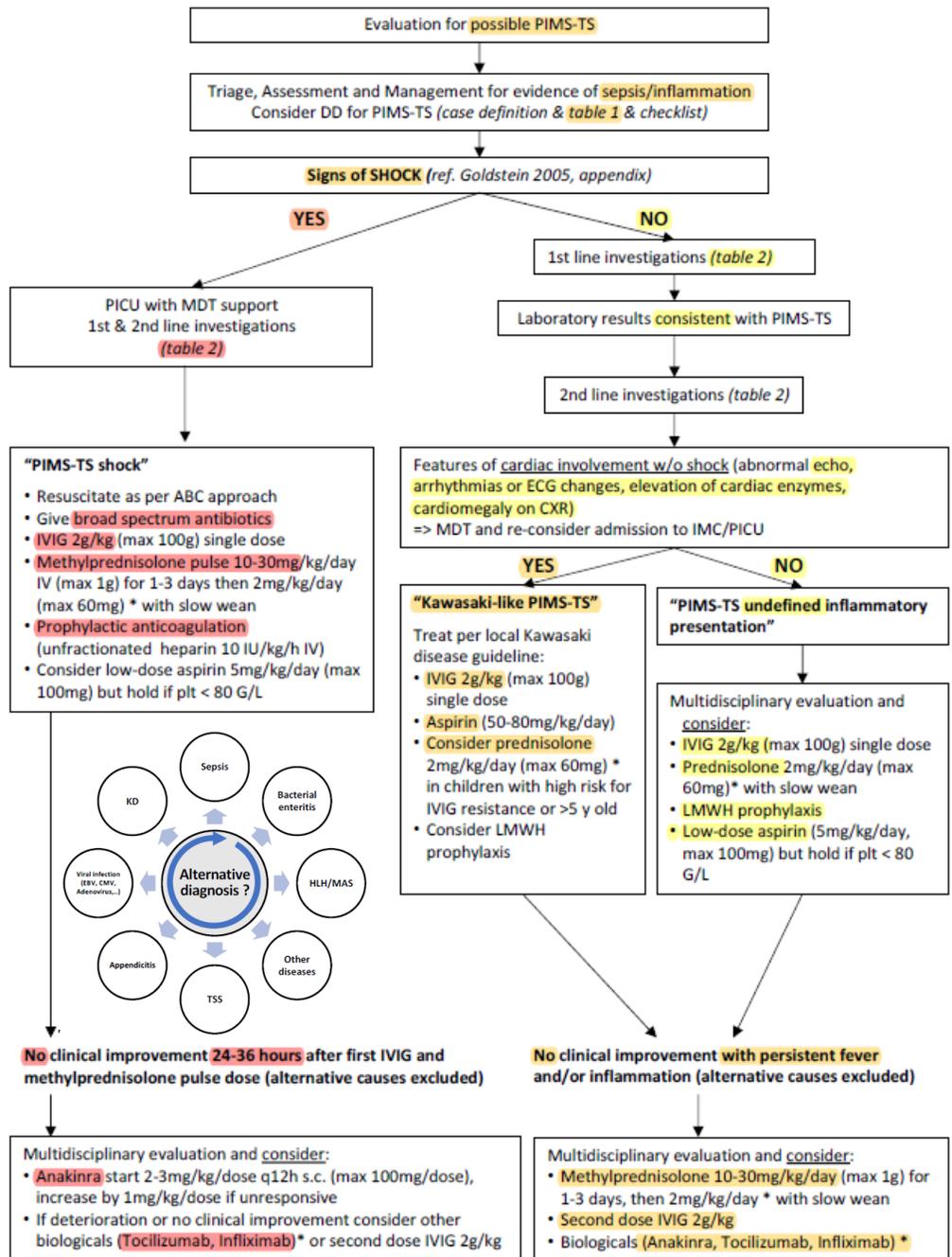


# PIMS-TS Diagnostic and Treatment Pathway



| Clinical features   |           | Criteria   |   |
|---|-----------|--|---|
| General   | Required  | Fever  | ○ |
| Organ systems   |           | Single or multi-organ involvement  |   |
| Gastrointestinal  |           | Abdominal pain, diarrhoea, vomiting  | ○ |
|   |           | Abnormal liver function tests  | ○ |
|   |           | Colitis, ileitis, ascites  | ○ |
| Cardiovascular  |           | Hypotension, shock, oliguria   | ○ |
|   |           | Myocardial dysfunction, pericardial effusion   | ○ |
|   |           | Coronary artery dilatation   | ○ |
| Respiratory   |           | Cough, sore throat   | ○ |
|   |           | Oxygen requirement   | ○ |
|   |           | Patchy infiltrates, pleural effusion   | ○ |
| Dermatologic  |           | Conjunctivitis, periorbital swelling/redness   | ○ |
|   |           | Mucous membrane changes  | ○ |
|   |           | Rash   | ○ |
|   |           | Lymphadenopathy  | ○ |
|   |           | Swollen hands and feet   | ○ |
| Neurologic  |           | Headache, confusion, irritability, reduced level of consciousness                            | ○ |
|   |           | Syncope  | ○ |
| <b>Abnormal laboratory findings indicating inflammation (any combination)</b> |           |  |   |
| Inflammatory markers  |           | Elevated CRP / fibrinogen / D-Dimers / ferritin, hypoalbuminaemia, lymphopenia, neutrophilia | ○ |
| Cardiac markers   |           | Elevated Troponin / NT-pro-BNP   | ○ |
| COVID-19 contact  | Confirmed | Either confirmed or putative   | ○ |
|   | Putative  | Positive for current or recent SARS-CoV-2 infection by PCR, serology, or antigen test        | ○ |
| Putative  |           | COVID-19 exposure within the 4 weeks prior to the onset of symptoms                          | ○ |
| <b>No alternative plausible diagnosis (microbial or inflammatory)</b>         |           |  |   |

