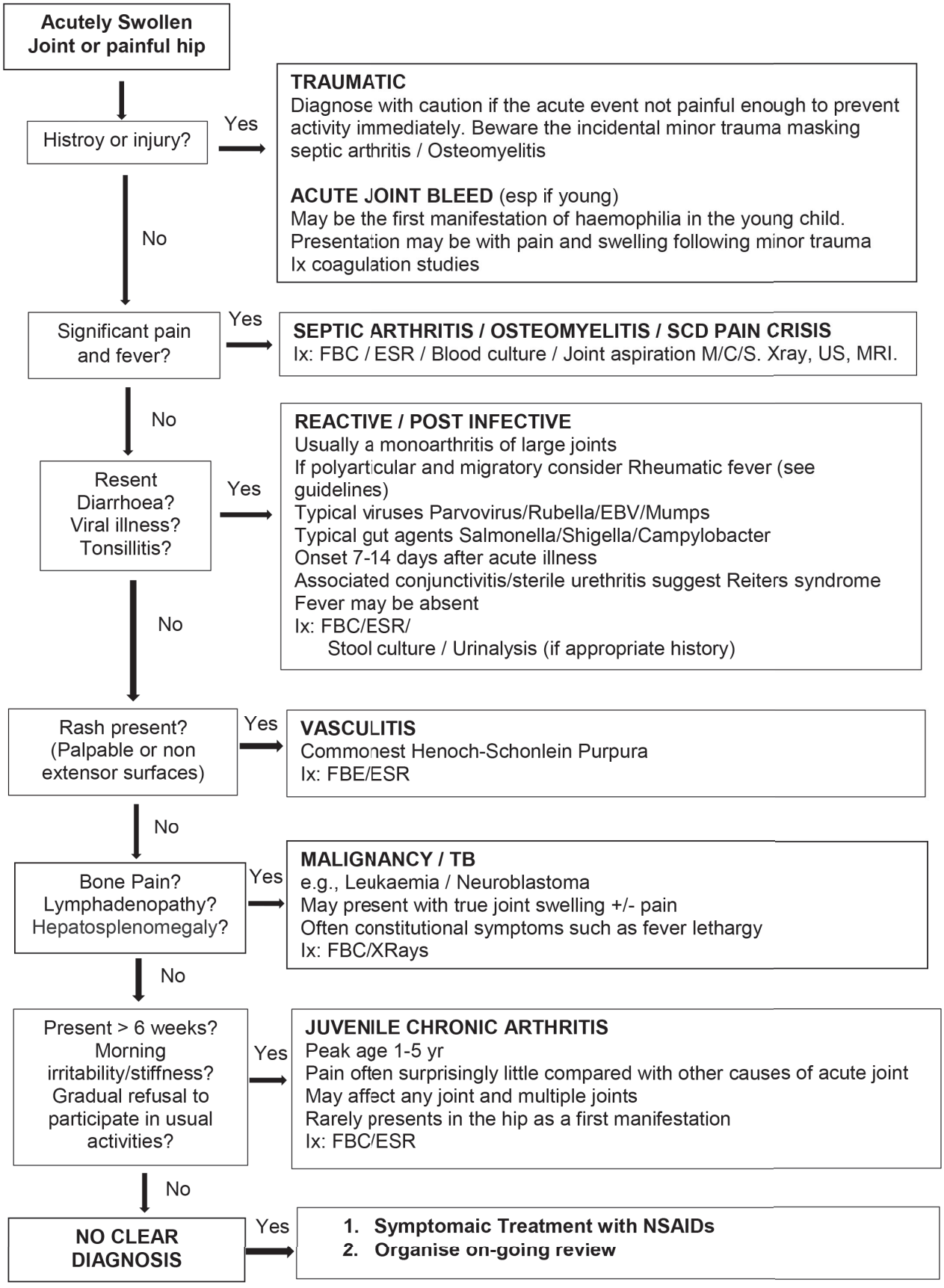
Chapter 13:

Rheumatolgy

Acronyms

ANA	Antinuclear Antibodies
CRP	C-Reactive Protein
CXR	Chest X-Ray
DCMO	Dilated Cardiomyopathy
DIC	Disseminated Intravascular Coagulopathy
DMARDs	Disease Modifying Antirheumatic Drugs
ECHO	Echocardiogram
ESR	Erythrocyte Sedimentation Rate
EULAR/ACR	European League Against Rheumatism/American College of Rheumatology
FB	Foreign Body
FBC	Full Blood Count
HSP	Henon-Schonlein Purpura
JDM	Juvenile Dermatomyositis
JIA	Juvenile Idiopathic Arthritis
KD	Kawasaki Disease
MAS	Macrophage Activation Syndrome
MCS	Microscopy, Culture and Sensitivity
MCP joints	Metacarpophalangeal Joints
MRI	Magnetic Resonance Imaging
NAI	Non Accidental Injury
NSAID	Non-Steroidal Anti-Inflammatory Drugs
Ortho	Orthopaedics
pGALS	Paediatric Gait Arms Legs and Spine
SCD	Sickle Cell Disease
SLE	Systemic Lupus Erythematosus
SO-JIA	Systemic Onset Juvenile Idiopathic Arthritis
US	Ultrasound
VDRL	Venereal Disease Research Laboratory Test

The Swollen Joint



Important points in history

- Length of history of swelling
- Any trauma or injury. Note: Beware the incidental minor trauma masking septic arthritis/ osteomyelitis
- Was the onset sudden or insidious
- Recent history of viral illness e.g. gastroenteritis, sore throat e.t.c
- History of migratory arthritis
- Fever
- Rash
- Maternal infection e.g. syphilis
- Any other joints involved or have been involved
- Decreased movement of the joint and pain
- Are symptoms worse in the morning or later in the day
- Past history of sickle cell disease, asplenia, or frequent malaria infections
- Previous admissions for same problem
- Family history of sickle cell disease, haemophilia or arthritis

Important points on examination

- Is the child 'toxic' e.g. looks unwell, listless
- Is the child in pain
- Is there fever
- Is the affected joint
  - Swollen (if so is there an effusion present?)
  - Warm?
  - Red?
  - Painful?
- Can the joint be moved by patient or observer?
- Any rashes or skin changes (including psoriasis, rheumatic nodules, or purpura)
- Are any other joints abnormal, and if so what is their distribution e.g. symmetrical/asymmetrical, large joint/small joint?
- Is there a cardiac murmur?
- Are there enlarged LNs or hepatosplenomegaly (consider leukaemia or systemic Juvenile Idiopathic Arthritis)

