A national consensus management pathway for Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS): The results of a national Delphi process

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Competing Interests:

All authors have completed the ICMJE uniform disclosure form at ww.icmje.org/coi_disclosure.pdf and declare: Marian Knight and Saul Faust are NIHR Senior Investigators. Benjamin Allin is funded by an NIHR Doctoral Research Fellowship. Rachel Harwood holds a KRUK training fellowship. There are no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing:

Relevant raw data will be provided in supplementary material. No further data will be available for sharing.

Transparency statement

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

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Summary Box

What was already known on this topic:

- In April 2020, a novel syndrome, Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS) was identified.
- This syndrome was identified as causing significant acute illness in children, including shock and features of Kawasaki's disease.
- No national consensus management pathway existed for children with PIMS-TS

What this study adds:

- This study has utilised a rapid, online Delphi process and virtual consensus meeting to develop a National consensus management pathway for children with suspected PIMS-TS.
- Until higher level evidence is available, this pathway can give clinicians a framework for managing children with suspected PIMS-TS.

Abstract

Objective:

The objective of this work was to develop a consensus management pathway for children with Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS), and to identify research priorities.

Design:

Statements for assessment in the consensus process were derived from existing evidence, local guidance documents and expert opinion. A three-phase online Delphi process and virtual consensus meeting were utilised to seek agreement with these statements from multidisciplinary participants involved in the care of children with PIMS-TS. Participants were grouped into three panels and asked to score each statement from 1 (disagree) to 9 (strongly agree). In phases two and three, participants were shown graphical and numerical representations of their panel's scores, and all panels' scores respectively for each statement.

Statements were defined as 'consensus agree' if ≥70% of participants in each panel scored the statement 7-9, and <15% scored the statement 1-3, and were defined as 'consensus disagree' if ≥70% of participants in each panel scored the statement 1-3, and <15% scored the statement 7-9. Where consensus had been achieved in two panels at the end of the Delphi process, statements were discussed at the consensus meeting, and those where ≥70% participants agreed or disagreed with the statement were defined as achieving consensus.

Participants:

98 people were invited to participate in the consensus process and 46 (47%) completed all three phases.

Results:

255 statements were assessed in total, with 'consensus agreement' achieved for 111 (44%), 'consensus disagreement' for 29 (11%), and no consensus for 115 (45%). The 140 consensus statements were used to derive the consensus management pathway.

Conclusions:

A national consensus management pathway has been developed for children suspected of having the novel syndrome PIMS-TS in a timely, cost-efficient manner, in the midst of a global pandemic. This pathway includes suggestions for integrating current and future research protocols into children's management. Use of a rapid online Delphi process has made this consensus process possible. Future evidence will inform updates to this guidance, which in the interim provides a solid framework to support clinicians caring for children with PIMS-TS.

Introduction

Since the first reports from London, UK, in late April 2020, many countries globally have reported children presenting severely unwell with features of significant inflammation temporally related to the COVID-19 pandemic. These include the United States of America(1), France(2, 3), Italy(4) and the United Kingdom(5, 6). Subsequently, parallels have been drawn between the presenting features of this syndrome and other known conditions, including complete, incomplete and atypical Kawasaki Disease (with or without coronary artery dilatation), toxic shock syndrome, and less commonly, Macrophage Activation Syndrome (MAS) or Haemophagocytic Lymphohistiocytosis (HLH). Definitions of this novel inflammatory condition have been published by the Royal College of Paediatrics and Child Health (RCPCH)(7), the Centre for Disease Control(8) and the World Health Organisation(9). As these definitions are based on relatively small numbers of children seen, variation exists. For the purposes of this paper, which focuses on the opinions of UK clinicians, the RCPCH definition, which names the condition '*Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS)'* has been used.

