Script: Management of multisystem inflammatory syndrome related to SARS-COV-2 in children

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I am Dr Jhuma Sankar, Associate Professor in the department of Pediatrics.

My topic for this series of webinar is – Management of multisystem inflammatory syndrome related to SARS-COV-2 in children.

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The outline of this webinar would be:

- We will attempt to understand the spectrum of the MISC.
- Review the investigations we can order and their relevance.
- The cardiovascular support we need to provide to these patients.
- The drugs available
- Suggested algorithm for tropical countries and
- Challenges anticipated while managing these cases.

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- I will start with the first case we managed in June 2020
- A 6yr boy presented to the ED with 4 days history of fever, malaise, poor appetite, maculopapular rash and shortness of breath

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- On examination in the ED he was found to be in shock and respiratory distress.
- In addition he had mucocutaneous involvement, bilateral cervical adenopathy and edema of hands and feet.

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- The child was started on high flow oxygen, administered a fluid bolus and stared on adrenaline infusion.

- The shock did not improve and nor-epinehrine and milrinone were added and the child was intubated and shifted to PICU.

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The differential diagnosis considered in the emergency and ICU were

- Kawasaki disease with shock
- Toxic shock syndrome and
- Sepsis MOD

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- The index care fulfilled the case definition of KD
- But was it KD? Or Covid-19 related MISC which was being increasingly reported during this pandemic from the west -we needed to explore.

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- The child's clinical picture also fit into toxic shock syndrome and therefore broad-spectrum antibiotics to cover possible organisms were initiated.

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- In view of KD with shock and / or TSS- both of which have good response to IVIG–ve decided to administer IVIG@2g/kg over 24 hours.

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- Investigations done at the time of admission revealed elevated markers of inflammation such as ESR, CRP, PCT and serum ferritin.
- We also got a COVID-19 test by RT-PCR which came negative.

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- Echocardiography showed LV dysfunctions and Troponin 15.7 pg/ml.
- Tests for common infections such as dengue, scrub, typhoid were all negative.
- As we wanted to rule out KD like illness due to SARS-COV-2 we sent serology for SARS-COV-2 and it was positive.

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These are the preliminary definitions laid down by the WHO and CDC.

- The index care fulfilled the case definition of MIS-C laid down by both organizations.

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- This table shows the list of investigations that could be done in a case of MIS-C.
- These include:
  Routine lab investigations such as total counts, COVID antibodies, PCR, blood culture, tests for tropical infections, markers of inflammation, left ventricular dysfunction and echo cardiogram.

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As of today the spectrum of MIS-C is not clearly understood.

- However we can broadly classify these patients as those presenting with
  1. Classic KD
  2. KD with shock
  3. Hyper-inflammation with myocarditis
  4. Hyper-inflammation and MODS without myocarditis

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- Accordingly, the cardio vascular support can be tailored to treat KD with shock, myocarditis and septic shock with multiorgan failure.
- Broadly, the treatment would comprise of antibiotics, IVIG, steroids, anti-platelet drugs and IL-1/IL-6 inhibitors in refractory cases.

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- Steroids could be considered as the first line therapy in these cases due to presentation which is similar to KD, potent anti-inflammatory effect and commonly used in pediatrics.
- Dose is 2mg/kg administered orally till markers of inflammation subside following which they are tapered over next 2 weeks.
- In severe cases with shock- pulse methyl prednisone may be administered at a dose of 30mg/kg/day for 5 days and tapered over 2 weeks.
- However, we need to bear in mind that there are no clinical trials and there are concerns with super added bacterial infections with the use of these agents.

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The other drugs considered as 1st line therapy in these cases are immunoglobulins.

- In view of the presentation similar to KD/TSS
- Commonly used in children and good clinical response has been observed in children with MISC.
- The dose is 2g/kg over 24 hours as infusion.
- Indication is KD/Atypical KD.
- The limitations of using this therapy include no clinical trials, high cost and availability issues.

