Clinical Medicine 2022 Vol 22, No 3: 266–70

Understanding the diagnosis and management of multisystem inflammatory syndrome in adults (MIS-A) in the UK: results of a national Delphi process

Authors: Lauren Hookham,[A] Corinne Fisher,[B] Jessica J Manson,[B] Matt Morgan,[C] Geraldine O'Hara,[D] Phil Riley,[E] Rachel S Tattersall[F] and Anna L Goodman[D]

ABSTRACT

Infection with SARS-CoV-2 may trigger a delayed hyper-inflammatory illness in children called paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS). A similar syndrome is increasingly recognised in adults termed multisystem inflammatory syndrome in adults (MIS-A) and may present acutely to medical or surgical specialties with severe symptoms, such as acute abdominal pain or cardiogenic shock. No national guidelines exist in the UK for the management of MIS-A and there is limited evidence to guide treatment plans. We undertook a national Delphi process to elicit opinions from experts in hyperinflammation about the diagnosis and management of MIS-A with the dual aim of improving recognition and producing a management guideline. Colleagues in paediatrics successfully initiated a national consensus management document that facilitated regional multidisciplinary referral and follow-up pathways for children with PIMS-TS, and we propose a similar system be developed for adult patients across the UK. This would facilitate better recognition and treatment of MIS-A across the multiple specialties to which it may present as well as enable follow-up with specialty services post-discharge.

KEYWORDS: COVID-19, MIS-A, PIMS-TS, hyperinflammation, multisystem inflammatory syndrome in adults

DOI: 10.7861/clinmed.2021-0700

Introduction

SARS-CoV-2 is recognised to trigger a rare, delayed critical inflammatory/hyperinflammatory illness some time (usually weeks) after infection. The diagnosis of or exposure history to SARS-CoV-2 may not be easily elicited and swabs for SARS-CoV-2 may be negative at presentation. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS; also known as multisystem inflammatory syndrome in children (MIS-C)) was reported in children and young people in the UK, USA and Europe as early as April 2020.[1–6]

This severe phenotype of SARS-CoV-2-related inflammatory disease is increasingly acknowledged to affect adults, with a review of cases first published by the Centers for Disease Control and Prevention (CDC) in October of 2020.[7] The clinical presentation may be with acute, severe abdominal pain (such that patients are triaged for surgical opinions) or unremitting fevers treated as sepsis refractory to antibiotics and, in severe cases, there is cardiogenic shock. A preliminary case definition for adults was devised, stating that multisystem inflammatory syndrome in adults (MIS-A) should be considered in adults with fever and inflammation (raised inflammatory markers) without evidence of a severe respiratory illness, involvement of one more extrapulmonary organ system and no evidence of an alternative diagnosis.[7] As knowledge of the illness has progressed over the course of the pandemic, the case definition has been updated to a patient aged >21 years, hospitalised for >24 hours or with an illness resulting in death, and meeting clinical and laboratory criteria. Clinical criteria must include subjective or documented fever for >24 hours prior to hospital admission or within the first 72 hours of admission. Primary clinical criteria include severe cardiac illness, rash and non-purulent conjunctivitis. Secondary clinical criteria include new onset neurological signs and symptoms; shock; or hypotension not attributable to medical therapy, abdominal signs, thrombocytopenia (platelet count $<150 \times 10^9$/L), and symptoms such as pain, vomiting or diarrhoea. Laboratory evidence should include elevated levels of at least two of C-reactive protein (CRP), ferritin, interleukin 6, erythrocyte sedimentation rate or procalcitonin. There should also be evidence of a positive SARS-CoV-2 test for either current or recent infection (RT-PCR, serology or antigen detection).[8]

Estimates for population-based incidence of PIMS-TS has been estimated at 316 cases per million SARS-CoV-2 infections.[9] In the USA, 11% of the 5,973 cases reported to the CDC in those under 21 years of age were over 16 years old. This suggests rates in those aged 16–20 years would be at least ~35 cases per million

