Pediatric Inflammatory Multisystem Syndrome: Statement by the Pediatric Section of the European Society for Emergency Medicine and European Academy of Pediatrics

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A rise in cases with a new hyperinflammatory disease in children has been reported in Europe and in the Unites States of America, named the Pediatric Inflammatory Multisystem Syndrome—temporally associated with SARS-CoV-2 (PIMS-TS). There appears to be a wide spectrum of signs and symptoms with varying degrees of severity, including a toxic shock like presentation with hypovolaemia and shock, and a Kawasaki-like presentation with involvement of the coronary arteries. Most of these children have evidence of a previous infection with SARS-CoV-2, or a history of significant exposure, but not all. Limited data exist on the incidence of PIMS-TS, but it remains a rare condition. Early recognition and escalation of care is important to prevent the development of serious sequelae, such as coronary artery aneurysms. Clinicians assessing febrile children in primary and secondary care should include PIMS-TS in their differential diagnoses. In children fulfilling the case definition, additional investigations should be undertaken to look for evidence of inflammation and multiorgan involvement. Suspected cases should be discussed with experts in pediatric infectious diseases at an early stage, and advice should be sought from critical care in more severe cases early. There is limited consensus on treatment; but most children have been treated with immunoglobulins or steroids, and with early consideration of biologicals such anti-TNF and anti-IL1 agents. Treatment should ideally be within the context of controlled treatment trials. Clinicians are encouraged to document and share their cases using research registries.

Keywords: children, COVID-19, SARS-CoV-2, PIMS-TS, MIS-C, Kawasaki-like disease, fever
According to the currently available evidence, SARS-CoV-2 infection in children is rarely associated with severe disease (1), children are less likely to be infected compared with adults, and children are likely to be less infectious compared with infective adults (2, 3). However, multiple cases of children with a new hyperinflammatory condition in children subsequent to SARS-CoV-2 infection have been reported in Europe and the United States of America (Tables 1, 2).

This statement has been written on behalf of both the Pediatric Section of the European Society for Emergency Medicine and the European Academy of Pediatrics to provide an update for health care professionals in primary or secondary care undertaking assessments of acutely unwell children. This statement aims to:

- provide information about the Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS);
- give initial guidance on the clinical assessment and management of children suspected of this new condition for health care professionals dealing with acutely unwell children;
- point out useful resources on the recognition and management of these children.

This statement does not address the management of children with PIMS-TS admitted under specialist care.

### TABLE 1 | Overview of studies reporting children with PIMS-TS.

| Population | Location | Number of children in study | Number of settings | Eligibility | Date of publication |
|------------|----------|-----------------------------|--------------------|-------------|---------------------|
| Riphagen et al. (4) | Children with hyperinflammatory shock | London, UK | 8 | 1 | Admitted to PICU | May 6th 2020 |
| Verdoni et al. (5) | Children with Kawasaki-like disease | Bergamo, Italy | 10 | 1 | Admitted to the general pediatric unit | May 13th 2020 |
| Belhadjer et al. (6) | Children with acute heart failure in MIS-C | France, Switzerland | 35 | 14 | Admitted to PICU | May 17th 2020 |
| Chiotos et al. (7) | Children with MIS-C | Philadelphia, US | 6 | 1 | Admitted to PICU | May 28th 2020 |
| Grimaud et al. (8) | Acute myocarditis and multisystem inflammatory emerging disease in critically ill children | Paris, France | 20 | 4 | Admitted to PICU | June 1st 2020 |
| Toubiana et al. (9) | Children with Kawasaki-like multisystem inflammatory syndrome | Paris, France | 21 | 1 | Admitted to general pediatric ward | June 3rd 2020 |
| Miller et al. (10) | Children with MIS-C | New York, US | 44 | 1 | Admitted to hospital | June 4th 2020 |
| Whittaker et al. (11) | Children with PIMS-TS | United Kingdom | 58 | 8 | Admitted to hospital | June 8th 2020 |
| Cheung et al. (12) | Children with MIS-C | New York, US | 17 | 1 | Admitted to hospital | June 8th 2020 |
| Capone et al. (13) | Children with MIS-C | New York, US | 33 | 1 | Admitted to hospital | June 10th 2020 |
| Pouletty et al. (14) | Children with PIMS-TS mimicking Kawasaki disease (Kawa-COVID-19) | Paris, France | 16 | 7 | Admitted to hospital | June 11th 2020 |
| Ramcharan et al. (15) | Children with PIMS-TS | Birmingham, UK | 15 | 1 | Admitted to hospital | June 12th 2020 |
| Kaushik et al. (16) | Children with MIS-C | New York, US | 33 | 3 | Admitted to PICU | June 14th 2020 |
| Riolano-Cruz et al. (17) | Children with MIS-C | New York, US | 15 | 1 | Admitted to hospital | June 25th 2020 |
| Hameed et al. (18) | Children with PIMS-TS | London, UK | 35 | 1 | Admitted to hospital | June 25th 2020 |
| Feldstein et al. (19) | Children with MIS-C | US | 186\(^a\) | 53 | Admitted to hospital | June 29th 2020 |
| Dufort et al. (20) | Children with MIS-C | New York, US | 99\(^b\) | 106 | Admitted to hospital | June 29th 2020 |

