different formulation, after pre-medicating with diphenhydramine and methylprednisolone (only for the first dose) and started on medium-dose aspirin (~39 g/kg/day).

The patient recovered on the pediatric floor with supportive therapy for COVID-19 [3] and was discharged after 6 days in the hospital. Hypotension with elevated inflammatory markers in patients with KD are the manifestations of KD shock syndrome (KDSS) [4]. Association between COVID-19 and KDSS [5] has been speculated, but warrants further investigation.

Adverse effects to IVIG infusion commonly include hypotension and anaphylactic reactions. This can be treated with steroids and antihistamines as pre-medication. However, there is a weak recommendation regarding avoidance of steroids in patients with COVID-19, with some indirect evidence of disease worsening [2]. Readers need to be aware of co-occurrence of Kawasaki disease with COVID-19, and the associated management issues.

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ELVIA I RIVERA-FIGUEROA[1], ROBERTO SANTOS[2], SCOTT SIMPSON[3] AND PADMA GARG[1]*
[1]Division of Pediatric Critical Care Medicine, [2]Division of Pediatric Infectious Disease, and [3]Division of Pediatric Cardiology, University of Mississippi Medical Center, Jackson, Mississippi, USA.
**ppgarg@umc.edu*

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Hyper-inflammatory Syndrome in a Child With COVID-19 Treated Successfully With Intravenous Immunoglobulin and Tocilizumab

Coronavirus disease (COVID-19) in children appears to be largely a benign condition. However, there are reports of children presenting significantly unwell across Europe and USA in the last couple of weeks with a new multisystem inflammatory syndrome [1]. We report a child with COVID-19 who had overlapping features of Toxic Shock Syndrome (TSS) and Kawasaki disease (KD).

A previously well, eight-year-old boy presented with fever, cough and throat pain. He was admitted to a local hospital on day 4 of illness in view of high-grade fever spikes. Investigations showed neutrophilic leukocytosis (total white blood cell count 23,000/μL, Neutrophils 89%) with raised acute phase reactants (C-reactive protein, CRP 120 mg/L). Chest *X*-ray showed right upper and middle lobe infiltrates. Reverse transcriptase polymerase chain reaction (RT-PCR) for severe acute respiratory illness novel coronavirus 2 (SARS-CoV-2) was negative. Treatment was empirically started with ceftriaxone and azithromycin. Despite treatment for three days, he continued to have high fever, worsening respiratory symptoms and was referred to our hospital.

On arrival, he was alert, had respiratory rate of 50/min, intercostal retractions and was maintaining SpO_2 in room air. He was febrile with tachycardia (HR 160/min), hypotension (80/31 mm Hg), warm extremities and a capillary refill time of 3 seconds. He was also noted to

have a generalized non-pruritic erythematous skin rash, non-purulent bulbar conjunctivitis, cracked lips, strawberry tongue, edema of limbs, tender hepatomegaly and abdominal distention. Investigations in our hospital showed haemoglobin of 8.9 g/dL, neutrophil predominant leukocytosis (total count 17,600/μL, 86% neutrophils), platelet count 3,95,000/μL, markedly raised CRP (317 mg/L), raised erytherocyte sedimentation rates (115 mm/h), hyper-ferritinemia (Ferritin 1,496 ng/mL), hypoalbuminemia (2.6 g/dL), hyponatremia (133 mEq/L), normal kidney and liver function, and 2+ proteinuria. He was given a fluid bolus and treatment empirically started with piperacillin-tazobactam and doxycycline. When reassessed after 30 minutes, he was febrile, hypotensive and had increased work of breathing. He was shifted to the pediatric intensive care unit. The initial differential diagnoses were pneumonia with septic shock, COVID-19 penumonitis, KD and TSS. High-flow nasal cannula (HFNC) support was started and antibiotics were modified to meropenem, vancomycin and clindamycin. The blood pressure was stable and urine output was normal. Intravenous Immunoglobulin (IVIG) was given (2 g/kg) with aspirin (75 mg once-a-day). Echocardiogram did not show any abnormalities and repeat chest *X*-ray showed increased right-sided infiltrates. Repeat nasopharyngeal COVID-19 RT-PCR was positive. Multiplex PCR of nasopharyngeal aspirate (BioFire FilmArray) detected Coronavirus OC43 and Human Rhino/Enterovirus. As he improved, he was gradually weaned off HFNC. Blood cultures showed no growth and antibiotics were changed to ceftriaxone. In light of the persistent high-grade fever and elevated CRP (121 mg/L), 72 hours after IVIG infusion, he was given tocilizumab (8 mg/kg IV over 2 hours). Twelve hours later, his fever spikes settled, and inflammatory parameters rapidly decreased to baseline (***Fig.* 1**). He was noted to have periungual peeling of skin and recovered completely after two weeks of illness.