Authors: [A]clinical research fellow, St George's University, London, UK; [B]consultant rheumatologist, University College Hospitals NHS Foundation Trust, London, UK; [C]consultant in adult critical care, University Hospital of Wales, Cardiff, UK; [D]consultant in infectious diseases, Guy's and St Thomas' NHS Foundation Trust, London, UK; [E]consultant in paediatric and adolescent rheumatologist, Manchester University NHS Foundation Trust, Manchester, UK; [F]consultant rheumatologist, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

SARS-CoV-2 infections, though the true incidence in those aged >20 years is not ascertained and is likely to be under-diagnosed.[10] A recent systematic review identified a total of 221 cases globally.[11] The true incidence of MIS-A is unknown and, although it is a rare condition, it is likely under-diagnosed.

In a US-based cohort of MIS-A patients (meeting the MIS-A criteria), the majority were not diagnosed by the primary clinical team, highlighting that many cases may be missed if physicians or surgeons of adults do not consider the diagnosis.[12] If the hyperinflammation of MIS-A progresses to cardiogenic shock, there may be resulting excess morbidity and mortality. Due to the small number of cases, there is no current evidence base to guide immune suppression, but steroids, intravenous immunoglobulin and biologic drugs are currently used based on treatments used in PIMS-TS; these, in turn, are being extrapolated from treatments for Kawasaki disease and other hyperinflammatory syndromes, such as haemophagocytic lymphohistiocytosis (HLH).

A Delphi process is an established way of achieving consensus from experts and stakeholders.[13] It has been utilised in healthcare settings and, of note, to create guidance for physicians in the UK on the diagnosis and management of PIMS-TS in children.[14–17] Given the uncertainties surrounding diagnosis and management with MIS-A, this working group sought to undertake a national Delphi process to elicit stakeholder opinions from experts in hyperinflammation about MIS-A. The aim was to produce a generic guideline to improve recognition of the syndrome in adult medicine and surgery as well as to increase awareness of delayed hyperinflammatory complications of SARS-CoV-2 in adults in the UK.

Methods

A survey was developed by working group members and sent to a national multidisciplinary panel designed to elucidate the approach to diagnosis and classification of MIS-A in a representative group of adult physicians. Statements in the questionnaire were derived by working group members from review of the existing literature, local and national guidelines available for PIMS-TS and MIS-A, and expert opinion. The full survey can be seen in supplementary material S1.

All participants were consultant clinicians who were selected by working group members to cover a range of multidisciplinary expertise and geographical areas. As MIS-A is a new condition, most adult physicians would have managed a small number of patients. However, paediatricians are likely to have seen more patients with PIMS-TS. Clinicians were, therefore, selected with a broad range of experience including rheumatology (including paediatric), infectious diseases, acute medicine and intensive care. Participants were invited personally by the study group to undertake the survey via e-mail. If participants were unable to complete the survey, they were offered the opportunity to nominate colleagues for the working group to approach. Patient groups and the public were not involved in the design or conduct of this study due to the specific clinician opinion nature of the questions.

Participants were given 2 weeks to complete the survey and a reminder e-mail was sent after 7 days. If there was no response to the survey or to e-mail communication after 2 weeks, then the participant was assumed to not be interested in being a participant. Alternative members were then sought from the same specialty to ensure an equal balance was met across the group. Feedback from Delphi participants regarding questionnaire statements were taken both within the survey and informally via e-mail to working group members. Surveys were completed between May 2021 and August 2021.

Table 1. Delphi members by specialty

Specialty	Participants (some are dual specialists), n
Infectious diseases	2
Intensive care	2
Immunology	1
Cardiology	1
Acute medicine	2
Respiratory	1
Rheumatology (including paediatric and adolescent rheumatology)	3
Haematology	1

Table 1 shows the breakdown of Delphi members by specialty.

A total of 35 experts were invited to complete the survey. Four members declined, stated they had not seen enough cases to consider themselves able to give advice. In total, 12 members completed the survey. The remaining invited experts did not complete the survey. The results of the survey were analysed, and statements with group consensus (agreement or disagreement) were included in the final report.