It rapidly became apparent that there are many clinical uncertainties regarding this new disease syndrome. These include the prevalence, apparent differing clinical phenotypes, variable severity, the clinical course, and optimal management. To provide clarity to UK clinicians, NHS England led a process to develop national clinical management guidance through a rapid consensus exercise. The process also explored where equipoise exists for the planning of formal research trials including children with PIMS-TS. Given the status of PIMS-TS as a new syndrome, clinical consensus combined with experience in treating the initial cases was the starting point in the process of constructing a clinical guideline and defining key areas of research. The UK Randomised Evaluation of COVID-19 (RECOVERY) trial (https://www.recoverytrial.net/) steering committee made the trial protocol (including anti-inflammatory agents) available to children with COVID-19 and related inflammation prior to NHS England initiating the consensus process. Therefore, enrolment to the RECOVERY trial, and future studies, were included within the scope of the consensus process.

A Delphi process is a well-established method for achieving consensus from multiple groups of stakeholders(10), and has been used within healthcare for multiple reasons, including development of core outcome sets and identification of metrics for monitoring quality of care (11-16). Broadly, a Delphi process involves asking respondents to complete sequential questionnaires with group opinion fed-back to individual participants in between completion of the questionnaires. Children with PIMS-TS require the expertise of clinicians who specialise in immunology, infectious diseases, rheumatology, cardiology, intensive care, general paediatrics, haematology and in some cases surgery, radiology and neurology. The aims of this study were therefore to seek consensus from participants within these key stakeholder groups regarding the diagnosis and management of children with suspected PIMS-TS, to identify areas where equipoise existed in order to inform subsequent research, and to explore whether consensus existed with regards to how children with PIMS-TS could be enrolled in the RECOVERY trial.

Methods

Ethics approval

This work was considered quality improvement by the Health Research Authority, and therefore approval by an ethics review board was not required.

Summary

A three-phase online Delphi process was used to identify statements where a national multidisciplinary panel agreed that consensus existed regarding the investigation and management of children with suspected PIMS-TS. A consensus meeting was conducted via a web-based platform to review statements where consensus had not been achieved during the Delphi process. A face to face consensus meeting was not conducted due to COVID-19 social distancing restrictions.

Scope

The consensus statements are applicable to children in the UK suspected of having PIMS-TS. They may also be applicable in other high-income countries, although the views described only represent those of UK clinicians. They are less likely to be applicable in countries where infrastructure and access to healthcare and treatments are significantly different to that of the UK.

Participants

Clinicians were purposively selected to cover the range of multidisciplinary clinical and research expertise needed to diagnose and manage children with PIMS-TS, and were invited personally, by email or by telephone to participate in the study through sub-speciality groups and personal contacts. Those who agreed to participate were divided into three panels in order to facilitate feedback throughout the Delphi process:

1. Paediatric Infectious Diseases and Immunology, Paediatric Rheumatology, Paediatric Respiratory, Pharmacist with specialist expertise in biological therapy
2. Paediatric Cardiology, Paediatric Intensive Care and Transport, Paediatric Haematology
3. General Paediatricians, Paediatric Radiologists and Paediatric Surgeons.

Representation in all three panels was sought, but experience in management of children with PIMS-TS, and the need to rapidly conclude the consensus process were prioritised over seeking wider engagement of clinicians or achieving numerical balance between the panels.

Information sources

Statements for assessment in phase one of the Delphi process were derived by the study management group from reviews of the existing literature and expert opinion, including draft local guidelines. Participants in the Delphi process were asked in phase one and phase two to propose additional statements which they considered necessary for assessment. These were reviewed by the study management group, and if falling within the scope of the study, were included for assessment in the subsequent phase.

Consensus process

A three-phase online Delphi process was conducted concurrently for the three panels. Results of the Delphi process were discussed in a virtual, online, consensus meeting attended by a representative sample of experts from each panel. The consensus meeting was chaired by an independent, non-voting, non-paediatric clinical academic experienced in Delphi methodology.

In phase one of the Delphi process, participants were asked to score statements from 1-9 based on how much they agreed with the statement. Scores of 1, 2 and 3 were 'disagree with statement', 4, 5 and 6 were 'agree with statement' and 7, 8 and 9 were 'strongly agree with statement. Participants were asked to score a statement 'don't know' if they did not consider themselves to have expertise in that area. In phase two, participants were shown graphical and numerical representations of how their panel overall had scored each statement and were asked to re-score the statements taking that information into account. In phase three, participants were shown graphical and numerical representations of how all three panels had scored each statement and asked to re-score the statements taking that information into account.