Overview of articles describing cases of PIMS-TS, SARS-CoV-2 related Kawasaki-like disease, or MIS-C [per 29-06-2020]; only articles with 5 or more cases included.

Search strategy: using MIS-C, PIMS-TS and Kawasaki Disease as search terms in Medline search, age range: 0–<21 years, from April 1st to June 29th 2020; only English articles were included: only peer reviewed and published articles were included, pre-print manuscripts were excluded.

MISc, Multisystem Inflammatory Syndrome in Children; PICU, Pediatric Intensive Care Unit; PIMS-TS, Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2.

\(^a\)Feldstein et al. (19) excluded cases in the cohort described by Dufort et al. (20) (n = 27), but included cases reported by Chiotos et al. (7) (n = 6) and Waltuch et al. (21) (n = 4). Feldstein et al. (13): 186 cases meeting the case definition included out of 234 reported cases.

\(^b\)Dufort et al. (20): details of 99 confirmed or suspected cases via Public Health reporting registry included; out of 191 potential reported cases.

### STATEMENT

**Abbreviations:** Anti-IL1, anti-Interleukin 1; Anti-IL6, anti-Interleukin 6; Anti-TNF, anti-Tumor Necrosis Factor; APTT, Activated Partial Thromboplastin Time; ECG, Electrocardiogram; ESR, Erythrocyte Sedimentation Rate; PCR, Polymerase Chain Reaction; PT, Prothrombin Time; IL-6, Interleukin-6; PIMS-TS, Pediatric Inflammatory Multisystem Syndrome-temporally associated with SARS-CoV-2; pro-BNP, pro-Brain Natriuretic Peptide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
### TABLE 2 | Presenting signs and symptoms, treatment, and outcomes in children with PIMS-TS.

