **Investigations**
  - Inflammatory changes in systemic vasculitis may include elevated inflammatory markers (CRP, ESR) and/or hyperferritinemia
  - Complete blood count may demonstrate neutrophilic leukocytosis and/or thrombocytosis due to persistent inflammation and/or anemia (may be due to chronic disease or acute blood loss)
  - Signs of end-organ damage or complications may include:
    - Kidneys: elevated creatinine, uremia, hyperkalemia, hyponatremia, and/or abnormal calcium metabolism
    - Lungs: scarring or fibrosis on X-ray or CT
    - Heart: pulmonary hypertension on echocardiogram and catheterization studies
    - Vessels: stenosis, fibrosis, and/or aneurysm may be identified on angiography (conventional, magnetic resonance, and/or CT); abnormalities may also be visible on Doppler ultrasound of involved vessels
    - Eyes: retinal vasculitis, cataracts, vision loss
    - Bones: fractures and/or decreased bone density on X-rays and/or DEXA
  - Immune serology (ANA, ANCA) may be helpful for diagnosis
  - Tissue biopsy may be essential in diagnosing certain types of vasculitis
  - Triggers for systemic vasculitis may include infections (e.g. hepatitis B or C, *Streptococcus*), drugs (e.g. cocaine), or malignancy
• **Treatment**
  o Typically involves immunosuppressive agents (corticosteroids, disease-modifying antirheumatic drugs, biologic agents) plus supportive therapy
  o Medications depend on specific diagnosis, organ involvement, and severity – please review the sections below for treatment of individual diseases

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

**References:**

**5B. Takayasu arteritis**

• **Overview**
  o Large vessel vasculitis involving the aorta and its branches (thoracic, abdominal, carotid) leading to thickening, stenosis, thrombus formation, aneurysms and possible dissection
  o Incidence rates higher in Asia, South America and Mediterranean region
  o Most commonly affects young women between 20 and 40 years of age and onset in childhood is much less frequent
  o Most patients experience a chronic relapsing-remitting disease course
  o Initially can present as non-specific inflammatory illness with fever
  o Evolution to chronic, fibrotic phase with signs and symptoms of chronic vascular insufficiency (pulse deficit, claudication, BP discrepancy, bruits) – ¼ of children are diagnosed during this late inactive phase

<table>
<thead>
<tr>
<th>2008 EULAR/PRINTO/PRES Classification Criteria for Childhood Takayasu arteritis *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic abnormalities of the aorta or its main branches and pulmonary arteries showing aneurysm/dilatation, narrowing, or thickened arterial wall (mandatory criterion)</td>
</tr>
<tr>
<td>Plus ≥ 1/5 of the following:</td>
</tr>
<tr>
<td>• Peripheral pulse deficit or claudication (focal muscle pain induced by physical activity)</td>
</tr>
<tr>
<td>• Discrepancy of four limb systolic BP &gt;10 mm Hg in any limb</td>
</tr>
<tr>
<td>• Bruits or thrills over the aorta and/or its major branches</td>
</tr>
<tr>
<td>• Hypertension (&gt;95th percentile for height)</td>
</tr>
<tr>
<td>• Acute phase reactants (ESR &gt;20 or increased CRP)</td>
</tr>
</tbody>
</table>

* 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
- Constitutional features are common and include fever, fatigue, weight loss, hypertension, headaches and myalgias
- Additional manifestations depend on which large vessels are involved
- CNS symptoms may occur due to involvement of carotid arteries or due to posterior reversible encephalopathy syndrome secondary to severe hypertension and include severe headache, stroke or transient ischemic attack, cognitive dysfunction, seizures, focal neurologic deficits, and visual disturbances
- Cardiovascular symptoms include chest pain, dyspnea, activity intolerance, or claudication when limb arteries are involved
- Pulmonary artery involvement leads to pulmonary hypertension characterized by dyspnea, activity intolerance, cough, and possible hemoptysis
- Gastrointestinal symptoms from celiac or mesenteric artery involvement include abdominal pain due to ischemia, diarrhea, bloody stools, and bowel perforation
- Renal artery involvement typically causes hypertension, but may rarely lead to proteinuria, hematuria, and renal dysfunction
- Skin lesions in patients with Takayasu arteritis are rare, but include livedo reticularis, purpura, erythema nodosum, and digital ischemia leading to ulcers and/or gangrene

Investigations
- Laboratory investigations are nonspecific and may include inflammatory changes, such as increased CRP and/or ESR, normocytic anemia, leukocytosis and thrombocytosis
- Imaging
  - Magnetic resonance angiography useful to show extension of disease and vessel wall inflammation; often used to follow disease (less invasive than conventional angiography)
  - Ultrasound Doppler is easily accessible and may be used a complement or precursor to MRA to identify decreased arterial flow and/or thrombus, but is not sensitive enough to exclude diagnosis if normal
  - CT angiogram may be used initially to identify anatomical areas of involvement (especially if MRI less accessible) but unable to distinguish active inflammatory lesions from late phase disease
- Rule out associated TB infection (PPD, chest X-ray) as this may be involved in pathogenesis and affect management by biologic agents
- Eye examination to assess for ocular ischemia and complications of hypertension or steroid therapy

Treatment
- Depends on phase of disease and degree of inflammation
  - If “active” disease (by acute phase reactants +/- wall enhancement on MRA):
    - Corticosteroids remain mainstay of treatment plus second line agent
    - Second line agents include Methotrexate, Mycophenolate mofetil, anti-TNF agents
    - May also use Tocilizumab, Cyclophosphamide, or Rituximab if refractory disease
    - Low dose aspirin is recommended to reduce risk of clots
  - If “inactive” disease:
    - Manage end-organ manifestations (medical therapy to control hypertension +/- vascular surgery/stenting to address organic ischemia caused by vessel stenosis, aneurysm and/or dissection)
• **Prognosis**
  o Early recognition is key for better outcome
  o Disease burden remains high in pediatric patients and damage accrues over time
  o Stroke, elevated CRP at disease onset, lower BMI and younger age at diagnosis associated with poor outcomes

**References:**

5C. **Kawasaki disease (KD)**

• **Overview**
  o Medium vessel vasculitis, with predilection for coronary arteries
  o Most common between 1 and 5 years of age
  o Ratio of males to females is ~1.5 to 1
  o Highest relative risk in children of Asian ethnicity, especially in Japanese ethnicity where recurrence rate is ~3% and relative risk in siblings is 10-fold higher
  o Most common cause of acquired heart disease in children in developed countries – coronary artery aneurysms from KD account for 5% of acute coronary syndromes in adults under 40 years of age
  o May be triggered by infectious agent (viral and/or bacterial super-antigen implicated)
  o Polygenic with genes identified that influence risk of KD and coronary artery involvement

---

**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 mucosa, fissured lips, strawberry tongue)
- Cervical lymphadenopathy (frequently unilateral, ≥1.5 cm)

* Other ways to make diagnosis of Kawasaki Disease (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 clinical features and compatible laboratory and/or echocardiographic findings – diagnosis aided by [American Heart Association algorithm for evaluation of suspected incomplete KD](#)
  c) **Atypical KD** diagnosed if KD with an unusual manifestation (e.g. gallbladder hydrops, pulmonary nodules, interstitial infiltrates, anterior uveitis, cranial nerve palsy)
Clinical features
- Diagnostic clinical features included in diagnostic criteria
- Additional common features: irritability (aseptic meningitis), arthritis (at onset or delayed), sterile pyuria (urethritis), gastroenteritis (abdominal pain, vomiting, diarrhea), uveitis, periungual desquamation 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)
- Disseminated intravascular coagulation

Investigations
- At diagnosis, laboratory investigations demonstrate inflammatory changes, including neutrophilic leukocytosis, normocytic anemia, elevated ESR/CRP, hyperferritinemia, and hypoalbuminemia; hyponatremia, elevated transaminases and sterile pyuria are also common
- Thrombocytosis develops in second week of illness with return to normal by 8 weeks
- Echoardiogram required at the time of diagnosis and 6 weeks later to assess for coronary artery dilatation and/or aneurysm
  - Severity of coronary artery dilatation classified based on Z-score

Treatment
- See treatment algorithm on next page
- Target treatment within 10 days of fever onset
- IVIG
  - Unequivocally reduces the occurrence of coronary artery aneurysms, especially if treated within first 10 days of illness
  - Recommended dose 2 g/kg over 10 to 12 hours
  - If still febrile 24-36 hours after IVIG → second dose of IVIG or may consider starting corticosteroids depending on patient features and response to first dose
  - 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 30 mg/kg/day for 1-3 days or prednisone PO 2 mg/kg/day for 3 days or for a longer course if high risk.

- **Anticoagulation**
  - Strongly consider for patients with increasing coronary artery dilation
  - *If large or giant coronary aneurysm* (e.g. Z-score > 5) → long-term therapy using ASA, a second antiplatelet agent, and low molecular weight heparin or warfarin may be considered

- **Supportive measures**
  - General counseling regarding healthy lifestyle and activity promotion recommended
  - Consider assessing diet, physical activity, blood pressure, lipid profile, body mass index, and smoking status (if relevant) regularly after KD diagnosis
  - No physical activity restrictions required for patients with mild dilatation or whose coronary artery dimensions return to normal on follow-up
  - Participation in competitive sports or high-intensity activities may be limited in patients with persistent medium or larger coronary artery aneurysm

### An algorithm for treatment of Kawasaki disease

![Algorithm](image)

- **Low risk patients**
  - IVIG infusion
  - ASA

- **High risk patients**
  - IVIG
  - ASA
  - **Plus**
    - Corticosteroid

### Treatment options for IVIG resistant patients

- **Most frequently administered**
  - IVIG – second infusion
  - IVIG + corticosteroid
  - Anti TNF-α agent - Infliximab

- **Alternative treatment**
  - Anti TNF-α agent - Etanercept
  - Interleukin -1 inhibitors - anakinra, canakinumab
  - Plasmapheresis – N/A
  - Other immunosuppressive agents – cyclophosphamide, cyclosporine, methotrexate.

**Figure from Oli A et al, Treatment options for refractory Kawasaki disease, Yangtze Medicine, 2019; 4(1):28-38 included with permission of publisher.**

**N.B.** High risk refers to risk of possible IVIG resistance at presentation and risk factors in various clinical scores include male gender, age <12 months, lower hemoglobin, lower platelet counts, hypoalbuminemia, hyponatremia, elevated CRP, increased AST, and neutrophilic leukocytosis.
A RESIDENT'S GUIDE TO PEDIATRIC RHEUMATOLOGY

- **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)

**References:**

5D. **Polyarteritis nodosa (PAN)**

- **Overview**
  - Necrotizing vasculitis in medium or small size muscular arteries
  - Very rare in childhood
  - Mild to severe inflammation leading to damage and early mortality
  - Early diagnosis challenging due to non-specific (may be constitutional only) symptoms

**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

- Clinical features
  - Constitutional symptoms, including prolonged fever, malaise, fatigue, weight loss, myalgias, and arthralgias
  - Specific manifestations include hypertension, renal artery abnormalities, skin lesions and peripheral or central nervous system involvement (see Classification Criteria above)
  - Additional clinical features include:
    - Testicular pain or tenderness
    - Stroke or coronary artery disease
    - Bruits
    - Ischemic abdominal pain

- Investigations
  - Non-specific inflammatory changes on laboratory testing in PAN include leukocytosis, thrombocytosis, normocytic anemia, and significant elevation of ESR and CRP
  - Typically negative autoantibodies, such as ANCA, ANA and extractable nuclear antigens
  - Renal involvement may lead to impaired renal function (e.g. elevated creatinine, uremia), proteinuria, hematuria, and red blood cell casts
  - Conventional angiogram is gold standard to identify aneurysmal / stenotic lesions
  - MR angiogram demonstrates vessel involvement but may fail to detect microaneurysms and over-estimate stenosis
  - CT angiogram is an excellent modality to identify stenotic and aneurysmal lesions
  - Positive hepatitis B serology can occur although it is unusual in pediatric patients

- Treatment
  - Aggressive therapy often indicated due to high disease burden and risk of damage
  - High-dose corticosteroids plus second line agent (e.g. Methotrexate, Cyclophosphamide, Mycophenolate mofetil) often used during remission induction in the first 3 to 6 months
  - Other second-line agents include azathioprine, infliximab, adalimumab, etanercept, or tocilizumab
  - Plasma exchange may be considered in acute life-threatening disease

Cutaneous PAN

- Clinical features
  - Cutaneous PAN characterized by absence of major organ involvement, but may involve skin, joints, muscles and peripheral nervous system
  - Skin findings include tender subcutaneous nodules, livedo reticularis, superficial or deep ulcers
  - Additional clinical features include constitutional features, myalgia, arthralgia, non-erosive arthritis, and 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 and another second line agent (e.g. IVIG, Methotrexate)
- Penicillin treatment (if proven associated *Streptococcal* infection) and prophylaxis

