Scottish Paediatric & Adolescent Rheumatology Network

Initial diagnosis of Macrophage Activation Syndrome

BACKGROUND

Macrophage activation syndrome (MAS) is a rare hyperinflammatory condition, one of the increasingly-recognised cytokine storms(1)(2), seen in children and adults with underlying rheumatological disorders. MAS requires prompt recognition and aggressive treatment as untreated the mortality rate is 8-22%(3)(4).

MAS is a known rare complication of rheumatological disorders, including systemic onset JIA (SoJIA), SLE, any vasculitis, Kawasaki's Disease and autoinflammatory conditions. There are published, diagnostic criteria for those with SoJIA and JSLE (see below). These may be helpful in a child already diagnosed with one of these conditions.

However, MAS may be the first presentation of disease and should still be considered if the child is not previously known to have a rheumatological diagnosis. A recent case series conducted in Scotland(5) showed that in the majority of cases of MAS (68%) occurred during the first presentation of illness. MAS should therefore be considered in any child presenting acutely unwell with a fever and without a clear diagnosis. Its precise incidence is not known but it is likely that it is under-diagnosed and therefore more common than is currently estimated.

MAS is part of a spectrum of cytokine storms and includes:

- Primary haemophagocytic lymphohistiocytosis (HLH)
- Secondary HLH (this includes MAS, the term used in the context of rheumatological disorders, and HLH driven by infection (especially EBV) and malignancy(6)(7)(8)
- PIMS-TS (Paediatric multisystem inflammatory syndrome temporally associated with covid-19). This is also described in some cohorts outwith the UK as MIS-C and a similar process in adults has been termed 'MIS-A'.

SCOPE

This guideline focusses on MAS in the context of rheumatological disorders. If the child does not have a known underlying diagnosis, the differential diagnoses of primary or secondary HLH and MAS as part of the initial presentation of a rheumatological disorder should be considered.

DEFINITION

Laboratory tests
Ferritin higher than would be expected for diagnosis (may be extremely high, however MAS should be considered even when levels ≥500µg/l)(9)
Low or falling ESR, in the context of active inflammatory disease or high CRP
Low leucocyte count
Low/falling/unexpected normal platelet count
Low/falling/unexpected normal fibrinogen
Abnormal coagulation
Elevated LDH
Elevated AST, ALT, GGT, Bilirubin
High triglycerides
Low sodium
Bone marrow aspiration showing haemophagocytosis *(not always present and only required if diagnostic uncertainty)*

Clinical signs
Fever (usually high and may be unremitting)
Rash
Hepatosplenomegaly (new)
Arthritis
Neurological manifestations (irritability, confusion, lethargy, headache, seizures, coma)

URGENT INVESTIGATIONS

These should be repeated daily if MAS suspected as trends are more helpful than absolute numbers.

- Ferritin – labs will have to be informed that test needs to be run urgently
- FBC
- ESR and CRP
- Coagulation screen, including fibrinogen
- D-dimers
- Triglycerides
- U+E, LFTs (including AST)
- LDH
- Troponin, NT pro-BNP

Investigations to be considered:

- Infection screen as appropriate: As clinical features of MAS and sepsis overlap
- Bone marrow aspiration (however, if this is normal it does not exclude MAS)
- Primary HLH screening assays: perforin, Granule Release Assay(GRA), and SAP/XIAP in males (see below)

PUBLISHED DIAGNOSTIC & CLASSIFICATION CRITERIA

The published classification criteria for diagnosis of MAS in SoJIA and SLE are outlined below. These were primarily developed for research purposes but can be a useful guide for making a diagnosis. Reaching a specific diagnostic cut-off is less important clinically and monitoring trends are more useful in making the diagnosis.

PRINTO/EULAR 2016 Classification criteria(10) for MAS in SoJIA

Febrile patient with known SoJIA with:	
Ferritin	>684ng/ml
And any 2 of the following:	
Platelet count	≤181 x 109/litre
Aspartate asminotransferase	>48 units/litre
Triglycerides	>156mg/dl
Fibrinogen	≤360mg/dl

Preliminary diagnostic guidelines for MAS complicating SoJIA(11)

Laboratory criteria	
Decreased platelet count	≤262 x 10^9/L
Elevated levels of aspartate aminotransferase	>59 U/L
Decreased white blood cell count	≤4.0 x 10^9/L
Hypofibrinogenemia	≤2.5 g/L
Clinical criteria	
Central nervous system dysfunction	Irritability, disorientation, lethargy, headache, seizures, coma
Haemorrhages	Purpura, easy bruising, mucosal bleeding
Hepatomegaly	≥3 cm below the costal arch
Histopathological criterion	
Evidence of macrophage hemophagocytosis in the bone marrow aspirate.	
- *The diagnosis of MAS requires the presence of 2 or more laboratory criteria or, 2 or 3 or more clinical and/or laboratory criteria. A bone marrow aspirate for the demonstration of haemophagocytosis may be required only in doubtful cases. The aforementioned criteria are of value only in patients with active SoJIA. The thresholds of laboratory criteria are provided by way of example only.* - *The clinical criteria are probably more useful as classification criteria rather than as diagnostic criteria because they often occur late in the course of MAS and may therefore be of limited value for early diagnosis of MAS.* - *Other abnormal clinical features in SoJIA-associated MAS may include: non-remitting high fever, splenomegaly, generalized lymphadenopathy, and paradoxical improvement of signs and symptoms of arthritis.* - *Other abnormal laboratory findings in SoJIA-associated MAS may include: anaemia, erythrocyte sedimentation rate fall, elevated levels of alanine aminotransferase, increased bilirubin, presence of fibrin degradation products, elevated lactate dehydrogenase, hypertriglyceridemia, low sodium levels, decreased albumin and hyperferritinaemia.*	