Relevant investigations

- Blood culture if febrile, FBC and diff
- X-ray of affected area (look for effusion, for bony changes or double periosteum in syphilis)
- Ultrasound, useful in hip involvement to demonstrate an effusion
- Inform ortho team if septic arthritis or osteomyelitis
- Consider MRI if uncertain diagnosis
- Maternal VDRL in infant

Indications for admission

- Unless obvious history of sprain or minor trauma admit for investigation and observation

Septic Arthritis

Definition

Intra-articular infection with bacteria or rarely, fungi

- Medical emergency (surgical emergency if hip or shoulder involved)
- Peak age 2 years, unwell febrile child & reduced range of movement of joint. Child may refuse to weight bear on the joint

Risk factors

- Trauma
- Young age
- Immune deficiency
- Poor wound care/treatment

Causes

- *Staphylococcus aureus* and non–Group A beta-haemolytic 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
- *Haemophilus influenzae* less likely due to immunizations

Prevention/promotion

- Early presentation to hospital
- Antibiotic treatment to be started early and should be a long course (only start after culture from blood and bone are done)
- Proper wound care

Signs and symptoms

- Systemic signs of illness (e.g. fever, vomiting, headache)
- May be a component of a more generalised infection that may include meningitis, cellulitis, osteomyelitis, or pharyngitis
- Joint pain is usually severe
- Infected joint and periarticular tissues are swollen, hot, and sometimes erythematous
- Joints of lower extremity are most common the sites of infection:
  Knees,
  Hips,
  Ankles, and
  Elbows

Investigations

- Joint aspirate prior to antibiotics/synovial fluid culture
  Characteristics of synovial fluid: Cloudy, very high White Blood Cell Count (WBC) of 50,000 -300,000, > 75% neutrophils and Gram stain positive
- FBC, elevated WBC with neutrophilia
- CRP and ESR
- Culture from subperiosteal space

- Blood culture
- Plain radiographs
- MRI/CT – MRI is 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

Management

Primary/secondary level
- Manage ABCDE
- Refer all cases to tertiary level

Tertiary level
- Analgesia – paracetamol, non-steroidal anti-inflammatory drugs (if available) and opiates may be required
- Rest the joint – sling for arm, bed rest for lower leg
- Intravenous antibiotics followed by high dose oral antibiotics (total antibiotic course of 2 weeks)
  - **NOTE:** Choice of antibiotics depends on presence of predisposing factors, age of child, suspected organism or positive culture and local resistance patterns
  - **Neonates: F**lucloxacillin & gentamicin IV until fever settles then oral treatment for 4 weeks depending on bacterial susceptibilities
  - **Older children:** Ceftriaxone 50mg/kg IV OD
    - Treat until fever is settled then oral ciprofloxacin for a maximum of 2 weeks if improving
- Surgical debridement, joint aspiration and injection of sterile fluid is done until joint aspirate is clear and is performed by orthopaedic surgery team

Complications
- Stiff immovable joint –is a late presentation of septic arthritis as articular surface may have been destroyed
- There may be a coexistent osteomyelitis in ~15% cases

Follow up
- Patients to be follow up in orthopedics and PEN-Plus clinic

Osteomyelitis

Definition
Intraosseous infection with bacteria or rarely, fungi. Classified as acute, subacute, or chronic.

Acute osteomyelitis:
- Is of recent onset and short duration. Most often haematogenous 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

Risk factors
- Young age
- Immunodeficiency
- Open fracture
- Sickle cell
- Untreated/under treated septic arthritis

Causes
- *Staphylococcus aureus*
- *Salmonella typhimurium*
- Salmonella spp (sickle cell disease)
- Group B streptococci (neonate)
- Coliforms (neonate - especially preterm)
- *Neisseria meningitidis*
- TB (note the following regarding TB):
  - Can cause osteomyelitis and septic arthritis
  - Signs are less marked than other bone infections, history more chronic
  - Signs of systemic TB are sometimes apparent
  - Spinal TB can cause paraplegia and deformity (Pott's disease)
  - Treatment is anti TB medications and surgery (discuss with orthopaedic surgeons)

Prevention/promotion
- Early presentation to hospital
- Antibiotic treatment to be started early and should be a long course (only start after culture from blood and bone are done)
- Proper wound care

Signs and symptoms
- Fever
- Severe bone pain and tenderness with or without local swelling should suggest the possibility of acute osteomyelitis

- Unique features:
  - Neonates may present with pseudoparalysis or sepsis. Fever is common, organisms frequently cross the physis and cause growth arrest
  - Patients with haemoglobinopathy frequently have salmonella and other gram-negative organisms

Investigations

- Elevated WBC, ESR, CRP are non-specific
- Blood cultures
- Bone cultures (sensitivity 80%)
- Imaging:
  - X-rays important for exclusion of other diagnoses (X-ray signs include soft-tissue swelling, soft tissue oedema, subperiosteal changes and bone destruction (diagnostic findings may not be clear until days 10 to 21)
  - Bone scan
  - MRI

Management

Primary/secondary level

- Manage ABCDE
- Refer all cases to tertiary level

Tertiary level

- Analgesia – paracetamol, non-steroidal anti-inflammatory drugs (if available) and opiates may be required
- Rest the joint – sling for arm, bed rest for lower leg
- Intravenous antibiotics followed by high dose oral antibiotics (total antibiotic course of 2 weeks)
  - **NOTE:** Choice of antibiotics depends on presence of predisposing factors, age of child, suspected organism or positive culture and local resistance patterns
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  - **Older children:** Ceftriaxone 50mg/kg IV OD
    - Treat until fever is settled then oral ciprofloxacin for a maximum of 4 weeks if improving
- Osteomyelitis abscess drainage required. Discuss with orthopaedic surgeons.
- Post surgery: Need physiotherapy and early mobilisation to prevent stiffness and to preserve function when pain free

<u>Treatment of Congenital Syphilis</u>

- 10 days IM/IV benzylpenicillin and treat both parents

Complications

- Chronic osteomyelitis. If acute osteomyelitis goes untreated pus escapes the intramedullary space to form a sequestrum (avascular cortical bone) by spreading proximally and distally This process lifts the periosteum and renders the cortex ischaemic. New bone is formed by the periosteum (involucrum). Management is difficult
- Consult orthopaedic surgeons and refer

