MEDICAL INSIGHTS

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ankura hospital for women & children

Message From The Editor

Dear friends,

Welcome to our monthly issue of Medical Insights. We are extremely happy to launch the first edition on the occasion of Children's day. On the occasion on children's day let us all take a pledge to practice 'evidence-based medicine'. It is the judicious use of current available scientific evidence in making decisions about the care of individual patients.

The advantages of practicing evidence-based medicine are several. These include the ability to choose the right options for the patient based on current available research and make better use of the limited resources. By following standard guidelines, we can provide uniform care to patients wherever they are located. This will help improve patient confidence in the doctors and thereby patient-doctor relationship. Following the current best scientific evidence also protects the doctors in case of medico legal issues.

The purpose of our magazine is to assist you in your pursuit of scientific evidence for the management of common as well as uncommon conditions. We therefore have two sections. Section A deals with the common conditions encountered in clinical practice and the questions that might arise in the management of these conditions. Section B deals with challenging cases or uncommon cases managed by us with an aim to share our experience gained. If people wish to have more detailed information about the above topics, they can browse the Annexures A and B which contain more detailed information on the above topics. Please contact the corresponding author.

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SECTION A: COVID IN CHILDREN-FREQUENTLY ASKED QUESTIONS

-Dr. Abhinav, Dr. Venkat, Dr. Vishnu Rao

What is the best test currently available test to diagnose Covid-19 infection in children ?

Currently the gold standard test for Covid-19 infection is detection of SARS-CoV-2 nucleic acid by RT-PCR. A systematic review reported false negative rates of between 2% and 29% (equating to sensitivity of 71-98%) [1]. Accuracy in clinical practice depends on factors such as site, quality and processing of the sample. The sample can be taken from nasopharynx, oropharynx, sputum, and BAL (intubated patients). In India, the MOHFW has advised sample collection from nasopharyngeal and throat swabs.

When should RT-PCR testing be done?

Respiratory shedding of virus peaks at the end of the first week after infection i.e. just before & at the onset of symptoms. It is therefore best to test as soon as symptoms appear as the viral load is highest in the upper respiratory tract in the early stages of infection [2] However, as viral shedding may be intermittent, if the initial testing is negative, repeat testing after 24 - 48 hours is warranted if clinical suspicion is high.

What is the role of rapid Antigen tests?

Rapid antigen tests are inexpensive and give quick results and hence can be used at the point-of-care. However, these tests are less sensitive than PCR based assays. Studies have shown their sensitivity to be around 30-35% 3. Hence if rapid antigen tests are negative and clinical suspicion remains high, RT-PCR testing must be done. They perform best when tested in early stages of infection when viral load is generally highest. The specimen is collected either from nasopharynx or oropharynx.

What is the role of rapid antibody-based tests?

Serologic testing by itself should not be used to establish the presence or absence of SARS-CoV-2 infection or reinfection[4]. This is because, antibodies may not be present when tested early in illness. Moreover, some people never develop detectable antibodies following the infection. In addition, the presence of antibodies may reflect previous infection and may be unrelated to the current illness. Serologic testing also should not be used to determine. immune status in individuals 4. However, a positive serology test may provide additional evidence of COVID-19 in a patient who has presented 9-14 days after illness onset in whom the RT-PCR is negative, and a CT chest is consistent with SARS-CoV-2 pneumonia. Antibody kits validated by ICMR should be used 5. However, a negative serology test does not, in any way, negate or refute the diagnosis if clinical & radiological findings are consistent. Serology tests may also be useful in children presenting with MIS-C like picture.

	DAYS 1-7	DAYS 8-14	DAYS 15-39
RNA by RT-PCR	67%	54%	45%
Total antibody	38%	90%	100%
IgM	29%	73%	94%
IgG	19%	54%	80%

The diagnostic sensitivity of various tests is given in tables 1

Table 1: Diagnostic sensitivity of various tests for SARS-CoV-2 infection
(Adapted from. Zhao J et al Antibody responses in SARS-CoV-2; Clin Infect Dis.2020 Mar 28)

What is the role of chest x ray and CT scan in pediatric Covid?

Chest X rays are not indicated in patients who are asymptomatic or have mild symptoms . They can be considered in patients with moderate to severe respiratory illness. The typical findings include bilateral patchy consolidations often at the periphery of the lungs, peribronchial thickening and ground-glass opacities. However, due to limited sensitivity and specificity, the use of chest x ray as a diagnostic utility in Covid is limited [6].

CT scan is more sensitive than chest x ray in the diagnosis of Covid infection in children. However, CT scan should not be used to screen for or as a first-line test to diagnose COVID-19 infection in children6. CT should be used sparingly and only for hospitalized children with specific clinical indications like severe disease and worsening respiratory status. The CT findings include ground-glass opacities with a peripheral lung distribution, unilateral or bilateral infiltrates, a crazy paving pattern, consolidation with surrounding halo sign [7].

Which group of Covid positive children can be managed at home ?