**Deficiency of Adenosine Deaminase 2 (DADA2)**

Overview
- First monogenic vasculitis syndrome that should be considered in differential diagnosis of polyarteritis nodosa, especially in early onset disease
- Autoimmune recessive disease caused by mutations in *ADA2* gene that encodes adenosine deaminase 2
- Parents of children with DADA2 are typically unaffected, which means that 50% of normal enzymatic activity is sufficient for protein function
- Clinical features are variable, depending on mutation type and number of affected alleles
- Compared to PAN, pediatric patients with DADA2 have fewer constitutional symptoms and fewer relapses, but increased cardiac and neurological involvement, increased hepatic fibrosis, and higher mortality

Clinical features:
- Constitutional symptoms include fever, arthralgia, myalgia, and weight loss
- Initial phenotype characterized by recurrent lacunar stroke (ischemic or hemorrhagic) with onset at young age
- Additional neurologic manifestations include peripheral polyneuropathy, neurosensory hearing loss, mononeuritis multiplex, labyrinthitis, and encephalopathy
- Livedo reticularis is very common
- Renal involvement may be characterized by arterial hypertension, renal vessel artery aneurysms, renal artery stenosis and glomerular scarring
- Gastrointestinal involvement may include hepatosplenomegaly, transaminitis, aphthous stomatitis, and abdominal ischemia due to aneurysm of the mesenteric or celiac arteries
- Some DADA2 patients may present with a phenotype similar to combined variable immunodeficiency with recurrent sinopulmonary infections and increased susceptibility to herpes virus infection (linked to hypogammaglobulinemia)

Investigations
- Diagnosis confirmed through genetic testing or reduced ADA2 levels
- Elevated inflammatory markers (CRP, ESR) may be identified during acute flare
- Cytopenias are common
- Assessment of immunoglobulins to screen for hypogammaglobulinemia should be performed and low serum immunoglobulin levels may correlate with inflammatory disease activity
- Screening for prothrombotic changes should be completed since patients may have positive lupus anticoagulant
- MRI brain used to assess for current or previous stroke
- Angiography (MR or conventional) to assess for aneurysm or stenosis
- Skin biopsy may be used to assess for vasculitis while awaiting genetic test results if other testing is inconclusive

Treatment
- TNF-inhibitors (etanercept, adalimumab, infliximab) have been successful in suppressing fever, vasculopathy and strokes
Anticoagulant and anti-platelet therapies (e.g. ASA) should be avoided due to high risk of intracranial hemorrhage.

- Corticosteroids and other second line agents commonly used in other vasculitides (e.g. methotrexate, mycophenolate mofetil) have limited benefit.
- Thalidomide may be used when biologic agents are not available.
- Hematopoetic stem cell transplantation may offer definitive treatment, especially in patients with immune dysregulation and/or bone marrow failure.
- Future therapies may include recombinant ADA2 protein or gene therapy.
- Genetic counselling should be offered to families.

References:

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

- **Overview**
  - Most common vasculitis in children
  - Characterized by diagnostic tetrad of purpuric rash, arthritis, abdominal pain, and renal abnormalities
  - Most frequently occurs between 3 and 15 years of age
  - Striking seasonal variation with most cases occurring in winter
  - 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
A RESIDENT’S GUIDE TO PEDIATRIC RHEUMATOLOGY

• Clinical features
  o Skin involvement (100% of patients)
    ▪ Cutaneous purpura (100%) with palpable non-blanchable lesions 2-10 mm in diameter, ranging from small petechiae to large ecchymosis, usually concentrated on lower extremities
    ▪ May not always present at onset of illness
    ▪ Subcutaneous edema over the hands and feet (often painful), and around the eyes, forehead, scalp and scrotum often occurs early in disease
  o Arthritis (75%)
    ▪ Usually affecting knees and ankles
    ▪ Associated with painful oedema
  o GI involvement (50-75%)
    ▪ Characterized by intermittent periumbilical abdominal pain, diarrhea, intussusception, and (less commonly) gastrointestinal hemorrhage
  o Renal involvement (40-50%)
    ▪ Renal abnormalities may not manifest initially, thus must regularly monitor blood pressure and urinalysis for at least 6 months after acute illness
    ▪ Most commonly microscopic hematuria
    ▪ Proteinuria accompanies hematuria in 25%
    ▪ Nephrotic syndrome in 5%
    ▪ Increased risk of nephritis in patients over 7 years of age, persistent purpuric lesions, severe abdominal complaints, and decreased factor XIII activity
  o Other uncommon manifestations
    ▪ Orchitis (10-20% of males) associated with pain and swelling
    ▪ Peripheral neuropathy
    ▪ Subconjunctival hemorrhage
    ▪ Pulmonary hemorrhage, interstitial pneumonitis

• Investigations
  o No distinctive or diagnostic laboratory abnormalities
  o May have non-specific inflammatory changes, such as elevated leukocytes, platelets, ESR and/or CRP
  o Coagulation profile must be normal and thrombocytopenia should be absent
  o Serum IgA increased in 50% of patients
  o Urinalysis (every 2 weeks for 3 months and then monthly up to 6-12 months after initial diagnosis of HSP) may show hematuria or proteinuria, less commonly associated with elevated creatinine and decreased ability to concentrate urine
  o Biopsy of skin or kidneys may be needed to confirm diagnosis if atypical features or if acute or persistent nephritic or nephrotic syndrome (see classification criteria above)

• Treatment
  o Largely supportive
  o NSAIDs may be used for joint pain (caution required due to potential renal and/or GI involvement)
  o Prednisone in select patients
    ▪ May decrease severity and duration of GI symptoms (and may need to be given IV due to GI inflammation affecting oral absorption) 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): high-dose oral or IV corticosteroids ± second line agent (e.g. azathioprine, mycophenolate mofetil, cyclophosphamide)

• Prognosis
  o Usually excellent since IgA vasculitis is typically a self-limited condition that resolves within 4 weeks (average)
  o Recurrence in about 1/3 of patients
  o Long-term prognosis depends on severity of nephritis (poorer prognosis with nephrotic syndrome or if >50% crescent formation on biopsy)
  o End-stage renal disease occurs in <5% of patients; in ~20% of those with nephritic or nephrotic syndrome

References:

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

• Overview
  o Predominantly small vessel vasculitis, characterized by severe granulomatous inflammation that may be life-threatening
  o Usually occurs as a triad involving airway, lower respiratory tract, and renal involvement
  o May present acutely as pulmonary-renal syndrome or evolve with a more chronic course
  o Generally occurs in the second decade of life with a female preponderance

**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
  - Clinical features listed in order of decreasing frequency:
    - Constitutional: fatigue, malaise, fever, weight loss
    - Pulmonary: dyspnea, chronic cough, hemoptysis/alveolar hemorrhage, lung nodules/cavitatios/ixed 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
  - Inflammatory changes on blood work are common, including elevated CRP and ESR, neutrophilic leukocytosis, normocytic anemia, and thrombocytosis
  - Renal involvement identified through proteinuria, hematuria, and red blood cell casts on urinalysis, while creatinine and urea are typically normal unless there is advanced disease
  - ANCA positive in >90% of patients (>80% are c-ANCA positive with anti-PR3 positivity)
  - Other autoantibodies may also be present, such as rheumatoid factor (~50%), ANA (20-40%) and antiphospholipid antibodies (~20%) that increase risk of thrombosis
  - Characteristic imaging findings include:
    - Chest X-ray – nodules, infiltrates
    - CT chest – pulmonary infiltrates, cavitations, alveolar hemorrhage, pleural effusion
    - CT sinus – mucosal thickening, opacification, mucosal and/or bony destruction
    - CT upper airway – subglottic stenosis
    - MRI upper airway – subglottic stenosis with airway wall thickening and enhancement in early disease
  - Pulmonary function test findings are non-specific, but may show decreased DLCO in interstitial lung disease and/or pulmonary hemorrhage
  - Biopsy may aid diagnosis
    - Kidney biopsy in GPA demonstrates pauci-immune crescentic glomerulonephritis
    - Lung biopsy shows granulomatous inflammation with no evidence of infection

- Treatment
  - Initial therapy involves combination of corticosteroids and a second-line agent, such as rituximab, cyclophosphamide, or methotrexate (choice depends on disease severity)
  - Rituximab is preferred for induction due to increased effectiveness and tolerance; however, other second-line agents may need to be trialed due to issues with access
  - Plasma exchange may be used as part of induction therapy for children with life-threatening disease
  - Maintenance therapy with rituximab, methotrexate, azathioprine, plus tapering doses of corticosteroids
  - May consider endoscopic intervention for subglottic stenosis and endobronchial disease
Supportive therapies include cotrimoxazole to prevent infections in patients treated with cyclophosphamide or rituximab and vitamin D and/or calcium to maintain bone health.

- **Prognosis**
  - Significant morbidity associated with disease and medications
  - Complications include nasal septal perforation, saddle nose deformity, upper airway stenosis, and renal failure
  - Rare complications include need for mechanical ventilation and/or dialysis in ~10% of patients

**References:**

**5G. Microscopic Polyangiitis (MPA)**

- **Overview**
  - Necrotizing, non-granulomatous small vessel vasculitis affecting capillaries, venules, or arterioles
  - Usually involves pulmonary capillaritis and glomerulonephritis
  - Rare in childhood, but mean age of onset in children is 9 to 12 years
  - No classification criteria have been developed

- **Clinical features**
  - Rapidly progressive glomerulonephritis (90% of patients) that typically presents with hypertension and abnormalities on urinalysis
  - Pulmonary capillaritis leading to hemorrhage (30-60%) that presents with bloody sputum, cough, pleuritic chest pain, and/or dyspnea
  - Pulmonary-renal syndrome (30-50%)
  - Hypertension (50-60%)
  - Palpable purpura (common), but other skin findings may include petechiae, livedo reticularis, ulcers, and urticaria

- **Investigations**
  - Inflammatory changes on blood work are common, including elevated CRP and ESR, neutrophilic leukocytosis, thrombocytosis, and normocytic (possibly refractory) anemia
  - Renal involvement is characterized by hematuria, proteinuria, and/or red blood cell casts on urinalysis and elevated urea and creatinine in advanced disease
  - ANCA positive in >95% with positive p-ANCA and anti-MPO specificity in >75%
  - ANCA titres may or not correlate with disease activity and risk of relapse or mortality
  - Diffuse pulmonary infiltrates, hemorrhage, and/or pleural effusion on chest X-ray and CT
Pulmonary function test findings are non-specific, but may show decreased DLCO in interstitial lung disease and/or pulmonary hemorrhage.

- Biopsy may aid diagnosis
  - Renal biopsy with immunofluorescence demonstrates necrotizing, pauci-immune crescentic glomerulonephritis
  - Lung biopsy shows non-granulomatous inflammation with absence of infection

- Treatment
  - Typically use similar treatment approach to GPA due to lack of trials in pediatric MPA
  - Induction therapy using corticosteroids and second-line agent, such as rituximab, cyclophosphamide, or methotrexate (depending on disease severity)
  - Maintenance therapy involves rituximab, methotrexate, or azathioprine with ongoing weaning of corticosteroids

References:

5H. Eosinophilic Granulomatosis with Polyangiitis (EGPA)

- Overview
  - Granulomatous small vessel vasculitis formerly known as Churg-Strauss syndrome
  - Characterized by extravascular granulomas and eosinophilic infiltration
  - Very rare in children and teenagers (1-3 per million) – no pediatric classification criteria

<table>
<thead>
<tr>
<th>2022 ACR/EULAR Classification Criteria for EGPA *</th>
</tr>
</thead>
<tbody>
<tr>
<td>A cumulative score of ≥ 6 points from the subsequent criteria needed to classify patient as having EGPA after confirming small or medium vessel vasculitis and excluding mimics:</td>
</tr>
<tr>
<td><strong>Clinical criteria</strong></td>
</tr>
<tr>
<td>• Obstructive airway disease +3 points</td>
</tr>
<tr>
<td>• Nasal polyps +3 points</td>
</tr>
<tr>
<td>• Mononeuritis multiplex or motor neuropathy not due to radiculopathy +1 point</td>
</tr>
<tr>
<td><strong>Laboratory and biopsy criteria</strong></td>
</tr>
<tr>
<td>• Blood eosinophil count ≥ 1 x 10⁹/L +5 points</td>
</tr>
<tr>
<td>• Extravascular eosinophilic predominant inflammation on biopsy +2 points</td>
</tr>
<tr>
<td>• Positive ANCA or anti-PR3 antibody -3 points</td>
</tr>
<tr>
<td>• Hematuria -1 point</td>
</tr>
</tbody>
</table>
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:
  - Characterized by history of “difficult to control” or severe chronic asthma, allergic rhinitis and/or nasal polyps
  - Sinusitis is common
  - Skin is also common, including vasculitic lesions, nodules, petechiae, purpura, livedo reticularis
  - Cardiovascular involvement (50%) includes myocarditis, pericarditis, cardiomyopathy, possible cardiac failure
  - Peripheral neuropathy presenting as mononeuritis multiplex
  - Other clinical features include ischemic abdominal pain, diarrhea and/or bloody stools, arthralgias, and myalgias

