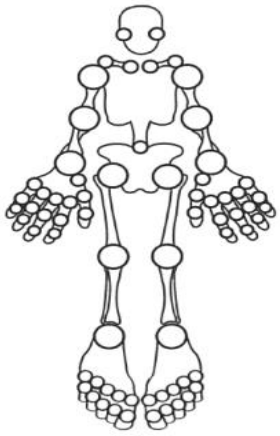

A RESIDENT'S GUIDE TO PEDIATRIC RHEUMATOLOGY

2016 Revised Edition

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SickKids®

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CANADIAN RHEUMATOLOGY ASSOCIATION | SOCIÉTÉ CANADIENNE DE RHUMATOLOGIE

This guide is intended to provide a brief introduction to basic topics in pediatric rheumatology. Each topic is accompanied by at least one up-to-date reference that will allow you to explore the topic in greater depth.

In addition, a list of several excellent textbooks and other resources for you to use to expand your knowledge is found in the Appendix.

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

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Notes:

Please consider that treatment regimens discussed in the guide are <u>suggestions</u> based on evidence-based guidelines and/or common practices by the pediatric rheumatologists who are section editors of the guide. Alternative treatment approaches may be used in other centres.

More detailed information on medications (class, action, dose, side effects, monitoring) may be found in the Medications section.

SECTION 1 – AN INTRODUCTION TO PEDIATRIC RHEUMATOLOGY

1A. Pediatric Rheumatologic History

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

History of presenting complaint

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

Past medical history

Chronic medical conditions
Admissions to hospital, surgeries
Eye examinations

Development

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

Immunizations

All childhood vaccinations
Varicella – Infection or vaccination?

Medications

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

Allergies

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

Family history

Ethnicity and consanguinuity

Rheumatologic diseases:	Juvenile idiopathic arthritis (JIA), rheumatoid arthritis (RA) Ankylosing spondylitis (AS) Premature osteoarthritis Inflammatory bowel disease (IBD) Psoriasis Systemic lupus erythematosus (SLE) Vasculitis Periodic fevers
Other autoimmune diseases:	Diabetes mellitus type I, Celiac disease, Thyroid disease

Social history

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

Review of systems

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

1B. Pediatric Rheumatologic Examination

Vital signs (including blood pressure percentiles)

Height, weight, BMI (percentiles, recent changes)

General appearance

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

1C. Laboratory Testing in Pediatric Rheumatology

General Principles

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

Complete blood cell count and differential

- Hemoglobin, red blood cell count and mean corpuscular volume
  - Normocytic or microcytic anemia in chronic inflammatory disease
  - Autoimmune hemolytic anemia in systemic lupus erythematosus (SLE)
  - Non-immune hemolytic anemia in macrophage activation syndrome (MAS)
  - Iron deficiency anemia if chronic blood loss (e.g. due to NSAIDs, inflammatory bowel disease)
- White blood cell count and differential
  - High white blood cell counts may be due to infection, systemic inflammation, or side-effect of corticosteroids
  - Leukopenia with lymphopenia and/or neutropenia may be due to systemic inflammation or medications Often leukopenia/lymphopenia in Lupus
- 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) or reduced platelet counts (e.g. SLE)

Acute phase response

- Acute phase reactants are plasma proteins produced by the liver that change production during acute phase of inflammation
- Acute phase response mediated by cytokines, such as IL-1, IL-6 and TNF (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 benign conditions, such as obesity, pregnancy, and strenuous exercises
- Overall effect of acute phase response is to protect host from damage
- Excessive or prolonged acute phase response may be deleterious itself (e.g. septic shock, MAS, malignancy)

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

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

- **Ferritin**
  - Protein central to iron homeostasis
  - Serum ferritin levels increase in setting of inflammation
  - May not be a reliable measure of iron status in setting of inflammatory disease

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

Complement

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

Autoantibodies

Antinuclear antibodies (ANA)

- Autoantibodies directed against nuclear, nucleolar or perinuclear antigens
- ANA should not be used as a screening tool
  - Low titres of ANA (e.g. ANA ≤ 1:80) may be present in up to 30% of normal healthy population and may revert to negative over time
  - ANA may also be present in non-rheumatologic diseases (e.g. infection, malignancy, medications)
- Low titres of non-specific ANA may be seen in JIA (e.g. ANA ≤ 1:160)
  - Positive ANA in JIA associated with higher risk of uveitis, asymmetric arthritis and early disease onset (do not need to repeat regularly once positive ANA established, as highlighted in *Choosing Wisely: Pediatric Rheumatology Top 5 by American College of Rheumatology*)

- Persistent high titres of ANA (e.g. ANA ≥ 1:160) in connective tissue diseases, such as SLE
  - Negative ANA makes diagnosis of SLE unlikely
- Specific antibodies (e.g. anti-double stranded DNA) should only be requested if ANA is positive and there is evidence of rheumatic disease *(highlighted in Choosing Wisely: Pediatric Rheumatology Top 5 by American College of Rheumatology)*

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

Antiphospholipid antibodies

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

Rheumatoid factor (RF)

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

Anti-citrullinated peptide antibodies (ACCP)

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

Antineutrophil cytoplasmic antibodies (ANCA)

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

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

Human Leukocyte Antigen (HLA) Genetics

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

HLA B27
- HLA class I gene that is present in only 7-10% of the general population (may be higher in some First Nations groups)
- Found in 90-95% of Caucasians with ankylosing spondylitis and many patients with JIA (particularly enthesitis related arthritis and psoriatic arthritis), inflammatory bowel disease, isolated acute anterior uveitis, and reactive arthritis
- HLA B27 may play a role in the pathogenesis of inflammatory disease

HLA B51
- May be associated with Behçet disease

Additional tests

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

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

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

Hepcidin
- Liver protein involved in iron absorption
- Used experimentally in assessment of immune response and may become part of work-up in the future

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3. Breda L, et al. Laboratory tests in the diagnosis and follow-up of pediatric rheumatic diseases: An update. *Semin Arthritis Rheum* 2010; 40(1):53-72.
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SECTION 2 – APPROACHES AND DIFFERENTIAL DIAGNOSES FOR COMMON COMPLAINTS REFERRED TO PEDIATRIC RHEUMATOLOGY

2A. Approach to Childhood Joint Pain

Differential diagnosis for pain involving a single joint:

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

Potential investigations for pain involving a single joint:

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

Differential diagnosis for pain involving multiple joints:

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

Potential investigations for pain involving multiple joints:

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

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

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

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5. Wolf M. Knee pain in children, Part III: Stress injuries, benign bone tumors, growing pains. *Pediatr Rev* 2016; 37(3):101-13.

2B. Approach to Childhood Back Pain

Differential diagnosis for back pain in children

Inflammatory	Juvenile idiopathic arthritis (JIA) Inflammatory bowel disease (IBD) Chronic non-bacterial osteomyelitis / chronic non-bacterial osteomyelitis
Infection-related	Acute infections (e.g. osteomyelitis, discitis, septic arthritis, epidural abscess) Chronic infections (e.g. tuberculosis (Pott disease)) Reactive arthritis
Neoplastic	Musculoskeletal tumors (e.g. osteoid osteoma) Leukemia, lymphoma Neurofibroma
Mechanical	Spondylolysis, spondylolisthesis Scoliosis Scheuermann disease Disc prolapse Degenerative disc disease
Trauma	Fracture
Hematologic	Sickle cell pain crisis
Pain syndrome	Fibromyalgia

Potential investigations for back pain in children:

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

References:

1. Altaf F, et al. Back pain in children and adolescents. *Bone Joint J* 2014; 96B:717-23.

2C. Approach to Fevers

Definition of fever of unknown origin:

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

Differential diagnosis for fever of unknown origin in children

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

Potential investigations for fever of unknown origin in children:

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

Definition of recurrent fevers:

- At least 3 episodes of unexplained fever in a 6-month period separated by at least 7 days of good health

Differential diagnosis for recurrent fevers

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

Potential investigations for recurrent fevers:

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

References:

1. Antoon JW, et al. Pediatric fever of unknown origin. *Pediatr Rev* 2015; 36(9):380-91.
2. Marshall GS. Prolonged and recurrent fevers in children. *J Infect* 2014; 68(Suppl1):S83-93.

2D. Approach to Recurrent Oral Ulcers

Differential diagnosis for recurrent oral ulcers in children

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

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

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

References:

1. Siu A, et al. Differential diagnosis and management of oral ulcers. *Semin Cutan Med Surg* 2015; 34(4):171-7.
2. Stoopler ET, Al Zamel G. How to manage a pediatric patient with oral ulcers. *J Can Dent Assoc* 2014; 80:e9.

2D. Additional differential diagnoses

Differential diagnosis for lymphadenopathy in children

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

Differential diagnosis for erythema nodosum in children

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

Differential diagnosis for recurrent parotitis

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

Differential diagnosis for muscle weakness

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

Differential diagnosis for chorea and abnormal movements in children

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

Differential diagnosis for stroke-like presentations in children

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

References:

1. Penn E, Goudy S. Pediatric inflammatory adenopathy. *Otolaryngol Clin North Am* 2015; 48(1):137-51.
2. Baszis K, et al. Recurrent parotitis as a presentation of primary pediatric Sjögren syndrome. *Pediatrics* 2012; 129:179-82.
3. Huber AM. Idiopathic inflammatory myopathies in childhood: Current concepts. *Pediatr Clin North Am* 2012; 59(2):365-80.
4. Gilbert DL. Acute and chronic chorea in childhood. *Semin Pediatr Neurol* 2009; 16(2):71-6.

SECTION 3 – JUVENILE IDIOPATHIC ARTHRITIS

3A. Introduction to Juvenile Idiopathic Arthritis (JIA)

- JIA encompasses a group of conditions with arthritis as the common feature.
- The current classification system by the International League of Associations for Rheumatology (ILAR) recognizes 7 distinct subtypes of JIA, based on their presentation within the first 6 months:

1. **Oligoarthritis**
2. **Polyarthritis (Rheumatoid Factor Negative)**
3. **Polyarthritis (Rheumatoid Factor Positive)**
4. **Systemic arthritis**
5. **Enthesitis-related arthritis**
6. **Psoriatic arthritis**
7. **Undifferentiated arthritis**

- Juvenile idiopathic arthritis is arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks and in which other known causes of arthritis are excluded.
- 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

Oligoarthritis

ILAR Criteria for Oligoarthritis

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

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

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

- Oligoarthritis is the most common subtype of JIA. The typical patient is a young girl with positive ANA who presents with a small number of swollen joints.
- The most frequent joints to be involved are knees, ankles, wrists, or elbows. Hip involvement is 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 11.)

Polyarthritis (Rheumatoid Factor Negative)

ILAR Criteria for Polyarthritis (Rheumatoid Factor Negative)

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

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

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

Polyarthritis (Rheumatoid Factor Positive)

ILAR Criteria for Polyarthritis (Rheumatoid Factor Positive)

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

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

- Patients with RF positive polyarthritis share many characteristics with adults with rheumatoid arthritis. All patients, by definition, are RF positive, many are positive for anti-CCP antibodies and ANA is positive in 75%.
- This affects mostly adolescent girls. The clinical symptoms are similar to the adult disease with symmetrical polyarthritis especially involving the PIP joints and MCP joints.
- Children may develop rheumatoid nodules and similar complications to adult disease, including joint erosions and Felty syndrome (neutropenia and splenomegaly).

Systemic Arthritis

ILAR Criteria for Systemic Arthritis

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

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

- The typical symptoms of systemic JIA include:
  - Once or twice daily fever spikes to >38.5°C, which then return to baseline or below. Children are usually acutely unwell during fever episodes.
  - Salmon-coloured, evanescent rash accompanying the fever, occasionally pruritic
  - Lymphadenopathy and hepatosplenomegaly
  - Arthritis may develop later (e.g. usually within the 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 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

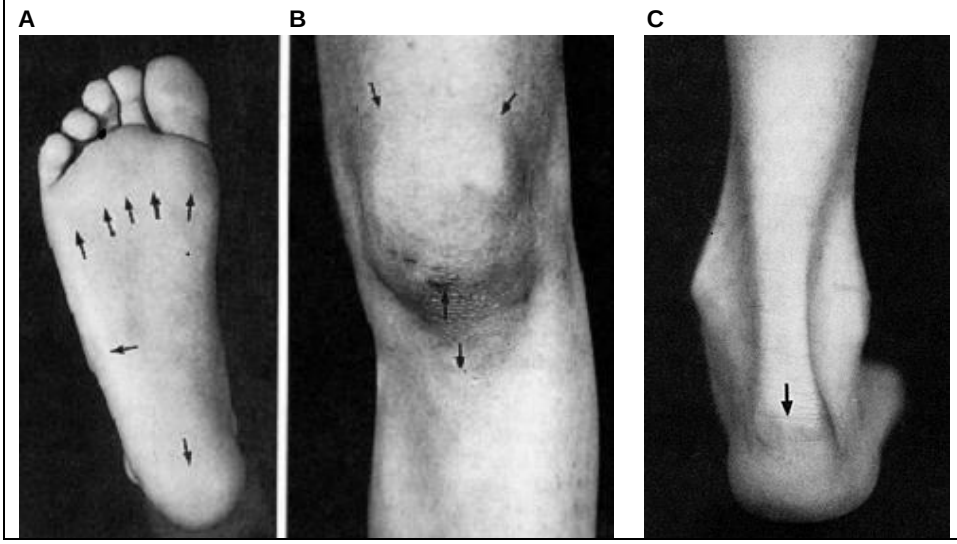
ILAR Criteria for Enthesitis Related Arthritis

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

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

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

Common sites of enthesitis in the lower body *



A. Insertions of plantar fascia

B. Insertions of quadriceps and patellar tendons

C. Insertion of Achilles tendon

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

Psoriatic Arthritis

ILAR Criteria for Psoriatic Arthritis

Definition:

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

Exclusions:

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

- Psoriatic arthritis can occur before or after manifestation of psoriasis. In fact, children may be re-classified as having psoriatic arthritis if they develop psoriasis after their arthritis is diagnosed.
- Psoriatic arthritis is typically asymmetric, and involves both large and small joints.
- A 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 Criteria for Undifferentiated Arthritis

Definition:

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

References:

