CHAPTER 12
RHEUMATOLOGY AND VASCULITIDES

12.1 IMMUNOGLOBULIN A VASCULITIS (PREVIOUSLY HENOCH SCHÖNLEIN PURPURA (HSP))

D69.0

DESCRIPTION

Immunoglobulin A vasculitis is an acute leucocytoclastic vasculitis of small blood vessels usually involving skin, gastrointestinal tract, joints and the kidney. Aetiology is unknown.

Complications include:

» acute severe abdominal pain, bowel infarction/perforation;
» nephritis with renal impairment or nephrotic syndrome.

DIAGNOSTIC CRITERIA

Clinical

Syndrome consisting of:

» Non-thrombocytopenic palpable purpuric skin **rash** with a very typical distribution on lower extremities and buttocks. The rash occurs in 100% of cases, but may not be present initially. Trunk and upper extremities may be involved. Angio-oedema of scalp, eyelids, lips and ears.
» **Arthralgia/arthritis** (60–70%): mostly of large joints, i.e. knees and ankles.
» **Abdominal pain** with 'colic' (60–70%): may develop gastrointestinal bleeding, intussusception, or infarction.
» **Renal involvement** (25–50%) manifesting with haematuria and/or proteinuria.

Investigations

» No specific diagnostic test.
» Full blood count (FBC): Platelets may be normal or increased (differentiating this form of purpura from that caused by thrombocytopenia), mild leucocytosis is seen in some children. Normochromic anaemia often related to gastro-intestinal loss.
» Coagulation studies are normal.
» Urine test strip to evaluate renal involvement.
» Serum urea, creatinine, electrolytes and albumin with renal involvement.
» Check stools for occult or frank bleeding.

GENERAL AND SUPPORTIVE MEASURES

» Short period of immobilisation during acute arthritis.
» Soft diet for acute gastrointestinal involvement.
» Clinical review with blood pressure monitoring and urine test strip testing weekly or biweekly for first 2 months, then monthly for the next year.

MEDICINE TREATMENT

For arthritis, oedema, fever, malaise:

- Paracetamol, oral, 15 mg/kg/dose, 6 hourly as required.

OR

- Ibuprofen, oral, 10 mg/kg/dose 6 hourly.
  - Reduce dosing interval to 8 hourly once pain starts improving.

For complicated HSP (severe pain, severe extrarenal symptoms or renal disease):

- Prednisone, oral, 1–2 mg/kg/dose once daily for 10 days in the morning.
  - Reduce dose gradually over 2 weeks.

REFERRAL

HSP with complications, i.e. in patients with:

» Persistent proteinuria, persistent microscopic haematuria, hypertension or worsening renal function for age (renal biopsy indicated).
» Persistent abdominal pain.

12.2 JUVENILE IDIOPATHIC ARTHRITIS (JIA)

M08.0

DESCRIPTION

Juvenile Idiopathic Arthritis (JIA) is of unknown origin with unexplained symptoms for at least 6 weeks with onset before the age of 16 years. Other causes of arthritis must be excluded, e.g. infections, malignancy, trauma, other autoimmune disease. Different clinical subgroups are recognised according to the pattern of onset that manifests within the first 6 months.

DIAGNOSTIC CRITERIA

Systemic onset JIA

» Arthritis in one or more joints.
» Plus at least 2 weeks of daily (quotidian) fever.
» With one of the following:
  > erythematous macular rash, or
  > serositis, i.e. pericarditis and pleuritis, or
  > hepato- or splenomegaly, or
  > generalised lymphadenopathy.

Note: There may be a prolonged delay between the onset of fever and the development of the arthritis.

Oligoarthritis

Always consider TB if only one joint is involved.
Arthritis affecting one to four joints for the first 6 months of disease.

» Two categories are recognised:
  > Persistent oligoarthritis: affects ≤ 4 joints throughout the disease course.
  > Extended oligoarthritis: affects > 4 joints after the first 6 months.

» Occurs more commonly in girls than in boys.
» Typically, onset is before 6 years of age.
» Usually asymmetric arthritis that affects mainly large joints.
» High risk of developing chronic iridocyclitis.
» Up to 70% of patients are anti-nuclear antibody (ANA) positive.

Polyarthritis (Rheumatoid factor (RF)-negative)

» Arthritis affecting ≥ 5 joints in the first 6 months of disease.
» Negative rheumatoid factor polyarthritis includes 2 subsets:
  > one that is similar to adult onset RF-negative rheumatoid arthritis, characterised by symmetric synovitis of large and small joints, onset at school age (between 10 and 14 years) and absence of ANA expression;
  > another that resembles oligoarthritis apart from the number of joints affected in the first 6 months of the disease. This subset of children usually presents between 2 and 5 years of age.