- Investigations
  - Peripheral eosinophilia (≥10% of leukocytes) and increased IgE levels
  - ANCA, usually anti-MPO, present in less than 50% of patients
  - Lung imaging shows diffuse, non-fixed pulmonary infiltrates
  - Pulmonary function tests show low DLCO
  - Echocardiogram needed to assess for myocarditis, pericarditis and decreased cardiac function
  - Diagnosis aided by lung or skin biopsy showing significant eosinophilic infiltration and granulomas

- Treatment
  - Typically involves corticosteroids plus second line agent
  - Cyclophosphamide or rituximab used for severe disease, especially if cardiac, GI or neurologic involvement
  - Alternate agents for less severe or steroid-dependent disease include methotrexate, azathioprine, or mycophenolate mofetil

References:

5. Behçet Disease

- Overview
  - Systemic vasculitis with characteristic triad of oral ulcers, genital ulcers, 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, but equally affects both genders

| 2016 Consensus Classification Criteria for Pediatric Behçet Disease |
| ≥ 3 of the following 6 criteria: |
| • Recurrent oral aphthosis (at least 3 attacks per year) |
| • Genital ulceration or aphthosis (typically with scarring) |
| • Skin involvement (necrotic folliculitis, acneiform lesions, or erythema nodosum) |
| • Ocular involvement (anterior uveitis, posterior uveitis, or retinal vasculitis) |
| • Neurological signs (with the exception of isolated headaches) |
| • Vascular signs (venous thrombosis, arterial thrombosis, arterial aneurysm) |

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

- Clinical features:
  - Mucocutaneous ulcers: crops of painful ulcers on lips, tongue, palate and GI tract that last for 3 to 10 days and heal without scarring
  - Genital ulcers: recurrent painful ulcers on penis, scrotum and perineum of males and on vulva in females that heal with scarring
  - Skin lesions: erythema nodosum, palpable purpura, papulopustular lesions, acneiform lesions, ulcers, folliculitis, positive pathergy test
  - Ocular inflammation: chronic relapsing bilateral posterior and anterior uveitis or retinal vasculitis; rare findings include hypopyon, corneal ulceration, cystoid macular edema, retinal detachment and retrobulbar neuritis
  - CNS involvement: aseptic meningitis, encephalitis, encephalomyelitis, cerebral venous sinus thrombosis, pseudotumour cerebri, cranial nerve paralysis
  - MSK: oligoarthritis or polyarthritis, acute localized myositis
  - GI: abdominal pain, diarrhea, colitis (difficult to distinguish from inflammatory bowel disease), hepatic vein occlusion
  - Vascular: arterial and/or venous thrombosis, superficial thrombophlebitis, cerebral sinus thrombosis
  - Rare manifestations: glomerulonephritis, carditis, dilation of proximal aorta, atrial septal aneurysm, mitral valve prolapse, pulmonary hemorrhage

- Investigations
  - Currently made clinically - no pathognomonic clinical finding or laboratory test to provide definitive diagnosis
  - Inflammatory changes on blood work are common, including elevated CRP and ESR, neutrophilic leukocytosis, thrombocytosis, and normocytic anemia
  - Pathergy test (rarely performed, characteristic but not pathognomonic of disease) with cutaneous pustular reaction occurring 24 to 48 hours after needle puncture of dermis
  - Genetics may be helpful – HLA-B51 (more prevalent in Mediterranean and Far East) and HLA-A26 (more prevalent in East Asian)
A RESIDENT’S GUIDE TO PEDIATRIC RHEUMATOLOGY

• Treatment
  - No controlled studies have been performed on children
  - Topical treatment of oral and genital ulcers using sucralfate and/or analgesics
  - Oral corticosteroids may be used during acute episode
  - Colchicine and thalidomide are helpful for recurrent oral and genital ulcers
  - Azathioprine may be used for recurrent mucocutaneous ulcers, ocular inflammation, CNS disease, or GI disease
  - Anti-TNF agents have been used for ocular, CNS disease and GI disease
  - Apremilast (an oral phosphodiesterase 4 inhibitor) has recently been demonstrated to be effective for treatment of oral ulcers in Behçet disease

• Prognosis
  - Long relapsing course
  - Young age at onset and male sex are indicators of prolonged disease
  - Severe ocular and CNS manifestations may lead to long-term morbidity and mortality
  - High risk of mortality in patients with vascular occlusion or aneurysm

References:
SECTION 6 – IDIOPATHIC INFLAMMATORY MYOPATHIES

6A. Juvenile Dermatomyositis (JDM)

- **Diagnosis**
  - 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); EMG and muscle biopsy are done less frequently
- 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
  - 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)
    - 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.

<table>
<thead>
<tr>
<th>MSA</th>
<th>Frequency</th>
<th>Associated Clinical Characteristics</th>
</tr>
</thead>
</table>
| Anti-p155/p140 (Anti-TIF1γ) | 60%       | Rash (Gottron papules, malar rash, “shawl-sign” rash)  
Photosensitivity  
Low CK levels  
Chronic illness course  
Generalized lipodystrophy |
| Anti-MJ (Anti-NXP2)       | 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 diagnosis |
| 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 severe 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
- 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, CRP), lipid abnormalities & organ involvement
- Consider echocardiogram and pulmonary function tests, as indicated

**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 or ulcerative skin disease
  - IVIG, cyclosporine, mycophenolate mofetil, rituximab, or Jak inhibitors may be used in resistant or refractory disease
  - Topical therapies may also be considered for resistant skin disease

**Prognosis**
- 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:**
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:

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:
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  
Stiff skin syndrome  
Lichen sclerosus |

*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

- **Overview**
  - Localized scleroderma, also known as morphea, is an idiopathic inflammatory and sclerosing disorder affecting the skin and subcutaneous structures characterized by excessive accumulation of collagen
  - Up to 50% of children can have extracutaneous manifestations, most often musculoskeletal (e.g. arthritis, joint contracture, myositis), as well as uveitis, neurologic findings (e.g. seizures, headache), and Raynaud phenomenon
  - Classified into 5 subtypes: circumscribed, linear, generalized, pansclerotic, and mixed

- **Circumscribed morphea**
  - Includes superficial round/ovoid 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 tissue atrophy, hyper- (or rarely hypo-) pigmentation and softening of lesions. More common on trunk than extremities.

**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% of cases
- Complications include joint flexion contractures, limb atrophy, leg length discrepancy
- Craniofacial linear scleroderma: may be associated with intracranial lesions, headaches, 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

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

**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, calcipotriol (vitamin D), Imiquimod 5%, Tacrolimus
- Systemic immunotherapy recommended for all lesions beyond superficial circumscribed morphea: corticosteroids, methotrexate, mycophenolate mofetil, biologic therapy such as abatacept or tocilizumab, rituximab, Jak inhibitors (may be considered in recalcitrant disease)
- Other: phototherapy with ultraviolet A rays
- Supportive: physiotherapy, occupational therapy, psychosocial support
- Corrective or cosmetic surgery for facial lesions, tendo-achilles lengthening, leg-length discrepancy

**References**

7C. **Systemic Sclerosis (SSc)**

- **Overview**
  - Rare autoimmune disease in children, characterized by symmetrical skin thickening and fibrosis of internal organs
  - Childhood onset accounts for 10% of cases
  - Sexes equally affected until onset age of 8 years, followed by 4:1 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)

<table>
<thead>
<tr>
<th>2013 ACR/EULAR Classification Criteria for SSc *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Items</strong></td>
</tr>
<tr>
<td>Skin thickening **</td>
</tr>
<tr>
<td>• Skin thickening of fingers of both hands extending proximal to metacarpophalangeal (MCP) joints</td>
</tr>
<tr>
<td>• Skin thickening of whole finger distal to MCP joints</td>
</tr>
<tr>
<td>• Puffy fingers</td>
</tr>
<tr>
<td>Fingertip lesions **</td>
</tr>
<tr>
<td>• Digital tip ulcers</td>
</tr>
<tr>
<td>• Pitting scars in fingertips</td>
</tr>
<tr>
<td>Telangiectasia</td>
</tr>
<tr>
<td>Abnormal nailfold capillaries (enlarged capillaries and/or capillary loss with or without peri-capillary hemorrhages)</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension and/or interstitial lung disease</td>
</tr>
<tr>
<td>Raynaud phenomenon</td>
</tr>
<tr>
<td>Scleroderma related antibodies (any of anti-centromere, anti-Scl70 (also known as anti-topoisomerase I), or anti-RNA polymerase III)</td>
</tr>
</tbody>
</table>

*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:

<table>
<thead>
<tr>
<th>Raynaud Phenomenon</th>
<th>Common in children with SSc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Associated with abnormal nail fold capillaries</td>
</tr>
<tr>
<td></td>
<td>Can lead to digital tip ulcers and gangrene</td>
</tr>
</tbody>
</table>

**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-ScI 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 and fluoroscopic swallowing study to look for dysmotility and GERD

### Treatment
- 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
  - Wound care and pain control for digital ischemia
- Symptomatic treatment
  - GERD: proton pump inhibitors (e.g. omeprazole)
  - Raynaud phenomenon: peripheral vasodilators (e.g. nifedipine)
  - Digital ischemia: prostacyclin analogs (e.g. iloprost)
  - Hypertension, renal disease: ACE Inhibitors (e.g. enalapril)
  - Pulmonary hypertension: endothelin-1 receptor antagonists (e.g. bosentan), prostacyclin analogs (epoprostenol)
- Systemic therapy
  - Systemic corticosteroids may be used in induction treatment for active inflammatory disease, but high and/or prolonged doses are associated with increased risk of renal crisis
  - Methotrexate and/or mycophenolate mofetil (MMF) for active inflammatory phase of skin disease
  - Cyclophosphamide, MMF and tocilizumab for alveolitis and interstitial lung disease; nintedanib (triple angiokinase inhibitor) used in adults for fibrotic lung disease
  - Tocilizumab or rituximab may be considered in severe or refractory cases
Autologous stem cell transplantation has been demonstrated to be efficacious and best candidates appear to be patients with moderate to severe disease of short duration before irreversible damage has occurred.

Prognosis
- 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

7D. Mixed Connective Tissue Disease (MCTD)
- Autoimmune disorder characterized by several clinical and laboratory features:
  - High titre anti-U1 RNP antibodies
  - Swollen hands/fingers or sclerodactyly
  - Raynaud phenomenon
  - Arthritis
  - Myositis
  - Skin rashes (may include malar rash, Gottron-like papules, sclerosis)
- Children may also develop GI manifestations (similar to SSc), interstitial lung and renal diseases over time.
- 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

7E. Raynaud Phenomenon
- Clinical features:
  - 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.
o Usually affects fingers and toes, but may also involve other areas (lips, tongue, tip of nose, earlobes)
o Precipitated by cold, physical or emotional stress, caffeine, medications or smoking
o Raynaud phenomenon may be primary or secondary
  ▪ Primary Raynaud phenomenon has no underlying etiology, but often a positive family history
  ▪ Secondary Raynaud phenomenon occurs due to underlying autoimmune disease (e.g. SLE, JDM, scleroderma, overlap syndromes, MCTD), mechanical obstruction (e.g. thoracic outlet syndrome, cervical rib), hyperviscosity (e.g. polycythemia), cryoglobulinemia, drugs/toxins, or vibration-induced phenomenon
o In isolated Raynaud phenomenon, two best predictive factors for future development of autoimmune diseases are: (1) positive ANA; and (2) abnormal nail fold capillaries

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

• Treatment
  o Preventative (avoid triggers; warm mittens, socks and boots in winter etc)
  o 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 phosphodiesterase (PDE5) inhibitor (e.g. sildenafil) or IV prostacyclin analog (e.g. iloprost)
  o Topical therapy (e.g. nitroglycerin 2% ointment) may be used for digital ulcers

References

7F. Sjögren Syndrome

• Clinical features
  o Multisystem autoimmune disease characterized by decreased secretion of lacrimal and salivary glands leading to dry eyes (keratoconjunctivitis sicca) and xerostomia (dry mouth)
  o Most common presentation in children is parotid swelling or parotitis
  o Clinical diagnosis, given lack of validated pediatric criteria
  o 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
A RESIDENT’S GUIDE TO PEDIATRIC RHEUMATOLOGY

- **Primary vs. secondary**
  - Primary (idiopathic) Sjögren syndrome has no underlying etiology
  - Secondary Sjögren syndrome 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: ultrasound, scintigraphy, minor salivary gland 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)
  - Pilocarpine trial for significant sicca symptoms
  - Hydroxychloroquine (Plaquenil) may be helpful
  - Systemic corticosteroids for acute salivary gland swelling or systemic inflammation

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

**References**

SECTION 8 – AUTOINFLAMMATORY DISEASES

8A. Periodic Fevers & Monogenic Autoinflammatory Syndromes

- Overview
  - The recurrent or periodic fever syndromes were traditionally 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; however, episodes may occur more or less frequently in some of the monogenic autoimmune inflammatory diseases
  - Please see Section 2 for differential diagnosis and approach to recurrent fevers
  - Fevers are typically associated with a constellation of symptoms, including ocular, oropharyngeal, gastrointestinal, dermatologic, and musculoskeletal manifestations
  - Interval between attacks of fever may be irregular or regular
  - Patients typically feel well between episodes