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- Some of the other drugs that are considered are antibiotics to cover infections, antiplatelet drugs such as aspirin in KD like illness @a dose of 30-50 mg/kg/day until patient is afebrile followed by 3-5mg/kg/day for 6-8 weeks.
- Anticoagulants such as Enoxapirin are considered in older children or in those with elevated D-dimers till 2 weeks after discharge.
- The prophylactic dose is 0.5 to 0.75 mg/kg SC 12 hourly and therapeutic dose is 1 to 1.5 mg/kg SC 12 hourly.

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- In patients with severe presentation and/or no response to IVIG and steroids in 24-48 hours we should consider Remdesivir.
- The median recovery time was shorter with Remdesivir in a preliminary study.

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- Tocilizumab, infliximab are considered in severe cases.
- In a retrospective cohort study the median duration of vasopressor support and medium time of clinical improvement was shorter in the Tocilizumab group.

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- In refractory cases-plasmapheresis and ECHO may be considered.

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- In a study of 58 children, 14% had coronary aneurysm and more than 60% received steroids and IVIG.

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This slide shows a suggested algorithmic approach to MIS-C.

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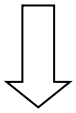
If a previously healthy child presents with a history of fever during the COVID-19 pandemic.



First of all we need to rule out the common causes including Dengue/Scrub/Laptosporosip/Malaria/Enteric and other suspected bacterial infection and also screen for COVID as per guidelines.

If there are features of KD then do Echo and send tests for markers of inflammation.

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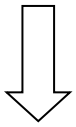
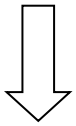
If the markers of inflammation are elevated then manage shock, respiratory distress, add antibiotics and start IVIG @2g/kg over 12-24 hours.

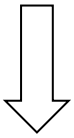
- Start Aspirin @30mg/kg/day.



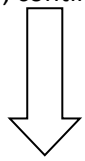
Assess for improvement in fever and inflammatory marker



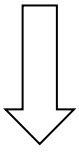
If no improvement/worsening



Consider repeat IVIG/IL-6 inhibitor, continue steroids, aspirin if COVID-19 positive antigen/antibody/close contact.

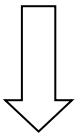


If improvement

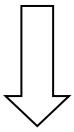


- Then taper steroids over 2 week.
- Continue aspirin for 6-8 weeks and review Echo at 2 and 6 weeks for Coronary artery involvement; if no involvement stop aspirin.

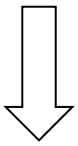
If there are no features of KD



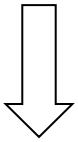
And presentation is not like sepsis/ septic shock/ TSS



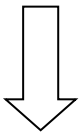
Then send appropriate investigation and start broad spectrum antibiotics.



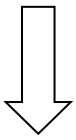
Perform Echo/ ECG for myocardial dysfunction.



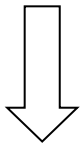
If there are features of myocardial dysfunction/injury



May consider IVIG/ Steroids on case to case basis.



If no response in 48 hours and repeat COVID-19 test is positive.



Repeat IVIG/IL-6 inhibiters

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Now let us see the index case.

- The shock and respiratory distress improved by day 5 and Echo was normal by day 7. The markers of inflammation decreased by day 3 along with fever and normalized by the end of 1st week. Finally, the Child was discharged after 10 days of ICU and hospital stay.

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- The challenges we faced while managing this child and may face for similar cases from our country include –
    - clinical challenges such as overlap with other topical infections,
    - non-availability of serology test for SARS COVID-2 and to decide about what drugs to be administered and when
    - there will be challenges with resource availability such Echocardiography may not be available for all cases, laboratory testing for inflammatory markers may be unavailable, PICU bed/ ventilators/IVIG may not be available or limited due to cost issues.

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To summarize

- MISC is an emerging spectrum of vasculitis and inflammation due to SARS COV-2 infection.
- Spectrum may vary from KD like illness to sepsis/ MODS like presentation similar to the West
- Treatment comprises of supportive care, anti-virals and immunomodulatory therapy
- While managing these patients we may face unique challenges and specially from resource-limited settings

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Thankyou