Polyarthritis (Rheumatoid factor (RF)-positive)

» Arthritis affecting ≥ 5 joints in the first 6 months of disease.
» Positive rheumatoid factor on 2 separate occasions at least 3 months apart.
» Involves large and small joints.
» Equivalent to RF-positive adult rheumatoid arthritis but with onset younger than 16 years of age.

Enthesitis-related arthritis

» Arthritis **and** enthesitis
  OR
» Arthritis **or** enthesitis, **and** 2 of the following:
  > sacroiliac joint involvement,
  > HLA-B27-positive,
  > first-degree relative with HLA-B27 associated disease,
  > arthritis in a boy after the age of 6 years,
  > anterior uveitis associated with pain, redness or photophobia.

Psoriatic arthritis

» Arthritis **and** psoriasis in a child,
  OR
» Arthritis **and** 2 of the following:
  > dactylitis,
  > nail pitting,
  > psoriasis in a first-degree relative.

Undifferentiated arthritis

» Arthritis not meeting criteria for one of the above categories or fitting more than one of the above groups.

Differential diagnosis

JIA is a clinical diagnosis and depends on the persistence of arthritis or typical systemic manifestations and by exclusion of other diseases:

» Pyogenic and tuberculous joint infection and osteomyelitis.
» Arthritis associated with other acute infectious illnesses.
» Acute leukaemia and other malignancies.
» Acute rheumatic fever.
» Autoimmune disorders, SLE or mixed connective tissue disease.
» Reiter syndrome, i.e. arthritis, urethritis and conjunctivitis.
» Arthritis associated with inflammatory bowel disease.

Investigations

Investigations must be tailored for each case; in consultation with a specialist, consider the following investigations:

» Full blood count with differential and platelet count.
» C-reactive protein and erythrocyte sedimentation rate.
» Liver function screen before starting methotrexate.
» Serum urea, creatinine and electrolytes.
» Muscle enzymes, albumin, calcium, phosphate and alkaline phosphatase.
» Auto-antibodies and rheumatoid factor.
» X–ray or ultrasound of affected joints.
» Arthroscopy and synovial biopsies in cases of possible TB arthritis.
» Eye screen for uveitis.

GENERAL AND SUPPORTIVE MEASURES

» Occupational and physiotherapy programs may provide the following:
  > exercises to increase range of movements of joints and to maintain muscle strength;
  > hot water baths, swimming pool exercises;
  > splints, e.g. nocturnal splints, for pain relief and prevention of contractures;
  > shoe inserts/raises;
  > aids for activities of daily living.
» Orthodontic treatment if temporomandibular joints are involved.
» All children should have a slit lamp examination initially, with follow-up thereafter, at the discretion of the ophthalmologist.
» Explore individualised evidence-based non-pharmacological strategies for management of pain.

MEDICINE TREATMENT

There is no cure for JIA.

The goal of treatment is to eliminate active disease, to normalise joint function, to preserve normal growth, to prevent long-term joint damage and disease complications. Outcome is improved with early aggressive therapy. Treatment should be decided in consultation with a specialist.

Oligoarthritis

NSAID, e.g.:

- Ibuprofen, oral, 10 mg/kg/dose 6–8 hourly.

LoE III[i]

NSAIDs as monotherapy are given for 1–2 months in patients with low disease activity and without joint contractures.

If no improvement:

ADD Intra-articular steroids.

- Intra-articular corticosteroid injection for all active joints (rheumatologist or orthopaedic specialist):
- Methylprednisolone acetate, 1 mg/kg with lignocaine 1%, 0.5 mL.
  - If no response: repeat in 3 months.
  - Young children may require light sedation with midazolam and ketamine.
  - Large joints, if possible, should be aspirated at the same time.
  - Can be repeated after 3 months if there was an initial response, but the disease is not yet in remission.
  - Intra-articular steroids can also be used as initial therapy.

If disease activity still present after 3 months:

ADD

- Methotrexate, oral, 10–15 mg/m^2/week as a single dose on an empty stomach. (Specialist initiated.)
  - Maximum dose: 25 mg/week.
  - Adverse effects include: nausea, mood changes, raised liver enzymes, bone marrow toxicity and proteinuria/haematuria.
  - Monitor: Pre-treatment FBC, liver transaminases and creatinine; then FBC and either ALT or AST 3 monthly. Serum creatinine 6 monthly.