Preliminary diagnostic guidelines for MAS as a complication of Juvenile SLE(12)

Clinical criteria
Fever (>38°C)
Hepatomegaly (≥3 cm below the costal arch)
Splenomegaly (≥3 cm below the costal arch)
Haemorrhagic manifestations (purpura, easy bruising, or mucosal bleeding)
CNS dysfunction (irritability, disorientation, lethargy, headache, seizures, or coma)
Laboratory criteria
Cytopenia affecting 2 or more cell lineages (white blood cell count ≤4.0x10^9/l haemoglobin ≤90 g/l, or platelet count ≤150 x 10^9/l)
Increased aspartate aminotransferase (>40 units/l)
Increased lactate dehydrogenase (>567 units/l)
Hypofibrinogenemia (fibrinogen ≤1.5 g/l)
Hypertriglyceridemia (triglycerides >178 mg/dl)
Hyperferritinemia (ferritin >500 µg/l)
Histopathologic criterion
Evidence of macrophage hemophagocytosis in the bone marrow aspirate
- *The diagnosis of macrophage activation syndrome requires the simultaneous presence of at least 1 clinical criterion and at least 2 laboratory criteria. Bone marrow aspiration for evidence of macrophage haemophagocytosis may be required only in doubtful cases.* - *These criteria were developed using patients with active juvenile systemic lupus erythematosus (SLE) without macrophage activation syndrome as a control group. As such, they may not be powerful enough to distinguish macrophage activation syndrome from particular infectious complications.*

INITIAL TREATMENT

MAS can be fatal if left untreated and urgent investigation and management is essential.

There should be a low threshold for seeking expert advice in any child with fever and hyperferritinaemia. Paediatric Rheumatology should be contacted for all children with a rheumatological diagnosis presenting with fever and hyperferritinaemia (especially serum ferritin ≥500µg/l).

Treatment is not standardised and should be directed towards treatment of the underlying disease. If there is diagnostic uncertainly BMA may be indicated prior to starting treatment and will involve multi-disciplinary discussion with Rheumatology, Haematology and often the ID teams.

Treatment should be started in consultation with a specialist in Paediatric Rheumatology but may include:

Steroids:

- Should be started promptly in most patients with MAS once relevant investigations have been taken. An exception to this might be found in SoJIA where monotherapy with anakinra maybe considered. This decision should be undertaken by an experienced Paediatric Rheumatology consultant.
- Dose: 30mg/kg IV Methylprednisolone per day (maximum dose 1gram) as single infusion (see separate guideline) given daily for 3 days
- Subsequently patients will be managed on 1-2mg/kg/day oral prednisolone
- Consideration should be given to gastro-protection (with omeprazole or lansoprazole) and calcium supplementation whilst the child is on steroids

Ciclosporin(13):

- Starting dose usually 3mg/kg BD(3) and adjust accordingly to trough levels
- 3-5mg/kg/day via enteral route(3) or 1-2mg/kg/day IV. ***Enteral route is almost always preferred.***
- Aim for trough levels between 100-150µg/L

Anakinra

Subcutaneous Anakinra(14)(15)(16):

- 1st choice biologic agent in treatment of MAS in context of SoJIA
- Has a short half life (approx 4 - 6 hours) and a wide therapeutic range
- Usually given S/C at dose of 2mg/kg once daily (max starting dose 100mg)
- Dose can be increased to a maximum of 5mg/kg/day or higher under the guidance of a specialist with experience in treating MAS
- Dose should be rounded to the nearest 10mg
- Use with caution if moderate to severe renal impairment

Intravenous Anakinra(17):

- This route is used if the child is critically unwell and there is concern about systemic absorption. This would usually be in the intensive care setting
- There are no published dose ranges for children
- Loading dose of 2mg/kg (max 100mg) given followed by continuous infusion starting at 2mg/kg/day but can be increased under specialist advice
- Anakinra has shown to be safe and does not increase mortality in patients with sepsis(18)

IV Immunoglobulin - for specific cases IVIG may also be used in combination following discussion with Paediatric Rheumatologist

Antibiotics:
Broad spectrum antibiotics should be given until bacterial infection has been excluded as per local antimicrobial guidelines.

ADDITIONAL CONSIDERATIONS

Primary HLH:

- Can have a similar presentation to secondary HLH
- Usually presents in younger children, most often in the first 2 years of life
- Discuss with ID/immunology if suspected
- Screening tests with perforin, granule release assay (GRA) and in males screening for X-linked lymphoproliferative disorders with SAP (Signal Lymphocyte Activating Molecule Associated Protein) and XIAP (X-linked Inhibitor of Apoptosis Protein) expression may be indicated

Infectious trigger:

- It is increasingly recognised that an episode of MAS may be triggered by an intercurrent infection in a child with a rheumatological diagnosis who is genetically susceptible. A thorough infectious screen should be sent including viral and bacterial throat swabs, blood cultures, urine cultures, viral and bacterial stool samples (if indicated), ASOT and viral serology/PCR for organisms such as adenovirus, EBV, CMV, HSV, VZV, HHV 6&7. Availability of viral pcr/serology testing may vary between hospitals and should be discussed on a local or regional basis.

Medications:

- In children with a rheumatological diagnosis, changing treatment may trigger an episode of MAS and biologics may affect clinical presentation (for example tocilizumab may prevent fever and CRP rise).

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NOTE
This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.