|                          | Whittaker et al. (11) | Feldstein et al. (19) | Dufort et al. (20) |
|--------------------------|-----------------------|-----------------------|--------------------|
| **Age (median, IQR, years)** | 9 (5.7–14)            | 8.3 (3.3–12.5)        | 31 (31%) <5 years, 42 (42%) 6–12 years |
| **Gender, female**       | 33 (57%)              | 71 (38%)              | 46 (46%)           |
| **Comorbidities**        | 7 (12%)               | 51 (27%)              | 36 (36%)           |
| Overweight, obesity a    | –                     | 45/153 (29%)          | 29 (29%)           |
| **Asthma**               | 3 (5%)                | 35 (18%)              | 12 (12%)           |
| Underlying cardiac disease | 0 (0%)               |                      | –                 |
| **Clinical signs and symptoms** |                      |                      |                   |
| **Fever**                | 58 (100%)             | 186 (100%)            | 99 (100%)          |
| **Duration of fever/symptoms (median, IQR, in days)** | 3–9 (range) | 6 (5–8) | 4 (3–6) |
| **Shock** b              | 29 (50%)              | 89 (48%)              | 10 (10%)           |
| **Gastro-intestinal symptoms** | –                     | –                     | 79 (80%) |
| **Abdominal pain**       | 31 (53%)              | –                     | 60 (61%)           |
| **Diarrhea**             | 30 (52%)              | –                     | 49 (49%)           |
| **Vomiting, nausea**     | 26 (45%)              | –                     | 57 (58%)           |
| **Kawasaki features**    |                       |                       |                   |
| **Kawasaki, complete c   | 7 (12%)               | 74 (40%)              | –                 |
| **Rash**                 | 30 (52%)              | 110 (60%)             | 59 (60%)           |
| **Conjunctival injection, conjunctivitis** | 26 (45%) | 103 (65%) | 55 (56%) |
| **Mucous membrane changes** | 17 (29%)             | 78 (42%)              | 27 (27%)           |
| (Cervical) lymphadenopathy, >1.5 cm diameter | 9 (16%) | 18 (10%) | 6 (6%) |
| **Swollen hand and feet** | 9 (16%)              | –                     | 9 (9%)             |
| **Changes to extremities** | –                     | –                     | 69 (37%)          |
| **Respiratory symptoms** | 12 (21%)              | –                     | 40 (40%)           |
| Sore throat              | 6 (10%)               | –                     | 16 (16%)           |
| Rhinorrhea, nasal congestion | –                      | –                     | 13 (13%)           |
| Chest pain               | –                     | –                     | 11 (11%)           |
| **Neurological symptoms** | –                     | –                     | 30 (30%)           |
| Confusion, altered mental state | 5 (9%)              | –                     | 2 (2%)             |
| Headaches                | 15 (26%)              | –                     | 29 (29%)           |
| Arthralgia, arthritis    | –                     | 4 (2%)                | 4 (4%)             |
| Myalgia, myositis        | –                     | 15 (8%)               | 17 (17%)           |
| **Virology results**     |                       |                       |                   |
| Nasopharyngeal SARS-CoV-2 RT-PCR | 15 (26%)          | 73 (56%)              | 50/98 (51%)        |
| Positive SARS-CoV-2 serology | 40/46 (83%)        | 85 (46%)              | 76/77 (99%)        |
| No positive SARS-CoV-2 result d | 13 (22%)          | 55 (30%)              | 4 (4%)             |
| **Immunomodulatory treatment** |                      |                       |                   |
| Nil immunomodulatory drugs | 13 (22%)          | –                     | –                 |
| Intravenous immunoglobulins | 41 (71%)          | 144 (77%)             | 69 (70%)           |
| Steroids                 | 37 (64%)              | 91 (49%)              | 63 (64%)           |
| **Biologics**            |                       |                       |                   |
| Anakinra (anti-IL1)      | 3 (5%)                | 24 (13%)              | –                 |
| Infliximab (anti-TNF-α)  | 8 (14%)               | 0 (0%)                | –                 |
| Tocilizumab (anti-IL6)   | 0 (0%)                | 14 (8%)               | –                 |
| **Outcomes**             |                       |                       |                   |
| Critical care admission  | 29 (50%)              | 148 (80%)             | 79 (80%)           |
| Inotropic/vasopressor support | 27 (47%)          | 89 (48%)              | 61 (62%)           |

(Continued)
TABLE 2 | Continued

| Whittaker et al. (11) | Feldstein et al. (19) | Dufort et al. (20) |
|----------------------|----------------------|-------------------|
| Mechanical invasive ventilation | 25 (43%) | 37 (20%) | 10 (10%) |
| Extracorporeal membrane oxygenation | 3 (5%) | 8 (4%) | 4 (4%) |
| Coronary artery aneurysm (z-score >2) | 8 (14%) | 15 (8%) | 9 (9%) |
| Death | 1 (2%) | 4 (2%) | 2 (2%) |

This is a summary table of clinical signs and symptoms, treatment, and outcomes from the three largest cohorts published up until June 29th 2020. Appendix 1 in Supplementary Materials includes these data from all published cohorts with 10 or more cases (as per June 29th 2020).