### Characteristic Features of Selected Periodic Fever Syndromes

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

AD: autosomal dominant, AR: autosomal recessive
Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis (PFAPA)

- **Overview**
  - 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)
  - As per Choosing Wisely Canada, genetic testing is not recommended in patients with classic presentation of PFAPA syndrome without features concerning for other genetic periodic fever syndromes

- **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 triad of small non-scarring aphthous ulcers (50-60%), pharyngitis (90%, exudative in 40%), and cervical adenitis (~80%) – only 40-50% of patients have all 3 cardinal symptoms
  - May have associated nausea, vomiting, abdominal pain and headache
  - Throat cultures are consistently negative

- **Treatment**
  - No consensus regarding treatment
  - Single dose of prednisone/prednisolone (1-2 mg/kg/dose) at onset of fever episode and, if necessary, the following day can abort the attack; however, interval between fever attacks may shorten in 10 to 20%
  - Tonsillectomy +/- adenoidectomy may improve or resolve symptoms in 60-80%
  - Supportive therapy with anti-pyretics, hydration and rest may be sufficient given that this is a self-resolving condition
  - Other options include daily cimetidine or colchicine to prevent fever episodes

Familial Mediterranean fever (FMF)

- **Overview**
  - 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
  - Major concern is with the development of amyloidosis, especially renal amyloidosis

- **Clinical features**
  - Fever episodes last for 1-3 days and occur at irregular intervals
  - Clinical hallmark is serositis (peritonitis, pleuritis, pericarditis)
  - Skin: Erysipelas-like rash on shins and dorsum of feet
  - MSK: Monoarthritis or oligoarthritis, arthralgia, myalgia

- **Treatment**
  - Colchicine is highly effective therapy for most patients with FMF to prevent fever episodes and reduce risk of amyloidosis
  - Anti-IL-1 therapy with anakinra, canakinumab or rilonacept is effective in colchicine-resistant or intolerant FMF
TNF-Receptor Associated Periodic Syndrome (TRAPS)

- **Overview**
  - Rare recurrent fever syndrome
  - Originally known as Familial Hibernian Fever
  - Autosomal dominant inheritance; linked to genetic mutation in *TNFRSF1A* gene that encodes TNF receptors
  - 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 is effective and may be considered if other therapies have failed

Hyperimmunoglobulinemia D Syndrome (HIDS)

- **Overview**
  - Also known as mevalonate kinase deficiency
  - 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)

- **Overview**
A RESIDENT’S GUIDE TO PEDIATRIC RHEUMATOLOGY

- 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 of CAPS**
  - Anti-IL-1 therapy with anakinra, canakinumab, or rilonacept are highly effective
  - Early treatment may reduce risk of amyloidosis, prevent hearing loss and improve quality of life and functional outcome

**Syndrome of Undifferentiated Recurrent Fever (SURF)**

- **Overview**
  - Recently described syndrome of recurrent, self-limiting inflammatory episodes without underlying genetic diagnosis or meeting criteria for PFAPA syndrome
  - Previously would have been described as atypical PFAPA syndrome or undifferentiated systemic autoinflammatory syndrome
A RESIDENT’S GUIDE TO PEDIATRIC RHEUMATOLOGY

- Clinical features
  - Recurrent fever episodes, often occurring monthly and lasting for 3 to 5 days
  - Multi-organ presentation – common symptoms include fatigue, malaise, arthralgia, myalgia, abdominal pain, and eye manifestations
  - Elevated inflammatory markers on blood work

- Treatment
  - Supportive therapy with anti-pyretics usually insufficient
  - Inconsistent response to on-demand corticosteroids during attacks
  - Higher response to daily colchicine to prevent flares

References:

8B. Other Inherited Autoinflammatory Diseases

- Overview
  - 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 (most common syndromes described in Section 8A) 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

- 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
  - Full panel testing for recurrent fever syndromes has become more accessible and cost-effective
  - Interpret “variants of uncertain significance” with caution and seek appropriate referrals as needed (e.g. rheumatology, genetics)
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.

**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
  - Avoid ASA, anticoagulants (strokes are hemorrhagic)
  - Reports of successful treatment with anti-TNF therapy
  - Hematopoietic stem cell transplantation considered for severe phenotypes
Type 1 Interferonopathies

- Rare diseases characterized by pathogenic variants in interferon genes coding for molecules that represent the cell’s first lines of defence against 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 (currently only available as a research 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

References:

8C. Chronic Non-Bacterial Osteomyelitis (CNO)

- Overview
  - 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.

### Bristol Diagnostic Criteria for CRMO

**Presence of typical clinical findings** (bone pain +/- localized swelling without significant local or systemic features of inflammation or infection)

AND

**Presence of typical radiologic findings** (plain X-ray demonstrating combination of lytic areas, sclerosis and new bone formation or preferably STIR MRI demonstrating bone marrow edema +/- bone expansion, lytic areas and periosteal reaction)

AND EITHER

**Criterion 1:** more than one involved bone (or clavicle alone) without significantly raised CRP (CRP <30 g/L)

OR

**Criterion 2:** if unifocal disease (other than clavicle) or CRP >30 g/L, bone biopsy showing inflammatory changes (plasma cells, osteoclasts, fibrosis or sclerosis) with no bacterial growth while not on antibiotic therapy.

*Adapted from Roderick et al, Pediatric Rheum, 2016.*

### 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

### Investigations

- Laboratory investigations may be normal or may demonstrate up to moderate inflammatory changes, although significant increases in CRP (>30 g/L) are atypical
- Markers of bone health are normal in CNO (e.g. calcium, magnesium, phosphate, LDH, ALP, PTH)
- HLA-B27 may be positive, especially in patients at higher risk of associated enthesitis related arthritis or inflammatory bowel disease
X-Rays may be normal or may demonstrate mixed osteolytic and sclerotic bone lesions localized in metaphyses close to growth plate with or without periosteal reaction; cortical thickening may occur later in disease.

- MRI (whole body, if available) demonstrates confluent bone marrow edema without abscess and with or without bone expansion, lytic areas and/or surrounding soft tissue swelling; most sensitive imaging 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.

### Jansson et al clinical score to direct work-up of suspected CNO

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal blood count</td>
<td>13</td>
</tr>
<tr>
<td>Symmetrical bone lesions</td>
<td>10</td>
</tr>
<tr>
<td>Lesions with marginal sclerosis</td>
<td>10</td>
</tr>
<tr>
<td>Normal body temperature</td>
<td>9</td>
</tr>
<tr>
<td>Vertebral, clavicular or sternal lesions</td>
<td>8</td>
</tr>
<tr>
<td>Radiographically proven lesions ≥ 2</td>
<td>7</td>
</tr>
<tr>
<td>CRP ≥ 1 mg/dL (10 mg/L)</td>
<td>6</td>
</tr>
</tbody>
</table>

Total clinical score * = 63

<table>
<thead>
<tr>
<th>* Total clinical score</th>
<th>Recommended diagnostic approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 28</td>
<td>Bone biopsy with culture</td>
</tr>
<tr>
<td>28-38</td>
<td>Clinical monitoring</td>
</tr>
<tr>
<td>≥ 39</td>
<td>Consistent with CNO diagnosis</td>
</tr>
</tbody>
</table>

Recommended diagnostic approach

Adapted from Jansson et al, Arthritis Rheum 2009.

- 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 60 to 80% of patients, but relapses are common.
  - Corticosteroids may be used to provide symptomatic relief while progressing therapy.
  - Second-line agents with demonstrated efficacy include bisphosphonates (e.g. pamidronate, zoledronate), anti-TNF agents (e.g. adalimumab, infliximab), methotrexate, and sulfasalazine.

### References:


**8D. Relapsing Polychondritis**

- **Overview**
  - 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 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 via clinical criteria (based on single-centre cohort studies, none validated)

<table>
<thead>
<tr>
<th>1976 McAdam et al Criteria for Relapsing Polychondritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3 of the following clinical features:</td>
</tr>
<tr>
<td>• Bilateral auricular chondritis</td>
</tr>
<tr>
<td>• Non-erosive, seronegative inflammatory polyarthritis</td>
</tr>
<tr>
<td>• Nasal chondritis</td>
</tr>
<tr>
<td>• Ocular inflammation (conjunctivitis, keratitis, scleritis/episcleritis, uveitis)</td>
</tr>
<tr>
<td>• Respiratory tract chondritis (laryngeal and/or tracheal cartilages)</td>
</tr>
<tr>
<td>• Cochlear and/or vestibular dysfunction (neurosensory hearing loss, tinnitus, vertigo)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1989 Modified Michet et al Criteria for Relapsing Polychondritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven chondritis in ≥2/3 cartilage sites of:</td>
</tr>
<tr>
<td>• Auricular cartilage</td>
</tr>
<tr>
<td>• Nasal cartilage</td>
</tr>
<tr>
<td>• Laryngotracheal cartilage</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>Proven inflammation in ≥1/3 of the above cartilage sites plus 2 other minor criteria:</td>
</tr>
<tr>
<td>• Occular inflammation</td>
</tr>
<tr>
<td>• Vestibular dysfunction</td>
</tr>
<tr>
<td>• Seronegative inflammatory arthritis</td>
</tr>
<tr>
<td>• Hearing loss</td>
</tr>
</tbody>
</table>

- **Treatment**
  - No evidence-based guidelines for treatment
In adults, largely empiric and based on disease severity
Options include NSAIDs, corticosteroids, dapsone, colchicine, methotrexate, azathioprine, and anti-TNF therapy

References:
9A. Uveitis

- **Overview**
  - Inflammation of the uvea, which is the middle layer of the eye and consists of the iris, ciliary body, and choroid.
  - May be asymptomatic or symptomatic and may be acute or chronic.
  - Uveitis is often idiopathic, but may also occur in the context of an underlying infection, malignancy, or systemic inflammatory disease.
  - Classification of uveitis is 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.


- **Complications of uncontrolled uveitis include:**
  - Cataracts
  - Glaucoma
  - Band keratopathy
  - Synechiae (adhesion of iris to lens)
  - Cystoid macular edema
  - Vision loss
• Treatment
  o Prompt and aggressive treatment to prevent or minimize visual complications
  o Minimize chronic use of topical corticosteroids (due to side effects such as cataract formation and glaucoma)
  o Close collaboration between rheumatologists and ophthalmologists is essential
  o Options include topical (corticosteroids, cycloplegics, mydriatics, anti-glaucoma agents) and systemic (methotrexate, mycophenolate, adalimumab, infliximab, tocilizumab) therapies

References:

9B. **Systemic Inflammatory Diseases Associated with Uveitis**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Acute/Chronic</th>
<th>Location</th>
<th>Associated clinical features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>Chronic, recurrent, asymptomatic</td>
<td>Anterior &gt; Posterior</td>
<td>Oligoarthritis &gt;&gt; Polyarthritis</td>
<td>ANA</td>
</tr>
<tr>
<td>(except enthesitis related arthritis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enthesitis related arthritis</td>
<td>Acute, often recurrent</td>
<td>Anterior</td>
<td>Enthesitis, sacroiliitis; often associated with reactive arthritis, IBD, or a family history of these conditions</td>
<td>HLA-B27</td>
</tr>
<tr>
<td>Behçet disease</td>
<td>Acute or chronic</td>
<td>Panuveitis, Posterior, Anterior</td>
<td>Recurrent oral and/or genital ulcers, arthritis, skin rash</td>
<td>HLA B51</td>
</tr>
<tr>
<td>Blau syndrome (familial form of sarcoidosis)</td>
<td>Chronic</td>
<td>Posterior, Anterior, Panuveitis</td>
<td>Skin rash, arthritis</td>
<td>Consider genetic testing (<em>NOD2/CARD15</em> mutations)</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Acute, asymptomatic</td>
<td>Anterior</td>
<td>Consider if patient presents with severe conjunctivitis and photophobia</td>
<td>Echocardiogram</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Chronic</td>
<td>Posterior, Anterior, Panuveitis</td>
<td>Skin rash, arthritis, lung involvement, lymphadenopathy</td>
<td>Biopsy, consider genetic testing (<em>NOD2/CARD15</em> mutations)</td>
</tr>
<tr>
<td>Tubulo-interstitial nephritis and uveitis (TINU)</td>
<td>Acute</td>
<td>Anterior</td>
<td>Fever, arthralgias, fatigue, abdominal pain, and nephritis; uveitis may present before or after renal disease</td>
<td>U/A, renal function</td>
</tr>
</tbody>
</table>
9C. Infectious Causes of Uveitis

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

9D. Treatment of Juvenile Idiopathic Arthritis (JIA)-Associated Uveitis

- Recommendations for treatment of JIA-associated uveitis have been published and updated since 2019 by various groups (see references below)
- Key recommendations for management include the following:
  - Initial therapy is typically topical corticosteroids as directed by ophthalmologists
  - Systemic therapy should be added in children with chronic anterior uveitis requiring more than 2 drops per day of prednisolone acetate 1% (or equivalent) after 3 months of therapy (and may be considered sooner at the discretion of the treating clinicians)
  - Methotrexate is typically suggested as first-line systemic therapy for ongoing chronic anterior uveitis
If adequate control of uveitis is not achieved after 3 months of optimal methotrexate therapy, the next recommended therapy is the addition of a monoclonal antibody targeting TNF (e.g. adalimumab, infliximab).