Follow up

- All patient to be follow up in orthopaedic and PEN-Plus clinic

The Limping Child

Definition
Abnormal gait

Risk factors (Indications for urgent assessment of a limping child)
- The very young (under 3 years of age)
- The ill and febrile
- The non-weight bearing
- Children with painful restricted hip movements
- The child who is immunosuppressed - when septic arthritis, osteomyelitis, malignancy, is suspected, fractures
- When non-accidental injury, SUFE (Slipped Upper Femoral Epiphysis) and malignancy are suspected

Causes of Limp by age

	0-3 years	4-10 years	11-16 years
Most common	• Trauma (including toddler's fracture) • Injury/FB/splinter to sole of foot	• Trauma • Transientsynovitis • Perthes' disease	• Trauma • Osgood-Schlatter disease
Conditions requiring urgent intervention	• Osteomyelitis • Septic arthritis • Non accidental injury (NAI) • Malignancy (e.g. neuroblastoma) • Testicular torsion • Inguinal hernia	• Osteomyelitis • Septic arthritis • NAI • Malignant disease e.g. Acute Lymphoblastic Leukaemia (ALL) • Testicular torsion • Appendicitis • Inguinal hernia	• Osteomyelitis • Septic arthritis • Slipped upper femoral epiphysis (SUFE) • Malignancy (e.g. bone tumours) • Testicular torsion • Appendicitis • Inguinal hernia
Other important conditions to consider	• Developmental dysplasia of the hip • Juvenile Idiopathic arthritisIdiopathic Arthritis	• Juvenile Idiopathic Arthritis	• Juvenile Idiopathic Arthritis
	• Metabolic (e.g. rickets) • Haematological disease (e.g. sickle cell disease) • Reactive arthritis • HSP • Multisystem diseases (e.g. Juvenile Systemic Lupus Erythematosus, Juvenile Dermatomyositis)		

Differential diagnoses

- Septic arthritis: Unilateral swollen joint, pain and fever needs urgent orthopaedic consultation.
- Malignancy (e.g. bone tumours, leukaemia). Perform diagnostic work-up if suspected
- Acute Rheumatic fever
- HIV arthropathy
- TB
- Joint bleeds e.g. in haemophilia
- Other autoimmune conditions and vasculitides e.g. Henoch Schonlein Purpura (HSP), Systemic Lupus Erythematosus (SLE), dermatomyositis

Investigations

- Will depend on the suspected cause of the limp.
- Discuss management with seniors (either consultant paediatrician or rheumatologist if available) and the orthopaedic team
- In patients without red flag features who have symptoms for > 6 weeks and are presumed to have JIA
  - HIV test
  - Malignancy/TB work-up if suspected
  - FBC (often normal in oligoarticular JIA. In systemic onset, polyarticular JIA it may reveal normo/microcytic anaemia, leucocytosis and/or thrombocytosis)
  - ESR
  - CXR/ECHO if suspecting alternative diagnosis or pleuritis/pericarditis
  - X-rays may reveal deformities, erosions, joint space narrowing, but can be normal in early disease
  - Ultrasound of joints useful if expertise exists to show joint effusions

Examination

- Joints:
  - **LOOK** (swelling, deformity, colour changes),
  - **FEEL** (heat, tenderness),
  - **MOVE** (passive and active) every joint
  - Don't forget spine and temporomandibular joints

pGALS is a good screening tool (see musculoskeletal assessment: pGALS questions and examination [versusarthritis.org] for details)

- Systemic: look for lymphadenopathy, hepatosplenomegaly, pleural/pericardial effusions (can all be seen in SO -JIA), features of psoriasis, rashes

Alert Box

Red flags to look out for in case of infection, malignancy or non-accidental Injury

- Fever, malaise, reduced appetite, weight loss, night sweats
- Bone or joint pain with fever
- Refractory or unremitting pain, persistent night waking
- Unclear history and presentation with regards to pattern of physical findings plus previous history of neglect

General Joint Screening
pGALS (paediatric gait, arms, legs, spine) screen-validated for use in school aged children

Screening questions
- Do you have any pain or difficulty in moving your arms, legs, neck or back?
- When you get dressed, are you able to do this yourself without any help?

Then conduct a physical examination (if all is normal it makes musculoskeletal pathology very unlikely)
- Observe the child from the back front and side
- Observe the patient walking
- Walk on your heels
- Walk on your tip-toes
- Put your hands out in front of you
- Turn your hand over and make a fist
- Touch the tips of your fingers
- Squeeze MCP joints.
- Put your hands and wrists together
- Put your hands back to back
- 3 fingers vertically inside
- Reach up as far as you can
- Look at the ceiling
- Put your hands behind your neck
- Place your ear on your shoulder
- Open your mouth wide and place 3 fingers inside
- Feel for effusion at the knee
- Bring your ankle up to your bottom
- Passive movement of hip and knee including rotation of hip
- Observe curvature of spine from the side and behind. Bend forwards

Treatment
- Depends on the underlying cause

Referral
- Refer to secondary or tertiary level depending on cause and treatment needed

Follow up
- Follow up will depend on cause and treatment needed

Juvenile Dermatomyositis

Definition
It is a rare systemic, autoimmune myopathy and vasculopathy in childhood. The skin and skeletal muscles are primary areas of involvement

Causes/risk factors
- Possible link to genetic susceptibility

Prevention/promotion
- There is no primary prevention
- Secondary and tertiary prevention should focus on controlling underlying myositis (to be discussed under management) and control of complications of the disease (contractures and calcinosis) and treatment (long term steroid use or immunosuppressive agents- to avoid acquisition of opportunistic infections like TB)
- Ambulatory support, if not able to walk (physiotherapy)
- School support- provide a letter of support for the teacher to consider child physical limitations
- Once diagnosis is made and a care plan instituted by a specialist- establish a mechanism for follow up at the nearest facility
- Adherence counselling and therapeutic monitoring and support
- Patient and family support group