PLUS

- Folic acid, oral, 5 mg weekly, (on the day after methotrexate) for the duration of the treatment.

If no remission in 6 months, refer to a rheumatologist.

Note: Screen all patients early for uveitis (highest risk if ANA positive).

Polyarthritis – early

Start NSAID as soon as possible.

- NSAID, e.g.:
  - Ibuprofen, oral, 10 mg/kg/dose 6–8 hourly.

LoE III[1]

If no significant improvement in 1 month, or if severe at onset, start disease-modifying drugs (DMARDs):

- Methotrexate, oral, 10–15 mg/m^2/week as a single dose on an empty stomach. (Specialist initiated.)
  - Maximum dose: 25 mg/week.

PLUS

- Folic acid, oral, 5 mg weekly (on the day after methotrexate) for the duration of the treatment.

Note:

Intra-articular steroids (IAS) may be used in conjunction with methotrexate.

For rapid relief of symptoms in severe early disease consider adding:

- Prednisone, oral, starting dose: 1 mg/kg/dose once daily.
  - Reduce dose gradually to 5–7.5 mg daily, depending on response.

Systemic onset JIA

Systemic JIA is an aggressive systemic disease. Refer to a rheumatologist early. Initiate treatment after consultation with a rheumatologist.

- **NSAID, e.g.:**
  - Ibuprofen, oral, 10 mg/kg/dose 6–8 hourly.

LoE III[i]

For patients with mild disease begin with:

- Prednisone, oral, 2 mg/kg as a single daily dose.
  - Once disease is controlled, reduce dose gradually.

Critically ill patients with internal organ involvement, such as pleuritis, pericarditis, myocarditis or evidence of early macrophage activation syndrome should be referred urgently:

- Methylprednisolone, IV, 30 mg/kg/day (maximum 1 gram) for 3 days.

Follow with:

- Prednisone, oral, 2 mg/kg as a single daily dose until disease is controlled.
  - These patients may respond to methotrexate or cyclosporine in the long-term, but the response is not as good as other JIA patients.

Psoriatic arthritis

Treat as for oligoarthritis if ≤ 4 joints, or polyarthritis if severe disease or > 4 joints at onset.

Refer early as most children will require a DMARD.

Enthesitis related arthritis

Start NSAID as soon as possible.

- NSAID, e.g.:
  - Ibuprofen, oral, 10 mg/kg/dose 6–8 hourly.

LoE III[i]

If severe disease:

- Prednisone, oral, 1–2 mg/kg as a single daily dose for 2 weeks and wean over 2 weeks (in discussion with a rheumatologist).
  - Refer all children early for consideration of a DMARD therapy.

Uveitis management

Manage in consultation with an ophthalmologist.

Management of a flare of disease

- NSAID, e.g.:
  - Ibuprofen, oral, 10 mg/kg/dose 6–8 hourly.

If severe flare, consider:

- Prednisone, oral, 1–2 mg/kg daily.

Prompt referral to a subspecialist.

With residual pain not relieved by DMARDs, NSAIDs and corticosteroids, consult a specialist for appropriate management. Adopt a holistic multimodal pain management plan, see Chapter 20: Pain Control.

REFERRAL

» **Urgent:** uncontrolled systemic disease.
» Paediatric specialist or subspecialist referral:
  > All for confirmation of diagnosis.
  > All patients requiring DMARD.
  > Adverse reaction to NSAID therapy.
  > Suspected JIA not responding to NSAID therapy.
» Ophthalmology referral:
  > For slit lamp examination.
  > Patients with iridocyclitis and uveitis.
» For orthopaedic treatment, e.g. where intra-articular corticosteroids are indicated, or if TB oligoarthritis is suspected.

12.3 KAWASAKI DISEASE/MUCOCUTANEOUS LYMPH NODE SYNDROME

M30.3

DESCRIPTION

Kawasaki disease is an acute systemic vasculitis of unknown aetiology occurring predominantly in children. It involves small and medium arteries. The most serious complication is coronary artery aneurysms.

Important: MIS-C, a complication of SARS-CoV-2, can mimic Kawasaki disease.

DIAGNOSTIC CRITERIA

Clinical

» There is no diagnostic test.
» Confirm diagnosis by the presence of fever for ≥ 5 days, lack of another known disease process to explain the illness and the presence of 4 of the 5 criteria listed below:
  1. Bilateral bulbar conjunctival injection without exudates.
  2. Changes of the lips and oral cavity: reddening of the oral mucosa, pharynx, lips, strawberry tongue, cracking of lips.
  3. Polymorphous rash, primarily on the trunk.
  4. Cervical lymphadenopathy (lymph nodes > 1.5 cm diameter).
  5. Changes of the extremities, including reddening of the palms and soles, oedema of the hands and/or feet and desquamation of the finger tips and toes.
» A high index of suspicion is required, especially in younger children, who may present without all the above or may have incomplete/atypical Kawasaki disease.
» Important differential diagnoses:

> aseptic/bacterial meningitis,
> viral or drug eruption,
> bacterial adenitis,
> diseases mediated by staphylococcal or streptococcal toxins,
> rickettsial diseases.