Further change or escalation in medications is recommended in children who have had a 3-month trial of systemic therapy and who remain on more than 2 drops per day of prednisolone acetate 1% (or equivalent).

Rheumatologists often use a similar treatment approach to guide systemic therapy for idiopathic uveitis (not associated with JIA or a systemic inflammatory disease).

References:
10A. Introduction to Inflammatory Brain Diseases

- Overview
  - 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
  - Management often involves a multidisciplinary team including Neurology and Rheumatology to help guide investigations, pharmacotherapy, and rehabilitation

Types of inflammatory brain diseases in children:

<table>
<thead>
<tr>
<th>Vasculitis</th>
<th>Primary Angiitis of the Central Nervous System in childhood (cPACNS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Angiography-positive cPACNS: progressive and non-progressive</td>
</tr>
<tr>
<td></td>
<td>• Angiography-negative cPACNS</td>
</tr>
<tr>
<td></td>
<td>Secondary CNS vasculitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-vasocentric neuroinflammatory disorders</th>
<th>Demyelinating disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Multiple sclerosis</td>
</tr>
<tr>
<td></td>
<td>• Acute demyelinating encephalomyelitis (ADEM)</td>
</tr>
<tr>
<td></td>
<td>• Optic neuritis</td>
</tr>
<tr>
<td></td>
<td>• Transverse myelitis</td>
</tr>
<tr>
<td>Antibody-mediated inflammatory brain disease</td>
<td>• Autoimmune encephalitis</td>
</tr>
<tr>
<td></td>
<td>• Neuromyelitis optica</td>
</tr>
<tr>
<td></td>
<td>• Hashimoto encephalopathy</td>
</tr>
</tbody>
</table>

| Systemic inflammatory diseases with CNS involvement | |
|-----------------------------------------------------| |
| • Systemic lupus erythematosus | |
| • Antiphospholipid syndrome | |
| • Celiac disease | |
| • Bechets disease | |
| • Sarcoidosis | |

| Post-infectious or infection-associated inflammatory encephalopathy | |
|-------------------------------------------------------------------| |
| • Acute rheumatic fever | |
| • Pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections (PANDAS) | |
| • Pediatric acute-onset neuropsychiatric syndrome (PANS) | |
| • 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)

- **Overview**
  - 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
  - Two clinically and radiology distinct types of cPACNS – angiography positive and angiography negative
  - Recovery is often excellent with early diagnosis and management, but complications may include persistent neurological deficits, seizures, and/or cognitive disability

1. **Angiography positive cPACNS** (Large-medium vessel CNS vasculitis)
   - Clinical features:
     - Stroke presentation with headache, acute hemiparesis, hemisensory deficits, and/or fine motor deficits
   - Investigations
     - 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
     - Ongoing monitoring required to distinguish between non-progressive and progressive disease
     - Non-progressive angiography-positive cPACNS is defined by absence of progression on imaging 3 months after diagnosis and is more common
     - Progressive angiography-positive cPACNS is defined by progression on neuroimaging 3 months after initial imaging and patients often present with focal and diffuse neurologic deficits, as well as multifocal lesions on imaging
   - Treatment
     - Corticosteroids improve outcome
     - Anti-coagulation is recommended with or without anti-platelet agent
     - If disease is progressive, then treatment is similar to angiography-negative cPACNS (see below)
     - Also need rehabilitation therapy to address cognitive, physical and psychological needs

2. **Angiography negative cPACNS** (Small vessel CNS vasculitis)
   - Clinical features:
     - May have systemic symptoms (fever, malaise)
     - Present with neuropsychiatric symptoms including headache, seizures, ataxia, cognitive decline and/or behaviour changes
   - Investigations
     - 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
    ▪ Induction therapy (first 6 months) using cyclophosphamide and corticosteroids
    ▪ Maintenance (up to 24 months) using mycophenolate mofetil and weaning corticosteroids
    ▪ Also need rehabilitation therapy to address cognitive, behavioural, physical, and psychological needs
    ▪ Adjunctive therapy may include anti-seizure medications, medications to address corticosteroid side effects (gastroprotective agent, vitamin D, ensuring calcium intake) and PJP prophylaxis while on cyclophosphamide

References:

10C. Secondary Central Nervous System Vasculitis

- Overview
  ▪ Occurs in context of an underlying systemic illness, such as infection or systemic autoimmune disease
  ▪ Treatment may involve corticosteroids as well as therapy directed to underlying cause

Causes of secondary CNS vasculitis:

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

References:

10D. Pediatric autoimmune encephalitis (AE)

- Overview
  - Brain inflammation caused by antibodies directed against intracellular neuronal antigens, synaptic receptors, ion channels and other neuronal proteins
  - Most common autoantibody targets in children:
    - N-methyl-D-aspartate (NMDA) receptor
    - Myelin oligodendrocyte glycoprotein (MOG)
    - Glutamic acid decarboxylase 65 (GAD65)
  - Additional antibody targets in children:
    - Aquaporin-4 (AQP4)
    - Dopamine-2 receptor
    - Gamma-aminobutyric acid (GABA) (A) receptor
    - GABA(B) receptor
    - Glycine receptor
    - Metabotropic glutamate receptor 5 (m-GluR5)
  - Clinical features of pediatric AE include seizures, memory deficits, behaviour changes, psychiatric symptoms, altered mental state, and focal neurological deficits
  - Diagnosis is challenging because of overlap in clinical presentations between the types of AE, other inflammatory brain diseases, infections, metabolic diseases, and psychiatric disorders
  - 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 (need to test both CSF and serum); however, children with a clinical phenotype of AE, inflammatory changes on CSF or imaging, and negative testing for anti-neuronal antibodies may meet criteria for *probable antibody-negative pediatric AE* since not all antibodies have been identified
  - If there is high suspicion for AE and infectious and other causes have been reasonably excluded, treatment should be started empirically while awaiting antibody confirmation
  - Treatment typically involves corticosteroids, IVIG and other immunosuppressants, such as rituximab and/or cyclophosphamide
  - Supportive therapies may include anti-seizure medications, anti-psychotics, sleep aids, and medications to address corticosteroid side effects
  - Better prognosis if antibody target is extracellular (e.g. synaptic receptors, ion channels)
Anti-NMDA receptor encephalitis

- 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 is less than in adults, but tumour removal is a key part of therapy if present)

- Treatment
  - First line immune suppressive therapy includes corticosteroids, IVIG and/or plasma exchange
  - Rituximab and/or cyclophosphamide 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 with antibodies to MOG

- Clinical features
  - Most common antibody associated with autoimmune demyelination
  - Patients typically 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 3 months of initiating therapy
  - Disappearance of antibodies associated with monophasic course, whereas persistent antibodies are associated with relapsing course
Autoimmune encephalitis associated with GAD65

- Clinical features
  - Broad range of neuropsychiatric symptoms including encephalitis with memory loss, cognitive impairment, cerebellar ataxia, and temporal lobe seizures
  - Associated with personal or family history of autoimmunity

- Investigations
  - Diagnosed by presence of high titres of anti-GAD65 antibodies in CSF (serum antibodies or low titres in CSF are not diagnostic)
  - MRI: may be normal initially; often progresses to lesions in the limbic system, cerebellum, and cortices with possible atrophy
  - CSF: leukocytosis may be mild with oligoclonal bands
  - EEG: epileptiform discharges may be multifocal

- Treatment
  - First line therapy with corticosteroids, IVIG and/or plasma exchange
  - Rituximab and cyclophosphamide may also be considered

- Outcome
  - Less is known about this autoantibody given limited published cases; however, there appears to be a higher predominance of treatment resistance and recurrences in patients with antibodies to GAD65 leading to a need for ongoing therapy
  - Cognition and fatigue may improve over time, whereas seizures, psychiatric symptoms, and sleep may be less likely to respond

Neuromyelitis optica (NMO)

- Clinical features
  - Neuroinflammatory and demyelinating disorder that mostly affects the spinal cord and optic nerves
  - 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 (AQP4) 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:
11A. Bone and Joint Infections

Osteomyelitis

- Overview
  - 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 (from bacterial seeding) 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 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/tortuous blood flow allows organisms to pass through fenestrations in vessel wall, migrate through Haversian canal to sub-periosteal space
  - May lead to adjacent osteomyelitis or septic arthritis
  - Organisms include *Staphylococcus aureus* (most common), Group A *Streptococcus*, MRSA, atypical gram-negative bacteria, and *Salmonella*

- Clinical features:
  - Key symptoms include fever, severe bone pain, and tenderness with or without local swelling
  - 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
  - Most common bones involved are femur, tibia, and humerus; may also involve fibula, calcaneus, or pelvis
  - Usually unifocal infection

- 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)
    - MRI is preferred modality (85% positive predictive value)
    - Bone scan could be considered if MRI is not available

- Treatment
  - Uncomplicated osteomyelitis: 2 to 4 days of intravenous antibiotics can be followed by high dose oral antibiotics, for a total antibiotic course of 3-4 weeks
Complicated osteomyelitis and/or failure to respond to antibiotics: consider surgical intervention

Septic Arthritis

- Overview
  - Intra-articular infection with bacteria or rarely, fungi, from hematogenous spread or direct trauma
  - Medical emergency (surgical emergency if hip or shoulder involved)
  - Organisms:
    - *Staphylococcus aureus* and non-Group A β *Streptococcus* are most common overall
    - *Streptococcus pneumoniae* is common in children younger than 2 years
    - *Neisseria gonorrhoeae* in sexually active adolescents
    - *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, as well as present with a milder clinical picture

- Clinical features
  - 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

- Investigations
  - Joint aspiration (prior to antibiotics)
    - Synovial fluid usually appears cloudy
    - Very high WBC count (50,000-300,000/mm³, >75% neutrophils)
    - Gram stain positive, may also send for PCR
  - 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 diagnostic evaluation
• Treatment
  o 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
  o Surgical
    ▪ May require urgent surgical or arthroscopic debridement, joint irrigation, drainage or recurrent aspiration for infections in deep joints (e.g. hips)

References:

11B. Reactive Arthritis

• Overview
  o A form of non-septic arthritis developing after an extra-articular infection (typically gastrointestinal, genitourinary or Group A Streptococcus); characterized as a spondyloarthropathy
  o Common GI pathogens: Salmonella, Shigella, Yersinia, Campylobacter
  o Common GU pathogens: Chlamydia, Ureaplasma

• Clinical features
  o Several stages involved:
    1. Clinical infection precedes appearance of arthritis and/or enthesitis by 1 to 4 weeks
    2. Active period of arthritis lasting for weeks up to 6 months
    3. Sustained remission or recurrent episodes which may evolve to ERA (about 25% develop chronic disease), especially in patients that are positive for HLA B27
  o Acute arthritis (marked pain, sometimes erythema over affected joint; often monoarthritis or oligoarthritis involving lower extremities) and/or enthesitis
  o May see tenosynovitis, bursitis, dactyliitis
  o Patients may continue to have fever, weight loss, fatigue and muscle weakness
  o Painless, shallow mucosal ulcers are common
  o Urethritis and cervicitis are rare
  o Conjunctivitis occurs in about 2/3 of children at onset
  o Skin lesions include erythema nodosum, circinate balanitis, keratoderma blennorrhagicum
A RESIDENT’S GUIDE TO PEDIATRIC RHEUMATOLOGY

- **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 50-80% of patients with reactive arthritis are HLA-B27 positive
  - Synovial fluid is sterile with an inflammatory infiltrate ($10,000$-$50,000$ WBC/mm$^3$)
  - Cultures (blood, urine, stool) obtained at the time of infection may be positive (<50% sensitivity)
  - Imaging may not be required; X-rays are often non-specific; MRI may be completed if arthritis persists and may show changes consistent with spondyloarthritis

- **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
  - Consider anti-TNF biologic agents if refractory to other treatments or if axial bone involvement

**References:**

11C. **Acute Rheumatic Fever (ARF)**

- **Overview**
  - 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

<table>
<thead>
<tr>
<th>Population risk</th>
<th>Low risk populations</th>
<th>Moderate- and high-risk populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases of ARF ≤ $2/100,000$ in school-aged children or rheumatic heart disease in ≤ $1/1000$ at any age</td>
<td>Cases of ARF &gt; $2/100,000$ in school-aged children or rheumatic heart disease in &gt; $1/1000$ at any age</td>
<td></td>
</tr>
</tbody>
</table>

- **Major criteria**
  1. Carditis (clinical and/or subclinical)
  2. Polyaarthritis
  3. Chorea
  4. Erythema marginatum
  5. Subcutaneous nodules
Minor criteria

