International Study to Define Best Available Treatment for Paediatric Inflammatory Syndromes Temporally Associated with SARS-CoV-2.

Paediatricians in many countries worldwide are seeing rapidly increasing numbers of children with a new spectrum of inflammatory diseases temporarily associated with the COVID-19 pandemic. Since the first reports of a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection, and establishment of a case definition in the UK (RCPCH, 1st May 2020), the disorder has been reported from many countries. However in addition to the critically ill children in the first reports, a wider spectrum of childhood inflammatory illness has emerged. Three related childhood syndromes have emerge which appear to represent a spectrum of illness temporally associated with SARS-CoV-2 pandemic:

1. Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS). Defined as:

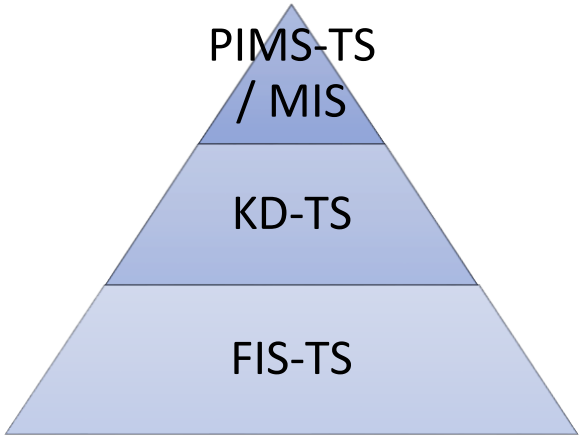
1. A child presenting with persistent fever, inflammation (which may be characterised by neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (see listed in Appendix 1). This may include children meeting full or partial criteria for Kawasaki disease.
2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
3. SARS-CoV-2 PCR testing may be positive or negative

2. Typical Kawasaki disease - Temporally associated with SARS-CoV-2 (KD-TS). Increasing numbers of children meeting the classical criteria for Kawasaki disease, but with evidence of SARS-CoV-2 infection or exposure. SARS-CoV-2PCR may be positive or negative, and SARS-CoV-2 antibodies positive or negative.

3. Febrile Inflammatory Syndrome - Temporally associated with SARS-CoV-2 (FIS-TS). Definition: Febrile children, without features of 1 or 2, but with inflammatory blood markers (such as raised CRP, neutrophilia, lymphopenia, elevated D-Dimers, ferritin), in whom other infectious or inflammatory causes cannot be identified, SARS-CoV-2 may be positive or negative by PCR and antibody.

4. Infection complicating 1,2,3. Some children in groups 1, 2 or 3 have evidence of invasive bacterial infections or opportunistic infections, suggesting that despite the intense inflammation seen in each of the three syndromes, immunity to common pathogens may be impaired.

Different acronyms and definitions for the syndrome have been proposed by the USA Centre for Disease Control and the WHO. CDC and WHO use the term: **Multisystem Inflammatory Syndrome (MIS)**; these definitions (which are shown in appendix below) are overlapping, and patients meeting any of the three definitions can be included.



Spectrum of Emerging Paediatric Inflammatory syndromes temporally associated with SARSCov2 pandemic. Note the term Multisystem Inflammatory Syndrome (MIS), and definitions used by WHO and CDC are largely overlapping with PIMS-TS

These emerging disorders appear to be an unusual response to SARS-Cov-2 infection mediated by the host innate and acquired immune systems.

These emerging disorders raise urgent questions on treatment: and progression.

1. Do patients progress from the less severe to more serious categories? ie. FIS-TS to KD-TS or PIMS-TS; or KD-TS to PIMS-TS.
2. What is the risk of coronary artery aneurysms in each group?
3. What is the relationship between KD-TS and KD prior to the pandemic?
4. Do the same treatments which reduce the risk of Coronary artery aneurysms in typical KD also reduce aneurysm risk in KD-TS?
5. Do anti-inflammatory and immuno-modulating treatment such as immunoglobulin, steroids, anti-TNF, anti-IL1, anti-IL6 or T cell inhibition, or anticoagulation or anti-platelet agents improve the outcome for critically ill children with PIMS-TS including reducing risk of coronary artery aneurysms?
6. Does treatment of children with fever and elevated inflammatory markers (FIS-TS) with any of the available immunomodulating agents prevent progression to the more severe syndromes of Kawasaki disease and PIMS-TS?
7. Should observation alone or treatment be given to the large number of children with FIS-TS, and if so, what levels of inflammation define need for treatment?
8. What are the risk and benefits of administering immunomodulating agents to large numbers of children who may have persistent SARS-CoV-2, or may have self-resolving inflammatory conditions?
9. Are there accurate biomarkers of progression and poor outcome?

The need for trials

The conventional method for addressing these questions and establishing which of the available treatments are beneficial and which may, in fact, be harmful would be to undertake randomised controlled trials. However, as randomised therapeutic trials take time to set up, require evaluation by

national ethics authorities and funding and support, it seems unlikely that formal randomised trials can be set up in time to be offered to the rapidly expanding numbers of children with these inflammatory syndromes, **except where existing trials are in progress.** Furthermore, many centres will not have biological agents available as there is a world-wide shortage of many agents as a result of their use in COVID-19 patients.

An alternative to randomised trials

As an alternative to randomised controlled treatment trials for the new SARS-CoV-2 associated disorders we invite paediatricians in any country to join a study which we term "**best available treatment study**". We believe that the approach outlined below will enable rapid evaluation of the available therapeutic modalities and rapidly provide answers on the questions as to which patients to treat, which treatments work, and which may be harmful.