Participants were sent a reminder email if they had not completed the phase with 24 hours remaining. Participants who did not complete a phase were deemed to have withdrawn from the study and were not invited to take part in subsequent phases.

Consensus definitions

'Consensus agreement' was defined as ≥70% of participants scoring a statement 7-9, and <15% of participants scoring a statement 1-3 in all three individual panels. 'Consensus disagreement' was defined as ≥70% of participants scoring a statement 1-3, and <15% of participants scoring a statement 7-9 in all three individual panels. Following phases two and three, if statements met 'consensus agreement' or 'consensus disagreement', they were excluded from the next stage of assessment.

Statements where consensus had been achieved in two out of three panels at the end of phase three were discussed in the consensus meeting. Statements discussed at the consensus meeting were assessed using a simple binary vote of 'agree' or 'disagree'. Those statements where more than 70% of participants either agreed or disagreed with the statement were deemed to have met consensus. If consensus was not met following the initial vote, in depth discussions were held to understand why disagreement existed and were followed up with a second vote. Where participants felt agreement could be achieved with minor modifications to the statements, these modifications were made.

Formation of the guidance

The final guidance is formed from those statements which met 'consensus agreement' or 'consensus disagreement' after phase two, phase three, or the consensus meeting.

Patient and public involvement

Whilst in most healthcare related Delphi processes it has been appropriate to involve patients or the public as key stakeholders, it was felt that the clinical expertise required to assess the statements around which consensus was required for development of this clinical management

pathway precluded inclusion of these groups. Patients and the public were therefore not involved in either the design or conduct of this study.

Results

A total of 98 participants were invited to contribute in phase one of the Delphi process, 46 (47%) of whom completed all three phases (Table 1). Nine participants attended the consensus meeting (Table 1).

Table 1: Participants

Panel	Invited to participate	Completed phase 1 n(% of invited)	Completed phase 2 n(% of invited)	Completed phase 3 n(% of invited)	Attended consensus meeting n(% of invited)
1	51	40 (78%)	32 (63%)	25 (49%)	3 (43%)
2	22	17 (77%)	11 (50%)	11 (50%)	4 (80%)
3	25	15 (60%)	13 (52%)	10 (40%)	2 (40%)
Total	98	72 (73%)	56 (57%)	46 (47%)	9 (53%)

Panel 1: Paediatric Infectious Diseases and Immunology, Paediatric Rheumatology, Paediatric Respiratory, Pharmacist with specialist expertise in biological therapy;
Panel 2: Paediatric Cardiology, Paediatric Intensive Care and Transport, Paediatric Haematology;
Panel 3: General Paediatricians, Paediatric Radiologists and Paediatric Surgeons.

217 statements were assessed in phase one, 35 statements were added for assessment in phase two, and 3 statements added for assessment in phase three. Following phase two, 68 statements met consensus agreement, and 14 statements met consensus disagreement, and therefore a total of 82 statements were dropped from phase three. Of the 173 statements assessed in phase three, 22 met consensus agreement, and 10 met consensus disagreement, and were therefore dropped from the consensus meeting. 102 statements achieved consensus in no panels or only one panel and were therefore excluded from discussion at the consensus meeting. 39 statements met consensus for agreement or disagreement in two out of three panels and were therefore eligible for discussion at the consensus meeting. Six of these statements, where 'consensus disagreement' had been achieved in two panels were not discussed, as their recommendations were already covered by statements where consensus agreement had been achieved, and they would have been superfluous in the final guidance. Of the statements discussed, 21 met consensus for agreement, and 5 met consensus for disagreement following the consensus meeting. At the end of the process, there was consensus agreement for 111 statements, consensus disagreement for 29 statements, and no consensus achieved for 115 statements. The final guidance is therefore formed from the 140 statements where consensus agreement was achieved throughout the consensus process (Figure 2). Supplementary material 1 lists all assessed statements and their final consensus decisions. Figure 3 and Boxes 1a – 4a summarise the guidance based upon the 140 statements where consensus was achieved.