Ethical approval was not sought or required for this service evaluation and development. The project was registered as an audit at Guy's and St Thomas' NHS Foundation Trust and was approved.

Results

All of the statements met group consensus for agreement. The full survey results may be seen in supplementary material S2. Of note, this survey was completed prior to the updated CDC case definition.[8]

Recognition and investigation

Essential diagnostic criteria (or major criteria) should include:

- fever
- severe dysfunction of one or more extrapulmonary organ systems (eg hypotension or shock; cardiac dysfunction; arterial or venous thrombosis or thromboembolism; or acute liver injury)
- evidence of severe inflammation (eg elevated CRP, ferritin, D-dimer or interleukin-6)
- no obvious microbial cause of illness
- evidence of COVID-19 (RT-PCR, antigen test or serology positive) or likely contact with patients with COVID-19.

Non-essential diagnostic criteria (or minor criteria) should include:

- acute abdominal pain, including gastroenteritis
- rash

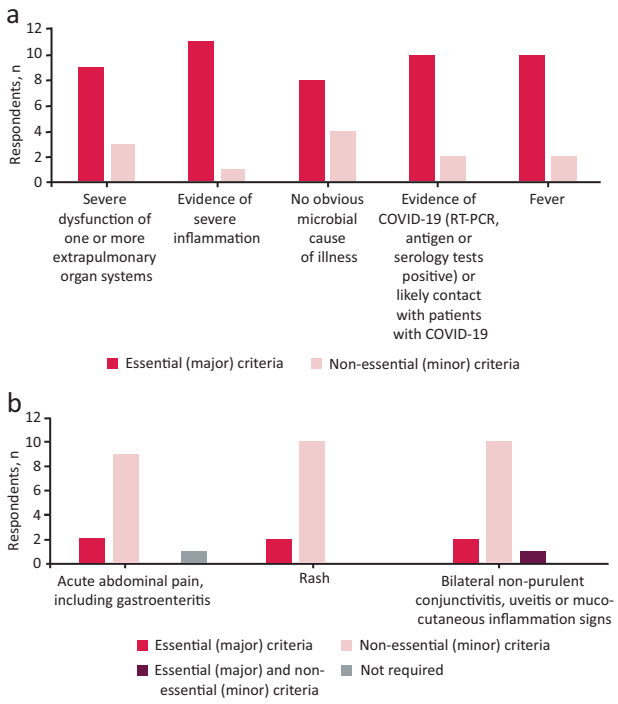

Fig 1. Criteria as defined by Delphi members. a) Major criteria. b) Minor criteria.

- bilateral non-purulent conjunctivitis, uveitis or muco-cutaneous inflammation signs.

The responses by Delphi members can be seen in Fig 1.

Members agreed that a broad panel of investigations should be undertaken for those with suspected MIS-A. These should include:

- SARS-CoV-2 status checked by RT-PCR and antibody tests
- Blood cultures, urine cultures, sputum culture and viral respiratory screen
- 12-lead electrocardiography (ECG)
- Chest X-ray
- Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, if neurological signs or symptoms.
- Abdominal imaging (ultrasound or CT depending on availability and urgency), if abdominal signs or symptoms.
- Echocardiography with a view of the coronary arteries.

Members noted that patients with MIS-A may develop cardiogenic shock necessitating investigations of cardiac function. They recommended that patients should have a daily ECG as an inpatient until stable for 3 days and at least weekly echocardiography while they are an inpatient regardless of whether they receive treatment. The echocardiography should review the coronary arteries and may be supported by additional CT angiography or cardiac MRI if available when echocardiography of coronary arteries is not. Adults with proven cardiac dysfunction should have a cardiac MRI with stable cardiac function being a criterion for discharge. Patients with coronary artery aneurysms should be discussed with a cardiologist and have an inpatient contrast-enhanced CT of the coronary vessels. All adults with coronary artery aneurysms should be discussed with a cardiologist and with a haematologist regarding long-term antiplatelet therapy and anticoagulation. There was no group consensus on the use of aspirin (high or low dose), however, the group did agree that adults who improve clinically and with improvement of inflammatory markers who are on high-dose aspirin can be stepped down to low-dose aspirin.