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

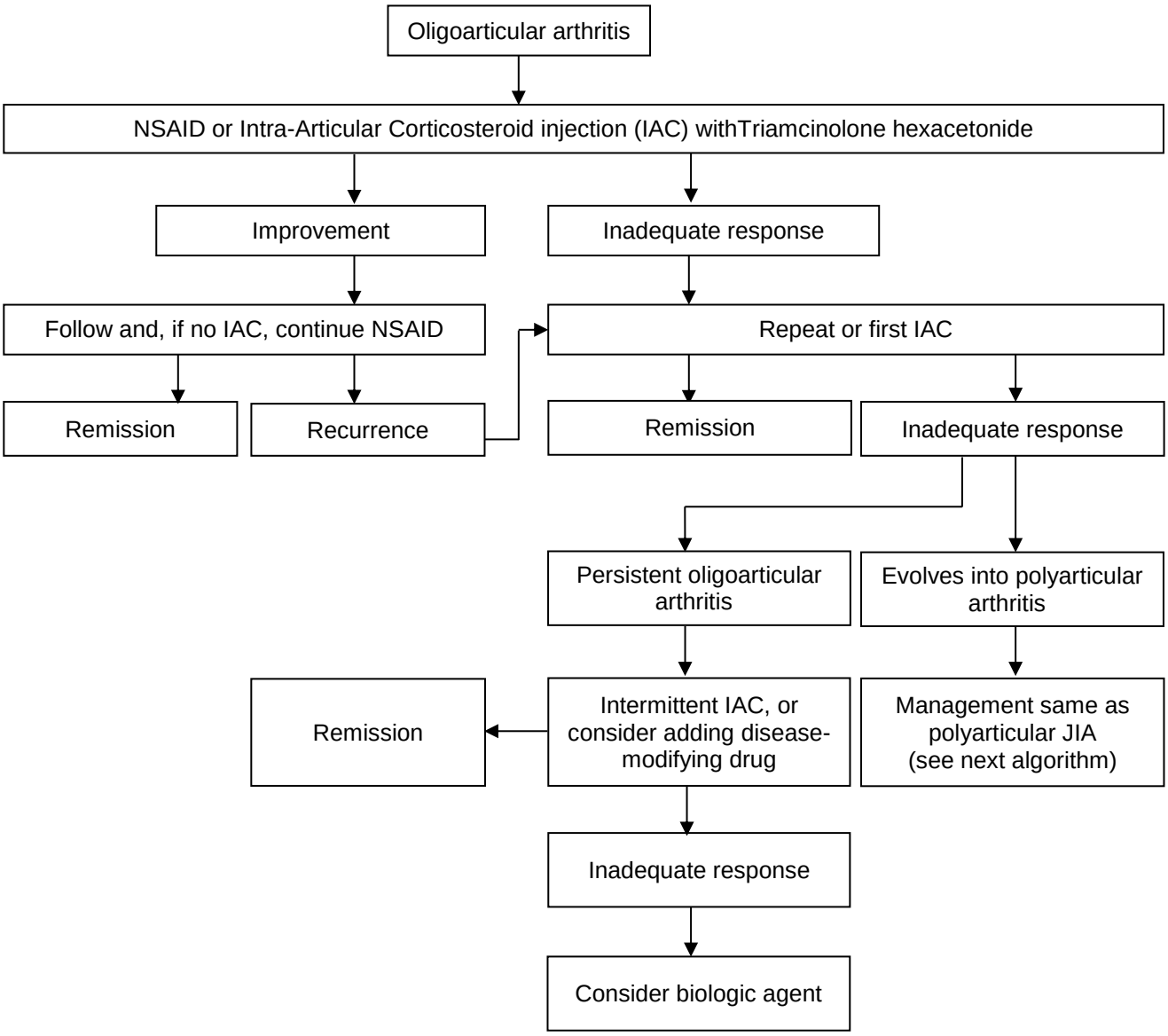
3B. Approach to Treatment of JIA

- **Goals of therapy:**

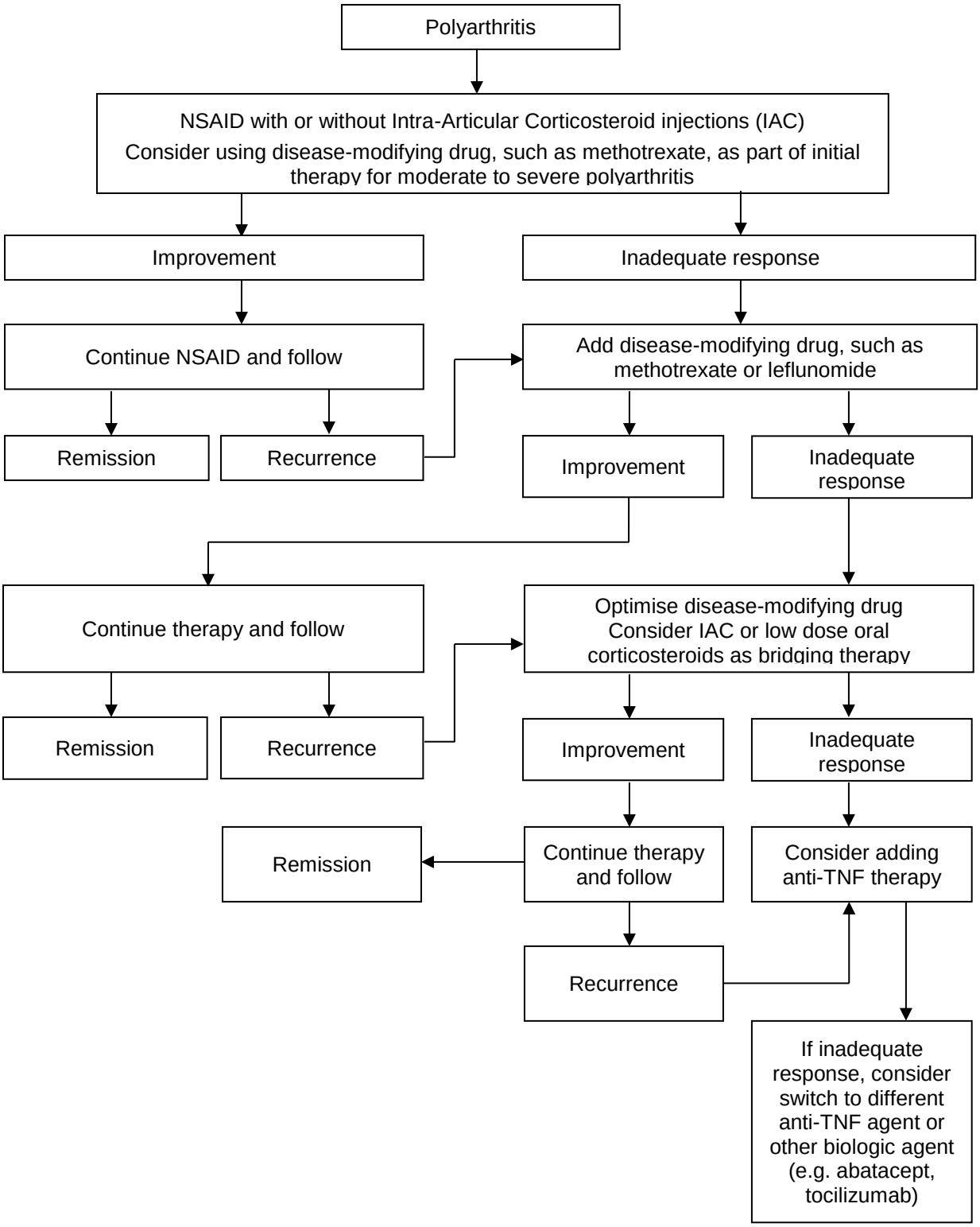
1. Eliminate inflammation with goal to achieve clinical remission
2. Prevent joint damage
3. Promote normal growth and development
4. Maintain normal function and optimize quality of life
5. Minimize medication toxicity

- Multidisciplinary approach 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
- Initial therapy with an NSAID may be started by a patient's primary care physician; however, a referral should be made to a pediatric rheumatologist as quickly as possible
- The goal of treatment is complete remission – rapid escalation of therapy may be required to achieve this goal
- Careful monitoring by an eye care provider is essential to assess for chronic anterior uveitis, especially in patients with oligoarthritis and positive ANA
- 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)*
- Potential algorithms for treatment of oligoarthritis, polyarthritis and systemic JIA are included in the following pages

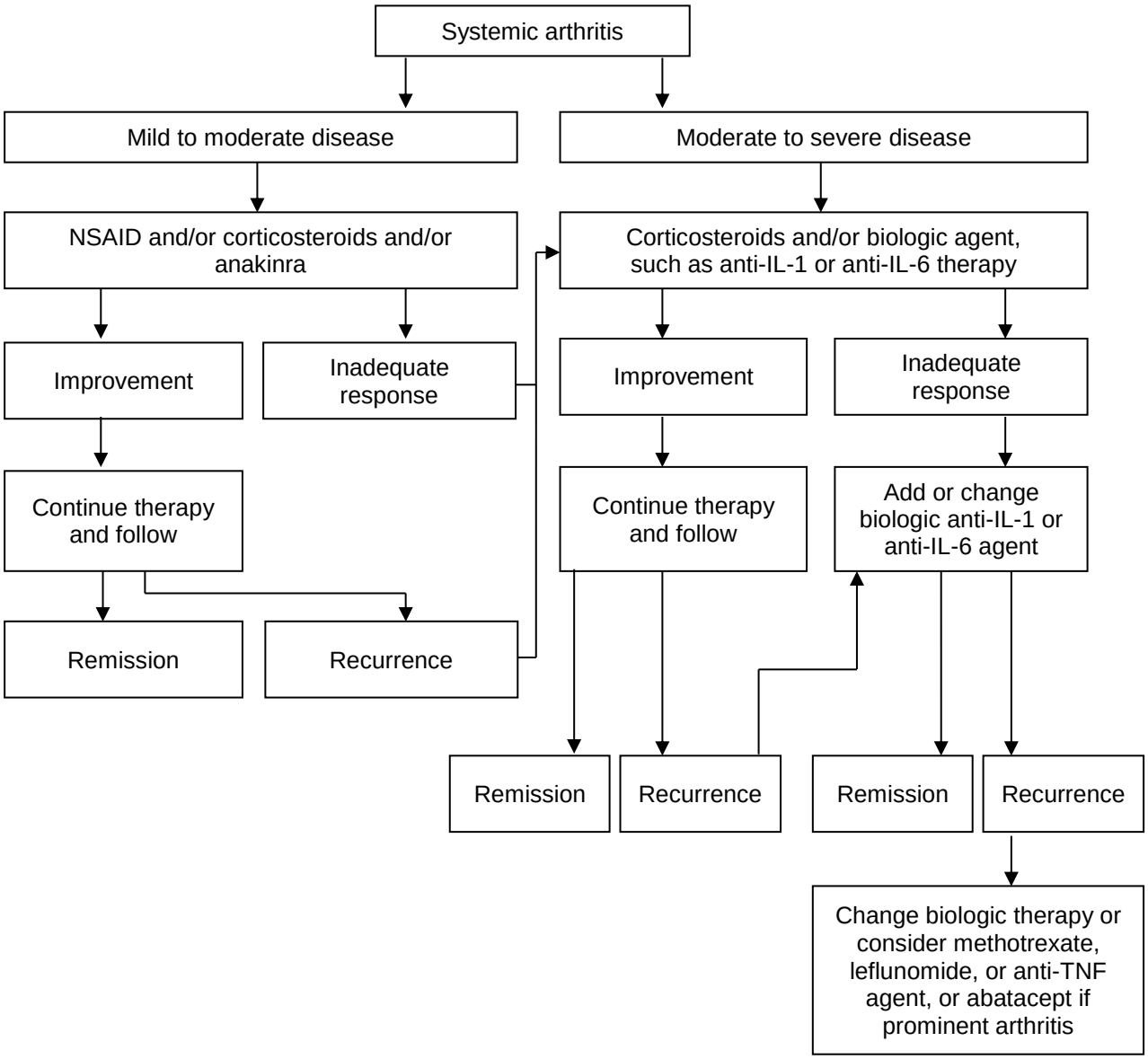
An Algorithm for Treatment of Oligoarthritis



An Algorithm for Treatment of Polyarthritis



An Algorithm for Treatment of Systemic JIA



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1. Beukelman T, et al. 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis... *Arthritis Care Res* 2011; 63(4):465-82.
2. Ringold S, et al. 2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis. *Arthritis Rheum* 2013; 65(10):2499-2512.
3. Stoll ML, Cron RQ. Treatment of juvenile idiopathic arthritis: A revolution in care. *Pediatr Rheumatol Online J* 2014; 12:13.
4. Zulian F, et al. Comparison of intra-articular triamcinolone hexacetonide and triamcinolone acetonide in oligoarticular juvenile idiopathic arthritis. *Rheumatology* 2003; 42(10):1254-9.

SECTION 4. SYSTEMIC LUPUS ERYTHEMATOSUS & RELATED CONDITIONS

4A. Systemic Lupus Erythematosus (SLE)

- Multi-system inflammatory disease characterized by autoantibody and immune-complex mediated inflammation of blood vessels and connective tissues
- 15-20% of cases of SLE are diagnosed before 16 years of age
- Female predominance, especially in adolescence and adulthood
- Ethnic predilection in Blacks, Hispanics, and Asians
- Positive family history of SLE in 10%

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

Need ≥ 4/11 of following criteria:

- Malar rash (butterfly rash sparing nasolabial folds)
- Discoid lupus rash*
- Photosensitivity
- Oral or nasal mucocutaneous ulcerations (usually painless)
- Non-erosive arthritis 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, antiphospholipid antibodies)

*Uncommon in children

- 1997 ACR Classification criteria were designed to identify a homogeneous population of SLE patients for research studies. However, the presence of ≥ 4 criteria is highly sensitive and specific for SLE (>95%) and so the criteria are widely used for diagnosis
- Other clinical features of SLE not included in above classification criteria:
  - Constitutional symptoms – fevers, fatigue, weight loss, anorexia
  - Other rashes (e.g. annular erythema, maculopapular or linear (nonspecific) rash, bullous lupus (rare), palmar/plantar/periungual erythema, livedo reticularis, or vasculitic rash)
  - Alopecia classically in the frontal area, but can be diffuse
  - Polyarthralgia, myalgia, and/ or myositis
  - Raynaud phenomenon (see Section 5A)
  - Lymphadenopathy
  - Hepatomegaly, splenomegaly
  - Hypertension
  - Decreased concentration and cognitive dysfunction, stroke, mood disorder, headache
  - Pneumonitis, pulmonary hemorrhage
  - Myocarditis, Libman-Sacks endocarditis

- Other common laboratory features of SLE:
  - Elevated ESR with normal CRP (except high CRP in infection and serositis)
  - Low complement (C3, C4) levels
  - Elevated IgG levels
  - Other autoantibodies: anti-Ro, anti-La, anti-RNP, Rheumatoid factor
- Presentation of SLE is not always "classic" → need to consider this diagnosis in adolescent females with polyarthritis; fever, rash and constitutional symptoms; ITP with positive ANA; unusual arterial or venous thrombosis; or chorea; may be accomplished 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)
    - Considered standard therapy for SLE
    - Proven efficacy in decreasing frequency and severity of disease flares
    - Improves serum lipid profile
    - May be helpful with anti-phospholipid antibodies
  - Corticosteroids
    - Often used in initial therapy for SLE with dose depending on severity and organ involvement
    - Pulse therapy is used for severe lupus nephritis, hematologic crisis, CNS disease or other life or organ-threatening manifestations
  - Azathioprine
    - Typically used for hematologic and renal manifestations
  - Mycophenolate mofetil
    - Used for hematologic, renal and CNS manifestations
  - Cyclophosphamide
    - Used for severe renal and CNS manifestations
  - Rituximab
    - Used for resistant thrombocytopenia
  - Belimumab
    - Adjunctive therapy for mild/moderate SLE (trials excluded those with severe CNS and renal involvement)

- Course and Outcomes
  - Relapsing and remitting course of disease
  - 10 year survival >90%
  - Most deaths related to infection, renal, CNS, cardiac, and pulmonary disease
  - Additional morbidity related to disease and/or treatment:
    - Early-onset coronary artery disease
    - Bone disease → osteopenia, avascular necrosis
    - Malignancy
  - Childhood-onset SLE vs. adult-onset SLE
    - Children have more active disease at presentation and over time
    - Children more likely to have active renal disease
    - Children receive more intensive drug therapy and sustain more long-term damage

References:

1. Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. *Ped Clin North Am* 2012; 59(2):345-64.
2. Weiss JE. Pediatric systemic lupus erythematosus: More than a positive antinuclear antibody. *Pediatr Rev* 2012; 33(2):62-73.
3. Malattia C, Martini A. Paediatric-onset systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2013; 27(3):351-62.