Investigations

» C-reactive protein.
» FBC: leucocytosis and thrombocytosis (thrombocytosis usually only occurs in the second week of illness).
» Urine test strip: transient pyuria.
» ESR: elevated.
» Cardiology assessment, including echocardiography to detect coronary artery aneurysms: 100% sensitivity, 97% specificity, done initially and 6 weeks after disease improvement.

GENERAL AND SUPPORTIVE MEASURES

» Routine supportive care.
» Maintain hydration with oral fluids.

MEDICINE TREATMENT

As soon as diagnosed and preferably within the first 10 days from onset of fever, after specialist consultation:

- Immunoglobulin, IV, 2 g/kg as a single dose administered over 12 hours.
  - Repeat dose, if necessary, if temperature does not normalise or rash does not resolve within 24 hours.

If fever continues after 2 doses:

- Methylprednisolone, IV, 30 mg/kg/dose. Specialist consultation.

All children:

- Aspirin (high dose), oral, 20 mg/kg/dose 6 hourly for 72 hrs or until fever settles.

Follow with:

- Aspirin, oral, 3–5 mg/kg/day until ESR and platelet count are normal if there are no coronary artery aneurysms.
  - If coronary aneurysms are present, continue for at least 2 years after aneurysms have resolved or lifelong if coronary aneurysms persist.

REFERRAL

» All patients for confirmation of diagnosis.
» For echocardiography to confirm the presence of coronary artery aneurysms.

12.4 SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

M32.9

DESCRIPTION

Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease characterised by the presence of auto-antibodies directed against various cellular components, particularly DNA. It is often associated with antiphospholipid-antibody-mediated hypercoagulability. In children it predominantly targets the kidneys (in 50–80%), central nervous system, skin and joints.

Treatment of acute lupus depends on severity of illness, with more aggressive treatment for CNS, renal and haematologic involvement.

DIAGNOSTIC CRITERIA

Clinical

Diagnosis may be elusive due to its variations in presentation and is confirmed with: **SLICC CLASSIFICATION FOR SLE**.

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria) ***OR*** *biopsy-proven lupus nephritis with positive ANA or anti-double stranded DNA antibody.*

CLINICAL CRITERIA	IMMUNOLOGIC CRITERIA (positive result)
1. Acute Cutaneous Lupus 2. Chronic Cutaneous Lupus 3. Oral or nasal ulcers 4. Non-scarring alopecia 5. Arthritis 6. Serositis 7. Renal 8. Neurologic 9. Haemolytic anaemia 10. Leukopenia 11. Thrombocytopenia (<100 000/mm^3)	1. ANA 2. Anti-double stranded DNA antibody 3. Anti-Sm 4. Antiphospholipid Ab 5. Low complement (C3, C4, CH50) 6. Direct Coombs test (do not count in the presence of haemolytic anaemia)

Investigations

Note: Normal urine analysis does not exclude renal disease.

» Urine test strip: haematuria and proteinuria.
» Urine microscopy: cellular casts.
» FBC: differential and platelet count.
» Complement, anti-nuclear antibodies, anti-double stranded DNA antibodies.
» Screen for thyroid involvement.
» Serum urea, creatinine, electrolytes, albumin and cholesterol.
» Clotting profile, antiphospholipid antibody and lupus anticoagulant.
» Electrocardiography and chest X-ray.

GENERAL AND SUPPORTIVE MEASURES

» Counselling, education and a team approach.
» Adequate rest and appropriate nutrition.
» Protect from sunlight: use sunscreen and hats; avoid sunlight if unprotected.
» Physiotherapy to relieve arthralgia.
» Psychological support.
» Immunisation, especially pneumococcal vaccine.
» Prompt management of infections.

MEDICINE TREATMENT

All children should be treated by a specialist.

- Vitamin D and calcium supplementation.

All children:

- Chloroquine (as base), oral, 5 mg/kg/dose daily, Monday to Friday.
- Maximum dose: 200 mg.
    - 6-monthly eye examination necessary.

Chloroquine has a disease-modifying role and is particularly useful for skin and joint disease; some patients can be managed with chloroquine alone or with the addition of low-dose steroids.