<table>
<thead>
<tr>
<th>1. Polyarthralgia</th>
<th>1. Monoarthralgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Fever ≥ 38.5 degrees Celsius</td>
<td>2. Fever ≥ 38 degrees Celsius</td>
</tr>
<tr>
<td>3. ESR ≥ 60 and/or CRP ≥ 3.0 mg/dL</td>
<td>3. ESR ≥ 30 and/or CRP ≥ 3.0 mg/dL</td>
</tr>
<tr>
<td>(30 mg/L)</td>
<td>(30 mg/L)</td>
</tr>
<tr>
<td>4. Prolonged PR interval (unless carditis is a major criterion)</td>
<td>4. Prolonged PR interval (unless carditis is a major criterion)</td>
</tr>
</tbody>
</table>

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

- Clinical features
  - Arthritis is the most common feature and has characteristics that help differentiate ARF 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
  - Carditis is the next most common feature (see echo findings below)
  - Chorea (Sydenham 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, autoimmune disease, familial chorea, etc…) have been excluded
  - Erythema marginatum is less common and may be difficult to distinguish from erythema migrans and other rashes
  - Subcutaneous nodules rarely 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 for eradication of GAS is required even if culture is negative; 10 days oral antibiotics, usually Penicillin, or a single dose of intramuscular penicillin G
  - Carditis therapy:
    - Mild-moderate: 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 NSAID)
    - Severe carditis, cardiomegaly and/or heart failure: prednisone +/- digoxin
  - Arthritis usually responds well to ASA and/or NSAID with improvement within a few days
  - Mild chorea may be treated with bed rest and stress avoidance; moderate to severe chorea may be treated with carbamazepine, phenobarbital, haloperidol, or chlorpromazine
  - Antibiotic 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:

11D. Post-Streptococcal Reactive Arthritis (PSRA)

- Overview
  - PSRA defined as inflammatory arthritis of ≥1 joint (with poor response to NSAID) associated with recent Group A Streptococcus (GAS) infection, but not meeting the Jones criteria to diagnose acute rheumatic fever (ARF) (see Section 11C)
  - PSRA is also different from reactive arthritis, which mostly involves large lower limb joints and is often associated with HLA B27 (see Section 11B)
  - Characteristics that help distinguish PSRA from ARF include the following:

<table>
<thead>
<tr>
<th></th>
<th>PSRA</th>
<th>ARF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age distribution</td>
<td>Bimodal: 8-14 years and 21-37 years</td>
<td>5-15 years with peak around 12 years</td>
</tr>
<tr>
<td>Timing of disease onset following GAS infection</td>
<td>7-10 days</td>
<td>10-28 days</td>
</tr>
<tr>
<td>Pattern of joint involvement</td>
<td>Additive and persistent, non-migratory arthritis involving large, small and axial joints</td>
<td>Migratory, transient arthritis involving mainly large joints</td>
</tr>
<tr>
<td>Response to ASA/NSAID</td>
<td>Poor to moderate</td>
<td>Dramatic improvement</td>
</tr>
<tr>
<td>Carditis</td>
<td>Uncommon</td>
<td>Occurs in 60-70% of ARF</td>
</tr>
</tbody>
</table>

- 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
A RESIDENT’S GUIDE TO PEDIATRIC RHEUMATOLOGY

Reference:

11E. Lyme Disease

- Overview
  - Complex tic-borne disease with multi-system 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*
  - Incidence continues to rise

- Clinical features
  - Early manifestations develop within weeks or few months of tick bite
  - Late manifestations begin several months or even years later

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Early Lyme disease</th>
<th>Late Lyme disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td><em>Erythema migrans</em></td>
<td>Acrodermatitis chronic atrophicans*</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Cranial nerve palsy</td>
<td>Chronic encephalomyelitis</td>
</tr>
<tr>
<td></td>
<td>Lymphocytic meningitis</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>Arthralgia or arthritis</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Carditis*</td>
<td></td>
</tr>
</tbody>
</table>

*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 monoarticular, but may sometimes involve several joints
  - Cardiac and neurological involvement are less common
  - Cranial nerve palsy usually involves the facial nerve

- Investigations
  - Non-specific inflammatory changes, such as elevated ESR and/or CRP are possible
  - CSF analysis (if indicated) demonstrates lymphocytic pleocytosis
  - Serologic confirmation is needed to confirm the diagnosis (initial screening performed with enzyme immunoassay, 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* and *Choosing Wisely Canada: Seven Tests and Treatments to Question in Pediatric Rheumatology*)

- Treatment
  - Varies according to disease manifestations
  - *Erythema migrans* only:
A RESIDENT’S GUIDE TO PEDIATRIC RHEUMATOLOGY

- 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)
  - No evidence to support chronic antibiotic therapy or retreatment for post-Lyme disease persistent symptoms (such as fatigue) once adequate initial antibiotic treatment has been completed

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

References:
SECTION 12 – PAIN SYNDROMES

12A. 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
- Management includes reassurance of parents and recommending comfort measures

Fibromyalgia (aka Generalized Amplified Musculoskeletal Pain)

- Clinical features
  - Chronic generalized pain syndrome that may be triggered by a change in physical activity due to injury, chronic illness, or psychosocial stressor(s)
  - Widespread pain with gradual onset and chronic course lasting at least 3 months
  - Associated with chronic fatigue, poor sleep, waking feeling unrefreshed, cognitive symptoms (“brain fog”), irritable bowel syndrome, and/or mood and anxiety disorders
  - 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)
  - May have significant functional impairment, including school absence, and reduced quality of life

- 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
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:

<table>
<thead>
<tr>
<th>Severity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No problem</td>
</tr>
<tr>
<td>1</td>
<td>Slight or mild problem: generally mild or intermittent</td>
</tr>
<tr>
<td>2</td>
<td>Moderate problem: often present and/or at moderate level of intensity</td>
</tr>
<tr>
<td>3</td>
<td>Severe problem: continuous, life-disturbing symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Trouble thinking or remembering</td>
<td></td>
</tr>
<tr>
<td>Waking up tired (unrefreshed)</td>
<td></td>
</tr>
<tr>
<td>Somatic symptoms* in general</td>
<td></td>
</tr>
</tbody>
</table>

* 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:

- Treatment
  - Education about chronic pain
  - Exercise and physiotherapy includes aerobic training to improve conditioning, strength training and movement-based therapy
  - Improvement of sleep hygiene and quality
  - Counselling, cognitive behavioural therapy (CBT), and other psychotherapy to facilitate development of coping strategies and to address anxiety, low mood and other consequences and contributors to pain
  - Intensive interdisciplinary pain treatment recommended for patients with severe pain-related disability
  - Evidence for use of medications in juvenile fibromyalgia is limited, but may include non-opioid analgesics, anticonvulsants, antidepressants, muscle relaxants, and nutritional supplements (e.g. vitamin D)
  - Limited evidence to support use of cannabis in children, while use of opioids is discouraged in juvenile fibromyalgia
  - Better outcomes in children compared to adults; however, the physical and psychosocial symptoms may become chronic for many patients
Complex Regional Pain Syndrome (CRPS)

- **Complex Regional Pain Syndrome Type I** (previously Reflex Sympathetic Dystrophy)
  - Chronic pain usually involving peripheral extremity (lower extremity more common in children and adolescents)
  - Often follows mild injury or cause of immobilization, such as surgery
  - Persistent pain, allodynia, and/or hyperalgesia in which pain is disproportionate in severity and duration in the context of the inciting event
  - Associated autonomic signs, including swelling, changes in skin blood flow leading to discolouration, and/or abnormal sweating in the region of pain
  - More common in females with mean age at diagnosis 12 years
  - Diagnosis using Budapest clinical criteria (see below) involves exclusion of other causes
  - Mainstay of treatment is intense physiotherapy (including desensitization strategies) with goal to restore function
  - Additional treatment strategies may include cognitive behaviour therapy or other psychotherapy, pharmacotherapy, and nerve blockade
  - Children have a better prognosis than adults with physiotherapy and cognitive behaviour therapy leading to remission in most

- **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
  - Very rare in children

**Budapest Clinical Criteria for Complex Regional Pain Syndrome**

_Beijing requires all 4 of the following criteria:_

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:**

12B. Hypermobile Joint Syndrome

• Overview
  o Joint pain caused by idiopathic increased flexibility secondary to ligamentous laxity – may be generalized or local
  o More common in females
  o Need to consider and exclude syndromes associated with generalized joint hypermobility, such as Ehlers-Danlos, Marfan, Down, Turner, Stickler, and osteogenesis imperfecta syndromes

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

• Clinical features
  o Joint pain typically occurs after activity
  o May be accompanied by transient joint swelling
  o Additional features consistent with hypermobility include flexible flat feet, ability to sit in “W” position, ability to touch elbows behind back, and/or ability to put heel behind head

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

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

References:
SECTION 13 – PEDIATRIC RHEUMATOLOGY EMERGENCIES

- 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

13A. Macrophage Activation Syndrome

- Overview
  - 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 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 (see Section 13B)
  - Primary and secondary HLH share similar clinical and biochemical features
  - Recent development of an MAS/HLH score to help discriminate between primary HLH and MAS includes age, splenomegaly, neutrophil count, platelet count, hemoglobin and fibrinogen

- Clinical features
  - Fever (continuous/persistent)
  - Splenomegaly
  - Lymphadenopathy
  - Tachycardia (even when afebrile) and hypotension are very common
  - Bleeding, bruising and petechiae
  - Acute respiratory distress syndrome
  - CNS dysfunction (headache, confusion, seizures, and coma) associated with poor prognosis
  - Rapid deterioration may occur and so it is critically important to reassess frequently

- Investigations
  - Cytopenias (anemia, thrombocytopenia, neutropenia) or, in systemic JIA, may see decrease in previously elevated cell counts
  - Persistently raised CRP, but decreasing ESR (due to consumption of fibrinogen)
  - Elevated ferritin
  - Elevated triglycerides
  - Coagulopathy characterized by prolonged INR/PTT, elevated D-dimers, decreased fibrinogen
  - Hepatic dysfunction with hepatomegaly, elevated bilirubin and liver enzymes
  - Elevated LDH
  - Hemophagocytosis on bone marrow, lymph node, liver or spleen biopsy
Additional suggested investigations prior to starting treatment

- Cultures of blood, urine, and throat to exclude an underlying bacterial infection
- Infectious serology and PCR (e.g. EBV, CMV, Parvovirus B19, Herpes viruses, SARS-CoV-2) may be helpful to diagnose underlying viral infection in primary or secondary HLH
- If the child does not have a pre-existing diagnosis and a systemic autoimmune rheumatic disease is suspected, autoantibodies (e.g. ANA, ENA panel, rheumatoid factor, ANCA) and direct antiglobulin test should be ordered prior to IVIG
- Soluble CD163, soluble IL-2 receptor, NK cell function, and lymphocyte typing may be helpful to identify underlying immune dysfunction and/or monitor inflammation
- Genetic testing for known mutations in primary HLH may be arranged after starting treatment, if indicated

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

Treatment

- Very close monitoring of labs, vital signs, and fluid status
- All patients require supportive management, which may include:
  - 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, 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
  - Biologic agents, in particular anakinra (anti-IL-1), may be effective treatments for MAS and may be used in lieu of cyclosporine and etoposide when IVIG and corticosteroids are insufficient
  - Plasmapheresis has been used in life-threatening disease
  - Rituximab should be used for EBV-associated MAS
  - In children with primary HLH or refractory HLH, bone marrow transplant is definitive treatment

References:

2. Minoia F, et al. Development and initial validation of the macrophage activation syndrome/primary hemophagocytic lymphohistiocytosis score, a diagnostic tool that


13B. Infection-Triggered Multisystem Inflammatory Syndromes

- Overview
  - Recently described group of severe multisystemic inflammatory syndromes caused by the immune system’s response to an infectious agentIncludes infection-triggered MAS, multisystem inflammatory syndrome in children temporally associated with COVID-19 (MIS-C), and COVID-19 associated hyperinflammation
  - List of defined syndromes may continue to expand in the coming years

Infection-triggered macrophage activation syndrome (MAS)

- Infection-triggered MAS is most commonly caused by viral infections, such as EBV, CMV, Parovirus B19, herpes viruses, Varicella zoster virus, Adenovirus, Influenza virus, Dengue virus, Coxsackie virus
- Other triggers include bacterial (e.g. Enterobacteriaceae, Salmonella, Pneumococcus, Mycobacteria, Mycoplasma), fungal (e.g. Candida, Histoplasma, Cryptococcus), and parasitic (e.g. Leishmania, Pneumocystis carinii) infections
- Clinical features, findings and treatment are similar to MAS due to other causes, but may include anti-infectious therapy as appropriate

Multisystem Inflammatory Syndrome in Children temporally associated with COVID-19 (MIS-C)

- Overview
  - Typically develops 2 to 6 weeks after COVID-19 infection or vaccine administration
  - Vast majority of children with COVID-19 present with mild symptoms and MIS-C is a rare but life-threatening complication
  - Several case definitions exist (e.g. World Health Organization, Centres for Disease Control and Prevention, Vogel et al publication in Vaccine 2021)
  - Overlapping features with Kawasaki disease and toxic shock syndrome
  - Epidemiologic studies suggest younger children are more likely to present with KD-like features, while older children are more likely to develop myocarditis and shock