Signs and symptoms
Diagnostic criteria according to Bohan and Peter criteria, 1975:
- Presence of pathognomonic rash (Gottron papules, Heliotrope rash) plus 3 or 4 of the following features for a "definite diagnosis"
  - Symmetrical proximal muscle weakness (Gower sign positive)
  - Elevated serum levels of muscle enzymes (CK, AST, LDH, aldolase)
  - Electromyographic changes of chronic inflammatory myositis
  - Muscle biopsy histopathological changes of inflammatory myositis)
  - Nailfold capillary microscopy abnormalities
- Probable diagnosis: would require presence of typical rash plus 2 of the above features
- **Note:** Typical muscle findings on MRI and ultrasound scan (MRI has become more important diagnostic tool for muscle inflammation)
- Other signs and symptoms include:
  - Calcinosis cutis,
  - Arthritis,
  - Constitutional symptoms (fever, weight loss, fatigue)
- 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
- 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
- JDM can also present with cardiopulmonary (conduction defects, myocarditis, DCMO) and gastrointestinal involvement

- Muscle biopsy has limited role in JDM diagnosis (consult rheumatologist if considered)

Investigations
- Laboratory tests
  - Full Blood count
  - Urea and Electrolytes
  - Inflammatory markers (ESR, CRP)
  - Muscle enzymes (creatinine kinase, lactate dehydrogenase, aspartate aminotransferase and aldolase). These may be normal at times
  - Lupus profile (ANA, extractable nuclear antigens[ENA])
  - Myositis-specific antibody assays (e.g. Anti MJ/Anti MDA5, Anti NXP2, Anti TIF1)
  - Antinuclear antibodies – ANA
- Imaging studies
  - Nailfold capillary microscopy
  - Muscle ultrasound scan (may be normal)
  - MRI
  - Electromyography

Differential diagnosis
- Consider other myopathies:
  - Non-inflammatory myopathies like muscular dystrophies
  - Inflammatory myopathies like viral myositis, pyomyositis
  - Metabolic myopathies

Management
- Goal: treat myositis, prevent mortality prevent calcinosis and long term morbidity
- All patients should be managed at a tertiary facility level with the supervision of a specialist (rheumatologist/neurologist)

Primary/secondary level
Refer all cases suspected of JDM to tertially level

Tertiary level

<u>First line: (mild to moderate disease)</u>

Pharmacological
- Corticosteroids (dose, route and duration depend on disease characteristics)
  - Methylprednisolone pulse 10-30mg/kg/day for 3 days (given over 1-4 hours in 100mL of normal saline and to measure BP during administration at 30 minutes intervals)
  - Prednisolone 1-2mg/kg slow weaning dose over the next 18 months
- Methotraxate 15mg/m^2 subcutaneous preferably
- Calcium and vitamin D supplementation
- TB INH Prophylaxis and folic acid for those on methotrexate
- Hydroxychloroquine at 3-6mg/day

Non-Pharmacological:
- Photoprotective measures
- Physio and occupational therapy

Second line: refer to rheumatologist
Pharmacological
- IV immunoglobulins
- Ciclosporin
- Azathioprine

Third Line: refer to rheumatologist
Pharmacological
- Cyclophosphamide
- MMF (mycophenolate mofetil)
- Tacrolimus
- Rituximab
- Anti-TNFα agents

Referral should be urgent to paediatrician/paediatric rheumatologist
- If suspected to have cardiopulmonary or gastrointestinal manifestations
- All patients requiring DMARD
- Adverse reaction to NSAID
- Severe JDM or suspected JDM not responding to first line therapy

Follow up and treatment monitoring
- Muscle enzymes should return to normal
- Inflammatory markers should return to normal
- Increase muscle strength subjectively and objectively using the childhood myositis assessment scale
- Resolution of skin rash
- Improvement in capillary nail fold changes

Systemic Lupus Erythematosus (SLE)

Definition
Multi-system inflammatory disease characterised by autoantibody and immune-complex mediated inflammation of blood vessels and connective tissues. It can lead to a spectrum of disease ranging from mild to life-threatening illness

- Common organs/systems involved: Skin, joints, kidneys, blood cells and nervous system

Risk factors

- Childhood onset average age is 12 years
- Affects more females than males
- RACE more common in blacks and hispanics
- Sun exposure
- Viral infections
- Genetic predisposition

Causes

- Aetiology unknown

Prevention/promotion

- Primary prevention to focus on disease progression reduction strategies for those not fulfilling SLE diagnosis criteria: Reduced sun exposure, vitamin D and calcium supplementation, hydroxychloroquine and close monitoring of biomarkers
- Secondary and tertiary prevention to consider: physiotherapy for joint involvement, prevention of drug toxicities (steroids) and infections
- Patient education on medication adherence
- Improve access to care: Development of care plan at tertiary facility inclusive of ongoing care and nearest primary care (follow up primary care could include physiotherapy, BP monitoring, urine dipsticks)
- Patient and family support groups

Signs and symptoms

- Malar rash
- Photosensitive rash

- Ulcers/mucocutaneous involvement
- Kidneys: Proteinuria, urinary cellular casts, hypertension, renal failure
- Seizures
- Thrombocytopaenia
- Haemolytic anaemia
- Fever
- Lymphadenopathy
- Pruritis
- Hepatosplenomegaly
- 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
    - Hypertension
    - Decreased concentration and cognitive dysfunction
    - Stroke
    - Mood disorder
    - Headache
    - Pneumonitis
    - Pulmonary hemorrhage
    - Myocarditis
    - Libman-Sacks endocarditis

EULAR/ACR Criteria for Classification of SLE: Entry criteria:

ANA positive (titres ≥1:80)

Clinical domain	Points
Constitutional • Fever • Weight loss • Fatigue	2
Cutaneous • Non-scaring alopecia • Oral ulcers • Subcutaneous/discoid lupus • Acute cutaneous lupus (malar rash)	 2 2 4 6
Arthritis • Synovitis or tenderness in at least 2 joints	 6
Neurologic • Delirium • Psychosis • Seizure	 2 3 5
Serositis • Pleural or pericardial effusion • Acute Pericarditis	 5 6

Haematology • Leucopaenia • Thrombocytopaenia • Autoimmune haemolysis	 3 4 4
Renal • Proteinuria >0.5g/24hour • Class II or V lupus nephritis • Class III or IV lupus nephritis	 4 8 10
Immunologic – Antiphospholipid antibody • Anticardiolipin igG>40GPL • or Anti-β2GP1 IgG>40 units • or Lupus anticoagulant	 2
Complement protein • Low C3 or Low C4 • Low C3 and Low C4	 3 4
Highly specific antibodies • Anti-dsDNA antibody • Anti-Sm antibody	 6 6

