Background
MAS requires prompt recognition and aggressive treatment to prevent fatalities from this rare complication of rheumatological disorders. It should be considered in ANY known inflammatory rheumatological condition (such as systemic onset JIA, SLE, any vasculitis, Kawasaki's Disease and autoinflammatory conditions). There are published, diagnostic criteria for those with systemic JIA (Appendix 2) and SLE (Appendix 3). 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 not be excluded if the child is not previously known to have a rheumatological diagnosis. A recent case series conducted in Scotland(1) 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.

Definition
Macrophage Activation Syndrome (MAS) is a recognised complication of childhood systemic inflammatory disorders which is severe and potentially fatal. This condition is characterised by pyrexia, hepatosplenomegaly, lymphadenopathy, profound cytopenia, deranged liver function tests, deranged coagulation, and central nervous system dysfunction.

Clinical Signs
- Pyrexia, which may be unremitting
- Rash
- Hepatosplenomegaly
- Arthritis
- Purpura, haemorrhages, mucosal bleeding
- CNS dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)

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

N.B. These should be repeated daily if clinical suspicion remains as trends may be more helpful than absolute numbers
- Ferritin – labs will have to be informed of URGENT nature of test to run immediately
- FBC
- ESR and CRP
- Coagulation screen, including fibrinogen
- D-dimers
- Triglycerides
- U+E, LDH, LFTs (including AST)
- **Infection screen as appropriate:** As clinical features of MAS and sepsis overlap many patients with MAS will require empirical treatment with broad spectrum antibiotics until active bacterial infection has been adequately excluded.

Investigations to be considered
- Bone marrow aspiration (however, if this is normal is does not exclude MAS)

Early discussion with the on call Paediatric Rheumatologist should be undertaken in all cases of suspected MAS, particularly if there are any clinical features as described above and a serum ferritin ≥500µg/l.

Notes
1. Primary HLH (Haemophagocytic Lymphohistiogytosis) presents in a very similar manner, has its own diagnostic guideline(2) and may also be considered, particularly in the very young (usually presents <2years of age).
2. Infection and MAS can co-exist (or even be a trigger) so evidence of one does not automatically exclude the other.
3. Biologic drug use may affect clinical presentation and investigation results, so these should be interpreted with care in those known to be on these medications (e.g. Tocilizumab prevents pyrexia and CRP rise).

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.
Appendix 1:
Initial Treatment of Rheumatological Related MAS

Treatment is not standardised and should be directed towards treatment of the underlying disease. This should be done in consultation with a specialist in Paediatric Rheumatology, but below is some guidance on the treatments you may be asked to initiate.

**Steroid Therapy**
- Should be started promptly in all patients with MAS
- Give 30mg/kg IV Methylprednisolone per day (maximum dose 1g) as single infusion
- This is usually given for 3 consecutive days in the first instance but patients with severe MAS may need further doses.
- Patients should subsequently be maintained on oral steroid of 1mg/kg/day prednisolone or equivalent

**Ciclosporin A**
- 3-5mg/kg/day via enteral route(3)
- Aim for trough levels between 100-150µg/L

**Subcutaneous Anakinra**
- 1st choice biologic agent in treatment of MAS in context of Systemic JIA
- 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(4) (max starting dose usually 100mg)
- Can also be given twice daily and dose increased beyond 100mg if needed(4) and under the guidance of a specialist with experience in treating MAS.

**Intravenous Anakinra**
- Systemic absorption of S/C Anakinra may be compromised if multi-organ failure is present
- In this context anecdotal evidence supports the use of Anakinra by IV infusion(5–9) in PICU
- There are no published dose ranges for children
- In this context, Anakinra may be diluted with 0.9% Saline as given as a 2mg/kg bolus, and then continued at 0.5mg/kg/hour as a continuous infusion(9)

**Plasma Exchange**
- Can be useful in severe cases for rapid control, but is not a definitive treatment

**IV Immunoglobulin**
- Has been found to be helpful in some cases of MAS, but not others(10)
Appendix 2:
Preliminary diagnostic guidelines for macrophage activation system complicating systemic juvenile idiopathic arthritis (11)

Laboratory criteria
1. Decreased platelet count (≤ 262 x 10^9/L)
2. Elevated levels of aspartate aminotransferase (> 59 U/L)
3. Decreased white blood cell count (≤ 4.0 x 10^9/L)
4. Hypofibrinogenemia (≤ 2.5 g/L)

Clinical criteria
1. Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)
2. Hemorrhages (purpura, easy bruising, mucosal bleeding)
3. Hepatomegaly (≥ 3 cm below the costal arch)

Histopathological criterion
Evidence of macrophage hemophagocytosis in the bone marrow aspirate.

Diagnostic rule
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.

Recommendations
The aforementioned criteria are of value only in patients with active S-JIA. The thresholds of laboratory criteria are provided by way of example only.

Comments
1. 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 be, therefore, of limited value for the early suspicion of the syndrome.

2. Other abnormal clinical features in S-JIA-associated MAS, not aforementioned, may include: nonremitting high fever, splenomegaly, generalized lymphoadenopathy, and paradoxical improvement of signs and symptoms of arthritis.

3. Other abnormal laboratory findings in S-JIA-associated MAS, not aforementioned, may include: anemia, erythrocyte sedimentation rate fall, elevated levels of alanine aminotransferase, increased bilirubin, presence of fibrin degradation products, elevated lactate dehydrogenase, hypertriglycerideridemia, low sodium levels, decreased albumin and hyperferritinaemia.
Appendix 3:

Preliminary diagnostic guidelines for macrophage activation syndrome as a complication of juvenile SLE(12)

Clinical criteria
1. Fever (>38°C)
2. Hepatomegaly (≥3 cm below the costal arch)
3. Splenomegaly (≥3 cm below the costal arch)
4. Hemorrhagic manifestations (purpura, easy bruising, or mucosal bleeding)
5. CNS dysfunction (irritability, disorientation, lethargy, headache, seizures, or coma)

Laboratory criteria
1. 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)
2. Increased aspartate aminotransferase (>40 units/l)
3. Increased lactate dehydrogenase (>567 units/l)
4. Hypofibrinogenemia (fibrinogen ≤1.5 g/l)
5. Hypertriglyceridemia (triglycerides >178 mg/dl)
6. 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 hemophagocytosis 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.
REFERENCES


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