Induction therapy

The options depend on the severity of the disease and major organ involvement.
For general systemic disease, serositis or musculoskeletal disease:

- Corticosteroid treatment:
- Prednisone, oral 2 mg/kg/day; maximum daily dose 60 mg.
    - Reduce dose to 0.5 mg/kg once daily by 2 months.

For major organ involvement (severe lupus nephritis class III or IV and neuropsychiatric lupus):

- Methylprednisolone, IV, 30 mg/kg/day (maximum 1000 mg) for 3 days followed by oral prednisone 2 mg/kg/day.
- Reduce dose to 0.5 mg/kg once daily by 2 months.

AND

- Cyclophosphamide, IV, 500–750 mg/m^2/dose, administered over 2 hours.
    - Repeat once a month for 6 months.
    - Cyclophosphamide must be given with pre-hydration and continue increased fluid intake for 24 hours after cyclophosphamide infusion.
    - Monitor vital signs during administration of cyclophosphamide.

Maintenance treatment (steroid sparing treatment)

For mild/moderate disease (vasculitic rash, cytopenia, serositis):

- Azathioprine, oral, 1–2.5 mg/kg/dose as a single daily dose.
    - Maximum dose: 150 mg.
    - Refer if contraindication to azathioprine or if patient develops adverse effects with treatment.

For musculoskeletal and skin disease:

- Methotrexate, oral, 10–15 mg/m^2/week as a single dose on an empty stomach. Specialist initiated.
  - Maximum dose: 25 mg/week.

PLUS

- Folic acid, oral, 5 mg weekly (on the day after methotrexate) for the duration of the treatment.

REFERRAL

Specialist referral:

» All patients for confirmation of diagnosis and initiation/supervision of treatment.
» All patients receiving chloroquine treatment must be referred for ophthalmologic examination.
» Macrophage activation syndrome.
» For kidney biopsy if any evidence of renal disease (deteriorating renal function, significant proteinuria/haematuria or hypertension).

12.5 TAKAYASU ARTERITIS

M31.4

DESCRIPTION

Takayasu arteritis is a chronic inflammatory disease involving large vessels, including the aorta and its main branches and the pulmonary vasculature. Lesions are typically segmental – obliterative and aneurysmal. Symptoms reflect end-organ ischaemia.

DIAGNOSTIC CRITERIA

EULAR/PRINTO/PRES CRITERIA

Angiographic abnormalities of the aorta or its main branches and pulmonary arteries (aneurysm/dilatation, narrowing, occlusion or arterial wall thickening not due to fibromuscular dysplasia).

AND

At least one of the following five:

» Pulse deficit (lost/decreased/unequal peripheral artery pulses and/or claudication induced by activity).
» Systolic blood pressure > 10 mmHg difference between any limbs.
» Bruits or thrills over the aorta and/or its major branches.
» Hypertension
» Elevated acute phase reactants.

May be associated with:

» Congestive cardiac failure associated with aortic regurgitation/dilated cardiomyopathy/hypertension.
» Neurologic signs secondary to hypertension/ischaemia.
» Any signs of unexplained inflammatory activity.
» Strongly positive Tuberculin Skin Test (TST).
» Discrepancy in kidney sizes.

Investigations

» C-reactive protein.
» ESR
» Plasma renin.
» Serum urea, creatinine and electrolytes.
» TST
» Electrocardiography
» Chest X-ray.

GENERAL AND SUPPORTIVE MEASURES

» Refer to Chapter 4: Cardiovascular System, section 4.11.1: Hypertension, acute severe.

MEDICINE TREATMENT

Treat hypertension – refer to Chapter 4: Cardiovascular System, section 4.11.1: Hypertension, acute severe.
Consider TB treatment if tuberculosis cannot be conclusively excluded.

- Aspirin soluble, oral, 5 mg/kg/day as a single daily dose.

Induction therapy

- Prednisone, oral, 2 mg/kg/day (maximum 60 mg) for maximum of 4 weeks.
  - Reduce dose slowly over 12 weeks to 0.25 mg/kg on alternate days.

LoE II[ii]

Continue maintenance treatment with:

- Methotrexate, oral, 10–15 mg/m^2/week. Specialist initiated.
  - Maximum dose: 25 mg/week.

PLUS

- Folic acid, oral, 5 mg weekly (on the day after methotrexate) for the duration of the treatment.

REFERRAL

Specialist referral:

» All patients for confirmation of diagnosis with conventional angiography or magnetic resonance imaging angiography.
» Poor response to initial therapy.

References

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