Important points to note:
- Patients must have ≥ 10 points to be classified as SLE
- Items counted only if no other likely cause suspected
- Count the highest criterion in the domain
- Points from at least 1 clinical domain required for classification
- Rare complication: Macrophage Activation Syndrome (MAS)

Investigations

Laboratory tests:
- FBC with differentials
- Urea and electrolytes
- Urinalysis with microscopy
- Inflammatory markers (CRP, ESR)
- Complement levels
- Liver function tests
- Creatinine kinase assay
- Spot protein/spot creatinine ratio
- Autoantibodies (ENA, ANA, antiphospholipid antibodies)
- Thyroid function test
- Coombs test

Imaging studies:
- Joint radiography
- Chest X-ray
- Echocardiography
- Abdominal ultrasound scan
- Brain MRI (contrast)

Procedures and other tests (depending on presentation):
- Lumbar puncture to rule out CNS infection in someone presenting with CNS symptoms

- Arthrocentesis
- Kidney biopsy (refer to American College of Rheumatology (ACR) guidelines for indications)
- Pleural or ascitic tap (send samples for chemistry, microbiology and cytology)
- Ophthalmology assessment
- Lung function test

Differential diagnosis

- Other connective tissues diseases (JDM, JIA, scleroderma)
- Autoinflammatory diseases (interferonopathy, monogenic autoinflammatory diseases)

Management and follow up

- Refer all patients to rheumatologist
- Goal: Prevent mortality and improve function and long term morbidity (organ damage)
- To be managed at a tertiary facility
- To be done in consultation with a paediatric rheumatologist and requires a multidisciplinary team
- To keep in mind disease and treatment complications (e.g. atherosclerosis, osteoporosis, neurocognitive impairment, renal complications)
- UV light protection

Primary/secondary level

- Refer all cases

Tertiary level

- Vitamin D and calcium supplementation
- All patients should be on hydroxychloroquine 200mg OD
- Corticosteroids
  - IV methylprednisolone followed by oral prednisolone
- Disease modifying drugs
  - Azathioprine
  - Mycophenolate mofetil (MMF)
  - Cyclophosphamide
  - Methotrexate
- Biological therapies
  - Rituximab
- Monitor inflammatory markers and renal functions

Juvenile Idiopathic Arthritis

Definition
Arthritis of unknown aetiology 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

Risk factors

- Girls more than boys (particularly oligoarticular)
- Other autoimmune diseases
- Trauma

Causes (inclusive of differential diagnosis)

- Consider other causes of arthritis (see approach to swollen joint section)
- For systemic arthritis rule out- Kawasaki's disease, scarlet fever, acute rheumatic fever
- Other autoimmune conditions or vasculitides (HSP, SLE)

Prevention/promotion

- Early diagnosis and treatment
- Secondary prevention of complication e.g. infection, deformity, reduced function
- Patient and family education about the disease and its management
- Provide emphasis of medication adherence and clinic follow ups
- Promote exercise to improve joint mobility and function (physiotherapy)
- Encourage regular eye examination
- Emotional support for patients and guardians through professional counselling and support groups

Signs and symptoms

- Arthritis is diagnosed in the presence of joint effusion OR two or more of the following:
  - limited range of movement with joint line tenderness
  - painful range of movement

(See general description above (limping child/the swollen joint)

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:

No	Class	Description

1	**Oligoarthritis**
	• Consider TB if only one joint is involved
		• Involve 1-4 joints during the first 6 months
		• Has two subtypes:
		  • Persistent (≤ 4 joints throughout the disease)
		  • Extended (> 4 joints after 6 months)
		• Has high risk of anterior uveitis (all need screening)
		• Most common in young girls with positive ANA (around 5 years old)
		• Frequent joints to be involved are knees, ankles, wrists, or elbows
		• Good prognosis unless extended

2	**Polyarthritis (Rheumatoid factor negative)**	• Affects >=5 joints in first 6 months • Negative rheumatoid factor • Joint involvement is frequently symmetrical, affecting large and small joints alike • Children with RF negative polyarthritis are frequently younger and have a better prognosis
3	**Polyarthritis (Rheumatoid factor positive)**	• Affects >=5 joints in the first 6 months • Positive rheumatoid factor on 2 occasions at least 3 months apart during first 6 months of disease • Share many characteristics with adults with rheumatoid arthritis (RA) • Affects mostly adolescent girls • Clinical symptoms are similar to the adult disease with symmetrical polyarthritis especially involving the PIP joints and MCP joints

4	**Systemic Arthritis**	• Arthritis in 1 or more joints (initially can lack arthritis)
		• 2 weeks of fever documented as daily quartan fever at least 3 days
		• Accompanied by 1 or more of:
		  • Erythematous macular rash (salmon rash)
		  • Serositis (pericarditis, and pleuritis)
		  • Hepatosplenomegaly
		  • Generalised lymphadenopathy
		• Strongly associated with macrophage activation syndrome

5	**Enthesitis related arthritis**	• Arthritis and enthesitis OR
		• Arthritis or Enthesitis and 2 of the following:
		  ◦ Sacroiliac joint tenderness and/or inflammatory back pain
		  ◦ HLA-B27 positive
		  ◦ First-degree or second-degree relatives with HLA-B27 related disease
		  ◦ Arthritis in a boy after 6 years
		  ◦ Acute (symptomatic) anterior uveitis, pain, redness or photophobia
		  ◦ History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, or acute anterior uveitis in a first-degree relative

6	**Psoriatic arthritis**	• Arthritis plus psoriasis in a child, OR
		• Arthritis and 2 of the following
		  ◦ Dactylitis
		  ◦ Nail pitting
		  ◦ Psoriasis in a first-degree relative
		• Arthritis is typically asymmetric, and involves both large and small joints.

