Multisystem Inflammatory Syndrome in Children: Clinical Features and Management—Intensive Care Experience from a Pediatric Public Hospital in Western India

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Abstract

Background: Multisystem inflammatory syndrome (MIS) associated with severe acute respiratory syndrome coronavirus (SARS-CoV-2) (MIS-C) in children is being increasingly reported across the world.

Materials and methods: Children fulfilling the World Health Organization criteria of MIS-C needing pediatric intensive care unit between April 15 and July 26, 2020 were studied.

Results: There were 21 patients with median age of 7 years [interquartile range (IQR) 1.9–12.1], of which 11 were females. SARS-CoV-2 real-time polymerase chain reaction positive in 8/21 and/or antibody positive 16/21. Fever was present in all patients, and gastrointestinal symptoms being second most frequent (16/21). One child had aplastic anemia, while the rest had no comorbidities. Nearly all presented with shock ($n = 20/21$) and 90% needed vasoactive drugs with a median Vasoactive Inotropic Score of 40 (IQR 20–95). Thirteen children needed ventilatory support and one needed peritoneal dialysis. Nine children had left ventricular dysfunction and five had dilatation of coronaries on echocardiography. Inflammatory markers C-reactive protein [98 mg/dL (IQR 89–119)], serum ferritin [710 mg/dL (IQR 422–1,609)], and serum interleukin-6 levels [215 ng/L (IQR 43–527)] were uniformly elevated. Eighteen children received pulse methyl-prednisolone, eleven intravenous immunoglobulins, and four tocilizumab. Eighteen children (86%) were discharged home while three died.

Conclusion: In our cohort, MIS-C was seen in previously healthy children with fever, gastrointestinal symptoms, and shock. Early and aggressive management of shock and immune modulation with methyl-prednisolone and intravenous immunoglobulin were used.

Keywords: Antibody, COVID-19, Intensive care, MIS-C, PICU, PIMS-TS, Refractory shock, SARS-CoV2.

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Introduction

The invisible virus has humbled the whole of mankind. Cases of severe acute respiratory syndrome coronavirus (SARS-CoV-2) pneumonia have been recognized in China as early as December 2019. The World Health Organization on March 11, 2020 declared SARS-CoV-2 as a pandemic. India has been the third most affected country with 1.64 million positive cases detected thus far. Data from the Ministry of Health website as on July 30, 2020 show Maharashtra had 406,651 SARS-CoV-2-positive cases and Mumbai had 111,991 COVID-19-positive cases of which around 5% were children below the age of 10 year.[1]

Historically, newer diseases always create new challenges for diagnosis and management. In children and adolescents, there is emerging evidence of a multisystem inflammatory syndrome presenting with a myriad combination of features such as shock, cardiac dysfunction, multiorgan affection, and some features of Kawasaki disease.[2–4] In the United Kingdom, this is known as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)[5] and in the United States as Multisystem Inflammatory Syndrome in Children (MIS-C).[6] At our pediatric tertiary care hospital in Mumbai Metropolitan Region, the first case was seen in late April 2020. We have had 105 COVID-positive children admitted to our hospital, and 21 children had MIS-C. It became imperative to collect standardized data and understand the clinical spectrum, laboratory profile, treatment provided, and outcome of these children.

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Materials and Methods

Study Design and Setting

This was an observational case series of all children, between 1 month and 18 years of age, presenting to the pediatric intensive care unit (PICU) and who fulfilled the case definition of MIS-C[7] between April and July 2020. Ethics committee approval was obtained.