- Clinical features
  - Characteristic features include high and persistent fever, tachycardia, and hypotension; mucocutaneous changes; bilateral non-exudative conjunctivitis; abdominal pain, nausea, vomiting, and/or diarrhea
  - Cardiac involvement may include myocardial dysfunction and coronary artery aneurysm
Bleeding, petechiae and purpuric rash may occur with coagulopathy
- Neurologic symptoms ranging in severity from headache to decreased level of conscious may occur
- Symptoms may quickly progress to multiorgan dysfunction requiring critical care for ventilatory and inotropic support

- Investigations
  - Characteristic laboratory features include hyperinflammation (elevated CRP, elevated ferritin, low albumin, elevated LDH, elevated IL-1β and IL-6 (if available)); cytopenias (most commonly lymphopenia, anemia and thrombocytopenia) but elevated neutrophil counts; coagulopathy (abnormal INR or PTT, elevated D-dimers)
  - Cardiac involvement demonstrated by elevated troponin, elevated NT-proBNP, sinus tachycardia on ECG, and myocardial dysfunction, pericardial effusion, and/or coronary artery abnormalities on echocardiogram
  - Evidence of recent COVID-19 infection (nasopharyngeal swab for SARS-Cov-2 positive on PCR; positive SARS-Cov-2 serology) OR history of recent COVID-19 immunization
  - Baseline assessment for multi-organ dysfunction is recommended
  - Need to exclude other infectious and non-infectious causes of this clinical presentation through bacterial cultures, viral cultures and serology, and/or other investigations, as indicated

- MIS-C vs. Kawasaki Disease (KD)
  - Significant similarities between MIS-C and KD
  - Increased incidence of MIS-C in patients of African, Afro-Caribbean and Hispanic descent, but a lower incidence in those of East Asian descent
  - Patients with MIS-C have more prominent gastrointestinal and neurologic symptoms, present more frequently in shock, and are more likely to display cardiac dysfunction
  - KD patients are more likely to develop coronary artery aneurysms
  - Patients with MIS-C tend to have lower platelet counts, lower lymphocyte counts, and higher CRP levels than those with KD
  - Patients with MIS-C encompass a broader age range than KD

- Treatment
  - Close monitoring of vital signs, fluid status, and laboratory abnormalities is recommended
  - Consider involving the intensive care unit early given the risk of rapid deterioration with need for inotropic support and mechanical ventilation
  - High dose or pulse IV corticosteroids are recommended as soon as possible to address hyperinflammatory state
  - IVIG 2 g/kg (maximum 70 g) is often included in management protocols given the risk for coronary artery aneurysm, similar to KD; if used, IVIG should be given at a slower infusion rate if significant cardiac dysfunction after assessment
  - Anakinra (anti-IL-1) or tocilizumab (anti-IL-6R) may be considered for treatment of MIS-C that is refractory to corticosteroids and IVIG
  - Duration of therapy determined by clinical and laboratory response and may range from 3 days to weeks
  - Anti-coagulation should be considered using low dose ASA for standard risk patients and low molecular weight heparin for patients with coagulopathy
  - Broad-spectrum antibiotics should be considered pending the results of bacterial cultures
COVID-19 associated hyperinflammation

- **Overview**
  - Vast majority of children with COVID-19 present with mild symptoms
  - Children, particularly infants, with medical complexity may be at higher risk for severe COVID-19
  - Racial and ethnic minorities may also be at higher risk

- **Clinical features**
  - Children admitted to hospital with COVID-19 typically present with fever, upper respiratory tract symptoms, abdominal pain, and diarrhea
  - Severe disease requiring supplemental oxygen or respiratory support may benefit from immunomodulatory therapy, especially if accompanied by laboratory findings of significant inflammation

- **Investigations**
  - Common findings on blood work include leukocytosis, increased inflammatory markers (CRP, ESR, ferritin), hypoalbuminemia, and transaminitis
  - If evidence of hyperinflammation is present, consider completing work-up for MIS-C
  - Infection confirmed by positive nasopharyngeal swab for SARS-CoV-2 PCR, but diagnosis should be considered in context of negative testing and positive close contacts
  - Consider investigating for other infectious and non-infectious causes of specific presentation

- **Treatment**
  - Treatment remains mainly supportive and may include hydration, anti-pyretics, supplemental oxygen, intubation, and mechanical ventilation
  - Antibiotic coverage may be considered in severe disease until diagnosis is confirmed and/or bacterial infection is excluded
  - Corticosteroids should be considered as first-line therapy for severe disease with significant inflammatory findings
  - Biologic agents such as anakinra (anti-IL-1), tocilizumab (anti-IL-6), or baricitinib (JAK inhibitor) may be considered as second line therapy

**References:**
13C. Kawasaki Disease Shock Syndrome (KDSS)

• Overview
  o Uncommon but life-threatening complication of KD
  o Occurs in <10% of children diagnosed with KD
  o Children often present with shock before the KD diagnosis is made and more likely to have incomplete KD presentation
  o May have more prominent inflammatory markers in early phase and higher risk of coronary artery dilatation
  o Given the overlapping clinical and laboratory features between KDSS, MAS and MIS-C, all of these diagnoses should be considered in the diagnostic work-up and preliminary management

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

• Investigations
  o 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
    ▪ Elevated troponin and NT-proBNP levels
    ▪ Higher levels of IL-6, IL-10 and IFN-γ (if testing available) may be seen in KDSS
  o ECG typically shows sinus tachycardia
  o Echocardiography:
    ▪ Impaired left ventricular systolic function with a lower ejection fraction and mitral regurgitation
    ▪ More likely to develop coronary artery abnormalities

• Treatment
  o Initial priority is to stabilize cardiorespiratory status
  o Requires careful fluid resuscitation – large fluid boluses not recommended as these may precipitate congestive heart failure
  o May require inotropic and/or vasopressor support
  o High dose corticosteroids should be given at onset, even prior to IVIG
  o IVIG and ASA remain mainstay of therapy; however, IVIG should be given at a slower rate as it may precipitate congestive heart failure and IVIG resistance is more common
  o If treated early and aggressively, most children survive without sequelae
References:

13D. Acute Adrenal Crisis

- Overview
  - Many children with rheumatic diseases are treated with systemic 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 features
  - 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 may include:
    - Arthralgias, myalgias, generalized weakness
    - Headache
    - Abdominal pain, nausea, vomiting, diarrhea
    - Fever
    - Hypotension
    - Decreased level of consciousness, lethargy
    - Unexplained hypoglycemia
    - Hyponatremia
    - Seizures, coma

- Investigations
  - Absence of laboratory abnormalities does not exclude the diagnosis of adrenal crisis
  - Hyponatremia is common, while hyperkalemia, metabolic acidosis, and hypoglycemia may also be present
  - Hypercalcemia is rare
  - Infectious and/or disease-specific investigations should be considered according to the patient's presentation
  - ACTH stimulation test should be arranged when the patient is off corticosteroids to assess for underlying adrenal insufficiency

- 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
A RESIDENT'S GUIDE TO PEDIATRIC RHEUMATOLOGY

(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:

13E. Pulmonary Renal Syndrome

- Overview
  - Characterized by diffuse alveolar hemorrhage in combination with rapidly progressive glomerulonephritis
  - Should be considered in any child presenting with respiratory distress and renal involvement
  - May be life-threatening with rapid deterioration from pulmonary hemorrhage and/or renal failure

Causes of pulmonary renal syndrome

<table>
<thead>
<tr>
<th>Specific</th>
<th>Non-specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematous (SLE)</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Granulomatosi with polyangiitis (GPA)</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Microscopic polyangiitis (MPA)</td>
<td>Pulmonary infection</td>
</tr>
<tr>
<td>Eosinophilic granulomatosi with polyangiitis (EGPA)</td>
<td>Renal disease in a child with pulmonary disease, usually infection</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura (HSP, now also known as IgA vasculitis)</td>
<td>Hemolytic uremic syndrome</td>
</tr>
<tr>
<td>Goodpasture syndrome</td>
<td>IgA nephropathy</td>
</tr>
</tbody>
</table>

- Clinical features
  - Respiratory involvement: dyspnea, cough, increased work of breathing, and hypoxemia; frank hemoptysis may be present
  - Renal involvement/acute kidney injury: oliguria, hypertension, nephritic syndrome, nephrotic syndrome
• Investigations
  o 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 bronchaleolar lavage (BAL) demonstrates presence of red blood cells and hemosiderin-laden macrophages; fluid should also be sent for culture to exclude infection
  o 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
  o Tests to determine underlying cause of pulmonary renal syndrome
    ▪ Autoantibodies and immune markers may be helpful to clarify underlying diagnosis, if not previously known (e.g. positive ANCA in GPA, MPA or EGPA; positive anti-glomerular basement membrane autoantibodies in Goodpasture syndrome; positive anti-dsDNA in SLE)
    ▪ Renal biopsy is often indicated to clarify underlying diagnosis and prognosis
    ▪ Skin biopsy may be helpful if rash is present
    ▪ Lung biopsy is rarely needed, but may be considered if diagnosis remains unclear despite complete work-up

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

References:

13F. Cardiac Tamponade

• Overview
  o Uncommon but life-threatening complication of pericarditis with effusion
  o 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 features**
- 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)

**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:**

**13G. Neonatal Lupus Erythematosus (NLE) with Complete Heart Block (CHB)**

**Overview**
- 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 features
- 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

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
- Initial priority is to stabilize cardiorespiratory status
- All infants require cardiology consultation and likely need close monitoring in an intensive care setting
- Infants with complete heart block may need pacemaker soon after birth
- If active inflammation is seen on echocardiogram, may consider corticosteroids +/- IVIG (treatment will depend on presence of CHF, myocarditis and EFE)

References:

13H. Catastrophic Antiphospholipid Syndrome (CAPS)

Overview
- A severe variant of the classic APS, characterized by multi-organ dysfunction and failure, evidence of multiple small vessel occlusions, and confirmation of the presence of antiphospholipid antibodies (aPL), usually in high titre
- 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
- Majority of catastrophic APS patients do not have underlying rheumatic disease
- Occurs in <1% of patients with APS with a mortality rate of 33-50%

**Diagnostic Criteria for Catastrophic Antiphospholipid Syndrome (CAPS)**

Definite diagnosis of CAPS 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 of CAPS 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

Clinical features
- May be mistaken for overwhelming sepsis
- Cardiopulmonary manifestations are the most frequent at presentation and may look like acute respiratory distress syndrome
- CNS features are next most common and may include cerebral infarction, seizures, encephalopathy, and cerebral venous sinus thrombosis
- Renal involvement is common, but may not present with symptoms
- 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

Investigations
- Assessment for signs of disseminated intravascular coagulation, including elevated INR and/or PTT, decreased fibrinogen, elevated D-dimers, and peripheral destruction of blood elements
- Findings of acute kidney injury may include proteinuria, hematuria, and/or abnormal renal function
- Cardiac dysfunction may be identified by increased troponin and decreased left ventricular function on echocardiography
- Imaging may show evidence of thrombosis (e.g. pulmonary embolus) or organ infarction
- Positive testing for aPL antibodies, including lupus anticoagulant, anti-cardiolipin, and anti-β2-glycoprotein I; novel aPL antibodies (e.g. anti-phosphatidylserine-prothrombin antibodies) are also reported in catastrophic APS, but testing is not widely available
- Important to investigate underlying triggers for the episode, including infectious testing, bone marrow biopsy or imaging to assess for underlying malignancy, and investigations for a possible systemic autoimmune rheumatic disease

Treatment
- Patients are often critically ill and intensive care requirement should be anticipated
- May need acute measures such as mechanical ventilation or dialysis
- Treatment aimed at removing triggering factor, if known, eliminating existing thrombus, and controlling systemic inflammatory response
- 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
  - Systemic inflammatory response: treated with systemic corticosteroids, therapeutic plasma exchange and IVIG (should be given after plasma exchange)
Other agents for severe or refractory cases include rituximab and eculizumab (anti-C5 agent)

References:

13I. Renal Crisis in Systemic Sclerosis (SSc)

- **Overview**
  - Rare and potentially life-threatening complication of SSc
  - High rate of mortality and progression into end-stage renal disease
  - 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 Features**
  - Reflects thrombotic microangiopathy of kidney similar to thrombotic thrombocytopenic purpura or hemolytic uremic syndrome
  - Acute renal failure without warning signs
  - Sudden onset of moderate to severe hypertension (although blood pressure is normal in up to 10% of renal crisis cases)
  - May be accompanied by hypertensive encephalopathy, congestive heart failure, arrhythmia, or acute cerebrovascular event

- **Investigations**
  - Elevated creatinine, proteinuria and hematuria on urinalysis
  - Thrombotic microangiopathy associated with 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
  - Chest X-ray 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 leads to stabilization of renal function in 70% of patients
  - ACE inhibitors (captopril most widely studied) are first line of therapy
  - Plasma exchange 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
Dialysis and possibly transplantation may be required for end-stage renal disease

References:
SECTION 14 – MEDICATIONS

Medications are listed in alphabetical order by their generic names with the exception of Corticosteroids and NSAIDs, which are listed under these categories. Biologic agents and biosimilar medications are listed by their generic names, but also included under the descriptions for these categories of medications.