Discussion

Use of an online Delphi process and virtual consensus meeting has enabled a National multidisciplinary panel to achieve consensus around 140 statements relating to the investigation and management of children with PIMS-TS, and participation of these children in studies including, but not limited to, DIAMONDS (https://www.diamonds2020.eu), ISARIC-CCP/UK (https://isaric4c.net) and the RECOVERY trial (https://www.recoverytrial.net). Based upon the results of this process, it has been possible to develop a national consensus management pathway for the care of children with suspected PIMS-TS within 6 weeks of the need for such guidance becoming apparent. However, all participants recognise that this process has relied on clinical opinion based upon the limited evidence currently available. Until further evidence materialises, this management pathway can provide a framework for managing children with suspected PIMS-TS. The sections relating to research will help ensure the views of a wide range of clinicians are taken into account when seeking amendments for existing trials or designing future trials. Taking account of these views could maximise clinicians' willingness to recruit to clinical trials.

The key strength of this work was the ability to achieve consensus relating to the management of a novel, complex condition, based upon quantitative data, from a relatively large number of participants, spread across multiple geographic regions. It was conducted in a short period of time, in the middle of a global pandemic, without the ability to conduct face to face meetings, large round table discussions, or focus groups. To our knowledge, such a process has not been attempted before. There are however three key limitations to the study. Firstly, the output and recommendations from a Delphi process can only ever be as robust as the statements that are assessed within it. As the statements assessed here were all developed based-upon level five evidence (expert opinion), the guidance can only ever seek to summarise this expert opinion. Once higher levels of evidence become available, these should be incorporated into future guidance in order to ensure that the management pathway remains relevant and up to date. Given the cost-efficient, timely nature of the conducted Delphi process, it would be feasible to re-run the process when significant new data comes to light, and to use the results of the process to inform development of guidance. The second limitation of the study is that a smaller number of participants were recruited from stakeholder groups than would normally be aimed for in conduct of a Delphi process, and the scope of the work precluded inclusion of parents, or members of the public in the process. Despite this, adequate representation was achieved across all panels, with multiple representatives from each stakeholder group participating. However, had time, and the need to ensure clinical expertise of participants not been such pressing factors, it would have been preferable to seek opinions from a larger number of stakeholders. Finally, the consensus meeting included only a few representatives of each stakeholder group due to the online format and need to ensure opinions from all stakeholder groups during the meeting.

The management pathway created from this consensus process generally aligns well with the small evidence base that currently exists for similar clinical conditions. In particular, the guidance focuses on the recognition of severe cardiac disease which has been described in both phenotypes of PIMS-TS(5, 17). It includes a management pathway for Kawasaki-like Disease which aligns with current guidance for the management of Kawasaki Disease(18), and may help to address the current variation in treatment which is occurring regarding the indications for intravenous immunoglobulin (IVIg)(17), and to support the use of IVIg in clinical trials in PIMS-TS.

Within the Delphi process, significant discrepancy was noted between panel one (paediatric medical specialists with training in immunology) and panel two (paediatric intensivists, cardiologists and haematologists) with regards to whether children with PIMS-TS should be cared for in units with extra-corporeal membrane oxygenation (ECMO) availability. 90% of panel two strongly agreed this should be the case, whilst 86% of panel one disagreed. Data collected by the national British Paediatric Surveillance Unit (https://www.rcpch.ac.uk/work-we-do/bpsu) PIMS-TS surveillance study will help to provide the underpinning research to resolve this discrepancy. Until such data are available, we would reinforce the need for significant clinical decisions relating to the management of children with PIMS-TS to be taken within a multi-disciplinary setting, with adequate representation from all core members of the multidisciplinary team. Other areas where the need for future research have been highlighted by this Delphi process include identification of the most appropriate immunomodulatory therapy for use in children with the non-specific PIMS-TS phenotype, and whether IVIG or methylprednisolone should be first line therapy for children with both phenotypes of PIMS-TS.

This is the first published consensus management pathway relating to the treatment of children with PIMS-TS(8, 19). It is based on consensus expert opinion and is intended to act as a framework for the safe management of children with this condition. As new, higher level evidence become available, the guidance will be updated.

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