4B. Neonatal Lupus Erythematosus (NLE)

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

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

- Clinical features
  - Cardiac
    - Most important and severe manifestation is complete congenital atrioventricular (AV) heart block
    - Complete heart block is associated with significant morbidity and mortality (congestive heart failure, fetal hydrops, intrauterine death)
    - Other manifestations include less severe conduction abnormalities, carditis
  - Skin
    - Classic NLE rash is annular, erythematous papulosquamous rash with fine scale and central clearing
    - Predilection for face and scalp (not malar distribution)
    - Typically photosensitive
    - Dermatitis may be present at birth, but more commonly develops within first 6 weeks of life
    - New lesions appear for several months, but rarely develop after 6 months and typically heal without scarring
    - Telangiectasias may develop starting at 6-12 months of age, may not be in areas affected by previous rash
  - Hematologic
    - Thrombocytopenia is most common
    - Neutropenia and anemia are less common
    - Usually resolve without sequelae and rarely require treatment
    - Neutropenia is not typically associated with increased risk of infection
  - Hepatic
    - Asymptomatic cholestatic hepatitis with mild to moderately elevated liver enzymes
    - Hepatomegaly and less commonly splenomegaly
    - May be the only manifestation of NLE

        - Typically resolves before 6 months without treatment
    - Neurologic
        - Reported CNS manifestations include macrocephaly, hydrocephalus, spastic paraparesis, asymptomatic neuroimaging abnormalities, and vasculopathy
        - Clinical significance still unclear
        - Important to monitor head circumference

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

References:

1. Izmirly PM, et al. Neonatal lupus syndromes. *Rheum Dis Clin North Am* 2007; 33(2):267-85.
2. Johnson B. Overview of neonatal lupus. *J Pediatr Health Care* 2014; 28(4):331-41.

4C. Drug-Induced Lupus

- Development of lupus-like symptoms that is temporally related to continuous drug exposure (>1 month) and that resolves with cessation of the offending drug
- Usually accompanied by serologic findings of positive ANA as well as anti-histone antibodies (in approximately 90% of patients)
- However, anti-histone antibodies can also be found in patients with SLE
- Variable time from drug exposure to onset of symptoms
- Onset generally insidious
- Patients commonly present with fever, arthralgias or arthritis, myalgias and serositis
- Usually mild, although life threatening disease has been reported
- Rarely involve classic malar or discoid rash, oral ulcers or major organ involvement
- Laboratory findings may include mild cytopenias, high ESR
- Drugs that have been implicated in drug-induced lupus include: Minocycline, anticonvulsants, Hydralazine, and biologic agents that target Tumor Necrosis Factor (TNF)
- Treatment
    - Stop the offending drug
    - Corticosteroids may be used for moderate to severe manifestations (e.g. cardiac tamponade)

References:

1. Vasoo S. Drug-induced lupus: an update. *Lupus* 2006; 15:757-61
2. Katz U, Zandman-Goddard G. Drug-induced lupus: an update. *Autoimmun Rev* 2010; 10(1):46-50.

4D. Antiphospholipid Syndrome (APS)

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

Adapted Classification Criteria for Antiphospholipid Syndrome in Pediatric Patients

Clinical criteria

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

Laboratory criteria

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

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

- Deep venous thrombosis is the most common type of venous thrombosis, while stroke is the most common type of arterial thrombosis (see Section 2: Differential Diagnosis of stroke-like presentations in children)

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

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

- Treatment
  - If primary, treat as a disorder of coagulation
  - If secondary, treat underlying disorder (often using Corticosteroids)

- Anticoagulation using heparin (e.g. low molecular weight heparin (LMWH)) is usually required at least initially, and patients could require LMWH or warfarin therapy lifelong
- Consider anti-platelet agents (e.g. ASA)
- May consider Rituximab as direct therapy to target pathogenic autoantibodies in APS

References:

1. Avcin T, et al. Pediatric antiphospholipid syndrome: Clinical and immunologic features of 121 patients in an international registry. *Pediatrics* 2008; 122(5):e1100-7.
2. Aguiar C, et al. Pediatric antiphospholipid syndrome. *Curr Rheumatol Rep* 2015; 17(4):27.

SECTION 5 – SYSTEMIC VASCULITIS

5A. Introduction to Vasculitis

- Group of multi-system inflammatory diseases characterized by inflammation and necrosis of blood vessels, resulting in vessel occlusion and tissue ischemia

- Consider vasculitis when:
  - Unexplained prolonged constitutional symptoms (fever, weight loss, fatigue)
  - Multiple organ system involvement
    - CNS (headache, seizures, stroke) and/or PNS (mononeuritis)
    - Cardiac (pericarditis, myocarditis, myocardial infarction)
    - Vascular (chronic vascular insufficiency, vascular bruits, claudication)
    - Pulmonary (hemorrhage, nodules, cavities, infiltrates)
    - Renal (nephritis, nephrotic syndrome, hypertension, rapidly progressive renal failure)
    - Opthalmologic (episcleritis, iritis, panuveitis, retinitis)
    - ENT (chronic sinusitis, epistaxis, chronic otitis, hearing loss, chondritis)
    - GI (ischemic abdominal pain)
    - MSK (arthritis, arthralgia, myalgias, calf pain)
    - Skin (palpable purpura, nodules, livedo, urticaria, ulcers)

Classification of vasculitis based on size of vessel involved	
Large vessel vasculitis	Takayasu arteritis Giant cell arteritis (older adults)
Medium vessel vasculitis	Kawasaki disease Polyarteritis nodosa (systemic, cutaneous)
Small vessel vasculitis	ANCA – associated vasculitis Microscopic polyangiitis Granulomatosis with polyangiitis (previously Wegener granulomatosis) Eosinophilic granulomatosis with polyangiitis (previously Churg-Strauss Syndrome) Immune complex vasculitis IgA vasculitis (Henoch-Schonlein purpura) Cryoglobulinemia Hypocomplementemic urticarial vasculitis
Variable vessel vasculitis	Behçet disease Cogan syndrome
Other vasculitis	Primary CNS vasculitis (see Section 5) Primary cutaneous vasculitis Vasculitis secondary to drugs, infection (e.g. hepatitis B virus, Parvovirus), or malignancy Monogenic disease causing vasculitis (e.g. Deficiency of Adenosine Deaminase 2)

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

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

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

References:

1. Jennette JC, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65(1):1-11.
2. Weiss P. Pediatric Vasculitis. *Pediatr Clin North Am* 2012; 59(2):407-23.
3. Barut K, et al. Pediatric Vasculitis. *Curr Opin Rheumatol* 2016; 28:29-38.

5B. Takayasu arteritis

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

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

Plus ≥ 1/5 of the following:

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

- Large vessel vasculitis involving the aorta and its branches (thoracic, abdominal, carotid)
- Chronic, relapsing disease
- Initially can present as non-specific inflammatory illness with fever
- Evolution to chronic, fibrotic phase with signs and symptoms of chronic vascular insufficiency (pulse deficit, claudication, BP discrepancy, bruits)

- Investigations
  - Magnetic resonance angiography useful to show extension of disease and vessel wall inflammation; often used to follow disease (less invasive than conventional angiography)
  - Rule out associated TB infection (PPD, chest X-ray)

- Treatment
  - Depends on degree of inflammation
  - If "active" disease (by acute phase reactants +/- wall enhancement on MRA):
    - Corticosteroids plus second line agent
    - Second line agent options include Methotrexate, Mycophenolate mofetil, Infliximab or Adalimumab
    - May also use Tocilizumab, Cyclophosphamide, or Rituximab if refractory disease
  - If "inactive" disease:
    - Manage end-organ manifestations (medical therapy +/- vascular surgery)

References:

1. Ozen S, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener's granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010; 69(5):798-806.
2. Brunner J, et al. Takayasu arteritis in children and adolescents. *Rheumatology* 2010; 49:1806-14.
3. de Ranieri D. Great vessels of children: Takayasu's arteritis. *Pediatr Ann* 2015; 44(6):e148-52.

5C. Kawasaki disease (KD)

Diagnostic Criteria for Kawasaki disease*

Fever persisting for ≥5 days

Plus ≥ 4/5 of the following:

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

* Other ways to make diagnosis of KD:
  a) In presence of fever and coronary artery involvement on echo, <4/5 criteria sufficient
  b) Incomplete KD diagnosed if ≥ 5 days of fever with 2 or 3 features (common in infants, who are at higher risk of coronary artery involvement)
  c) Atypical KD diagnosed if KD with an unusual manifestation (e.g. renal failure)

- Medium vessel vasculitis, with predilection for coronary arteries
- Most common between 1 and 5 years of age

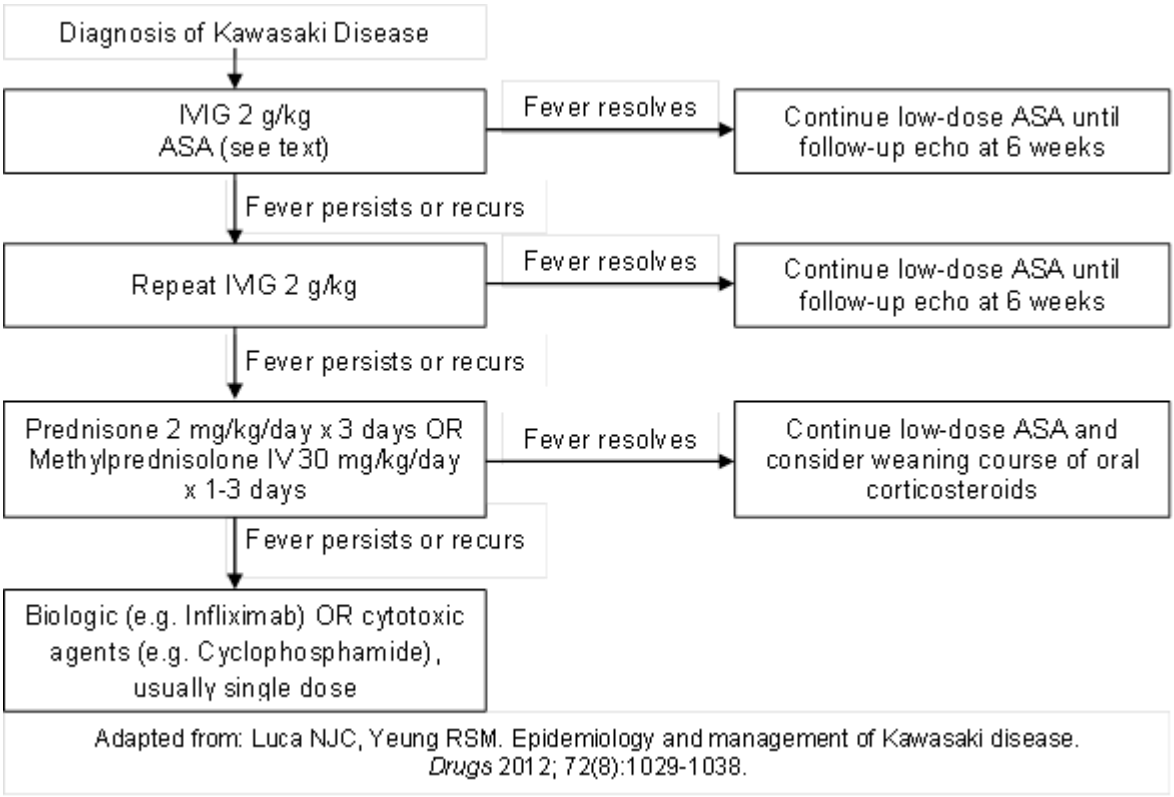
- Most common cause of acquired heart disease in children in developed countries
- May be triggered by infectious agent (viral and/or bacterial super-antigen implicated)
- Probable genetic predisposition; polygenic with genes identified that influence risk of KD and coronary artery involvement
- Common clinical manifestations: irritability (aseptic meningitis), arthritis (at onset or delayed), sterile pyuria (urethritis), gastroenteritis (abdominal pain, vomiting, diarrhea), uveitis, periungual desquamantion in weeks 2 or 3
- Uncommon features include gallbladder hydrops, GI ischemia, jaundice
- Cardiac involvement: myocarditis, pericarditis, cardiac failure, valvular regurgitation
- May be complicated by macrophage activation syndrome (MAS), DIC
- KD shock syndrome characterized by hypotension or poor perfusion
- Coronary artery disease in KD
  - 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

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

- Treatment
  - See treatment algorithm on next page
  - Target treatment within 10 days of fever onset
  - IVIG 2g/kg (unequivocally reduces the occurrence of coronary artery aneurysms)
    - *If still febrile 24-36 hours after IVIG* → second dose of IVIG
    - Consider monitoring for IVIG-related hemolysis with CBC, blood film, reticulocytes and direct antiglobulin test 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
  - *Myocarditis, MAS* → add Corticosteroids
  - *If large coronary aneurysm* → Abciximab (glycoprotein IIb/IIIa receptor inhibitor) in acute or subacute phase; long-term antiplatelet (+ Heparin or Warfarin if giant aneurysm)

- Prognosis
  - In-hospital mortality 0.17% (all cardiac-related)
  - ~ 2% risk of recurrent KD
  - Without treatment, coronary artery aneurysms occur in ~25% of patients → reduced to ~4% if IVIG treatment within 10 days
  - If coronary artery aneurysm → risk for thrombosis, obstruction and stenosis, ventricular dysfunction/arrhythmia, early atherosclerosis, myocardial infarction (highest if ≥8 mm)

An algorithm for treatment of Kawasaki disease



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

References:

1. Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A statement for health professionals by the committee on rheumatic diseases, endocarditis, and Kawasaki disease, American Heart Association. *Pediatrics* 2004; 114: 1708-1733.
2. Yellen ES, et al. Performance of 2004 American Heart Association recommendations for treatment of Kawasaki disease. *Pediatrics* 2010; 125(2): e234-e241.
3. Scuccimarri R. Kawasaki disease. *Ped Clin North Am* 2012; 59(2):425-445.

5D. Polyarteritis nodosa (PAN)

2008 EULAR/PRINTO/PRES Classification Criteria for Childhood PAN

Systemic illness characterized by:

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

Plus ≥ 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)

Systemic PAN

- Very rare in childhood
- Additional clinical features
  - Constitutional symptoms
  - Prolonged fever
  - Testicular pain or tenderness
  - Stroke or coronary artery disease
  - Bruits
  - Ischemic abdominal pain

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

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

Cutaneous PAN

- Clinical syndrome characterized by absence of major organ involvement, but may involve skin, joints, muscles and peripheral nervous system
- Skin findings (tender subcutaneous nodules, livedo reticularis, superficial or deep ulcers)
- Additional clinical features
  - Constitutional features
  - Myalgia, arthralgia, non-erosive arthritis
  - Peripheral neuropathy

- Investigations
  - Diagnosis requires deep skin biopsy to get small muscular arteries showing necrotizing, non-granulomatous vasculitis
  - Negative testing for ANCA
  - May be associated with serological (ASOT) or culture evidence of Streptococcal infection

- Treatment
  - Corticosteroids with rapid wean or another second line agent (e.g. IVIG, Methotrexate)
  - Penicillin treatment (if proven associated *Streptococcal* infection) and prophylaxis

Deficiency of Adenosine Deaminase 2 (DADA2)

- Consider in differential diagnosis of polyarteritis nodosa
- Recently identified monogenic autoimmune recessive disease (mutations in *CECR1* gene) leading to vasculitis
- Clinical features are variable, depending on mutation type and number of affected alleles
- Common features:
  - Recurrent lacunar stroke (ischemic or hemorrhagic) with onset at young age
  - Fever
  - Vasculitis, including polyarteritis nodosa
  - Livedo reticularis
  - Hepatosplenomegaly
  - Various ophthalmologic manifestations

- Investigations
  - Elevated inflammatory markers
  - Diagnosis confirmed through genetic testing

- Treatment
  - Not established
  - Consider disease modifying medications and biologic agents for inflammatory component

References:

1. Ozen S, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener's granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010; 69(5):798-806.
2. Kawakami T. A review of pediatric vasculitis with a focus on juvenile polyarteritis nodosa. *Am J Clin Dermatol* 2012; 13(6):389-98.
3. Beckum KM, et al. Polyarteritis nodosa in childhood: recognition of early dermatologic signs may prevent morbidity. *Pediatr Dermatol* 2014; 31(1):e6-9.
4. Falcini F, et al. Clinical overview and outcome in a cohort of children with polyarteritis nodosa. *Clin Exp Rheumatol* 2014; 32(3 Suppl 82):S134-7.
5. Navon Elkan P, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. *N Engl J Med* 2014; 370(10):921-31.