IL1, Interleukin 1; IL6, Interleukin 6; IQR, Interquartile range; IVIG, Intravenous Immunoglobulin; RT-PCR, Reverse Transcriptase Polymerase Chain Reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, Tumor Necrosis Factor.

1Whittaker et al. (11): report both clinically diagnosed obesity (n = 12/153, 8%) and BMI based obesity (n = 45/153, 29%).
2Feldstein et al. (19): number of children with asthma included all children with respiratory comorbidity.
3Feldstein et al. (19): number of children with asthma included all children with respiratory comorbidity.
4Feldstein et al. (19): showed gastro-intestinal involvement in 170 (91%) children, respiratory insufficiency or failure in 109 (59%) children, and neurological complications (encephalitis, aseptic meningitis, demyelinating disorder, seizures, coma or unresponsive within 24 h of admission) in 10 (6%) children; 132 (71%) children had four or more organ systems involved, 36 (19%) children had three organ systems involved, 18 (10%) children had two organ systems involved.
5Feldstein et al. (19): z-score = 2.5.
6Dufort et al. (20): a total of 36 patients (36%) received a diagnosis of Kawasaki Disease or atypical (or incomplete) Kawasaki Disease.
7Dufort et al. (20): including cough n = 31 (31%), shortness of breath n = 19 (19%), wheezing n = 1 (1%).

The three case definitions have in common that they describe a population of children at risk with (1) persistent fever, (2) clinical signs and biochemical profiles reflecting ongoing inflammation, (3) the potential of multiorgan involvement (and most importantly the risk of cardiac involvement), (4) the absence of other reasonable explanations of the acute illness, and (5) evidence of a preceding SARS-CoV-2 infection or exposure to a suspected or confirmed case. Notably, children of all ages appear affected, but it has been more commonly reported in the adolescent age group, which is distinctly different from the children with classic Kawasaki Disease and children with toxic shock syndrome (5, 11). Also, boys and girls appear affected similarly (Table 2, Appendix 1 in Supplementary Materials), whereas children of black and minority ethnicity backgrounds appear affected more often (4, 9, 11).

It is important to stress that the incidence of PIMS-TS is rare with an estimated incidence at 2 in 100,000 persons <21 years of age (20). Also, although some deaths in children with PIMS-TS have been reported, as well as children requiring extracorporeal membrane oxygenation (27), many affected children don’t require critical care and have a full, and rapid clinical recovery (Table 2, Appendix 1 in Supplementary Materials).

There appears to be a wide spectrum of signs and symptoms with varying degree of severity (Table 2, Appendix 1 in Supplementary Materials). All children present with persistent fever. Typically, a substantial proportion of children present with abdominal symptoms, with some having symptoms of such severity that they had US and CT imaging, and some undergoing...
TABLE 3 | Available resources, guidelines and ongoing studies.

### Resources and guidelines

- **European Center for Disease Prevention and Control (ECDC)**
  - [https://www.ecdc.europa.eu/en/publications-data/paediatric-inflammatory-multisystem-syndrome-and-SARS-CoV-2-rapid-risk-assessment](https://www.ecdc.europa.eu/en/publications-data/paediatric-inflammatory-multisystem-syndrome-and-SARS-CoV-2-rapid-risk-assessment)

- **British Pediatric Allergy, Immunity and infection Group (UK)**
  - [https://www.bpaig.org/news-bpaig-position-statement-SARS-CoV-2-treatment-guidance-version-12](https://www.bpaig.org/news-bpaig-position-statement-SARS-CoV-2-treatment-guidance-version-12)

- **Royal College of Pediatrics and Child Health (UK)**
  - [https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19](https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19)

- **Don’t forget the bubbles**
  - [https://dontforgetthebubbles.com/pims-ts/](https://dontforgetthebubbles.com/pims-ts/)

- **World Health organization (WHO)**
  - [https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19](https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19)