Data included demographic details with special reference to close contact with COVID-19 case, residence in containment

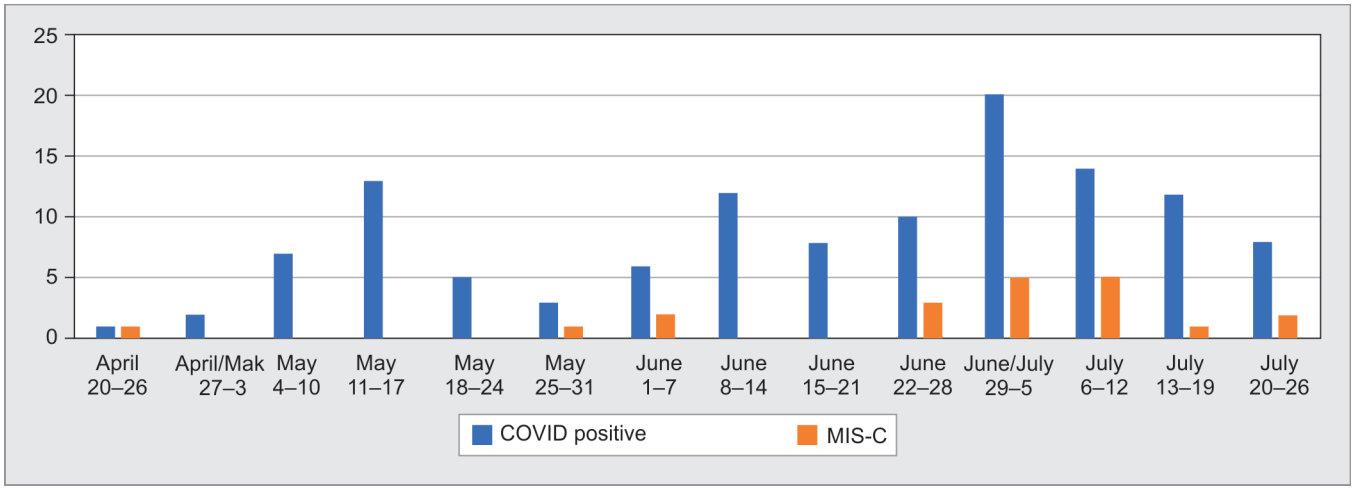

Fig. 1: Weekly distribution of COVID-19 PCR-positive cases and MIS-C children

zones, and clinical features on presentation. All patients were tested by reverse-transcriptase polymerase chain reaction (PCR) for SARS-CoV-2. SARS-CoV-2 immunoglobulin G antibody ELISA testing by Indian Council of Medical Research approved kit (Zydus Diagnostics, Ahmedabad, Gujarat, India) was done as available. Shock was considered to be present if clinical features of low perfusion persisted despite a 20 mL/kg bolus of crystalloid and the need for further fluid resuscitation and/or vasoactive drugs. Data were also collected for underlying comorbidities. Laboratory markers, including C-reactive protein (CRP), serum ferritin, interleukin-6 (IL-6), D-dimer, and Fibrinogen, were done at presentation prior to start of specific therapy. Immunomodulatory therapy was decided on a case-to-case basis by the intensive care team with inputs from multidisciplinary team of experts. Echocardiography was done by cardiologist and the findings of ejection fraction (EF), systolic and diastolic function, and the size of the coronaries expressed as SD scores were noted. Evaluation of cardiac involvement was done by checking markers in the blood, such as creatinine phosphokinase (CPK), CPK MB, and Troponin I. PRISM III score at admission was recorded. Vasoactive drugs requirement was graded based on Vasoactive Inotropic Score (VIS). Ventilatory support was noted as invasive or noninvasive ventilation. Patients received intensive care support as per standard of care in PICU.

Statistical analysis was performed using STATA version 11.1. Continuous data are presented as median and categorical data as percentages. *T* test was applied to look for association of demographic or laboratory parameters with outcome.

Results

Demographic Data

Twenty-one children fitting the case definition of MIS-C presenting between April 20 and July 26, 2020 were studied. The median age at presentation was 7 years [interquartile range (IQR) 5.1; range 9 months to 14 years], and 11 (52%) were girls. The duration of illness prior to presentation to the hospital was 5 days (range 3–10 days). Figure 1 depicts weekly distribution of SARS-CoV-2 PCR-positive cases and children with features of MIS-C admitted to our hospital over the study period.