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

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)

- Predominantly small vessel vasculitis, characterized by granulomatous inflammation
- Generally occurs in the second decade of life, with a female preponderance
- Hallmark of GPA is triad of upper and lower respiratory tract inflammation and renal disease
- Common presenting features (in order of decreasing frequency)
  - Constitutional – fatigue, malaise, fever, weight loss
  - Pulmonary – SOB, chronic cough, hemoptysis/alveolar hemorrhage, lung nodules/cavitations/fixed infiltrates, abnormal PFTs (obstructive and restrictive)
  - ENT – nasal involvement (epistaxis, ulcers), sinusitis, otitis/mastoiditis, hearing loss, subglottic involvement
  - Renal – abnormal urinalysis, biopsy-proven GN, elevated creatinine, acute renal failure
  - MSK – arthralgia/myalgia, arthritis
  - GI – nonspecific abdominal pain, chronic nausea
  - Eye – nonspecific red eye, conjunctivitis, scleritis
  - Cutaneous – palpable purpura/petechiae
  - CNS – severe headache, dizziness

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

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

- Prognosis
  - Significant morbidity associated with disease and medications
  - Severe pulmonary disease requiring mechanical ventilation in 11%
  - Dialysis required in 11%

References:

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

5F. Microscopic Polyangiitis (MPA)

- No 2008 EULAR/PRINTO/PRES classification criteria
- Pauci-immune, necrotizing, non-granulomatous small vessel vasculitis
- Rare in childhood

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

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

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

References:

1. Cabral D, et al. Comparing presenting clinical features in 48 children with microscopic polyangiitis to 183 children who have granulomatosis with polyangiitis (Wegener's): An ARChiVe Cohort Study. *Arthritis Rheumatol* 2016; 68(10):2514-26.
2. Sun L, et al. Clinical and pathological features of microscopic polyangiitis in 20 children. *J Rheumatol* 2014; 41(8):1712-9.
3. Peco-Antic A, et al. Childhood microscopic polyangiitis associated with MPO-ANCA. *Pediatr Nephrol* 2006; 21:46–53.

5G. IgA Vasculitis (also known as Henoch-Schonlein Purpura, or HSP)

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)

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

- Most common vasculitis in children
- Often follows a respiratory infection, most commonly Group A *Streptococcus*
- Predominantly small vessel vasculitis, characterized by IgA deposition and leukocytoclastic vasculitis

- Clinical features
  - Cutaneous purpura (100% of patients) with palpable lesions 2-10 mm in diameter, usually concentrated on lower extremities
  - Arthritis (75%) usually affecting knees and ankles, associated with painful oedema
  - GI involvement (50-75%), including abdominal pain and intussusception
  - Renal involvement (40-50%)
    - Most commonly microscopic hematuria
    - Proteinuria accompanies hematuria in 25%
    - Nephrotic syndrome in 5%
    - Renal abnormalities may not manifest initially, thus must regularly monitor blood pressure and urinalysis x 6 mos after acute illness
  - Orchitis (10-20% of males) associated with pain and swelling

- No distinctive or diagnostic laboratory abnormalities
  - May have elevated WBC, platelets and/or ESR; coagulation profile must be normal and thrombocytopenia should be absent
  - Serum IgA increased in 50% of patients

- Treatment
  - Largely supportive
  - NSAIDS for joint pain
  - Prednisone in select patients
    - May decrease the severity and duration of GI symptoms
    - Unclear impact on risk of persistent renal disease (controversial)
    - No definite benefit for prevention of HSP recurrence
    - May be helpful for bullous lesions

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

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

References:

1. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener's granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010; 69(5):798-806.
2. Trnka P. Henoch-Schönlein purpura in children. *J Paediatr Child Health* 2013; 49(12):995-1003.
3. Hahn D, et al. Interventions for preventing and treating kidney disease in Henoch-Schönlein Pupura (HSP). *Cochrane Database of Systematic Reviews* 2015; 8:CD005128.
4. Weiss PK, et al. Corticosteroids may improve clinical outcomes during hospitalization for Henoch-Schönlein purpura. *Pediatrics* 2010; 126(4):674-81.

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

- No 2008 EULAR/PRINTO/PRES classification criteria – very rare in children

- Granulomatous small vessel vasculitis characterized by:
  - Preceding history of "difficult to control" chronic asthma
  - Paranasal sinus abnormalities
  - Peripheral eosinophilia (≥10%) + eosinophilic infiltration on biopsy
  - Non-fixed pulmonary infiltrates
  - Peripheral neuropathy

- Additional clinical features
  - Cardiovascular (50%): Myocardial ischemia, pericarditis, cardiac failure
  - Ischemic abdominal pain
  - Cutaneous nodules

- Diagnosis
  - Biopsy (lung, skin) showing eosinophilic infiltrates and granulomas
  - Peripheral eosinophilia and increased IgE levels
  - ANCA, usually anti-MPO, present in less than 50% patients

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

References;

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

5J. Behçet Disease

1990 International Study Group for Behçet Disease Criteria for Diagnosis

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

Plus ≥ 2 of the following criteria:

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

2014 International Criteria for Behçet Disease

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

Simple classification: Add points from above and score ≥4 consistent with Behçet disease

- Systemic vasculitis with characteristic oral and genital ulcers, vasculopathy and uveitis
- Among the systemic vasculitides, Behçet disease is remarkable for its ability to involve blood vessels of all sizes - small, medium, and large - on both the arterial and venous sides of the circulation
- More common in certain ethnic groups along the "Silk Route" (Turks, Greeks)
- Uncommon in children

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

- Diagnosis
  - Currently based on clinical criteria
  - HLA B51 may be helpful

- Treatment
  - No controlled studies have been performed on children
  - Corticosteroids, colchicine, thalidomide, and anti-TNF agents (e.g. Infliximab) have been shown to be helpful
  - May treat isolated oral and/or genital ulcers with topical therapy, including analgesics and/or steroids

References:

1. Koné-Paut I. Behçet's disease in children, an overview. *Pediatr Rheumatol Online J* 2016; 14(1):10.
2. Ozen S, Eroglu FK. Pediatric-onset Behçet disease. *Curr Opin Rheumatol* 2013; 25(5):636-42.
3. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's Disease. *Lancet* 1990; 335: 1078-80.
4. International Team for the Revision of the International Criteria for Behçet's Disease, *JEADV* 2014; 28:338-457
5. Hatemi G, *et al*. EULAR recommendations for the management of Behçet disease. *Ann Rheum Dis* 2008; 67: 1656-1662.

SECTION 6 – INFLAMMATORY BRAIN DISEASES

6A. Introduction to Inflammatory Brain Diseases

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

Types of inflammatory brain diseases in children:

Vasculitis	Primary Angiitis of the Central Nervous System in childhood (cPACNS) • Angiography-positive cPACNS: progressive and non-progressive • Angiography-negative cPACNS Secondary CNS vasculitis
Non-vasocentric inflammatory disorders	Demyelinating disorders • Multiple sclerosis, acute demyelinating encephalomyelitis, optic neuritis and transverse myelitis Antibody mediated inflammatory brain disease: • Anti-NMDA receptor encephalitis, other autoimmune encephalitis, neuromyelitis optica, Systemic inflammatory diseases with CNS involvement • Systemic lupus erythematosus, Beçhet disease, celiac disease, sarcoidosis, acute rheumatic fever, Hashimoto encephalitis Rasmussen encephalitis Neurosarcoidosis Febrile infection-related epilepsy syndrome (FIRES)

6B. Childhood Primary Angiitis of the Central Nervous System (cPACNS)

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

- 2 clinically and radiologically distinct types of cPACNS

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

   - Clinical features: headache, acute hemiparesis, hemisensory deficits, and/or fine motor deficits
   - Inflammatory markers: often normal
   - CSF: often normal
   - MRI: unilateral focal areas of acute ischemia in a vascular distribution
   - Evidence of vasculitis on angiography (conventional angiography or MRA)
   - Brain biopsy not required

- Further divided into progressive and non-progressive subtypes
- Non-progressive cPACNS
  - Defined by absence of progression on imaging 3 months after initial angiography (i.e. monophasic disease)
  - More common than progressive cPACNS
- Progressive cPACNS
  - Defined by progression on neuroimaging 3 months after initial angiography
  - Presents with both focal and diffuse neurologic deficits
  - Multifocal T2 lesions on MRI, proximal and distal stenosis on angiography

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

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

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

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

References:

1. Gowdie P, et al. Primary and secondary CNS vasculitis. *J Child Neurol*. 2012; 27(11):1448-59.
2. Twilt M, Benseler SM. The spectrum of CNS Vasculitis in children and adults. *Nature Reviews Rheumatol* 2011: 8(2):97-107.
3. Cellucci T, Benseler SM. Diagnosing central nervous system vasculitis in children. *Curr Opin Pediatr* 2010; 22:731-8.

6C. Secondary Central Nervous System Vasculitis

- Occurs in context of an underlying systemic illness
- Can occur in context of infections, as well as other systemic inflammatory and autoimmune diseases

Causes of secondary CNS vasculitis:

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

References:

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

6D. Autoimmune encephalitis

- Inflammation of the brain occurs as a result of antibodies directed against neuronal proteins
- Antibody targets have been increasingly identified in children over past decade and include the NMDA receptor, aquaporin 4, Dopamine-2 receptor, GABA(A) receptor, GABA(B) receptor, GAD, AMPA receptor, and m-GluR5 receptor
- Better prognosis if antibody target is extracellular or synaptic protein
- Clinical features include memory deficits, behaviour changes, psychiatric symptoms, altered mental state, seizures, and focal neurological deficits
- Investigations
  - MRI may be normal or abnormal (findings often depend on antibody)
  - Serum testing may show inflammatory changes
  - CSF often shows increased white blood cell counts
  - EEG is often abnormal with seizures, epileptiform discharges and/or slowing
  - Psychoeducational testing often shows cognitive dysfunction, including impaired memory and slow cognitive processing speeds
- Diagnosis confirmed by identification of anti-neuronal antibodies in CSF or serum
- Treatment typically involves corticosteroids, IVIG and other immunosuppressants

Anti N-methyl-D-aspartate (NMDA) receptor encephalitis

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

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

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

- Outcome
  - 80% of patients have full recovery
  - Continued improvement may be seen up to 2 years after onset of symptoms

Neuromyelitis Optica (NMO)

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

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

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

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

- Outcome
  - Frequent relapsing course with accumulation of neurological deficits

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SECTION 7 – IDIOPATHIC INFLAMMATORY MYOPATHIES

7A. Juvenile Dermatomyositis (JDM)

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

Bohan and Peter Criteria for Diagnostic of Juvenile Dermatomyositis

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

- Recently, MRI has become an important diagnostic tool to look for muscle inflammation and to direct a site for biopsy (if needed)

- Clinical features
  - Proximal muscle weakness (which is present in 95% of patients) may be described on history as difficulty getting up from sitting or lying, difficulty climbing stairs, and frequent falls. Children may demonstrate a Gower 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%), heliotrope rash (66-100%), malar rash (42-73%) and photosensitive rashes. These may be confused with psoriasis, especially given the location of Gottron papules on extensor surfaces. In severe cases, there may be skin ulceration.
  - Capillary vasculopathy can be seen using capillaroscopy to look at changes in the nail fold capillaries (91%) such as tortuosity, dilatation, and dropout.
  - Other organ systems may also be involved:
    - Arthritis (23-58%)
    - GI tract symptoms (22-37%), including dysphagia, GI ulceration, perforation
    - Lungs (interstitial lung disease)
    - Heart (cardiomyopathy) – very rare
  - Constitutional features, such as fever and fatigue, are common.
  - 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 frequently recommended in this patient group

- Investigations
  - Positive ANA is common (up to 70% of patients) but not specific
  - Myositis-specific antibodies (MSA) are identified in up to 2/3 of children with JDM, but are not routinely available in all laboratories

MSA	Frequency	Associated Clinical Characteristics
Anti-p155/p140	60%	• rash (Gottron papules, malar rash, "shawl-sign" rash) • photosensitivity • low CK levels • chronic illness course
Anti-MJ	20%	• muscles cramps • dysphonia • high rate of hospitalization • monocyclic disease course
Anti-synthetase	5-10%	• interstitial lung disease • "mechanic's hands" • arthralgia • older age at diganosis
Anti-Mi2	5%	• Hispanic ethnicity • rash (Gottron papules, heliotrope rash, malar rash) • high CK • low mortality
Anti-SRP **In patients with polymyositis	25%	• black race • severe onset • distal weakness • Raynaud phenomenon • cardiac involvement • high CK levels • chronic disease course • wheelchair use

  - Myositis-associated antibodies
    - Anti-p155 and anti-p140 found in 30% of JDM patients
    - Other myositis-associated antibodies are more common in overlap syndromes

- 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 can include infection, osteoporosis, growth delay, cataracts and glaucoma, type 2 diabetes, and hypertension

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

- Treatment
  - Supportive: adequate nutrition, physiotherapy, sunscreen for photosensitive rash
  - Medications:
    - Induction therapy using Corticosteroids starting from 1-2 mg/kg/day with slow taper and Methotrexate 15 mg/m^{2}SC
    - Cyclophosphamide may be used for interstitial lung disease and vasculitis
    - IVIG, Cyclosporine, Mycophenolate mofetil or Rituximab if resistant or refractory
    - Topical therapies may also be considered for resistant skin disease

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

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2. Batthish M, Feldman BF. Juvenile dermatomyositis. *Curr Rheumatol Rep* 2011; 13(3):216–24.
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7B. 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:

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2. Rider LG, et al. Developments in the classification and treatment of the juvenile idiopathic inflammatory myopathies. *Rheum Dis Clin North Am* 2013; 39(4):10.
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7C. 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
- 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

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SECTION 8 – SYSTEMIC SCLEROSIS & RELATED SYNDROMES

8A. Classification of Scleroderma and Scleroderma-like Disorders

Morphea/ Localized scleroderma (See Section 6B)	Circumscribed morphea Linear scleroderma Generalized morphea Pansclerotic morphea Mixed morphea
Systemic sclerosis (See Section 6C)	Diffuse* Limited† 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 Premature aging syndromes

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

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

8B. Localized Scleroderma or Morphea

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

- **Circumscribed morphea**
  - Includes superficial lesions previously known as "plaque" morphea
  - May involve superficial and deep dermis as well as subcutaneous tissues
  - Early lesions are firm, ivory-coloured oval lesions surrounded by reddish-lilac coloured ring suggesting active inflammation
  - Later, there is atrophy, hyper-(rarely hypo-) pigmentation and softening of lesions

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

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

- **Pansclerotic morphea**
  - Least common subtype, but most disabling
  - Circumferential changes (often affecting a limb) that extend into tissues below dermis including muscle, tendon and bone
  - Frequently spares the fingers and toes

- **Mixed morphea**
  - Morphea of ≥ 2 subtypes in an individual patient

- Diagnosis
  - Clinical, although skin biopsy may be performed (usually to exclude other disorders)
  - MRI may be useful to determine extent of deep lesions

- Treatment
  - Topical: emollients, Corticosteroids, Calcipotriene (vitamin D), Imiquimod 5%, Tacrolimus
  - Systemic: Corticosteroids, Methotrexate, Mycophenolate mofetil, Cyclosporine
  - Other: Psoralen with Ultraviolet A radiation (PUVA) therapy, UV light
  - Supportive: physiotherapy, psychosocial support
  - Surgery for facial lesions, tendo-achilles lengthening

References

1. Zulian F. Systemic sclerosis and localized scleroderma in childhood. *Rheum Dis Clin North Am* 2008; 34(1):239-55.
2. Torok KS. Pediatric scleroderma: systemic and localized forms. *Ped Clin North Am* 2012; 59:381-406.