- **American Academy of Pediatrics (US)**
  - [https://www.aappublications.org/news/2020/05/14/covid19inflammatory051420?cct=2287](https://www.aappublications.org/news/2020/05/14/covid19inflammatory051420?cct=2287)

- **Center of Disease Control and prevention (US)**
  - [https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html#anchor_1589580133375](https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html#anchor_1589580133375)
  - [https://emergency.cdc.gov/han/2020/han00432.asp](https://emergency.cdc.gov/han/2020/han00432.asp)

- **PENTA network**
  - [https://penta-id.org/covid-19-outbreak/](https://penta-id.org/covid-19-outbreak/)

- **European Society of Medicine**
  - [https://eusem.org/news/corona-virus](https://eusem.org/news/corona-virus)

- **European Academy of Pediatrics**
  - [https://www.eapaediatrics.eu/covid-19-resource-centre/](https://www.eapaediatrics.eu/covid-19-resource-centre/)

### PIMS-TS studies and registries

- **Clinical data collection:**
  - **ISARIC study, International Severe Acute Respiratory and emerging Infection Consortium:** [https://isaric.tghn.org](https://isaric.tghn.org)
  - **British Pediatric Surveillance Unit (UK)**
    - [https://www.rcpch.ac.uk/work-we-do/bpsu/study-multisystem-inflammatory-syndrome-kawasaki-disease-toxic-shock-syndrome](https://www.rcpch.ac.uk/work-we-do/bpsu/study-multisystem-inflammatory-syndrome-kawasaki-disease-toxic-shock-syndrome)
  - **World Health organization (WHO)**
    - [https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19](https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19)

- **Diagnostics and -omics studies:**
  - **DIAMONDS study, Diagnosis and Management of Febrile Illness using RNA Personalized Molecular Signature Diagnosis (Europe):** [https://www.diamonds2020.eu](https://www.diamonds2020.eu)

- **Treatment studies:**
  - **Registry: Best Available Treatment Study for the Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (BATS-study):** [https://bestavailabletreatmentstudy.co.uk](https://bestavailabletreatmentstudy.co.uk)
  - **Clinical trial: RECOVERY trial, Randomized Evaluation of COVID-19 Therapy:** [https://www.recoverytrial.net](https://www.recoverytrial.net)

Surgical procedures (10, 11, 31). The PIMS-TS spectrum includes disease entities that need urgent recognition and treatment, such as a toxic shock like presentation with hypovolaemia and shock, as well as Kawasaki-like disease with involvement of the coronary arteries (4–6). Children with Kawasaki-like disease will have all or some of the typical features, such as a rash and skin changes, conjunctival injection, mucous membrane changes, unilateral lymphadenopathy, and swollen hands and feet (6, 11). A majority of the reported children with PIMS-TS had evidence of multiorgan involvement (19). A number of these children will subsequently need critical care with (multiorgan) supportive care, whereas others can be managed safely on normal pediatric wards. Almost exclusively, these children appear ill and present in a manner that warrants enough concern to admit them to hospital and to perform additional diagnostic tests. By now, it appears that the biochemical profile of children with PIMS-TS is distinct from that of children with classic Kawasaki Disease and Kawasaki Disease with shock, with children with PIMS-TS having noticeably higher markers of inflammation (e.g., CRP, ferritin), marked lymphopaenia, greater elevation of troponin, and higher levels of fibrinogen; it is less clear how the biochemical profiles differ from children with toxic shock syndrome (11). Lastly, it is important to note, however, that the cases reported in the literature are likely to represent the more severe spectrum of disease.
| Population | Clinical signs and symptoms | Evidence of multiorgan involvement | Markers of inflammation | Evidence of other infections | Evidence of SARS-CoV-2 infection | Additional comments |
|------------|-----------------------------|-----------------------------------|------------------------|-----------------------------|--------------------------------|---------------------|
| World Health Organization (30) | Children and adolescents 0–19 years of age | Fever > 3 days And two of the following: Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet). Hypotension or shock. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) | Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities, including echocardiogram findings or elevated Troponin/NT-proBNP Evidence of coagulopathy (by PT, APTT, elevated d-Dimers) | Elevated markers of inflammation such as erythrocyte sedimentation rate, C-reactive protein, or procalcitonin | No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal, or streptococcal shock syndromes | Evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19 |
| Center of Disease Control and Prevention (CDC) (US) (29) | An individual under 21 years | Presenting with fever The CDC note the fever should be at least 38 degrees Celsius for at least 24 h or a subjective fever lasting 24 h | Evidence of clinically severe illness requiring hospitalization with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) | Evidence of inflammation could include but is not limited to an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes, and low albumin | No alternative plausible diagnoses | Positive for current or recent SARS-CoV-2 infection by reverse-transcriptase polymerase chain reaction, serology or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection |
| Royal College of Pediatrics and Child Health (UK) (28) | Any child | Persistent fever | Evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with other additional clinical, laboratory or imagining, and ECG features | Neutrophilia, elevated CRP, and lymphopaenia | Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus | SARS-CoV-2 PCR testing positive or negative Children fulfilling full or partial criteria for Kawasaki disease may be included |