7	**Undifferentiated arthritis**	• Arthritis not fitting any of the above or more than one group

Alert box (important points to note)
- See above under the limping child and the swollen joint

Investigations (primary secondary and tertiary level)
- See above under the limping child and the swollen joint

Differential Diagnosis
- See above under the limping child and the swollen joint

Management

Treatment goals:
- Eliminate inflammation with goal to achieve clinical remission (rapid escalation of therapy may be required to achieve this goal)
- Prevent joint damage
- Promote normal growth and development
- Maintain normal function and optimize quality of life
- Minimize medication toxicity

Treatment in general:
- 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

Primary/secondary level

- Pharmacotherapy, initial therapy:

Oligoarticular JIA/polyarticular JIA

- NSAID and/or intraarticular steroids
  - E.g. Ibuprofen 10mg/kg/dose 6-8 hourly for 1-2 months if no joint contractures and low disease activity
- Refer all patients to tertiary level of care

SJIA, psoriatic, enthesitis, non-specific

- Refer to tertiary level

Tertiary level

- To be managed in consultation with paediatric rheumatologist

Oligoarticular; if no improvement after initial therapy

- Intra articular injections for all active joints
  - Methylprednisolone or Triamcinolone hexacetonide 1mg/kg with 1%lignocaine, 0.5ml
  - Repeat after 2 months if no response or response but not in remission
- If disease still active after 3 months
  - Methotrexate 10-15mg/m^2/week (Maximum 25mg/week) stat on empty stomach
  - Increase dose at 1mg/kg/week until response and maintain same dose
- Note: screen for uveitis
- Add folic acid 5mg PO weekly during treatment with MTX
- Monitor FBC, LFT, 3 monthly and creatinine 6 monthly
- If no improvement, start biologic. TNF inhibitor (consult rheumatologist)

Polyarticular JIA

- If no improvement after a month of initial therapy
  - Consider MTX as above
  - Intra articular steroids can be used together with methotrexate
  - For rapid symptom relief: Prednisolone 1mg/kg/day starting dose and reduce to 5mg - 7.5mg/day if good response

SJIA

- Mild disease
  - Prednisolone 2mg/kg PO daily- tapper if remission achieved
- Critically ill patients with serositis
  - Methylprednsolone 30mg/kg/day IV for 3 days
  - Followed by prednisolone 2mg/kg/day until disease controlled
  - Start biologic therapy (IL-1 or IL-6 inhibitor); this can be initiated at diagnosis
- Note: Monitor for development of Macrophage Activation Syndrome.
- If possible start with IL-1 inhibitor without prior steroids