Most children with COVID-19 do not require hospitalization. Children who are asymptomatic or with mild symptoms can be managed at home. However, caregivers of these children should monitor for warning signs of clinical deterioration[8].

What are the criteria for hospital admission in children?

Children with moderate, severe, or critical disease as per the WHO criteria9 should be admitted to the hospital. These include:

1. Hypoxia, respiratory distress, cyanosis
2. Poor oral intake, signs of dehydration and shock
3. Lethargy, drowsiness, seizures, and encephalopathy

How long should COVID positive children be isolated? Do they require repeat testing?

In majority of Covid positive children, isolation and precautions can generally be discontinued 10 days after symptom onset and resolution of fever for at least 24 hours (without the use of fever-reducing medications),

and with improvement of other symptoms. There is currently a shift from test-based strategy to symptom-based strategy for isolation. As per CDC guidelines the vast majority of children and adults who are asymptomatic or mildly symptomatic do not require repeat testing to come out of isolation 10. The exceptions include patients with severe illness and the immunosuppressed. Moreover, RT- PCR positivity does not necessarily translate to having infectious virus. Patients who have recovered can continue to have SARS-CoV-2 RNA detected in their upper respiratory specimens for up to 12 weeks10.

What is the current evidence for various therapies in Covid disease?

The drugs used in Covid fall in two main categories: antivirals and immune modulators. Most of the studies have been done in adult population. In mild to moderate disease, no specific therapy is found to be effective as per currently available evidence. In severe and critical disease, only corticosteroids have been proven effective as per current available evidence.

The RECOVERY trial from UK has shown that steroids reduced mortality by 33% in ventilated patients and by 20% in patients requiring supplemental oxygen11.

Steroids can be considered in children with moderate to severe disease with increasing oxygen requirements or requiring escalation of respiratory support. The Solidarity Trial found that all 4 treatments evaluated (Remdesivir, Hydroxychloroquine, Lopinavir/Ritonavir and Interferon) had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients 12. The PLACID trial on convalescent plasma in the management of moderate covid-19 in adults in India showed no difference in 28-day mortality or progression to severe disease among patients with moderate COVID-19 treated with convalescent plasma13. There is no clinical evidence for rest of the drugs including Azithromycin, Ivermectin, Doxycycline, Tocilizumab in acute Covid infection in children14.

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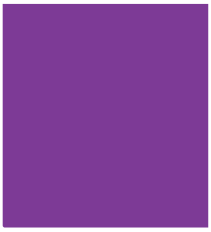
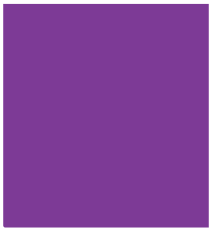
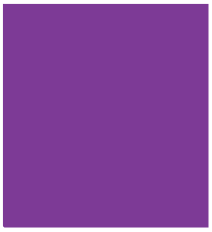
SECTION B: MULTISYSTEM INFLAMMATION SYNDROME (MIS-C) IN CHILDREN

-Dr. Kishore, Dr. Khalil, Dr. Sagar Bhattad

Case report:

Presenting symptoms: A 9-year-old developmentally normal child with no significant past history was brought with complaints of fever for 8 days; high grade temperature (around103 F), every 4th to 6th hourly subsiding with paracetamol. It was associated with maculopapular rash all over the body for 5 days. Decreased activity for 5 days and increasing irritability for 2 days.

Examination findings: On examination, there was maculopapular rash all over the body, periorbital puffiness, conjunctival injection, and red lips. Saturations were 90% in air; signs of respiratory distress in form of tachypnoea (RR-70 /min), intercostal & subcoastal retractions were noted. Examination of CVS revealed compensated shock with heart rate of 170-180 per min, CRT>3sec, and normal blood pressure. On examination of CNS, he was irritable but oriented.

Investigations & management: He was admitted in the PICU and started on non-invasive ventilation. Fluid bolus was given and started on empiric antibiotics. Initial investigations showed leucocytosis with neutrophilia and high CRP (150). Urine microscopy revealed 8-10 pus cells. CSF analysis revealed white cell count of 8 with 50% neutrophils (other CSF parameters being normal). CT scan brain was normal. His blood, urine & CSF culture were sterile. Echocardiogram was normal. In view of persisting fever, antibiotics were upgraded & repeat set of cultures, Covid antibodies and inflammatory markers were sent. The repeat cultures were sterile but Covid antibodies (IgG and IgM) were positive. Inflammatory markers (ferritin, LDH, IL-6, d-dimers) were high.

In view of the above clinical and investigation findings, a diagnosis of multisystem inflammatory syndrome in children (MIS-C) was made. He was started on IVIG and steroids following which his oxygen requirement, fever, rash, and irritability improved. He became afebrile and repeat inflammatory markers showed a decreasing trend following which he was discharged home.

Pathogenesis

The relationship MIS-C to SARS-CoV-2 infection suggests that the pathogenesis involves post-infectious immune dysregulation[1].