*Two of the following of clinical signs and symptoms, or evidence of multiorgan involvement.*
Some of these children test positive for SARS-CoV-2 on PCR, and most have evidence of a previous infection with positive SARS-CoV-2 serology (Table 2, Appendix 1 in Supplementary Materials); however, some cases do not have a history of exposure to SARS-CoV-2 and do not have clear evidence of a (previous) SARS-CoV-2 infection (11). It remains important to perform (serial) tests to confirm the presence of active or previous infection with SARS-CoV-2, and to further our understanding of the relationship between and the underlying mechanisms of infection with SARS-CoV-2 and PIMS-TS (32).

After a reduction in the number of presentations to emergency departments during the lockdown periods across Europe (33), the raised awareness of PIMS-TS in the media might lead to an increase of presentations of children with fever and other infectious symptoms to acute care facilities. Public health bodies should communicate clearly with the general public about the warning signs of PIMS-TS and about when to seek care as to prevent delayed presentations (34, 35). Moreover, an increase in incidence of PIMS-TS has a 4–6 weeks delay after the onset of a COVID-19 outbreak (19, 20, 36).

As with any emerging disease, it might not immediately be straightforward deciding who is at risk of PIMS-TS, and in whom to perform additional investigations. This could adversely lead to false positive test results creating clinical uncertainty, erroneous clinical decision making, and heightened parental anxiety. Similarly, there is a risk that children will be classified as having sepsis, exacerbated by the risk of delayed presentations during a pandemic (34), and that they will be managed as such in their local hospital, without appropriate investigations and escalation of care. There is also a risk that many children with other, more common, childhood infections will be classified as suspected PIMS-TS and will undergo unnecessary diagnostic tests and treatment. For children with abdominal symptoms, an early diagnosis of PIMS-TS may inadvertently lead to a delay in surgical review, and concerns of surgical abdominal pathology could inversely lead to a delay in recognition of a diagnosis of PIMS-TS. Involvement of senior clinical decision makers and adherence to up-to-date case definitions and guidance are advisable.

Altogether, the emergence of PIMS-TS dictates careful clinical decision making when dealing with febrile children presenting to acute care facilities across Europe:

1. The need for additional investigations should be based on the initial clinical assessment of a febrile child by a clinician experienced in pediatric care.
2. The management of febrile children who appear clinically well, with a clear focus of infection, and who would previously have been deemed well enough for discharge from our care without any interventions should generally not change; this is likely to reflect the management of the vast majority of febrile children presenting to acute care facilities.
3. Ensure that the presence or absence of all Kawasaki-like features are documented for all febrile children; ensure that a blood pressure and a full set of vital parameters are recorded.
4. Clinicians should be aware of and follow published guidance on PIMS-TS by (inter)national societies (Table 3).
5. Perform additional investigations at an early stage in unwell appearing febrile children with sufficient heightened clinical concern as based on the case definition, or with clinical signs of inflammation and/or shock.
6. Additional laboratory investigations should include markers of myocardial involvement (such as troponin, pro-BNP), hypercoagulation (including APTT, PT, fibrinogen, D-Dimer), markers of inflammation (such as C-reactive protein, procalcitonin, ferritin, IL-6, erythrocyte sedimentation rate), creatine kinase, lactate dehydrogenase, full blood count, renal profile, vitamin D level, and liver function tests, including triglycerides; include amylase in the presence of abdominal symptoms (Table 5).
7. Request appropriate microbiology, including a blood culture, and virology tests to rule out any other infectious cause of the illness (Table 5). We also suggest PCR of oropharyngeal swab for SARS-CoV-2 in first instance. Save an EDTA and

| Table 5 | List of investigations in PIMS-TS. |
|---------|----------------------------------|
| **Blood tests** | Blood gas with lactate |
|         | Full blood count and film |
|         | Renal profile |
|         | Liver function tests, LDH, Triglycerides, CK |
|         | Amylase in presence of abdominal symptoms |
|         | C-reactive protein, procalcitonin, ferritin, ESR |
|         | Coagulation screen with fibrinogen and |
|         | D-Dimer |
|         | Troponin, pro-BNP |
|         | Vitamin D |
| **Imaging** | Chest X ray |
|         | ECG, echocardiogram |
| **Microbiology and virology** | Abdominal US with abdominal symptoms |
|         | Blood culture |
|         | Urine culture |
|         | Stools culture |
|         | Throat culture |
|         | Nasopharyngeal aspirate or throat swab for |
|         | PCR for respiratory viruses |
|         | Mycoplasma pneumoniae titres, ASOT |
|         | PCR for bacterial pathogens (e.g., |
|         | meningococcal, pneumococcal, streptococcal, |
|         | and staphylococcal PCR) on blood |
|         | PCR for EBV, CMV, adenovirus, parvovirus, |
|         | enterovirus, and parechovirus on blood |
|         | HIV |
|         | Save samples for PCR and serology studies |
|         | (prior to IGW) |

Proposed list of initial investigations in children with suspected PIMS-TS needing hospital admission. This list is not exhaustive and additional investigations should be tailored to each individual patient.

**Antibodies**
- Anti-Streptolysin O Titer; CK; Creatine Kinase; EBV; Epstein-Barr Virus; ECG, electrocardiogram; ESR, Erythrocyte Sedimentation Rate; HIV, Human Immunodeficiency Virus; LDH, lactate dehydrogenase; PCR, Polymerase Chain Reaction; pro-BNP, pro-Brain Natriuretic Peptide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; US, Ultrasound.
serum sample for PCR and serology studies prior to giving intravenous immunoglobulins.
8. An ECG and echocardiogram should be part of the diagnostic work-up of all children with suspected PIMS-TS.
9. We recommend early discussion with a specialist pediatric infectious diseases team if there is clinical and biochemical evidence of inflammation and suspicion of PIMS-TS. We also recommend early discussion with a pediatric critical care team in children in need for single or multiple organ support. Any evidence of myocardial involvement (for example, raised troponin or pro-BNP, or concerning ECG or echocardiogram) warrants early escalation to a center with pediatric cardiology expertise.

This statement does not cover the specific treatment of individual children with PIMS-TS; all these children should be discussed with a pediatric expertise center. At present, there is no high-level evidence to support any best care recommendations about the treatment of these children outside providing optimal supportive care. For children with Kawasaki-like disease, the mainstay of treatment consists of intravenous immunoglobulins, steroids and possibly additional biologicals, such as anti-TNF, anti-IL1, or anti-IL6, and aspirin. For children presenting with a toxic shock like picture, treatment should focus on early cardiovascular support, treatment and reversal of shock, and intravenous immunoglobulins. Fluid boluses should be titrated carefully in view of the risk of myocardial impairment; inotropes and immunoglobulins. Fluid boluses should be titrated carefully in view of the risk of myocardial impairment; inotropes and immunoglobulins. 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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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