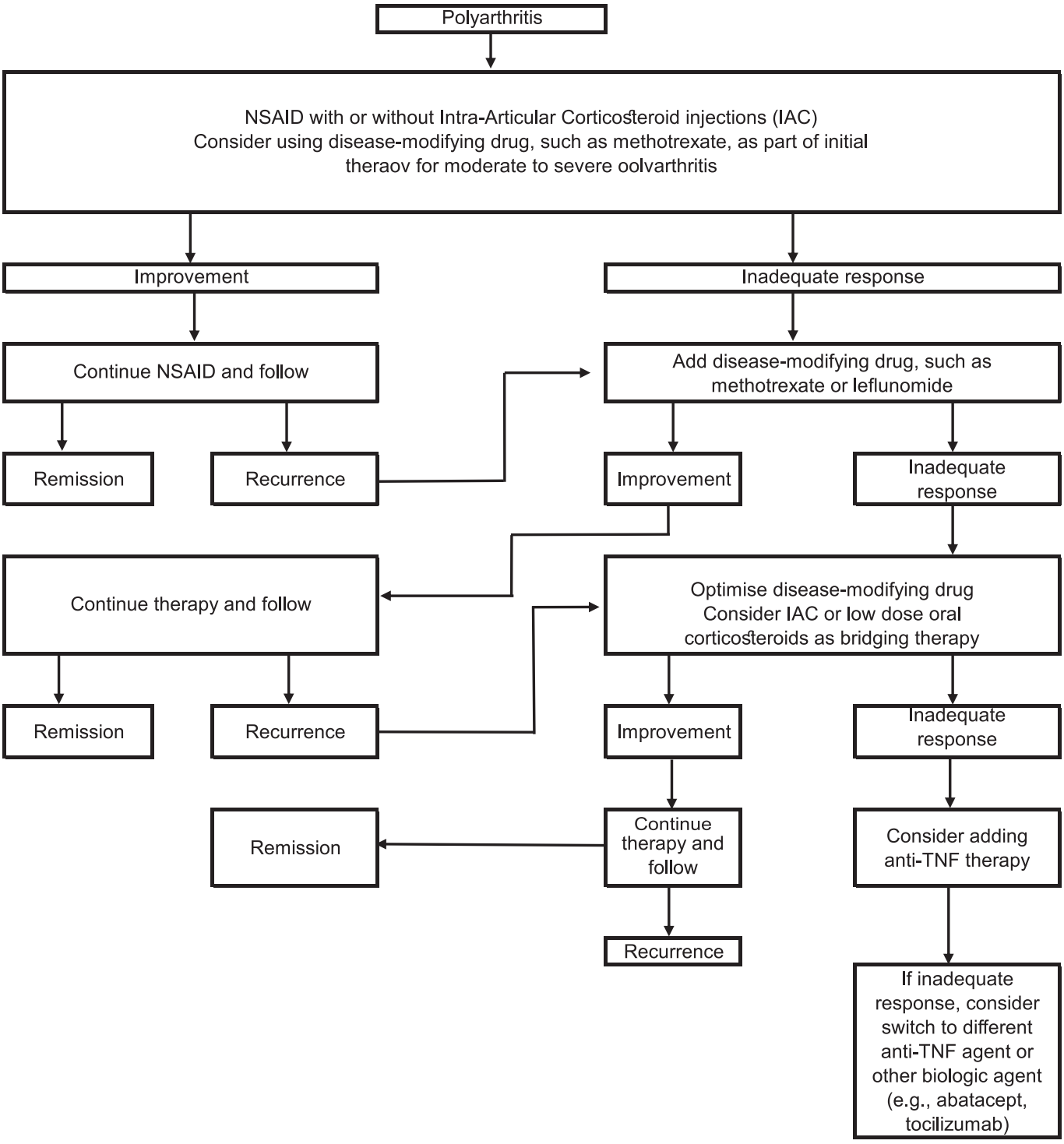
Psoriatic JIA

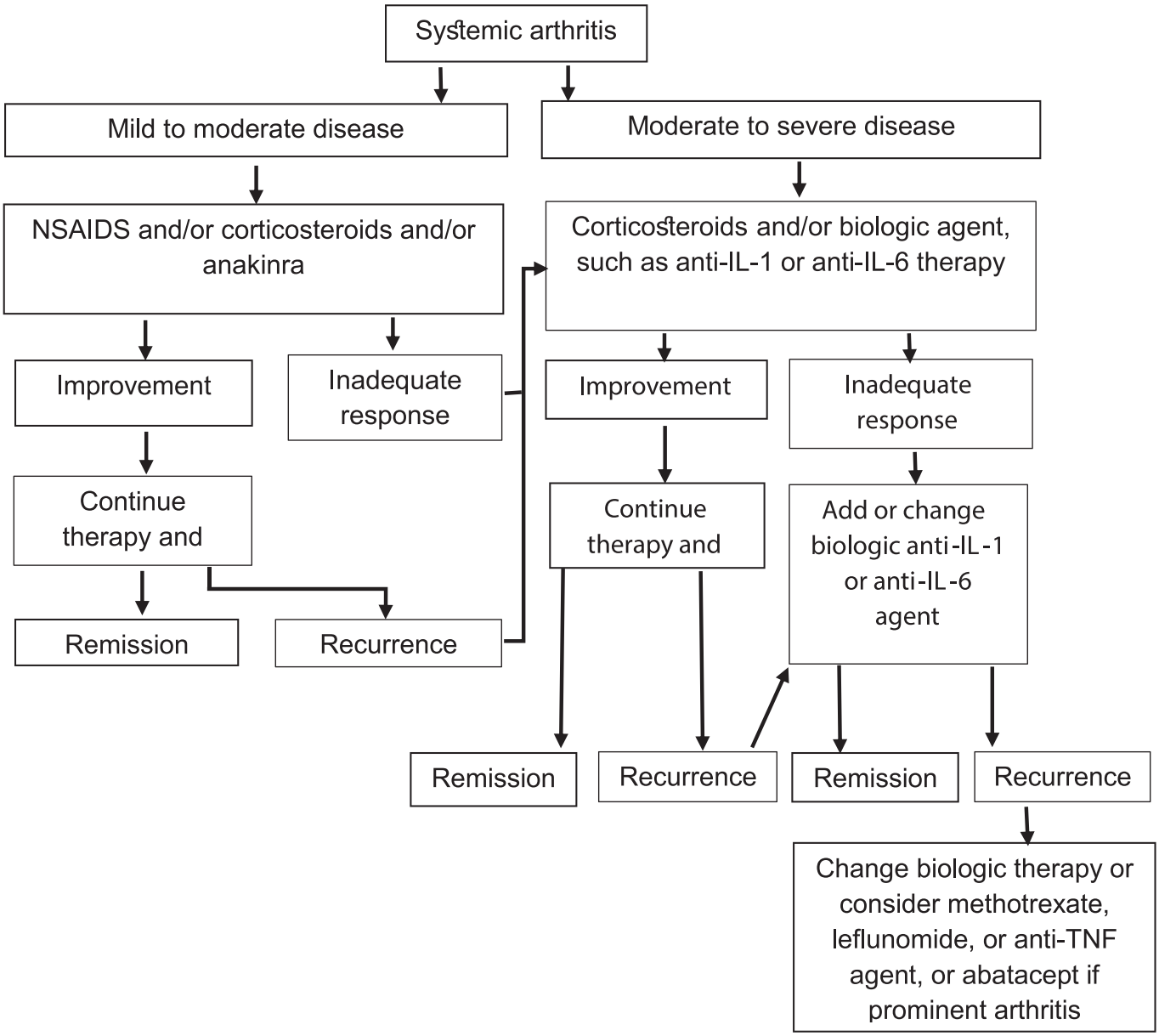
- NSAIDs e.g. Ibuprofen 10mg/kg/dose 6-8 hours for 1-2 months if no joint contractures and low disease activity

- Treat like oligoarticular arthritis above.
- If no improvement, biologic therapy with an - anti-IL-17 secukinumab

<u>Enthesitis related arthritis</u>

- Primary treatment as per primary level, using NSAIDs
- In severe disease
  - Prednisolone 2mg/kg/day oral
  - Consult paediatric rheumatologist





Follow up

- New patients need a monthly follow up
- Stable patients need 3 monthly follow up

Kawasaki Disease

Definition
- A medium vessel vasculitis of unknown aetiology characterised by fever, rash, conjunctival injection, oral mucositis, extremity changes, cervical lymphadenopathy and in a proportion of cases, dilation or aneurysms of the coronary arteries.
- The commonest vasculitides in children < 5 years of age

Risk factors
- Males
- Prolonged fever
- Infants >1 year or <5 years of age
- Asian or Hispanic ethnicity
- Familial risk is uncertain

Causes (including differential diagnoses)
- Aetiology is unknown
- May be an immunologic response
- Infectious trigger (viral and/or bacterial)
- Genetic susceptibility is one of the suggested factors in the pathophysiological process

Prevention/promotion
- No primary prevention of the disease
- Secondary prevention should consider early diagnosis and treatment of children suspected to have the disease
- Patient support
- Educating patients about the disease and its complications

Signs and symptoms
- Diagnostic criteria for Kawasaki disease

Diagnostic Criteria for Kawasaki Disease
Fever lasting at least 5 days.
At least 4 out of 5 of the following: • Bilateral non-purulent conjunctivitis. • Mucosal changes of the oropharynx (injected pharynx, red lips, dry fissured lips, strawberry tongue). • Changes in extremities (oedema and/or erythema of the hands or feet, desquamation, beginning periungually). • Rash (usually truncal), polymorphous but non vesicular. • Cervical lymphadenopathy.
Illness not explained by other disease process.

Important points to note:
- In presence of fever and coronary artery involvement on echo, <4/5 criteria sufficient
- Incomplete KD if ≥ 5 days of fever with 2 or 3 features (common in infants who are at higher risk of coronary artery involvement)

- Atypical KD refers to KD with unusual manifestations (e.g. renal failure)

Other clinical manifestations:
- Relatively common: Irritability (aseptic meningitis), skin peeling in groin, arthritis, sterile pyuria (urethritis), gastroenteritis (abdominal pain, vomiting, diarrhoea), uveitis
- Uncommon – gallbladder hydrops, gastrointestinal ischaemia, jaundice
- Cardiac – myocarditis, pericarditis, cardiac failure, valvular regurgitation
- May be complicated with macrophage activation syndrome (MAS), DIC
- Periungual desquamation in weeks 2 or 3

Coronary artery disease in KD:
- Major concern is the development of coronary artery aneurysms, which most commonly occurs at 6-8 weeks after the acute illness (can occur earlier)

Investigations
- Full blood count: Anaemia, leukocytosis with left shift, thrombocytosis
- ESR and CRP (usually elevated)
- Serum albumin < 3g /dL; raised transaminases
- Urine > 10 WBC/HPF
- Chest X-ray, ECG
- Echocardiogram in the acute phase; repeat at 6-8 wks/earlier if indicated

Differential diagnosis
- COVID MIS-C
- Meningitis
- Viral infections (adenovirus)
- Polyarteritis nodosa (systemic, cutaneous)
- SJS (Stevens Johnson Syndrome)
- IgA vasculitis (once known as HSP)

Management

Primary/secondary level
- Refer all suspected cases to tertiary level.