Viral entry into cell (binding to Angiotensin converting enzyme 2)

↓

Dysregulated innate immunity

↓

Cytokine storm

↓

Endothelial damage, myocarditis, shock, multi organ failure

Definition: WHO and CDC have developed case definition for MIS-C in children and adolescents. Here we present the WHO case definition for MIS-C 2

All 6 criteria must be met:

1. Age 0 to 19 years
2. Fever for ≥3 days
3. Clinical signs of multisystem involvement (at least 2 of the following):
   Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
   Hypotension or shock Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP) Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer) Acute gastrointestinal symptoms (diarrhoea, vomiting, or abdominal pain)
4. Elevated markers of inflammation (e.g., ESR, CRP, or procalcitonin)
5. No other obvious microbial cause of inflammation, including bacterial sepsis & staphylococcal/ streptococcal toxic shock syndromes
6. Evidence of SARS-CoV-2 infection: any of the following:
   Positive SARS-CoV-2 RT-PCR
   Positive serology
   Positive antigen test
   Contact with an individual with COVID-19

Clinical features:

MIS-C has a wide spectrum of presenting signs and symptoms and disease severity. In a systematic review of 655 patients, fever, gastrointestinal symptoms, and Kawasaki disease-like symptoms were reported at presentation in most of the children 3. Co morbidities were seen in significant (23%) proportion of the children.

The clinical features include:

1. Generalized symptoms: fever, myalgia
2. Mucocutaneous features similar to Kawasaki disease (conjunctivitis, rash, stomatitis, lymphadenopathy, erythema and swelling of extremities, peeling of skin).
3. Gastrointestinal symptoms: nausea, vomiting, abdominal pain, diarrhoea, acute surgical abdomen like picture.
4. CNS: headache, lethargy, irritability, aseptic meningitis, encephalopathy.
5. CVS: tachycardia, hypotension, shock
6. Respiratory: cough, hypoxia, respiratory distress, chest pain
7. Renal: features of acute kidney injury
8. Serositis: signs of pleural, pericardial, and peritoneal effusions

Differential diagnosis

MIS-C in children may mimic the following conditions 4:

1. Bacterial sepsis/toxic shock syndrome
2. Kawasaki disease
3. HLH/MAS
4. Vasculitis

Investigations

The following findings may be noted 5:

Biochemical tests

1. Inflammatory markers: elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin, ferritin, LDH, IL-6 etc.
2. Renal function tests: hyponatremia, hypoalbuminemia, elevated BUN and creatinine
3. Cardiac markers: elevated troponin and pro-B-type natriuretic peptide (pro BNP)
4. Liver function tests: elevated AST, ALT
5. Abnormalities in blood gas with lactate

Haematological tests

1. CBP with peripheral smear: neutrophilia, lymphopenia, anaemia, thrombocytopenia
2. Clotting tests: elevated PT, APTT, D-dimers, fibrinogen.

Radiological investigations

1. Ultrasound: evidence of pleural, pericardial, and peritoneal effusions
2. Echocardiogram: myocarditis, depressed ventricular function, valvular regurgitation, dilated coronaries, coronary aneurysms
3. CT chest: pulmonary infiltrates/opacities

Microbiological investigations

1. NPA or lower respiratory samples for RT-PCR and serological tests for Covid
2. Cultures of blood, urine and CSF where indicated

Other investigations

1. 12 lead ECG
2. Tests to rule out other differential diagnoses

Management

The treatment options include IVIG, steroids, Aspirin, and anticoagulation therapy 6.

IVIG: The indications include:

Kawasaki disease-like illness

Evidence of myocarditis, coronary artery dilatation/aneurysms

Worsening clinical status with rising inflammatory parameters

Presence of shock

Dosage: 1-2 g/kg over 12 – 24 hrs

Steroids: The indications include:

Patients with severe disease – given upfront along with IVIG

Patients refractory to IVIG

Dosage: IV Methyl prednisolone 2-10 mg/kg/day for 3- 5 days (Max 1 g/day); high dose IV pulse steroids in life threatening complications like severe shock.

At discharge: oral steroids 1-2 mg/kg/day to be tapered over 4-6 weeks.

Aspirin: indicated in following:

Kawasaki disease like picture

Thrombocytosis

Coronary aneurysms with Z score 2.5 - 10

Anticoagulation: indicated in

Elevated d-dimers

Coronary aneurysms with Z score > 10

Documented thrombosis

Ejection fraction < 35%

Others: Drugs like Tocilizumab and Anakinra (not available in India) are indicated in MIS-C refractory to IVIG and steroids or where the drugs are contraindicated.

In a systematic review of 655 patients 3, all patients were hospitalized, and the majority (68%) of patients with MIS-C required intensive care admission. For treatment of MIS-C, IVIG was used in 63% patients, corticosteroids in 49% and Anakinra in 8%. Inotropes were required in 40%, anticoagulant therapy in 34% and mechanical ventilation in 15%. Despite most children requiring intensive care and immunomodulatory therapies, favourable outcomes were reported in the majority with low mortality rates3.

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