Table 1: Demographic and clinical characteristics

Characteristics	*N* = 21
Female, *n* (%)	11 (52%)
Age in years, median (IQR)	7 (5·1)
Duration of symptoms prior to hospitalization, median (IQR)	5 days (range 3–10 days)
Comorbidity (aplastic anemia), *n* (%)	1 (4%)
Symptoms (*n*) (%)	
Fever	21 (100%)
GI symptoms	16 (76%)
Skin rash	7 (33%)
Conjunctival congestion	9 (42%)
Breathing difficulty	5 (23%)
Oliguria facial puffiness	4 (19%)
Duration of symptoms days, median (IQR)	5 days (2–8)
Pediatric risk of mortality (PRISM) III, median (IQR)	9 (4–14)

Vasoactive infusion dose calculation (VIS) = dopamine (μg/kg/minute) + dobutamine (μg/kg/minute) + 100 × adrenaline (μg/kg/minute) + 10 × milrinone (μg/kg/minute) + 10,000 × vasopressin (units/kg/minute) + 100 × noradrenaline (μg/kg/minute)

Clinical Characteristics

All children had fever at presentation. Other associated symptoms included vomiting, abdominal pain and loose motions (*n* = 16/21; 76%), respiratory distress (*n* = 5/21; 23%), macular rash (*n* = 7/21; 33%), nonpurulent conjunctivitis (*n* = 9/21; 42%), and oliguria with facial puffiness (*n* = 4/21; 19%). One child was a diagnosed case of aplastic anemia and the others (*n* = 20/21; 95%) did not have any comorbidity. Nearly all (*n* = 20/21; 95%) children presented with shock requiring fluid boluses and vasoactive drugs. Median VIS was 40 (IQR 20–95). PRISM III score of greater than 8 was found in 9 (42%) children (Table 1). Two children had radial artery thrombus related to arterial catheter; both had forearm skin discoloration which resolved. We would like to describe an unusual central nervous system manifestation in a child with MIS-C. A 12-year-

old girl with catecholamine refractory shock, dilated coronaries, and hemophagocytes on bone marrow aspiration developed right upper limb monoparesis with confusional state. On day 7 of PICU stay, magnetic resonance imaging (MRI) of brain revealed a subacute infarct with area of restricted diffusion in the left posterior periventricular white matter and multiple tiny microhemorrhages in subcortical white matter and splenium of corpus callosum. MR angiogram and venogram did not reveal any abnormality. She was discharged from PICU care after 12 days of stay.

Temporal Relation with SARS-CoV-2

All the 21 children with MIS-C were tested for SARS-CoV-2 by real-time PCR (RT-PCR). About 8 (38%) children were positive and 13 (62%) SARS-CoV-2 PCR negative. Of the negative cases, anti-SARS-CoV-2 antibodies were tested in 11 (85%) that was positive in all. Five children who were SARS-CoV-2, PCR positive also had positive antibody tests (Flowchart 1). Two children could not be tested for SARS-CoV-2 antibody, but had come from containment zones.

Laboratory Investigations

All children underwent basic hemogram analysis. Leukocytosis was seen in 57% ($n = 12/21$) cases. Absolute lymphocyte count less than $1,500 \times 10^3/mm^3$ was seen in 80% ($n = 17/21$) (median of 1,344 c/mm^3; IQR 970–2,400) and neutrophil to lymphocyte (N:L) ratio of more than 3.5 was seen in 57% ($n = 12/21$) children (median of 4.5; IQR 2.7–8.3). Platelet count less than 150×10^9/L was seen in 71% ($n = 15/21$) children (median of $0.99 \times 10^5/mm^3$; IQR $0.90–1.45 \times 10^5$/cu.mm). Inflammatory markers were high in all cases with raised CRP median value of 98 mg/L (IQR 89–119) and serum ferritin, median value of 710 ng/mL (IQR 422–1,609). Serum IL-6 done in 61% ($n = 13/21$) cases and was raised with a median of 215 ng/L (IQR 43–527). Procalcitonin done in 43% ($n = 9/21$) cases had median value of 37.2 ng/mL (IQR 7.5–39). Coagulation screen also showed high D-dimers median value of 2,664 ng/mL (IQR 1,469–6,910) in all patients. Prothrombin time and INR was normal in all. Blood cultures were negative in all. Table 2 summarizes the laboratory results of the children with MIS-C.