8C. Systemic Sclerosis (SSc)

- Rare autoimmune disease in children, characterized by symmetrical sclerodermatous changes and visceral involvement
- Mean age of onset ~ 8 years and majority of patients are female (80%)
- 90% of pediatric patients who develop SSc have diffuse subtype and 10% have limited disease (also known as CREST syndrome – calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia)

2007 EULAR/PRINTO/PRES Provisional Classification Criteria for Juvenile SSc

Major criterion (mandatory): Proximal skin sclerosis/induration of the skin

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-topoisomerase1))

Common clinical features of SSc:

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

Renal	Major cause of morbidity prior to development of ACE inhibitors Renal vasculopathy leads to renal hypertension (may be life-threatening) Proteinuria (may precede hypertension) Glomerular disease is unusual
Neurologic	Rare (e.g. trigeminal neuropathy, carpal tunnel syndrome)

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

- Treatment
  - Primarily supportive care
    - Avoid cold, stress, caffeine (to prevent Raynaud phenomenon)
    - Eat small meals, avoid foods that exacerbate gastric acidity, remain upright after eating and elevate head of bed (for dysmotility and GERD)
    - Physiotherapy and occupational therapy
  - Symptomatic treatment
    - GERD: Proton pump inhibitors (e.g. Omeprazole)
    - Raynaud phenomenon: peripheral vasodilators (e.g. Nifedipine)
    - Hypertension, renal disease: ACE Inhibitors (e.g. Enalapril)
    - Pulmonary hypertension: endothelin-1 receptor antagonists (e.g. Bosentan), prostacyclin analogs (Epoprostenol)
  - Systemic therapy
    - Methotrexate for active skin disease
    - Cyclophosphamide, Mycophnolate mofetil and Corticosteroids for alveolitis and interstitial lung disease
    - Other immunomodulatory agents (e.g. Anti-thymocyte globulin) have unclear efficacy in treatment of SSc
    - Autologous stem cell transplantation has been successful in progressive, resistant disease

- Prognosis and outcome
  - Prognosis depends on degree of organ dysfunction, which either later stabilizes or progresses to significant morbidity and mortality
  - Survival much better in children (5 year survival >90%) compared to adults

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8D. Mixed Connective Tissue Disease (MCTD)

- Autoimmune disorder characterized by several clinical and laboratory features:
  - High titre anti-U1 RNP antibodies
  - Swollen hands
  - Raynaud phenomenon
  - Arthritis
  - Myositis
  - Skin rashes (may include malar rash, Gottron-like papules, sclerosis)

- Children may also develop over time GI manifestations (similar to SSc), interstitial lung and renal diseases
- Multiple different diagnostic criteria for MCTD exist (e.g. Sharp, Alarcon-Segovia, Kasukawa, Kahn), but no single set of criteria is validated in children
- Investigations should be directed to assess for multi-organ involvement
- Treatment depends on severity of clinical manifestations and organ involvement

Reference

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8E. Raynaud Phenomenon

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

- Raynaud phenomenon may be primary or secondary
  - *Primary*
    - No underlying etiology, but often positive family history
    - No peripheral ulcerations
  - *Secondary*
    - Due to underlying autoimmune disease (scleroderma, overlap syndromes, MCTD, SLE, JDM), mechanical obstruction (thoracic outlet syndrome, cervical rib), hyperviscosity (polycythemia), cryoglobulinemia, drugs/toxins, or vibration-induced phenomenon

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

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

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

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1. Nigrovic PA, et al. Raynaud's phenomenon in children: a retrospective review of 123 patients. *Pediatrics* 2003; 111(4):715-721.
2. Falcini F, et al. Anti-nuclear antibodies as predictor of outcome in a multi-center cohort of Italian children and adolescents with Raynaud's phenomenon. *Clin Rheumatol* 2015; 34(1):167-9.
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8F. Sjögren Syndrome

- Multisystem autoimmune disease characterized by decreased secretion of lacrimal and salivary glands leading to dry eyes (keratoconjunctivitis sicca) and xerostomia (dry mouth)
- May present as isolated parotid swelling or parotitis
- Diagnosis requires 2 of the following:
  - Positive ANA>1:320 *and* positive RF or positive anti-Ro and/or anti-La
  - Keratoconjunctivitis sicca
  - Presence of focal lymphocytic sialadenitis in labial salivary gland biopsy

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

- Investigations
  - Ocular: Schirmer's test (tear production ≤ 5 mm in 5 minutes is abnormal), tear break-up time, Rose Bengal staining of devitalized areas
  - Salivary glands: scintigraphy, biopsy

  - Blood work: complete blood count and differential, inflammatory markers, immunoglobulin levels, serology (ANA, anti-Ro, anti-La, specific autoantibodies, RF)

- Treatment
  - Supportive (artificial tears for dry eyes; increase fluid intake, chewing gum for dry mouth)
  - Pilocarpine or Cevimuline may be used to stimulate saliva production in severe disease

- 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

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SECTION 9 – PERIODIC FEVER SYNDROMES & OTHER INHERITED AUTOINFLAMMATORY DISEASES

9A. Periodic Fever/Autoinflammatory Syndromes

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

Characteristic Features of the Periodic Fever Syndromes

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

AD: autosomal dominant, AR: autosomal recessive

- Other autoinflammatory syndromes include Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome and Deficiency of the Interleukin-1 Receptor Antagonist (DIRA)
- New autoinflammatory diseases continue to be described

Familial Mediterranean Fever (FMF)

- Most common hereditary autoinflammatory disease
- Autosomal recessive inheritance; linked to genetic mutation in *MEFV* gene encoding pyrin
- Ethnic predilection among Sephardi and Ashkenazi Jewish, Arab, Armenian, Italian, and Turkish populations with carrier rates as high as 1:3 to 1:5
- Usually presents in childhood with 60% of patients presenting prior to 10 years of age
- Clinical features
  - Fever episodes last for 1-3 days and occur without true periodicity
  - Clinical hallmark is serositis (peritonitis, pleuritis, synovitis)
  - Skin: Erysipelas-like rash on shins and dorsum of feet
  - MSK: Monoarthritis, myalgia
- Morbidity is associated with amyloidosis, especially renal amyloidosis
- Treatment
  - Colchicine is highly effective therapy for 85% of patients with FMF
  - Anti-IL-1 therapy with Anakinra, Canakinumab or Rilonacept is effective in Colchicine-resistant FMF

TNF-Receptor Associated Periodic Syndrome (TRAPS)

- Originally known as Familial Hibernian Fever
- Autosomal dominant inheritance
- TRAPS is linked to genetic mutation in *TNFRSF1A* gene that encodes TNF receptor
- Age of onset ranges from early childhood to several decades
- Clinical features
  - Distinguishing feature is relatively long duration of most attacks, which can last 3-4 weeks and occur at irregular intervals
  - Skin: Migrating erythematous, maculopapular rash that spreads from trunk to extremities
  - MSK: Severe migratory myalgias associated with rash, arthralgias
  - Ocular: Conjunctivitis, periorbital edema
  - GI: Severe abdominal pain
- Treatment
  - Standard therapy is unproven
  - Corticosteroids provide symptomatic relief but do not diminish frequency
  - Anti-TNF agents (e.g. Etanercept) thought to be promising, but results of studies disappointing
  - Some patients will respond to anti-IL-1 therapy

Mevalonate kinase deficiency- Hyperimmunoglobulinemia D Syndrome (HIDS)

- Rare recurrent fever syndrome
- Caused by genetic mutations in mevalonate kinase (*MVK*) gene
- 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 and diarrhea
- Other common features include tender cervical lymphadenopathy, oral ulcers, arthralgias, and large joint symmetric arthritis
- Elevated inflammatory markers and WBC
- Often 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-TNF and anti-IL-1) may be more effective

Cryopyrin Associated Periodic Syndrome (CAPS)

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

1. **Familial Cold Autoinflammatory Syndrome (FCAS)**
   - Children develop fever, chills and generalized, non-pruritic urticarial skin lesions within 30 minutes to 6 hours of exposure to cold
   - Symptoms persist up to 24 hours
   - Associated symptoms during attacks include conjunctivitis and arthralgias
   - Amyloidosis extremely rare

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

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

- Treatment
  - Anti-IL-1 therapy with Anakinra, Canakinumab, or Rilonacept are highly effective treatment for CAPS
  - Early treatment may reduce risk of amyloidosis and improve functional outcome

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

- Most common recurrent fever syndrome in children in North America
- No known genetic association or inheritance pattern
- Typically starts in early childhood before 5 years and is self-limited (resolves within 5 years)
- Clinical features
  - Episodes of high fever that occur with regular periodicity every 4-6 weeks
  - Fever episodes generally last up to 5 days
  - Characteristic findings of small non-scarring aphthous ulcers, non-exudative pharyngitis, and cervical adenitis
  - May be associated nausea, vomiting, abdominal pain and headache
  - Throat cultures are consistently negative
- Treatment
  - No consensus regarding treatment
  - Single dose of prednisone at onset of symptoms and, if necessary, the following day can abort the attack; however, interval between fever attacks may shorten
  - Other options include cimetidine and tonsillectomy +/- adenoidectomy

References:

1. Federici S, Gattorno M. A practical approach to the diagnosis of autoinflammatory diseases in childhood. *Best Pract Res Clin Rheumatol.* 2014; 28(2):263-76.
2. Goldsmith DP. Periodic fever syndromes. *Pediatr Rev* 2009; 30(5):e34-41.
3. Hashkes PJ, Toker O. Autoinflammatory syndromes. *Pediatr Clin North Am* 2012; 59(2):447-70.

9B. Other Inherited Autoinflammatory Diseases

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

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

- Rare autosomal dominant autoinflammatory syndrome
- Clinical features
  - Recurrent episodes of sterile, erosive arthritis in early childhood

  - As patients progress to puberty, skin involvement may predominate
  - Characterized by cystic acne, recurrent and often debilitating aggressive ulcerative skin lesions of the lower extremities indistinguishable from pyoderma gangrenosum
- Treatment
  - Arthritis may respond to corticosteroids, but adverse effects often limit their use
  - Reports of successful treatment with Anakinra, Etanercept, and Infliximab

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 5: Systemic Vasculitis)

- Newly recognized recessively inherited disorder with presentation very early in life
- Clinical features
  - Recurrent fevers, fatigue, arthralgia
  - Livedoid skin rash, cutaneous vasculitis
  - Vascular involvement (may include recurrent lacunar strokes, cerebral haemorrhage, polyarteritis nodosa)
  - Also possible hypertension, hepatosplenomegaly
- Treatment
  - Consider DMARD or Anti-TNF therapy; bone marrow transplantation has been described

Diseases linked to the proteasome and/or interferon-γ (IFN-γ)

- Three previously described independent syndromes have been linked to abnormalities in IFN-γ pathway
  - JMP (joint contractures, muscle atrophy and panniculitis-induced lipodystrophy) syndrome
  - CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) syndrome
  - NNS (Nakajo-Nishimura syndrome)
- Clinical features
  - Recurrent fevers

  - Violaceous skin rashes, progressive lipodystrophy
  - Arthralgia and arthritis with varying degrees of joint contractures
- Treatment
  - High dose corticosteroids (but symptoms often rebound with tapering)
  - Variable response to anti-TNF, anti-IL-1, and anti-IL-6 agents

References:

1. Federici S, Gattorno M. A practical approach to the diagnosis of autoinflammatory diseases in childhood. *Best Pract Res Clin Rheumatol.* 2014; 28(2):263-76.
2. Hashkes PJ, Toker O. Autoinflammatory syndromes. *Pediatr Clin North Am* 2012; 59(2):447-70.

9C. Role of Genetic Testing

- Genetic testing may be used to confirm a diagnosis when the clinical pattern fits with one of the autoinflammatory diseases
- A genetic diagnosis should be pursued in a logical manner recognizing the cost and limitations of testing, although panels of genetic mutations associated with these conditions are now more accessible and cost-effective
- A simple interactive tool is available online (http://www.printo.it/periodicfever/) to guide ordering of genetic tests for autoinflammatory diseases

References:

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

9D. Chronic Non-Bacterial Osteomyelitis (CNO)

- If multiple sites of involvement, may be called chronic recurrent multifocal osteomyelitis (CRMO)
- Some cases (20-30%) are unifocal at diagnosis, whereas others (20-30%) may be multifocal without recurrence
- A non-infectious, autoinflammatory disease involving bone that may be associated with other organ involvement (e.g. skin, gastrointestinal tract)
- Presents with acute or insidious onset of bone pain; some patients also have localized swelling, fever, malaise
- Clinical and radiographic findings initially mimic septic osteomyelitis; however, no abscess formation is noted, cultures are negative, and there is a poor response to antibiotic therapy
- Must consider bone malignancy, infection, and histiocytosis in work-up as CNO is a diagnosis of exclusion
- There are no validated diagnostic criterial for CNO/CRMO, but a clinical score may aid in differentiating non-bacterial osteitis from other bone lesions

2007 Proposed major and minor diagnostic criteria for nonbacterial osteitis (Jansson)

Major criteria

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

Minor criteria

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

* Diagnosis confirmed by 2 major criteria *or* 1 major plus 3 minor criteria

- Pathophysiology poorly understood, probably neutrophil mediated
- CNO is associated with inflammatory disorders of skin (e.g. palmoplantar pustulosis, psoriasis, generalized pustulosis, severe acne, pyoderma gangrenosum), and disorders of the gastrointestinal tract (e.g. inflammatory bowel disease), as well as 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
- CNO affects females > males and is more common in children and adolescents
- Clinical course characterized by periods of exacerbation with symptom-free intervals
- Typical sites of involvement include clavicles, tibia, femur, metaphyses of tubular bones

- Imaging
  - X-Rays:
    - Osteolytic bone lesions localized in the metaphyses close to the growth plate
    - Sclerosis and periosteal reaction
  - MRI (whole body, if available): sensitive to assess extent and activity of lesions, as well as asymptomatic lesions
  - Bone scan: may be helpful to assess the extent of lesions

- Treatment
  - Most lesions resolve without significant sequelae and spontaneous remission can occur; however severe pain, recurrences, and functional limitations may necessitate therapy
  - First-line therapy: NSAIDs provide symptomatic relief in up to 80% of patients
  - Second-line agents include Cordicosteroids, Bisphosphonates (e.g Pamidronate), Sulfasalazine, Methotrexate, anti-TNF agent (e.g Infliximab), and IL-1 inhibitors

References:

1. Twilt M, Laxer RM. Clinical care of children with sterile bone inflammation. *Curr Opin Rheumatol* 2012; 23(5):424-31.

2. Catalano-Pons C, et al. Clinical outcome in children with chronic recurrent multifocal osteomyelitis. *Rheumatol* (Oxford) 2008; 47(9):1397-9.

9E. Relapsing Polychondritis

- A rare immune-mediated condition associated with inflammation in cartilage and other tissues (particularly ears, nose, eyes, joints, respiratory tract, and heart valves)
- Children with relapsing polychondritis have similar clinical features to adults, but are more likely to have a 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) mandatory

1979 Modified McAdam's Criteria for Relapsing Polychondritis

(1) ≥ 3 of the following criteria:

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

(2) ≥1 of the above clinical criteria plus positive histologic confirmation

(3) ≥2 separate anatomic locations of chondritis plus response to steroids and/or dapsone

- Diagnosis requires any of the above 3 criteria

- Treatment
  - In adults, largely empiric and based on severity of disease
  - Options include NSAIDs, corticosteroids, methotrexate, dapsone, azathioprine

References:

1. Belot A, et al. Pediatric-onset relapsing polychondritis: case series and systematic review. *J Pediatr* 2010;156(3):484-9.