Table 1. List of diagnostic criteria for PIMS-TS. Patients must be below 18 years and meet at least one criterion for each group, including i) presence of fever, ii) organ involvement, iii) laboratory evidence of inflammation, iv) microbiologically proven or putative COVID-19 contact, and v) exclusion of other causes.

| Initial investigations in case of suspected PIMS-TS (according to disease severity) | Full blood count (FBC)   |
|---|--|
|   | C-reactive protein (CRP)   |
|   | Blood gas, lactate, glucose  |
|   | Urea, creatinine, electrolytes (U&E)   |
|   | Liver function tests (LFTs)  |
|   | Coagulation: INR, aPTT, Fibrinogen   |
|   | Blood cultures (always before starting antibiotics)  |
|   | Urine microscopy and culture   |
|   | NPA: respiratory panel, SARS-CoV-2 PCR   |
|   | Urine  |
|   | Lumbar puncture if clinically indicated  |
| Second line investigations: (in addition to initial bloods)                         | Erythrocyte sedimentation rate (ESR)   |
|   | Ferritin   |
|   | D-dimers   |
|   | Troponin   |
|   | NT-pro-BNP   |
|   | LDH  |
|   | CK   |
|   | Albumin  |
|   | Triglycerides  |
|   | Store serum and EDTA blood (before administration of IVIG)   |
|   | EBV/CMV/Adeno-/Enterovirus blood PCR   |
|   | SARS-CoV-2 serology  |
|   | 12-lead ECG and echokardiography   |
|   | Chest radiograph   |
|   | Abdominal ultrasound (if gastrointestinal symptoms)  |
| Desirable measures which should NOT delay seeking expert opinion or treatment       | IL-10, IL-6, sCD25*<br>* consider full HLH screen if suggestive features present (e.g. splenomegaly, fibrinogen normal or low; ferritin >2000); Perforin-, SAP- and XIAP-expression, NK cell degranulation and consider HLH-directed therapy (MDT) |

Table 2. Recommendations for diagnostic work-up in children evaluated for PIMS-TS. Note: where possible, PIMS-TS patients should be enrolled in observational or interventional studies, which may include additional diagnostics.

| Class           | Drug   | Route | Dose  | Duration                | Comments and side effects  |
|-----------------|--|-------|---|-------------------------|--|
| Blood products  | IVIG   | IV    | 2 g/kg (max 100g)   | Infusion over 12 hours  | Side effects: Aseptic meningitis, volume load, systemic inflammation, haemolytic anaemia, neutropenia. Slower the rate or divide the dose over two days if signs of volume overload or severe cardiac dysfunction  |
| Corticosteroids | Methylprednisolone   | IV    | 2 mg/kg daily (max 60 mg/day) or 10-30 mg/kg daily for 1-3 days (max 1 g/day)       | 1-3 days discuss in MDT | Side effects: Hyperglycaemia, hypertension, agitation  |
|                 | Prednisolone   | PO    | 1 mg/kg q12h or 2 mg/kg q24h  | Up to 2-6 weeks         | Taper: over 2-6 weeks  |
| Biologicals     | Anakinra (recombinant interleukin-1 receptor antagonist)               | SC    | start at 2-3 mg/kg q12 hours (max. 100mg/dose)                                      | Discuss in MDT          | Escalation/taper: MDT decision. IV administration possible under different dosing scheme. Side effects: neutropenia, leukopenia, thrombocytopenia, eosinophilia, headache, abdominal pain, nausea/vomiting, diarrhea, hepatitis, increased serum transaminases, hypersensitivity reactions, injection-site reactions, skin rash, arthralgia  |
|                 | Tocilizumab (recombinant interleukin-6 receptor)                       | IV    | < 30kg: 12 mg/kg single dose (max 800mg)<br>≥ 30kg: 8 mg/kg single dose (max 800mg) | Discuss in MDT          | Escalation: If no clinical improvement after initial dose, may repeat dose 8-12 hours after the initial dose after MDT discussion. Side effects: neutropenia, leukopenia, thrombocytopenia, anemia, pain, headache, dizziness, insomnia, demyelinating disorders, ulcerations, nausea, increased serum transaminases, liver impairment, increase in serum lipids, pancreatitis, hypertension, hypothyroidism, hypersensitivity reactions, Steven-Johnson-Syndrome, conjunctivitis, nephrolithiasis, injection-site reactions, rash |
|                 | Infliximab (chimeric tumour necrosis factor TNF α monoclonal antibody) | IV    | 5 mg/kg single dose   | Discuss in MDT          | Side effects: neutropenia, leukopenia/agranulocytosis, thrombocytopenia, anemia, pain, headache, dizziness, insomnia, demyelinating disorders, hypersensitivity reactions, injection-site reactions, skin rash   |

Table 3. Anti-inflammatory therapies in patients with PIMS-TS. DISCLAIMER: Medication dosing and administration should be checked with the local hospital pharmacists and considering recent evidence updates. Where possible, PIMS-TS patients should be enrolled in interventional studies

\* Refer to the treatment Table 3 for more details