Tertiary level
- IV immunoglobulins 2 g/kg infusion over 10 - 12 hours
    - Therapy < 10 days of onset effective in preventing coronary vascular damage
- Oral aspirin (anti-inflammatory dose) 30-50mg/kg/day in 3 divided doses till day 14 of illness or until patient is afebrile for 2-3 days (view algorithm below)

Maintenance
- Oral aspirin 3-5 mg/kg daily (anti-platelet dose) for 6 - 8 weeks or until ESR and platelet count normalise

Tertiary level

- To be managed in consultation with paediatric rheumatologist

Oligoarticular; if no improvement after initial therapy

- Intra articular injections for all active joints
  - Methylprednisolone or Triamcinolone hexacetonide 1mg/kg with 1%lignocaine, 0.5ml
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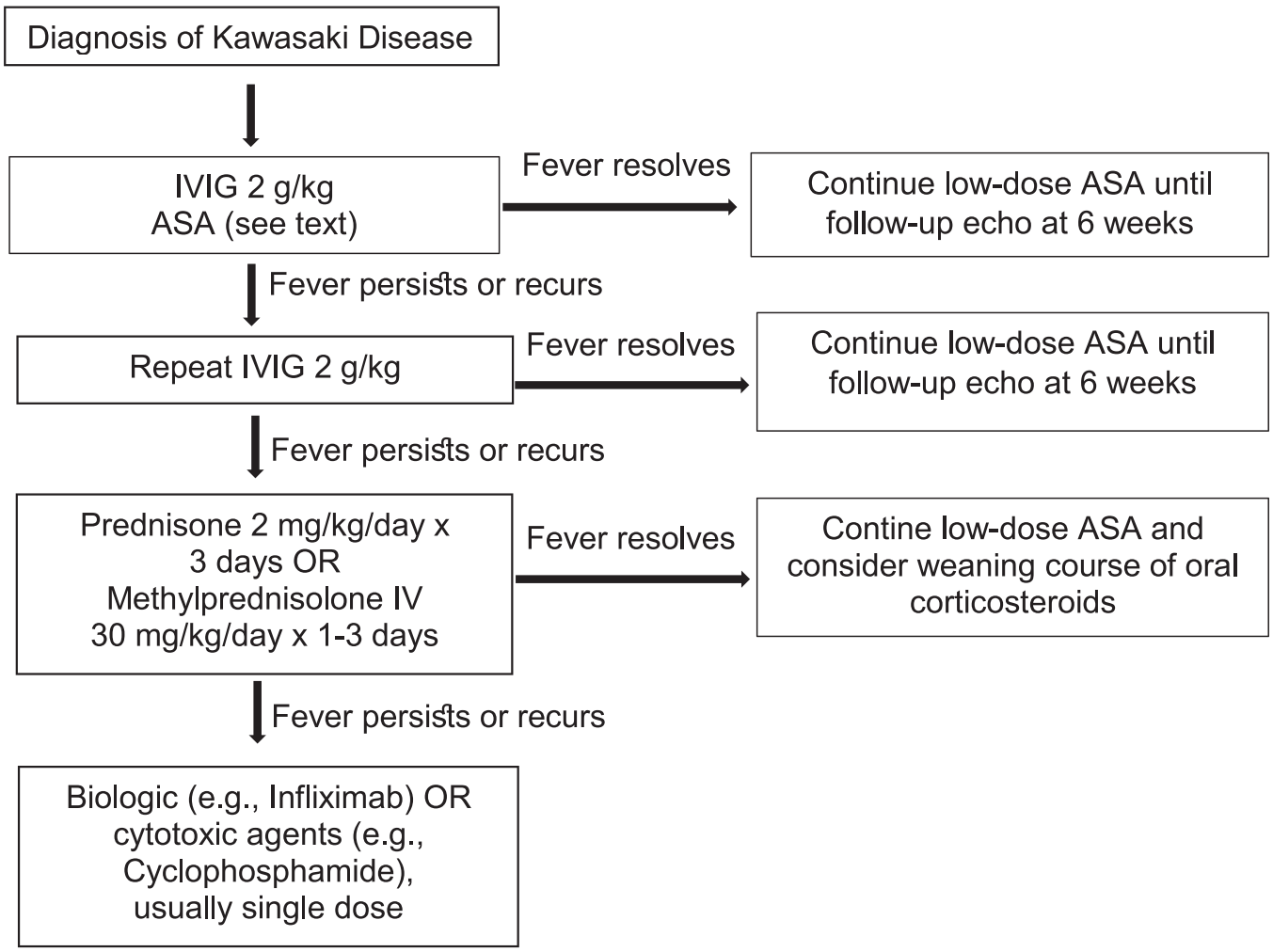
- Treat like oligoarticular arthritis above.
- If no improvement, biologic therapy with an - anti-IL-17 secukinumab
-

Enthesitis related arthritis

- Primary treatment as per primary level, using NSAIDs
- In severe disease
  - Prednisolone 2mg/kg/day oral
  - Consult paediatric rheumatologist
- If coronary aneurysm present, then continue aspirin until resolves
- Note: Kawasaki Disease not responding to primary treatment is defined as persistent or recrudescent fever ≥ 36hours after completion of initial dose of IV Immunoglobulins
  - Repeat IV immunoglobulins 2mg/kg infusion over 10 - 12 hours

An algorithm for treatment of Kawasaki disease



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

Routine echocardiography [Note in-hospital mortality is 0.17% (all cardiac-related)]

- ~ 2% risk of recurrent KD
- Without treatment, coronary artery aneurysms occur in ~25% of patients → reduced to ~4% if IV immunoglobulins treatment within 10 days
- If coronary artery aneurysm → risk of thrombosis, obstruction and stenosis at inlet/outlet of aneurysm, ventricular dysfunction/arrhythmia, early atherosclerosis, myocardial infarction (highest risk if aneurysm ≥8 mm)

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