SECTION 10 – INFECTION & INFECTION-RELATED CONDITIONS

10A. Bone and Joint Infections

Osteomyelitis

- Intraosseous infection with bacteria or rarely, fungi
- Classified as acute, subacute, or chronic
  - Acute osteomyelitis is of recent onset and short duration
    - Most often hematogenous in origin but may result from trauma such as a compound fracture or puncture wound
    - Can be metaphyseal, epiphyseal, or diaphyseal in location
  - Subacute osteomyelitis is of longer duration and is usually caused by less virulent organisms
  - Chronic osteomyelitis results from ineffective treatment of acute osteomyelitis and is characterized by necrosis and sequestration of bone
- Source may be (1) hematogenous (2) local invasion from contiguous source (3) direct invasion of bone
- Usually blood-borne to metaphysis, slow blood flow allows organisms to pass through fenestrations in vessel wall, migrate through haversian canal to sub-periosteal space
- Unique features:
  - Neonates may present with pseudoparalysis or sepsis; fever is common; organisms frequently cross the physis and cause growth arrest
  - Patients with hemoglobinopathy frequently have *Salmonella* and other gram-negative organisms
- Key symptoms:
  - Fever, severe bone pain, and tenderness with or without local swelling should suggest the possibility of acute osteomyelitis
- Bones involved:
  - Femur, tibia, humerus, fibula, calcaneus, pelvis
- Organisms:
  - *Staphylococcus* most common
  - Group A *Streptococcus*, MRSA, atypical Gram negative bacteria and *Salmonella*

- Investigations
  - Blood work: Elevated WBC, ESR, CRP are non-specific
  - Blood cultures (sensitivity 60%), bone cultures (sensitivity 80%)
  - Imaging:
    - X-rays important for exclusion of other diagnoses
    - X-ray signs include soft-tissue swelling, soft tissue edema, subperiosteal changes and bone destruction (diagnostic findings may not be clear until days 10 to 21)
    - Bone scan has positive predictive value of 83% (MRI 85%) and allows detection of other sites

- Treatment
  - For the treatment of uncomplicated osteomyelitis, in which fever and symptoms resolve rapidly, 2 to 4 days of intravenous antibiotics can be followed by high dose oral antibiotics, for a total antibiotic course of 3 weeks.

Septic Arthritis

- Intra-articular infection with bacteria or rarely, fungi
- Medical emergency (surgical emergency if hip or shoulder involved)
- Key symptoms:
  - Usually accompanied by systemic signs of illness (e.g., fever, vomiting, headache)
  - May be a component of a more generalized infection that may include meningitis, cellulitis, osteomyelitis, or pharyngitis
  - Joint pain is usually severe, and the infected joint and periarticular tissues are swollen, hot, and sometimes erythematous
- Joints involved:
  - Joints of lower extremity are most commonly the sites of infection
  - Knees, hips, ankles, and elbows account for 90% of infected joints in children
- Organisms:
  - *Staphylococcus aureus* and non–Group A β *Streptococcus* are most common overall
  - *Streptococcus pneumoniae* is common in children younger than 2 years
  - *Neisseria gonorrheae* in sexually active adolescents
  - *Salmonella* is commonly associated with sickle cell disease
  - *Mycobacterium tuberculosis* is an unusual cause of septic monarthritis in childhood
  - *Kingella kingae* is emerging as an important pathogen in children with septic arthritis and may also account for a significant portion of culture negative cases

- Investigations
  - Need to aspirate joint prior to antibiotics
  - Characteristics of synovial fluid:
    - Cloudy, very high WBC count (50,000-300,000, > 75% neutrophils)
    - Gram stain positive
  - Elevated WBC with neutrophilia, CRP and ESR are non-specific
  - Synovial fluid culture (sensitivity 80%), blood culture (sensitivity 10%)
    - Cultures require special handling if suspect *Neisseria* or *Mycobacterium tuberculosis*
    - *Kingella kingae* may require cultures for 7 days to isolate the organism
  - Imaging
    - Plain radiographs are not diagnostic, but may be helpful in excluding other disorders, and may show an underlying osteomyelitis as the etiology of the septic arthritis
    - X-rays may demonstrate only increased soft tissue and capsular swelling
    - 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

- Treatment
  - For the treatment of uncomplicated septic arthritis, in which fever and symptoms resolve rapidly, 2 to 4 days of intravenous antibiotics can be followed by high dose oral antibiotics, for a total antibiotic course of 2 weeks
  - Often surgical debridement and joint irrigation performed by orthopedic surgery
  - Choice of antibiotics depends on presence of predisposing factors, age of child and suspected organism
  - NSAIDs can be used to control fever and to contribute to pain relief

References:
1. Paakkonen M, Peltola H. Bone and Joint Infections. *Ped Clinic North Am* 2013; 60(2);425-436.
2. Castellazzi L, et al. Update on the management of pediatric acute osteomyelitis and septic arthritis. *Int J Mol Sci* 2016; 17(6):855-63.
3. Montgomery NI, Rosenfeld S. Pediatric osteoarticular infection update*. J Pediatr Orthop 2015;* 35(1):74-81.

10B. Reactive Arthritis

- A form of non-septic arthritis developing after an extra-articular infection
- Arthritogenic bacteria:
  - GI: *Salmonella, Shigella, Yersinia, Campylobacter*
  - GU: *Chlamydia, Ureaplasma*

- Clinical manifestations
  - Several stages involved:
    1. Clinical infection precedes appearance of arthritis and/or enthesitis by 1 to 4 weeks
    2. Active period of weeks to months
    3. Sustained remission or recurrent episodes which may evolve to ERA, especially in patients that are positive for HLA B27
  - Acute arthritis (marked pain, sometimes erythema over affected joint) and/or enthesitis
  - May see tenosynovitis, bursitis, dactylitis
  - Patients may continue to have fever, weight loss, fatigue and muscle weakness
  - Painless, shallow mucosal ulcers are common
  - Urethritis and cervicitis are rare
  - Conjuctivitis occurs in about two thirds of children at onset
  - Skin lesions include erythema nodosum, circinate balanitis and keratoderma blennorrhagicum

- Investigations
  - Mild decrease in hemoglobin, mild leukocytosis with neutrophilia
  - Elevated inflammatory markers (platelets, immunoglobulins, ESR and CRP)
  - Autoantibodies (RF and ANA) are usually absent, but reactive arthritis most frequently occurs in HLA-B27 positive individuals
  - Synovial fluid is sterile
  - Cultures (blood, urine, stool) obtained at the time of infection may be positive

- Treatment:
  - NSAIDs
  - No clear evidence that antibiotics during inflammatory phase alter course of disease
  - Rarely, Corticosteroids (oral or intra-articular) may be required
  - Sulfasalazine is recommended in the management of resistant arthritis and enthesitis

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

10C. Acute Rheumatic Fever (ARF)

- The arthritis in ARF has characteristics that help in its differentiation 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

Modified Jones Criteria for diagnosis of initial attack of ARF

MAJOR Manifestations*	MINOR Manifestations*	Supporting evidence of antecedent GAS infection*
Polyarthritis Carditis Sydenham's chorea Erythema marginatum Subcutaneous nodules	Clinical: o Fever o Arthralgia Laboratory: o Elevated ESR, CRP o Prolonged PR interval	Elevated or rising streptococcal antibody titers Positive throat culture

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

- Treatment
  - 10 days oral antibiotics (usually Penicillin)
  - ASA 100 mg/kg/day divided QID PO for 3–5 days, then 75 mg/kg/day divided QID PO for 4 weeks (or may consider Naproxen instead)
  - Prednisone may be used for carditis/cardiomegaly and heart failure +/- Digoxin
  - Carbamazepine, Phenobarbital, Haloperidol, or Chlorpromazine for chorea
  - Prophylaxis for recurrence:
    - Without carditis: Up to age 21 or 5 years post initial attack, whichever is later
    - With carditis, but without residual heart disease: Up to age 21 or 10 years post initial attack, whichever is later
    - With carditis and residual heart disease: Up to age 40 or 10 years post initial attack, whichever is later

References:

1. Dajani AS, et al. Guidelines for the diagnosis of rheumatic fever: Jones criteria, Updated 1992. *Circulation* 1993; 87:302-7.
2. Webb RH, et al. Acute Rheumatic Fever. *BMJ 2015* Jul 14; 351;h3443.
3. Gerber MA, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. *Circulation* 2009; 119:1541-51.

10D. Post-Streptococcal Reactive Arthritis (PSRA)

- Characteristics that help distinguish PSRA from ARF include:
  - Non-migratory arthritis
  - Typically asymmetric oligoarthritis of lower extremities with axial involvement in 25%
  - Shorter latency in PSRA (<10 days) compared to ARF (14-21 days)

  - Protracted course
  - Less dramatic response to ASA/NSAIDs than ARF
  - Carditis develops in 5% of children with PSRA (compared to 50% with ARF)

- Treatment
  - 10 days oral antibiotics (usually Penicillin)
  - ASA or NSAID
  - Antibiotic prophylaxis has been recommended by some, but this issue is controversial. Prophylaxis can be given for up to 1 year after the onset of symptoms.

Reference:

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

10E. Lyme Disease

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

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

*Rare in childhood

- Erythema migrans usually begins as a round, erythematous macule or papule that rapidly expands, often with central clearing, to a diameter of at least 5 cm and resolves within four weeks if untreated
- Arthritis is typically monoarthritis, but may sometimes be polyarthritis

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

- Treatment
  - Varies according to disease manifestations
  - Erythema migrans only:
    - Amoxicillin or Doxycycline (only if >10 years of age) PO x 14-21 days
  - Early Lyme disease (except isolated rash) or Late Lyme disease:
    - Ceftriaxone or Cefotaxime IV x 2-4 weeks, or
    - Amoxicillin or Doxycycline (only if >10 years of age) PO x 4 weeks

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

References:

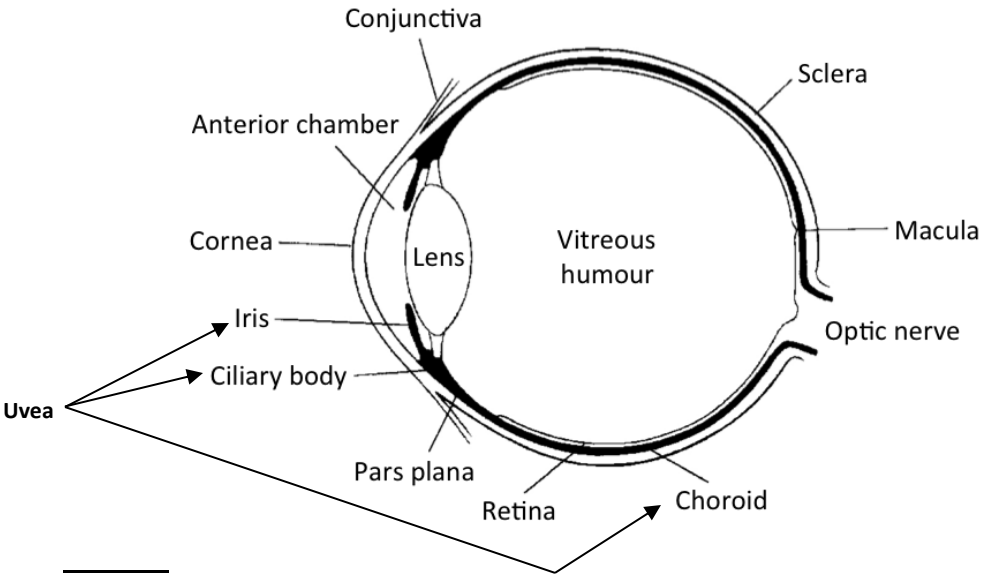
1. Shapiro ED. Lyme disease. *New Engl J Med* 2014; 370(18):1724-31.
2. Sood SK. Lyme disease in children. *Infect Dis Clin North Am* 2015 Jun: 29(2);281-94.

SECTION 11 – UVEITIS

11A. Uveitis

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

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



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

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

11B. Systemic Inflammatory Diseases Associated with Uveitis

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

11C. Infectious Causes of Uveitis

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

References:

1. Sauberan DP. Pediatric uveitis. *Int Ophthalmol Clin* 2010; 50(4):73-85.
2. Heilingenhaus A, et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. *Rheumatol Int* 2012; 32(5):1121-33.
3. Sen ES, et al. Uveitis associated with juvenile idiopathic arthritis. *Nat Rev Rheumatol* 2015; 11(6):338-48.

SECTION 12 – PAIN SYNDROMES

12A. Chronic Pain Syndromes

- Primary pain syndromes may have a greater impact on patients' and families' quality of life than inflammatory disease
- Many children with chronic musculoskeletal (MSK) pain do not have an identified cause
- Potential role of psychosocial stress in development of chronic pain syndromes

Growing Pains

- Onset usually between 4 and 10 years of age
- Typical history is deep aching cramping pain in bilateral thighs or calves, usually at night and intermittently waking the patient from sleep
- Improve with gentle massage, heat and/or analgesia
- Symptoms disappear by morning
- Normal physical examination
- Investigations not necessary for diagnosis

Fibromyalgia (aka Generalized Amplified Musculoskeletal Pain)

- Chronic generalized pain syndrome
- May be triggered by change in physical activity due to injury or chronic illness
- Treatment strategies for chronic pain in children and adolescents that are supported by research evidence include:
    - Education about chronic pain
    - Progressively increasing aerobic physical activity over time to a target of 60 minutes daily
    - Improving sleep hygiene, including consistent bed and waking times, and eliminating long naps during the day
    - Learning coping strategies for chronic pain
    - Counselling, cognitive behaviour therapy (CBT) and/or other psychotherapy to manage anxiety, low mood and other consequences and contributors to pain
- Medications less effective in childhood fibromyalgia
- Better outcomes in children compared to adults

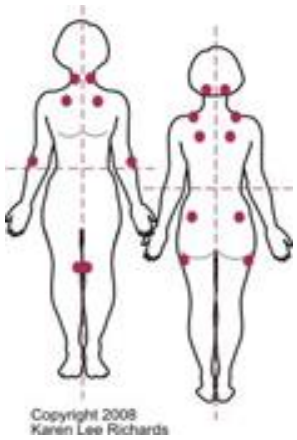
Yunus and Masi Diagnostic Criteria for Fibromyalgia in Children
Major criteria • Generalized musculoskeletal pain in at least 3 areas lasting more than 3 months • Absence of underlying condition or cause • Normal test results • At least 5 out of 18 typical tender points*

Minor criteria

- Fatigue
- Poor sleep
- Headaches
- Chronic anxiety or tension
- Irritable bowel syndrome
- Pain affected by weather
- Subjective soft tissue swelling
- Pain affected by anxiety and stress
- Paresthesia
- Pain affected by activities

Diagnosis requires all 4 major criteria plus 3 of 10 minor criteria, or may have first 3 major criteria plus 4 tender points and 5 minor criteria

*Please see table below for specific tender points.

Fibromyalgia Tender Points *		
	**Occiput**	Suboccipital muscle insertions
	Low Cervical	Anterior aspects of C5-C7
	Trapezius	Midpoint of the upper border
	Supraspinatous	Medial border of scapula
	Second Rib	Second costochondral junctions
	Lateral Epicondyle	2 cm distal to epicondyles
	Gluteal	Upper outer quadrants of buttocks
	Greater Trochanter	Posterior to trochanteric prominence
	Knee	Medial fat pad

N.B. Nine areas of body x 2 sides = 18 tender points. Apply approximate pressure of 4 kg, or until fingernail blanches.