The principles of the proposed study are:

- We do not know which immunomodulating treatments are beneficial or harmful for SARS-CoV-2 associated inflammatory conditions.
- Paediatricians try to provide the best available care to their patients.
- Anti-inflammatory and immuno-modulatory treatments are in short supply as their use in adults with COVID-19 are exhausting supplies of many of the biological agents. The numbers of cases with Kawasaki like syndromes may also strain supplies of intravenous immunoglobulin.
- Faced with variable availability of treatment options paediatricians will offer their patients their "best guess" of which of the available therapies are likely to be beneficial in their setting.
- We have excellent biological markers of the inflammatory process. Elevation of CRP, ferritin, troponin, BNP, D-dimers, liver function tests and conventional blood markers are indicative of the intensity of the inflammatory process and return to normal as inflammation subsides.
- We have simple clinical markers to evaluate improvement, need for intensive care, need for oxygen, inotropes or other support.
- We have accurate clinical markers of outcome: frequency and severity of coronary artery aneurysms, length of stay in hospital, requirements for inotropes and ventilation, and overall survival.

The hypothesis underlying this study is that the administration of immunoglobulin, steroids or other immunomodulating agents such as immunoglobulin, anti-TNF, anti-IL1, or anti-IL6 therapies, steroids or cyclosporin, will result in more rapid resolution of inflammatory markers, prevent progression from FIS-TS to KD-TS or PIMS-TS, reduce the need for intensive care or organ support and reduce coronary artery aneurysm rate.

Conduct of the study:

Study population

Patients meeting any of the three SARS-CoV-2 associated inflammatory condition definitions (see Box 1 for Paediatric Inflammatory Multi-system Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS), Kawasaki Disease - Temporally associated with SARS-CoV-2 (KD-TS), and Febrile Inflammatory Syndrome - Temporally associated with SARS-Cov-2(FIS-TS) can be enrolled in the study. Patients meeting the

overlapping definitions of Multisystem Inflammatory Syndrome (MIS) from CDC and WHO (listed in Appendix) can also be enrolled.

Methodology

1. Systematic data collection on all patients with FIS-TS, KD-TS, and PIMS-TS using an on-line case report form. Patients are anonymised and identified only by the clinician reporting the case, hospital and country, and age of the child in months and years.
2. The severity of each patient's clinical findings, inflammatory markers and organ dysfunction are recorded
3. Rate of change in inflammatory markers following Initiation of immunomodulating agents, **or during observation** (if no specific treatment given) is recorded.
4. Outcome including presence of coronary artery aneurysms, time in PICU, duration of organ support, or death, and progression from FIS-TS to KD-TS or PIMS-TS is documented
5. Rate of change in inflammatory markers, organ failure or need for interventions is compared between the no intervention group, and each of the individual immunomodulating agents or combinations, using machine learning and other mathematical approaches.

This approach is likely to be successful because:

- There is genuine equipoise in treatment, as there is no clear evidence on which to base any specific agent or regime.
- Paediatricians in different countries are choosing treatments based on agents that are available, and their personal practice and preferences.
- The different rates of improvement in inflammation and outcome associated with each agent, or combinations of agents, can be detected in a non-randomised study by matching patients for severity and degrees of inflammation and studying the rates of improvement of the available markers of inflammation and the outcome variables of coronary artery aneurysms, intensive care and organ support duration and mortality.
- **Patients who are included in randomised trials can be included as long as treatment arm is known**
- Machine learning and other mathematical models are likely to reveal genuine differences in outcome as long as the numbers of patients in the trial are large, and matching for severity at the time of initiation of treatment is undertaken.

Does the study require ethics approval and patient consent?

Regulations vary in different countries, and paediatricians enrolling patients should check with their own institution and country guidance. As no patient identifiable data is collected, patients and families consent is not required to utilise routinely collected hospital data. As many international studies using similar non identified data are in progress the principle is widely accepted, and most countries would not require ethics approval for this data collection exercise, but please comply with your local regulations.

How to participate

The entry point to the study is **recognition of a case of FIS-TS, KD-TS, or PIMS-TS (this can be prospective, or retrospective).**

Exclusions: The only exclusions are identification of an alternative diagnosis once all investigations are available.

1. To participate in the study and provide data: log onto the online study entry site and provide contact details (**email, address, country and institution**). You will be asked to enter **only the date of admission to hospital and the age in years and months of your patient.**

2. You will then be asked to provide **basic information from a tick box list of the presenting features and enter laboratory findings that document the severity of inflammation on the day of trial entry as well as indicators of the severity of illness.**

3. Your own choice of of best available therapy is administered and recorded. If no specific therapy is given this is recorded.

4. Record daily (if possible) changes in the child's condition and the results of subsequent blood tests, severity markers and follow up echocardiography.

Analysis

Electronically captured data following treatment with any of the agents will be analysed by the machine learning and data monitoring group at Imperial College who have led application of machine learning techniques to large scale patient data

Acknowledgement, participation and ownership of data

All clinicians submitting patients to this study will be listed as a member of the international consortium, have access to the data for their own analyses and included in all subsequent reports.

Appendix: Case definitions for inclusion

PIMS-TS case definition

KD-TS case definition

FI-TS case definition

WHO Preliminary Case Definition

Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19

Preliminary case definition [a]

Children and adolescents 0–19 years of age with fever > 3 days

AND two of the following:

Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
Hypotension or shock.
Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

AND

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

[a] Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome

CDC Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

An individual aged <21 years presenting with fever[i], laboratory evidence of inflammation[ii], and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological);

AND
No alternative plausible diagnoses;

AND
Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

i. Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
ii. Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

Additional comments

Some individuals may fulfil 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