- Abatacept
  - Class: biologic agent (see Biologic agents for summary table)
  - Original biologic agent: Orencia
  - Biosimilar medications: not available yet
  - Mechanism of action: Selectively inhibits co-stimulatory signal for T-cell activation
  - Dose:
    - IV: 500 mg if <60 kg; 750 mg if 60-100 kg; or 1000 mg if >100 kg via IV every 2 weeks for 3 doses then every 4 weeks
    - SC: 125 mg SC weekly after IV loading dose based on weight
  - 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)
  - Original biologic agent: Humira
  - Biosimilar medications: Abrilada, Amgevita, Amsparity, Cyltezo, Hadlima, Hefiya, Hukyndra, Hulio, Hyrimoz, Idacio, Imraldi, Libmyris, Simlandi, Yuflyma, Yusimry
  - Mechanism of action: recombinant monoclonal antibody that binds to circulating and cell surface TNFα
  - Dose: 20 mg if <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), paradoxical psoriasis
  - Monitoring: CBC, differential, AST, ALT, creatinine every 6-12 months

- Anakinra
  - Class: biologic agent (see Biologic agents for summary table)
  - Original biologic agent: Kineret
  - Biosimilar medications: not available yet
  - 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, neutropenia, increased transaminases
  - 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)
  - **Original biologic agent:** Benlysta
  - **Biosimilar medications:** not available yet
  - **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**

<table>
<thead>
<tr>
<th>Biologic Class</th>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Approved in pediatrics (Health Canada)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B cell depletion</td>
<td>Belimumab</td>
<td>• Human monoclonal antibody directed against BLyS&lt;br&gt;• Inhibits BLyS-induced proliferation of B cells and decreases survival of autoreactive B cells</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
<td>• Chimeric mouse-human monoclonal antibody directed against CD20 on pre-B and mature B cells&lt;br&gt;• Selectively depletes B cells</td>
<td>No</td>
</tr>
<tr>
<td>IL-1 inhibitors</td>
<td>Anakinra</td>
<td>• IL-1 receptor antagonist&lt;br&gt;• Blocks IL-1 receptor to prevent pro-inflammatory signaling (both IL-1α and IL-1β)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Canakinumab</td>
<td>• Human monoclonal antibody directed against IL-1β&lt;br&gt;• Binds to IL-1β to prevent pro-inflammatory signaling</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Rilonacept</td>
<td>• Fully human dimeric fusion protein consisting of extracellular portion of IL-1 receptor and constant region of human immunoglobulin&lt;br&gt;• Binds to IL-1 to prevent pro-inflammatory signaling</td>
<td>No</td>
</tr>
<tr>
<td>IL-6 inhibitor</td>
<td>Tocilizumab</td>
<td>• Humanized monoclonal antibody against IL-6 receptor&lt;br&gt;• Blocks IL-6 mediated pro-inflammatory signaling</td>
<td>Yes</td>
</tr>
<tr>
<td>IL-12/IL-23 inhibitor</td>
<td>Ustekinumab</td>
<td>• Humanized monoclonal antibody against IL-12 and IL-23&lt;br&gt;• Blocks IL-12/23 to prevent pro-inflammatory signaling</td>
<td>No</td>
</tr>
<tr>
<td>IL-17A inhibitor</td>
<td>Secukinumab</td>
<td>• Humanized monoclonal antibody against IL-17A&lt;br&gt;• Blocks IL-17A mediated pro-inflammatory signaling, which is mainly produced by T helper 17 cells</td>
<td>No</td>
</tr>
<tr>
<td>T cell co-stimulatory modulator</td>
<td>Abatacept</td>
<td>• Fusion protein consisting of extracellular portion of CTLA-4 and constant region of human immunoglobulin&lt;br&gt;• Blocks co-stimulation and activation of T cells</td>
<td>Yes</td>
</tr>
<tr>
<td>TNF inhibitors</td>
<td>Adalimumab</td>
<td>• Human monoclonal antibody directed against circulating and membrane-bound TNFα&lt;br&gt;• Binds to TNFα to block pro-inflammatory signaling&lt;br&gt;• May result in cell lysis in presence of complement</td>
<td>Yes</td>
</tr>
</tbody>
</table>
| **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 “generic” biologic medication that is designed to be identical to an existing biologic medication, but is created using a different process
  - Comparison studies seem to demonstrate equivalent efficacy and safety profiles between biosimilars and the original biologic agents
  - Biosimilars often more cost-effective than the biologic agents that they replicated

- **Canakinumab**
  - **Class:** biologic agent (see Biologic agents for summary table)  
  - **Original biologic agent:** Ilaris  
  - **Biosimilar medications:** not available yet  
  - **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 (higher doses at shorter intervals required for NOMID)  
  - **Side effects:** injection site reactions, headache, flu-like symptoms, GI upset, infections

- **Colchicine**
  - **Class:** alkaloid; immune modulating but not immunosuppressive  
  - **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 two to three times daily doses if side effects  
  - **Side effects:** nausea, vomiting, diarrhea, bloating, 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; doses range from 0.5 mg/kg/day oral dosing for mild disease activity to 30 mg/kg/day (max 1000 mg) IV methylprednisolone for severe or life-threatening disease
  - **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
    - Intra-articular administration: septic arthritis, subcutaneous atrophy, intra-articular and/or peri-articular calcifications
  - **Monitoring:** clinical (including blood pressure); consider monitoring bone health carefully if long-term corticosteroids are used

- **Cyclophosphamide**
  - **Class:** cytotoxic alkaulating 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/m²/dose IV every 2 to 4 weeks up to 6 months; occasionally used orally
  - **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)
  - **Original biologic agent:** Enbrel
  - **Biosimilar medications:** Benepali, Brenzys, Enticovo, Erelzi, Nepexto
  - **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
• Hydroxychloroquine
  o **Class:** antimalarial agent; immune modulating but not immunosuppressive
  o **Mechanism of action:** interferes with antigen processing and antigen-antibody interactions, inhibits nucleic acid and protein synthesis
  o **Dose:** up to 4-6 mg/kg/day (max 400 mg) PO daily
  o **Side effects:** nausea, anorexia, skin rash, headache, dizziness, photosensitivity, retinal toxicity
  o **Monitoring:** eye examinations every 12 months to assess for retinal deposits

• Infliximab
  o **Class:** biologic agent (see Biologic agents for summary table)
  o **Original biologic agent:** Remicade
  o **Biosimilar medications:** Avsola, Flixabi, Inflectra, Infixi, Remsimia, Zessly
  o **Mechanism of action:** monoclonal chimeric human-mouse antibody that binds to circulating and cell surface anti-TNFα
  o **Dose:** 6-10 mg/kg/dose on week 0, 2, 6 then every 4 to 8 weeks (may occasionally require higher doses)
  o **Side effects:** infusion reactions, anaphylaxis (especially with second or third infusions), headaches, infections, cytopenias, potential risk of future malignancy, demyelinating disease, new or worsening heart failure
  o **Monitoring:** CBC, differential, AST, ALT, creatinine every 3-6 months
  o **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
  o **Class:** plasma-derived protein; immune modulating but not immunosuppressive
  o **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
  o **Dose:** 2 g/kg/dose IV
  o **Side effects:** infusion reactions, haemolysis, aseptic meningitis 18-36 hours post infusion (headache and vomiting), cough, acute renal failure
  o **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
  o **Class:** disease-modifying antirheumatic drug (DMARD)
  o **Mechanism of action:** inhibits enzyme involved in DNA synthesis and interferes with lymphocyte proliferation
  o **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
  o **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/m²/dose (max 25 mg) PO or SC weekly (note: there may be a better response and fewer side effects with SC route)
- **Side effects:** GI upset, nausea, “mental fog” (24-36 hours following weekly dose), 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 for patients on stable doses
- **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/m²/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 may be considered

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin/ASA</td>
<td>High dose (anti-inflammatory): 50-100 mg/kg/day PO div QID</td>
<td>Used mostly in the setting of Kawasaki disease and acute rheumatic fever</td>
</tr>
<tr>
<td></td>
<td>Low dose (anti-platelet): 3-5 mg/kg/day PO OD</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>50 mg PO BID if 10-25 kg</td>
<td>Selective COX-2 inhibitor; expensive</td>
</tr>
<tr>
<td></td>
<td>100 mg PO BID if &gt;25 kg</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>20-40 mg/kg/day PO div TID or QID</td>
<td>Commonly used in childhood JIA</td>
</tr>
</tbody>
</table>

© Copyright of The Hospital For Sick Children
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin</td>
<td>2-3 mg/kg/day (max 150 mg/day) PO div TID</td>
<td>Commonly used in ERA and sJIA, can be compounded into liquid</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>0.125 mg/kg (max 15 mg/day) PO daily</td>
<td>Used in JIA, can be compounded into liquid</td>
</tr>
<tr>
<td>Naproxen</td>
<td>20 mg/kg/day (max 500 mg/dose) PO div BID</td>
<td>Frequently used in childhood JIA</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>0.4 mg/kg (max 20 g/day) PO daily</td>
<td>Used in JIA, capsule may be opened and sprinkled on food</td>
</tr>
</tbody>
</table>

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 (max 60 mg) IV monthly for 3 months (N.B.: first dose to be divided 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)
  - **Original biologic agent**: Arcalyst
  - **Biosimilar medications**: not available yet
  - **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)
  - **Original biologic medication**: Rituxan
  - **Biosimilar medications**: Blitzima, Rixathon, Riximyo, Ruxience, Riabni, Truxima
  - **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/m² once weekly for 2-4 doses or 750 mg/m² on days 1 and 15; for polyarticular RF-positive JIA patients 500 mg/m² (max 1000 mg) every 2 weeks for 2 doses or 375 mg/m² once weekly for 4 doses (used in ANCA vasculitis)
  - **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

**Secukinumab**
- **Class:** biologic agent (see Biologics agents for summary table)
- **Original biologic agent:** Cosentyx
- **Biosimilar medications:** not available yet
- **Mechanism of action:** humanized monoclonal antibody that binds soluble and membrane bound IL-17A
- **Dose:** for enthesitis related arthritis and psoriatic arthritis 75 mg if <50 kg or 150 mg if ≥50 kg 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

**Sulfasalazine**
- **Class:** disease-modifying antirheumatic drug (DMARD); analogue of 5-ASA linked to a sulfonamide; immune modulating but not immunosuppressive
- **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 Biologics agents for summary table)
- **Original biologic agent:** Actemra
- **Biosimilar medications:** not available yet
- **Mechanism of action:** humanized monoclonal antibody that binds both soluble and membrane-bound IL-6 receptor
- **Dose:**
  - Systemic JIA IV dosing: 12 mg/kg/dose every 2 weeks if <30 kg or 8 mg/kg/dose (max 800 mg) every 2 weeks if ≥30 kg
  - Systemic JIA SC dosing: 162 mg SC every 2 weeks if <30 kg or 162 mg weekly if ≥30 kg
  - Polyarticular JIA or uveitis IV dosing: 10 mg/kg/dose every 4 weeks if <30 kg or 8 mg/kg/dose (max 800 mg) every 4 weeks if ≥30 kg
  - Polyarticular JIA or uveitis SC dosing: 162 mg SC every 3 weeks if <30 kg or 162 mg SC every 2 weeks if ≥30 kg
- **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:** 2-4 mg PO twice daily if <40 kg; or 5 mg PO twice daily if ≥40 kg
  - **Side effects:** infections, viral reactivation, anemia, thrombocytopenia, neutropenia, lymphopenia, hypercholesterolemia, increased liver transaminases, GI perforation, potential risk of future malignancy, potential risk of cardiovascular events in adults

- **Ustekinumab**
  - **Class:** biologic agents (see Biologic agents for summary table)
  - **Original biologic agent:** Stelara
  - **Biosimilar medications:** not available yet
  - **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

- **Zoledronate**
  - **Class:** bisphosphonate
  - **Mechanism of action:** inhibits bone resorption, decreases mineralization by inhibiting osteoclast activity
  - **Dose:** 0.1 mg/kg/year; starting dose 0.025 mg/kg IV every 3 months and may increase to 0.05 mg/kg (max 4 mg) IV every 6 months
  - **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
APPENDIX – HELPFUL RESOURCES IN PEDIATRIC RHEUMATOLOGY

**Expert Clinical Reviews**


Kimura Y, Schanberg LE, Eds.


**Internet Resources for Images in Rheumatology**


Free access online journal: Pediatric Rheumatology ( [https://ped-rheum.biomedcentral.com/](https://ped-rheum.biomedcentral.com/) )

**Textbooks**


**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](https://www.printo.it/pediatric-rheumatology/IE/info/IE)

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

About Kids Health – provides information on multiple childhood rheumatic diseases from a general pediatric perspective  [https://www.aboutkidshealth.ca/](https://www.aboutkidshealth.ca/)
A RESIDENT'S GUIDE TO PEDIATRIC RHEUMATOLOGY

Cassie+Friends – patient support organization that provides information on childhood rheumatic diseases and treatments from a patient/parent perspective
https://cassieandfriends.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