Delphi members advised that a multidisciplinary team (MDT) discussion should be a priority for patients with suspected MIS-A and this should occur within 24 hours to aid risk stratification. Though this will require resources and organisation, a similar system was initiated by paediatric colleagues for the management of children with PIMS-TS.

Specialty teams can aid the management of patients with MIS-A. This includes a spectrum of specialties that includes but is not limited to infectious diseases, immunology, rheumatology, cardiology, intensive care, haematology, surgery, respiratory, neurology and pharmacy. People with MIS-A can deteriorate rapidly. Delphi respondents agreed that escalation to level 3 care should be considered for adults with single or multiple organ dysfunction who meet criteria for MIS-A. Patients with evidence of cardiac involvement (elevated troponin, elevated brain natriuretic peptide (BNP), abnormal ECG, abnormal coronary arteries on echocardiography or abnormal coronary arteries on contrast-enhanced CT) should also be cared for in a level 2/3 unit with availability of cardiology on site where possible.

Management

Severe disease can be identified as those patients with shock (prolonged capillary refill time, multiple fluid boluses, resistant hypotension, raised lactate and need for inotropes). Cardiac features of severe disease include abnormal ECG and abnormal echocardiography (including left ventricular failure and coronary aneurysm). Other cardiac features that may indicate the need for treatment include an elevated or rising troponin, and elevated or rising BNP.

Other investigations that may indicate that treatment is required include:

- elevated creatinine
- elevated or rising lactate dehydrogenase
- rising or elevated D-dimer
- high CRP
- rising or elevated ferritin
- elevated or rising lactate.

Delphi members agreed that management of severe disease should include intravenous (IV) immunoglobulin (IG) if there is evidence of coronary artery abnormality or toxic shock syndrome. The dose of IVIG should be 2 g/kg (calculated using ideal body mass index; in single or divided dose depending on clinical picture and cardiac function). Patients should receive early IV methylprednisolone and receive gastro-protection (ie with a proton pump inhibitor). Broad spectrum antibiotic cover should be initiated, with antibiotic focus after culture results. Antibiotics may be stopped if cultures are negative and there is no other evidence of sepsis. If patients meet the criteria for HLH, then they should be managed according to HLH guidelines.

IV methylprednisolone (if not already commenced) should be considered the next treatment option in adults who remain unwell 24 hours after IVIG infusion. Patients on IV methylprednisolone may be stepped down to oral prednisolone when they show an

improvement in their inflammatory markers, are apyrexial and are clinically stable.

Adults who remain unwell 24 hours after commencing IVIG and IV methylprednisolone should be considered for biological agents. The decision to commence a biologic, as well as the agent of choice, should be an MDT decision.

If patients do not have criteria of severe disease, consider treating with IVIG or parenteral steroids if there is symptomatic evidence of progressive disease, prolonged fever or evidence of coronary artery disease.

Discharge and follow-up

Delphi members agreed that patients should be followed up initially 1–2 weeks after discharge and should have a follow-up appointment offered 6 weeks after discharge (even if seen earlier than this). All patients should have follow-up echocardiography after discharge, even if the initial echocardiography is normal. An early outpatient contrast-enhanced CT of the coronary vessels (if not performed as an inpatient) should be undertaken for adults who had a severe phenotype of MIS-A. All patients should be approached to consider biobanking for future research. Patients should also be advised to be vaccinated against SARS-CoV-2.

Discussion

This national multidisciplinary Delphi process has enabled key components of the diagnosis, management and follow-up of patients with MIS-Ato be developed. There are limitations to our approach. Our Delphi group participation represents a small number of clinicians. We would ideally have recruited more participants and included patient and next of kin stakeholder groups. Recruitment was limited by the relative inexperience of adult physicians in PIMS-TS/MIS-A: a key reason for completing this work. We did not recruit patients or patient representatives as this Delphi was a physician only paper exercise but in a wider repetition of this work, we would seek to do this.