The clinical characteristics of COVID-19 disease progression and outcome in children and young adults appear significantly milder compared to older individuals [2]. However, there is now a growing recognition of a small number of children presenting with a multisystem inflammatory syndrome. This rare syndrome shares common features with other pediatric inflammatory conditions, including KD, Staphylococcal/streptococcal toxic shock, bacterial sepsis and macrophage activation syndrome. It can also present with unusual abdominal symptoms with elevated inflammatory markers. Recently 8 children have been reported to present with hyper-inflammatory shock [3]. This has been labelled as Pediatric multisystem inflammatory syndrome temp-orally associated with COVID-19 and a case definition has been suggested [1]: a child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features, which may include fulfilling full or partial criteria for KD; exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes; and SARS-CoV-2 PCR testing may be positive or negative

Our case fulfils these criteria. It is likely that cytokine storm (CS) is one of the major causes of acute respiratory distress syndrome (ARDS), multi-organ dysfunction and possibly pediatric multisystem inflammatory syndrome [4]. IL-6 is a key cytokine in this process and few studies suggest that CS is positively correlated with disease severity [5]. Various immunomodulators have been discussed and tried for controlling the inflammatory response [6]. Tocilizumab, an IL-6 receptor antagonist approved by the US FDA for treating of Cytokine release syndrome (CRS), is now in clinical trials for treating severe COVID-19 pneumonia [7]. Tocilizumab blocks downstream signal transduction by binding membrane IL-6 receptor and soluble IL-6 receptor and plays a role in the treatment of CS in COVID-19 [8]. High CRP levels seen in our case shows that this inflammatory syndrome is likely mediated by IL-6. Our case suggests that immunomodulation with IVIG and IL-6 blockade can be an effective therapeutic strategy, which has a scientific rationale. It is clear from Europe and the USA that appearance of this syndrome in children follows the peak of infections in affected areas. The immunopathology behind this phenomenon is yet to ascertained. We believe that children across India may present with this inflammatory syndrome related to COVID-19 in the weeks ahead and would like to highlight this to pediatricians across India. Tocilizumab may prove to be an effective second line agent in IVIG refractory children with COVID-19 hyper-inflammatory syndrome

Though most SARS-CoV-2 infections in children are likely to present with mild features, some may develop a hyper-inflammatory syndrome, which may require treatment with IVIG and Tocilizumab. Pediatricians should be aware of such presentation and immunomodulatory treatment modalities.

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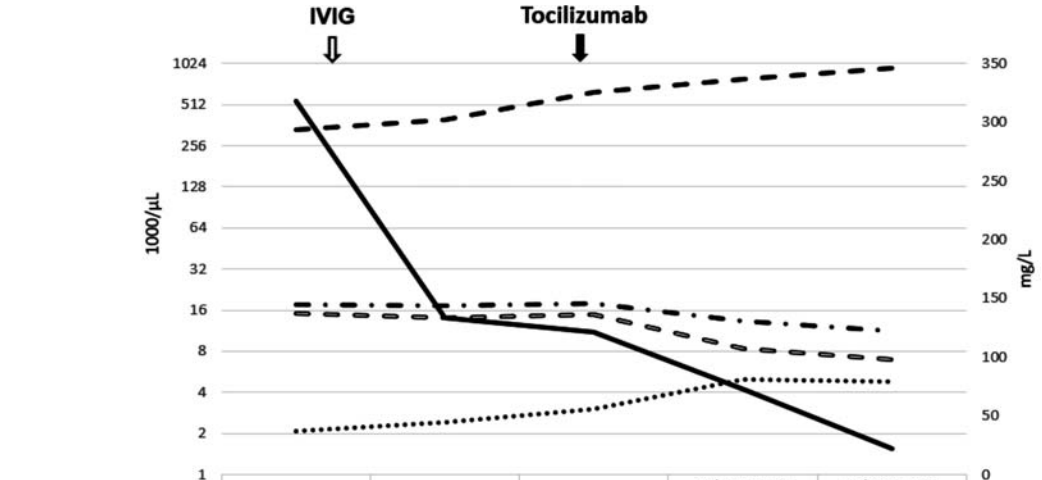

	At admission	24hours post IVIG	72hours post IVIG	12hours post Tocilizumab	72hours post Tocilizumab
TWBC(1,000/µL)	17.6	17.3	17.8	13.2	11.2
Lymphocyte(1,000/µL)	15.1	14.2	14.8	8.3	7
Neutrophil(1,000/µL)	2.1	2.4	3	5	4.8
Platelet(1000/µL)	333	400	630	780	950
CRP(mg/L)	318	134	121	73	22

Fig. 1 *Trend of inflammatory markers in a child with hyper-inflammatory syndrome and COVID-19.*

S BALASUBRAMANIAN[1], TM NAGENDRAN[2]*, B RAMACHANDRAN[2] AND AV RAMANAN[3]

*[1]Department of Pediatrics and [2]Pediatric Intensive Care Unit, Kanchi Kamakoti CHILDS Trust Hospital, Chennai, India; and [3]Department of Pediatric Rheumatology; Bristol Royal Hospital for Children, Bristol, UK and [3]Translational Health Sciences, University of Bristol, UK. *nagupeds@gmail.com*

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