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

- Chronic pain often involving peripheral extremity (lower extremities more common in kids)
- Initiating injury or cause of immobilization can lead to CRPS
- Continuing pain, allodynia, and/or hyperalgesia in which pain is disproportionate to inciting event
- Associated swelling, changes in skin blood flow leading to discolouration, and/or abnormal sweating in the region of pain
- Diagnosis of exclusion, therefore no other condition should account for the degree of pain and dysfunction
- Treatment involves intense physiotherapy with manipulation of extremity with goal to restore function; another potential treatment option is desensitization

Diagnostic Criteria for Complex Regional Pain Syndrome

Regional pain *and 2 symptoms from each of the following types of symptoms*

Neuropathic symptoms

- Burning
- Dysesthesia
- Paresthesia
- Allodynia
- Cold hyperalgesia

Autonomic dysfunction

- Cyanosis
- Mottling
- Hyperhidrosis
- Coolness (by at least 3 degrees Celsius)
- Edema

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

References:

1. Anthony KK, Schanberg LE. Pediatric pain syndromes and management of pain in children and adolescents with rheumatic disease. *Pediatr Clin North Am* 2005; 52(2):611-39.
2. Weiser P. Approach to the patient with noninflammatory musculoskeletal pain. *Pediatr Clin North Am* 2012; 59(2):471-92.
3. Sherry DD, et al. The treatment of juvenile fibromyalgia with an intensive physical and psychosocial program. *J Pediatr* 2015; 167(3):731-7.
4. Kashikar-Zuck S, et al. Longitudinal evaluation of patient-reported outcomes measurement information systems measures in pediatric chronic pain. *Pain* 2016; 157(2):339-47.

12B. <u>Hypermobile joint syndrome</u>

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

Beighton Criteria for Hypermobile Joint Syndrome *

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

* Diagnosis requires ≥ 6/9 points

- Additional features consistent with hypermobility include:
  - Flat feet
  - Able to sit in "W" position
  - Able to touch elbows behind back
  - Able to put heel behind head

- Treatment
  - Education
  - Activity modification (avoid exacerbating activity)
  - Physiotherapy to strengthen muscles around affected joints
  - Orthotics

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

References:

1. Murray KJ. Hypermobility disorders in children and adolescents. *Best Pract Res Clin Rheumatol* 2006; 20(2):329-51.
2. Pacey V, et al. Joint hypermobility syndrome: A review for clinicians. *J Paediatr Child Health* 2015; 51(4):373-80.

SECTION 13: PEDIATRIC RHEUMATOLOGY EMERGENCIES

13A. Introduction to Pediatric Rheumatologic Emergencies

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

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

- 85% of neonates with CHB have transplacentally acquired maternal antibodies to Ro/SSA or La/SSB
- 1 year mortality up to 54% if untreated
- Rheumatology consultation may be requested urgently for complete heart block with signs of active inflammation (such as pericardial effusion or carditis), congestive heart failure or antenatal fetal hydrops

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

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

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

References:

1. Izmirly PM, et al. Neonatal Lupus: advances in understanding pathogenesis and identifying treatments of cardiac disease. *Curr Opin Rheumatol* 2012: 24(5): 466-7
2. Jaeggi ET, et al. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block: A single institution's experience of 30 years. *J Am Coll Cardiol* 2002; 39(1):130-7.

13C. Macrophage Activation Syndrome

- Macrophage activation syndrome (MAS) is a multisystem inflammatory emergency
- Consider in the broad differential of an unexplained persistently febrile child, especially in the presence of pancytopenia – a high index of suspicion is required

- MAS may complicate a number of autoimmune diseases (e.g. systemic arthritis/JIA, SLE, Kawasaki disease most commonly)
- May occur at any time during the disease course (especially following a change in therapy) or may be part of the initial presentation
- Classified as a form of secondary hemophagocytic lymphohistiocytosis (HLH)
    - Primary HLH is an inherited multi-system inflammatory disease caused by congenital abnormalities affecting natural killer cell, macrophage and T cell function
    - Similar abnormalities have recently been identified in patients with systemic JIA
    - Secondary HLH in children can also be triggered by infection, especially EBV

- Diagnostic clinical and laboratory features of MAS
    - Fever (continuous/persistent)
    - Splenomegaly
    - Cytopenias (anemia, thrombocytopenia, neutropenia) or, in systemic JIA, may see decrease in previously elevated cell counts
    - Elevated triglycerides
    - Decreased fibrinogen
    - Elevated ferritin
    - Hemophagocytosis on bone marrow, lymph node, liver or spleen biopsy

- Other important clinical and laboratory features
    - Bleeding, bruising, petechiae, due to DIC-like picture with prolonged INR/PTT, elevated D-dimers
    - Hepatic dysfunction with hepatomegaly, elevated bilirubin and liver enzymes
    - Elevated LDH
    - Persistently raised CRP, but decreasing ESR (due to consumption of fibrinogen)
    - CNS dysfunction, including headache, confusion, seizures, and coma
    - Respiratory distress including ARDS, pulmonary dysfunction
    - Lymphadenopathy
    - Changes in blood pressure and heart rate
    - MAS may be life-threatening and can result in death

- 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

- Urgent investigations prior to starting treatment (in addition to the diagnostic investigations listed above)
    - Cultures of blood, urine and throat should be ordered to rule out an underlying bacterial infection since it will take time to receive results
    - Infectious serology and PCR (e.g. EBV, CMV, Parvovirus B19, Herpes viruses) may be helpful to diagnose an underlying viral infection in primary or secondary HLH and must be ordered before the child receives IVIG
    - If the child does not have an established diagnosis and a systemic rheumatologic condition is suspected, autoantibodies (e.g. ANA. ENA panel, rheumatoid factor, ANCA) must be ordered before the child receives IVIG

  - Soluble CD163, IL-2 receptor, NK cell function and lymphocyte typing may be helpful to identify underlying immune dysfunction and/or monitor inflammation, but they should be ordered prior to starting treatment
  - If needed, a direct antiglobulin test should be ordered prior to the child being given any IVIG

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

References:

1. Sen ES, et al. Macrophage activation syndrome. *Indian J Pediatr* 2016; 83(3):248-53.
2. Cron RQ, et al. Clinical features and correct diagnosis of macrophage activation syndrome. *Exp Rev Clin Immunol* 2015; 11(9):1043-53.
3. Minoia F, et al. Clinical features, treatment and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. *Arthritis Rheumatol* 2014; 66(11):3160-9.
4. Wang W, et al. Macrophage activation syndrome in Kawasaki disease: more common than we thought? *Semin Arthritis Rheum* 2015; 44(4):405-10.
5. Parodi A, et al. Macrophage activation syndrome in juvenile systemic lupus erythematosus: a multinational multicenter study of thirty-eight patients. *Arthritis Rheum* 2009; 60(11):3388-99.

13D. Pulmonary Renal Syndrome

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

Causes of pulmonary renal syndrome

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

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

- Diagnostic Investigations
  - Tests to assess presence of pulmonary hemorrhage or vasculitis
    - Complete blood count showing anemia (often microcytic) or decreasing hemoglobin, elevated reticulocyte count
    - Chest X-ray may show diffuse alveolar infiltrates
    - Chest CT may show patchy ground glass opacities or nodules
    - Pulmonary function tests may show an increase in DLCO consistent with intra-alveolar bleeding
    - Bronchoalveolar lavage demonstrates presence of red blood cells and hemosiderin-laden macrophages
  - Tests to assess presence of renal involvement
    - Urinalysis demonstrating proteinuria, hematuria and/or cellular casts
    - Increases in creatinine and/or urea
  - Tests to determine underlying cause of pulmonary renal syndrome
    - Autoantibodies:
      - Positive ANCA in GPA, MPA, E-GPS (see Section 5)
      - ANA, anti-dsDNA, antibodies to extractable nuclear antigens, and antiphospholipid antibodies may be positive in SLE
      - Anti-glomerular basement membrane (GBM) antibodies seen in Goodpasture syndrome
    - Renal biopsy:
      - ANCA-associated vasculitis: pauci-immune necrotizing crescentic glomerulonephritis
      - SLE: glomerular immune deposits with histologic changes of lupus nephritis

        - Goodpasture syndrome: IgG deposition along glomerular basement membrane with crescentric changes
        - HSP: deposition of IgA-containing immune complexes in glomeruli with mesangial cell proliferation, glomerular sclerosis and crescent formation
    - Skin biopsy:
        - HSP: leukocytoclastic vasculitis with IgA deposits
        - SLE: immunofluorescence demonstrates immunoglobulins and complement at the dermal-epidermal junction; may see damage of keratinocytes, follicular plugging, basal layer vacuolation, perivascular infiltrates and dermal mucin deposition
- Treatment
    - Early recognition and management of pulmonary renal syndrome is critical
    - Initial therapy is identical for any underlying cause of pulmonary renal syndrome and should be started promptly
    - Supportive therapy may include oxygen, intubation, ventilation, plasmapheresis and/or dialysis
    - Initial immunomodulatory therapy with pulse IV methylprednisolone followed by high dose prednisone (1-2 mg/kg/day)
    - Cyclophosphamide or Rituximab may be used depending on the underlying disease
    - If concurrent infection cannot be excluded, appropriate anti-microbial coverage should be considered

References:

1. Gallagher H, et al. Pulmonary renal syndrome: a 4 year, single-center experience. *Am J Kidney Dis* 2002; 39(1);42-7.
2. West SC, et al. Pulmonary Renal Syndrome: a life threatening but treatable condition. *Postgrad Med J* 2013: 89(1051):274-83.
3. Cabral DA, et al. Classification, presentation, and initial treatment of Wegener's granulomatosis in childhood. *Arthritis Rheum* 2009; 60(11):3413-24.

13E. Catastrophic Antiphospholipid Syndrome (APS)

- A severe variant of the classic APS, characterized by:
    - Clinical evidence of multiple organ involvement developing over short period of time
    - Histopathological evidence of multiple small vessel occlusions, although the patient may not have obvious thrombosis
    - Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and anti-cardiolipin), usually in high titre
- Multisystem microvascular thrombosis with a secondary systemic inflammatory response due to tissue damage
- 2/3 of patients have an underlying trigger (infection, surgery, trauma, malignancy, and flares of SLE) and children are more likely to have infectious trigger compared to adults
- Catastrophic APS more likely to be first manifestation of APS in children compared to adults

- Clinical Presentation
    - May be mistaken for overwhelming sepsis
    - Cardiopulmonary manifestations are the most frequent at presentation
        - May look like acute respiratory distress syndrome

        - Pulmonary embolus or alveolar hemorrhage may occur
    - CNS features are next most common
        - Cerebral infarction, seizures, and encephalopathy
        - Cerebral venous sinus thrombosis
    - Renal and abdominal involvement is common
        - Renal failure, proteinuria, significant abdominal pain
        - 80% of patients experience an intra-abdominal thrombotic event over the course of an episode
    - Clinical signs of systemic inflammation and lab features of DIC

Diagnostic Criteria for Catastrophic Antiphospholipid syndrome

Definite diagnosis requires all of the following criteria:

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

Probable diagnosis if:

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

- Diagnostic Investigations
    - Tests to confirm presence of thrombotic disorder
        - Look for organ infarction (kidney, spleen, or bowel) on imaging or organ failure (cardiac or renal) with markers of DIC, coagulation dysfunction, and/or peripheral destruction of blood elements
        - May require tissue sample
    - Tests to confirm presence of antiphospholipid antibodies
        - Lupus anticoagulant, anti-cardiolipin, anti-beta 2 microglobulin
    - Investigate underlying triggers for the episode
        - Cultures and infectious serology to assess for infection (respiratory, skin, urinary tract)
        - Bone marrow biopsy or imaging may be needed to assess for an underlying malignancy
        - Investigations for a systemic inflammatory condition, such as SLE, may be indicated if the child does not have a previous diagnosis

- Treatment
    - Patients are often critically ill
    - ICU support should be available and anticipated
    - May need acute measures such as mechanical ventilation or dialysis
    - Empiric antibiotics until infection ruled out

- Targeting two main pathologic processes may reduce mortality from 50% to 30%
  - Thrombosis treated with parenteral and subsequently oral anticoagulation; may need vasodilators, fibrinolytics, and embolectomy
  - Secondary systemic inflammatory response treated with systemic corticosteroids, plasmapheresis and/or IVIG

References:

1. Berman H, et al. Pediatric catastrophic antiphospholipid syndrome: descriptive analysis of 45 patients from the "CAPS Registry". *Autoimmun Rev* 2014; 13(2):157-62.
2. Cervera R, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. *Ann Rheum Dis* 2015; 74(6):1011-8.
3. Asherson RA, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus* 2003; 12(7):530-4.

13F. Cardiac Tamponade

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

- Clinical Presentation
  - Typically presents with dyspnea, tachypnea and chest pain
  - May have distended neck veins, 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, such as systemic lupus erythematosus or systemic arthritis

- Diagnostic Investigations
  - ECG typically shows sinus tachycardia and may also show low voltage, pattern of pericarditis may be present
  - 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
  - Temporizing measures can be used such as IV fluids or sympathomimetics
  - More specific treatment depends on the underlying cause of pericarditis
  - Corticosteroids are the mainstay of acute treatment for life-threatening conditions, but other immunosuppressive agents may be added if there is insufficient improvement or if required to treat an underlying rheumatic disease

References:

1. Mok GC, Menahem S. Large pericardial effusions of inflammatory origin in childhood. *Cardiol Young* 2003; 13(2):131-6.

2. Sagrista-Sauleda J, et al. Diagnosis and management of pericardial effusion. *World J Cardiol* 2011; 3(5):135-43.
3. Maharaj SS, Chang SM. Cardiac tamponade as the initial presentation of systemic lupus erythematosus: a case report and review of the literature. *Pediatr Rheumatol Online J* 2015; 13:9.

13G. Kawasaki Disease Shock Syndrome

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

- Clinical Presentation
    - Hemodynamic instability with tachycardia, hypotension and poor peripheral perfusion
    - Typically associated with more severe manifestations of Kawasaki disease, although not necessarily longer duration of fever
    - May be associated with more gastrointestinal symptoms (e.g. vomiting), respiratory failure, encephalopathy, acute renal injury and multiple organ dysfunction
    - More likely to demonstrate IVIG resistance

- Diagnostic Investigations
    - Compared to children with Kawasaki disease who are hemodynamically stable, children with Kawasaki disease shock syndrome were more likely to have:
        - Higher CRP and ESR
        - Higher neutrophil counts with bands
        - Lower hemoglobin and platelet counts
        - Lower albumin levels
        - Consumptive coagulopathy with low platelet counts, increased D-dimers and prolonged PTT
    - ECG typically shows sinus tachycardia
    - Echocardiography:
        - Impaired left ventricular systolic function with a lower ejection fraction and mitral regurgitation
        - More likely to develop coronary artery abnormalities

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

References:

1. Kanegaye JY, et al. Recognition of a Kawasaki Shock Syndrome. *Pediatrics* 2009; 123(5):e783-9.
2. Chen PS, et al. Clinical manifestations of Kawasaki disease shock syndrome: A case-control study. *J Microbiol Immunol Infect* 2015; 48(1):43-50.
3. Gatterre P, et al. Kawasaki disease: an unexpected etiology of shock and multiple organ dysfunction syndrome. *Intensive Care Med* 2012; 38(5):872-8.