The major and minor criteria in this Delphi process are a clinical aid and not a definitive diagnostic tree. The aim of this piece of work was to raise awareness of a rare condition in an at-risk patient group. The CDC, subsequent to our survey, has provided an updated case definition that should be utilised by clinicians.[8]

The group did not reach consensus on the preferred name of the syndrome, with MIS-A/AIMS, MIS-A/AIMS-TS, adult-onset PIMS-TS and COVID-associated hyperinflammation receiving support from Delphi members (Fig 2). Nor was there consensus on the lower age of diagnosis. The variability in naming the syndrome may lead to confusion. In the meantime, MIS-A has gathered traction internationally with associated ICD-10 coding and an amended case definition.[8,18] The results of this Delphi survey mirror this new case definition. MIS-A represents a spectrum of disease in continuity with PIMS-TS, and so the age of diagnosis between the two clinical conditions is likely to be arbitrary. We believe it is reasonable to state that if a patient is triaged to the adult-take and be managed by adult general medicine or specialty teams, then the prefix or suffix 'adult' may be added.

Treatment guidelines for PIMS-TS have been recently updated (after completion of this Delphi study) to prioritise corticosteroids over IVIG.[19] It is likely that if the Delphi process were repeated, a similar approach would be recommended in MIS-A. The level of experience of this condition among physicians is likely to increase as the pandemic continues and as evidence accumulates over the pandemic, treatment recommendations are likely to change and treating clinicians will need to keep abreast of these developments.

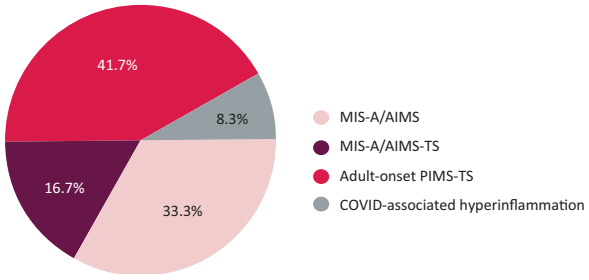

Fig 2. Preferred name of syndrome.

Recognition of MIS-A and prompt management should be the focus for healthcare professionals.

Multidisciplinary management is vital for patients with MIS-A, however, not all hospitals will have inpatient referral services for some of the specialties required. It is likely that regional hubs of expertise and knowledge will be required so that district general hospitals can quickly access the opinion and advice of tertiary specialists in one referral. This would facilitate access to multiple specialties simultaneously as well as enable follow-up with specialty services once discharged. This model was utilised with success for the management of children with PIMS-TS and sets the standard for care in adult patients. An example of guidelines for the management of PIMS-TS are provided by Evelina London Children's Healthcare.[20] PIMS-TS is currently included as an indication for IVIG in the commissioning criteria, however, at the current time, MIS-A is not. This requires an application to a panel for approval of use.[21] There is subsequently inequity in access to IVIG for the same condition presenting across different age groups.

The recruitment of children with PIMS-TS into clinical trials also enabled clinicians to develop treatment guidelines from expert level advice to more robust evidence from randomised controlled trials. Similar clinical trials are needed in the adult population to elicit evidence-based practices and guidelines for the management of these patients.

As SARS-CoV-2 continues to infect thousands of adults per day in the UK, it is inevitable that adults will continue to present to health services with MIS-A. Physicians across all specialties and in all settings should be aware of its presentation and of the urgency of triage and treatment to prevent unnecessary morbidity and mortality. ■

Supplementary material

Additional supplementary material may be found in the online version of this article at www.rcpjournals.org/clinmedicine:
S1 – Full MIS-A Delphi survey.
S2 – Full MIS-A survey results.

Acknowledgements

We would like to thank the Delphi survey respondents for taking time to complete this survey.

Conflicts of interest

Dr Anna Goodman is on the editorial board for *Clinical Medicine*.

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Address for correspondence: Dr Lauren Hookham, Department of Infection and Immunity, St George's University, London, Cranmer Terrace, London SW17 0RE, UK.
Email: lhookham@sgul.ac.uk
Twitter: @lauren_hookham