13H. Renal Crisis in Systemic Scleroderma (SSc)

- Renal impairment is a frequent symptom in SSc
- Severe renal crisis is an acute and life threatening event
- Incidence of 8-10% in limited SSc, 10-0% in diffuse SSc
- Usually develops within the first 5 years of onset of the disease
- Risk factors: rapidly progressing disease, high dose glucocorticoids, presence of anti-RNA polymerase abs

- Clinical Presentation
    - Reflects thrombic microangiopathy of kidney similar to thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
    - Acute renal failure without warning signs
    - Sudden onset of moderate to severe hypertension
    - May be accompanied by encephalopathy, left sided heart failure, or acute cerebrovascular event

- Diagnostic Investigations
    - Urine sediment studies show proteinuria and hematuria
    - Renal biopsy findings include proliferation and thickening of arcuate and interlobar arteriole intima, leading to narrowing or full obliteration of vessels
    - CXR may demonstrate pulmonary edema
    - Eye exam may identify retinal hemorrhages or exudates
    - MRI/CT head may show signs of stroke

- Treatment
    - Rapid (within 72 hr) control of blood pressure
        - Provides stabilization of renal function in 70% of patients
    - ACE inhibitors (captopril most widely studied)
    - Dialysis

References:

1. Denton CP, et al. Renal complications and scleroderma renal crisis. *Rheumatology (Oxford)* 2009; 48(Suppl 3):S32-5.
2. Mouthon L, et al. Scleroderma renal crisis. *J Rheumatol*. 2014; 41(6):1040-8.

13I. Acute Adrenal Crisis

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

- Clinical Presentation
    - May be variable
    - Many signs and symptoms are non-specific and can be mistaken for symptoms of an intercurrent illness or the underlying condition being treated
    - Signs and symptoms include:
        - Arthralgias, myalgias, generalized weakness
        - Headache
        - Abdominal pain, nausea, vomiting, diarrhea
        - Fever
        - Hypotension
        - Decreased level of consciousness, lethargy
        - Unexplained hypoglycemia
        - Hyponatremia
        - Seizures, coma

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

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

References:

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

SECTION 14 – MEDICATIONS

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

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

- **Adalimumab**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: recombinant mAb that binds to circulating and cell surface TNFα
  - Dose: 24 mg/m^2/dose if <15 kg; 20 mg if 15-30 kg; or 40 mg if >30 kg via SC injection every 2 weeks
  - Side effects: injection site reactions, headaches, infections, cytopenias, potential risk of future malignancy, demyelinating disease, new or worsening heart failure
  - Monitoring: CBC, differential, AST, ALT, albumin every 4-12 weeks

- **Anakinra**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: human recombinant form of IL-1 receptor antagonist (IL-1Ra)
  - Dose: 1-2 mg/kg/dose (max 100 mg) SC daily; in sJIA, may titrate up to 4 mg/kg/dose (max 200 mg) SC daily
  - Side effects: injection site reactions, infections, GI upset, potential risk of future malignancy
  - 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: 0.5-2.5 mg/kg/day (max 150 mg) PO daily
  - Side effects: GI upset, oral ulcers, rash, cytopenias, hepatotoxicity
  - Monitoring: CBC, differential and liver enzymes weekly until achieve stable dose then monthly; consider thiopurine methyltransferase (TPMT) genetic testing if abnormally low CBC (e.g., neutropenia) unresponsive to dose reduction

- **Belimumab**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: human IgG1 neutralizing monoclonal antibody against B-lymphocyte stimulating factor (also known as B-lymphocyte simulator [BLyS])
  - Dose: 10 mg/kg via IV over 1 hr at 2-week intervals for 3 doses then every 4 weeks
  - Side effects: infusion reactions, infections, potential risk of future malignancy
  - Monitoring: CBC (e.g., leukopenia) and liver enzymes with each infusion

- **Biologic agents**
  - See table below for class and mechanism of action
  - See individual drug listing for dosing and side effects

Biologic Class	Medication	Mechanism of Action
B cell depletion	Belimumab	• Human monoclonal antibody directed against BLyS • Inhibits BLyS-induced proliferation of B cells and decreases survival of autoreactive B cells
	Rituximab	• Chimeric mouse-human monoclonal antibody directed against CD20 on pre-B and mature B cells • Selectively depletes B cells
IL-1 inhibitors	Anakinra	• IL-1 receptor antagonist • Blocks IL-1 receptor to prevent pro-inflammatory signaling
	Canakinumab	• Human monoclonal antibody directed against IL-1β • Binds to IL-1β to prevent pro-inflammatory signaling
	Rilonacept	• Fully human dimeric fusion protein consisting of extracellular portion of IL-1 receptor and constant region of human immunoglobulin • Binds to IL-1 to prevent pro-inflammatory signaling
IL-6 inhibitor	Tocilizumab	• Humanized monoclonal antibody against IL-6 receptor • Blocks IL-6 mediated pro-inflammatory signaling
T cell co-stimulatory modulator	Abatacept	• Fusion protein consisting of extracellular portion of CTLA-4 and constant region of human immunoglobulin • Blocks co-stimulation and activation of T cells
TNF inhibitors	Adalimumab	• Human monoclonal antibody directed against circulating and membrane-bound TNFα • Binds to TNFα to block pro-inflammatory signaling • May result in cell lysis in presence of complement
	Certolizumab	• PEGylated Fab fragment of humanized monoclonal antibody directed against TNFα • Binds to TNFα to block pro-inflammatory signaling
	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
	Golimumab	• Human monoclonal antibody directed against TNFα • Binds to TNFα to block pro-inflammatory signaling
	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

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 biotherapeutic product similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product
  - Uncertain whether biosimilars will have identical effects to reference biologic product since even minor modifications may alter pharmacokinetic, immunogenetic, glycosylation, sialylation, stability, safety, and efficacy

- Rare events and long-term safety will be assessed in postmarketing surveillance studies

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

- **Colchicine**
  - Class: alkaloid; commonly used to treat familial Mediterranean fever and Behçet disease
  - Mechanism of action: binds to microtubules to prevent activation, proliferation and functioning of inflammatory cells
  - Dose: 0.3-1.8 mg/day; may divide into twice daily doses if side effects
  - Side effects: GI upset, 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, prednisolone (PO)
    - Methylprednisolone (IV)
    - Dexamethasone (PO or IV)
    - Triamcinolone hexacetonide (intra-articular)
  - Dose: depends on severity of inflammation
  - Side effects:
    - Early: increased appetite, GI upset, gastritis, mood and behaviour changes
    - Late: infections, Cushing syndrome (truncal obesity, moon facies, cutaneous striae), acne, growth suppression, osteoporosis, AVN, psychosis, hypertension, dyslipidemia, hyperglycemia, myopathy, cataracts, glaucoma
  - Monitoring: clinical (including blood pressure); consider monitoring bone health carefully if long-term corticosteroids are used

- **Cyclophosphamide**
  - Class: cytotoxic alkalating agent
  - Mechanism of action: alkylating agent preventing cell division and leading to B and T cell lymphopenia
  - Dose: 500-1000 mg/m^2/dose IV every 2 to 4 weeks up to 6 months
  - Side effects:
    - Short-term: GI upset, alopecia, cytopenias, opportunistic infections, hemorrhagic cystitis, SIADH, teratogenicity, gonadal dysfunction
    - Long-term: bladder fibrosis, bladder carcinoma, fertility issues, malignancy
  - 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: renal toxicity, hypertension, hepatotoxicity, GI upset, tremor, paresthesias, gingival hyperplasia
    - Monitoring: BP, renal function, urinalysis, CBC, differential, and liver enzymes monthly

- **Etanercept**
    - Class: biologic agent (see Biologic agents for summary table)
    - Mechanism of action: fully human dimeric fusion protein that binds to circulating TNFα
    - Dose: 0.4 mg/kg/dose (max 25 mg) twice weekly or 0.8 mg/kg/dose (max 50 mg) weekly via SC injection
    - Side effects: injection site reactions, headaches, infections, cytopenias, potential risk of future malignancy, demyelinating disease, new or worsening heart failure
    - Monitoring: CBC, differential, AST, ALT, albumin every 4-12 weeks

- **Hydroxychloroquine**
    - Class: disease-modifying antirheumatic drug (DMARD); antimalarial agent
    - Mechanism of action: interferes with antigen processing and antigen-antibody interactions, inhibits nucleic acid and protein synthesis
    - Dose: up to 6.5 mg/kg/day (max 400 mg) PO daily
    - Side effects: retinal toxicity, GI upset, headache, tinnitus, neuropathy, myopathy
    - Monitoring: eye examinations every 6 months to assess for retinal deposits

- **Infliximab**
    - Class: biologic agent (see Biologic agents for summary table)
    - Mechanism of action: monoclonal chimeric human-mouse antibody that binds to circulating and cell surface anti-TNFα
    - Dose: 3-10 mg/kg/dose on week 0, 2, 6 then every 4 to 8 weeks (may occasionally require higher doses)
    - Side effects: injection site reactions, headaches, infections, cytopenias, potential risk of future malignancy, demyelinating disease, new or worsening heart failure
    - Monitoring: CBC, differential, AST, ALT, albumin every 4-12 weeks
    - Special consideration: human anti-chimeric antibodies (HACAs) can develop and decrease efficacy and increase risk of infusion reactions; incidence is lower in patients receiving continuous (rather than intermittent) therapy and concomitant immunosuppressive therapy (e.g., methotrexate)

- **IVIG**
    - Class: biologic agent; plasma-derived protein
    - Mechanism of action: multiple anti-inflammatory mechanisms including inhibition of antibody-mediated cytotoxicity; attenuation of complement-mediated damage; modulation of cytokine production; and neutralization of superantigens
    - Dose: 2 g/kg/dose IV

  - Side effects: infusion reactions, haemolysis, anaphylaxis or allergic reactions, acute aseptic meningitis, acute renal failure
  - Special consideration: need to delay future immunizations by 11 months due to possible inefficacy of subsequent vaccines for this time period

- **Leflunomide**
  - Class: disease-modifying antirheumatic drug (DMARD)
  - Mechanism of action: inhibits enzyme involved in DNA synthesis and interferes with lymphocyte proliferation
  - Dose: 10-20 mg PO daily
  - Side effects: GI upset, allergic rash, hepatotoxicity, teratogenicity, potential risk of future malignancy
  - Monitoring: CBC, differential, liver enzymes every 4-6 weeks
  - Special consideration: need to discuss alcohol avoidance and birth control

- **Methotrexate**
  - Class: disease-modifying antirheumatic drug (DMARD)
  - Mechanism of action: inhibitor of folate pathway and DNA synthesis
  - Dose: 10-15 mg/m^2/dose (max 25 mg) PO or SC weekly (note: often better response and fewer side effects with SC route)
  - Side effects: GI upset, oral ulcers, hepatotoxicity, bone marrow suppression, teratogenicity, potential risk of future malignancy
  - Monitoring: CBC, differential, liver enzymes every 4-6 weeks (consider reducing frequency to every 12 weeks after patients on stable dose for 6 months – highlighted in *Choosing Wisely: Pediatric Rheumatology Top 5 by American College of Rheumatology)*
  - Special considerations: need to discuss alcohol avoidance and birth control; prophylaxis against oral ulcers with folic acid 1 mg PO daily (6x/week) or 5 mg PO weekly

- **Mycophenolate mofetil**
  - Class: antimetabolic agent
  - Mechanism of action: inhibits enzyme in DNA synthesis leading to inhibition of B and T cell proliferation, suppresses antibody response
  - Dose: 800-1200 mg/m^2/day (max 3000 mg/day) PO divided twice daily
    - Typical starting dose is 250 mg daily
    - Use drug levels (MMF kinetics) to optimize dose
  - Side effects: GI upset, headaches, cytopenias, infections, teratogenicity, potential risk of future malignancy, progressive multifocal leukoencephalopathy (PML)
  - Monitoring: CBC and differential every 4-6 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: GI upset, gastritis, GI bleeding, renal toxicity, hepatotoxicity, ototoxicity
  - Monitoring: hemoglobin, renal function and liver enzymes with clinic visits

NSAID	Dose	Comments
Aspirin	High dose (anti-inflammatory): 50-100 mg/kg/day PO div QID Low dose (anti-platelet): 3-5 mg/kg/day PO OD	Used mostly in the setting of Kawasaki disease and acute rheumatic fever
Celecoxib	50 mg PO BID if 10-25 kg 100 mg PO BID if >25 kg	Selective COX-2 inhibitor; expensive
Ibuprofen	20-40 mg/kg/day PO div TID or QID	Commonly used in childhood JIA
Indomethacin	2-3 mg/kg/day (max 200 mg/day) PO div TID	Commonly used in ERA and sJIA
Naproxen	20 mg/kg/day (max 500 mg/dose) PO div BID	Frequently used in childhood JIA

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: 0.75 mg/kg/day if 2-3 yrs; or 1 mg/kg/day if >3 yrs (max 60 mg/day) monthly for 3 months (note: first dose to be given over 2 days)
  - Side effects: bone pain, fever, headaches, lethargy, fetal toxicity, unclear risk of osteonecrosis of the jaw
  - Monitoring: calcium and PTH prior to each infusion

- **Rilonacept**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: fully human dimeric fusion protein that blocks IL-1 by acting as a soluble decoy receptor; also known as "IL-1 Trap"
  - Dose: loading dose 4.4 mg/kg/dose (max 320 mg) then 2.2 mg/kg/dose SC weekly (max 160mg)
  - Side effects: injection reactions, infections, dyslipidemia, potential risk of future malignancy
  - Monitoring: serum lipid monitoring after 2-3 months; CBC and liver transaminases at one month, then every 3 months

- **Rituximab**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: chimeric mouse-human monoclonal antibody that binds to the B cell CD20 receptor (on pre-B and mature B cells but not on stem cells or plasma cells)
  - Dose: 375 mg/m^2 once weekly for 2-4 doses; or 750 mg/m^2 on days 1 and 15
  - 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

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

- **Tocilizumab**
  - Class: biologic agent (see Biologic agents for summary table)
  - Mechanism of action: humanized monoclonal antibody that binds both soluble and membrane-bound IL-6 receptor
  - Dose:
    - Systemic JIA: 12 mg/kg/dose if <30 kg; or 8 mg/kg/dose (max 800 mg) if ≥ 30 kg via IV *every 2 weeks*
    - Polyarticular JIA: 10 mg/kg/dose if <30 kg; or 8 mg/kg/dose (max 800 mg) if ≥ 30 kg via IV *every 4 weeks*
  - Side effects: infusion reactions, headaches, GI upset, gastritis, infections, hepatotoxicity, dyslipidemia, cytopenias, potential risk of future malignancy
  - Monitoring: AST, ALT, absolute neutrophil count at baseline, second infusion, then every 2-4 weeks; lipid panel 4-8 weeks after start of treatment then every 6 months

- **Tofacitinib**
  - Class: disease-modifying antirheumatic drug (DMARD); kinase inhibitor
  - Mechanism of action: interferes with Jak-stat system and subsequent production of selective interleukins and interferons
  - Dose: adult RA $\rightarrow$ 5 mg PO twice daily; or extended release 11 mg PO daily
  - Side effects: infections, anemia, thrombocytopenia, neutropenia, hypercholesterolemia, increased liver transaminases, GI perforation, potential risk of future malignancy

APPENDIX – HELPFUL RESOURCES IN PEDIATRIC RHEUMATOLOGY

Textbooks

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

Foster HE, Brogan P. *Paediatric Rheumatology.* 2012: Oxford University Press.

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

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

Firestein GS, Budd RC, Harris ED, McInnes IB, Ruddy S, Sergent JS. *Kelley and Firestein's Textbook of Rheumatology, 10th Edition.* 2016: Saunders Elsevier Publishing.

Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, Eds. *Rheumatology, Sixth Edition.* 2015: Mosby Elsevier Publishing.

Journals

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

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

Internet Resources for Images in Rheumatology

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

Rheumatlas website:
http://rheumatlas.org

IRHEUM by the European League against Rheumatism:
http://www.irheum.eu/

Clinical Cases and Images by the University of Chicago:
http://clinicalcases.org/2009/08/rheumatology-images-in-clinical.html

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

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