Two-dimensional echocardiography was done in all children and nine (43%) had EF less than 55% of whom two had EF less than 30%. Two children with cardiac dysfunction expired and the remaining seven had normal cardiac function at discharge. Coronary dilatation at more than 2.5 *Z* score for age was seen in five children of whom one child died and remaining had normal coronaries at discharge. Electrocardiography abnormalities noted in

Flowchart 1: RT-PCR SARS-CoV-2 and anti-SARS-CoV-2 antibody profile

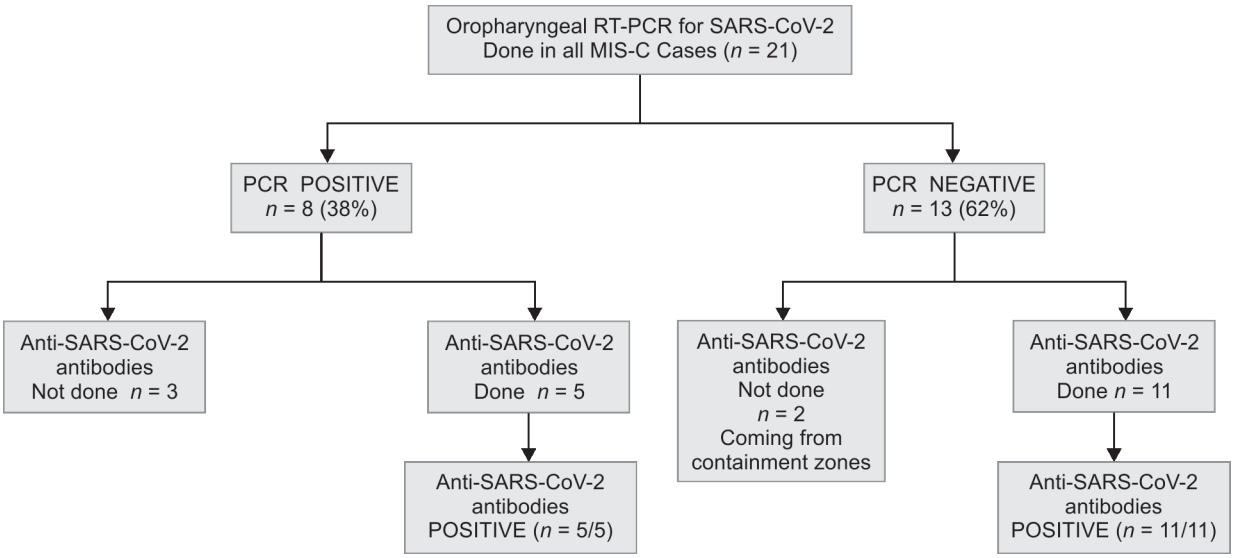

Table 2: Laboratory profile of children with MIS-C

Laboratory test (units) (n)		*Median (IQR)*	*Normal range*
Hemogram	Hemoglobin (g/dL)	9.6 (9–11.1)	11–16
	Total leukocyte count ($\times 10^3/mm^3$)	9,790 (2,885–14,150)	2,000–7,000
	Absolute lymphocyte count ($\times 10^3/mm^3$)	1,334 (970–2,400)	4,000–8,000
	Neutrophil to lymphocyte ratio	4.5 (2.7–8.3)	<3.5
	Platelet count ($\times 10^5/mm^3$) ($n = 21$)	0.99 (0.99–1.45)	1.5–4.5
Inflammatory markers	CRP, mg/mL ($n = 21$)	98 (89–119)	Up to 6 mg/mL
	S. Ferritin (ng/mL) ($n = 21$)	710 (422–1,609)	4.63–264
	Serum IL-6 (pg/mL) ($n = 12$)	215 (43–527)	0–7
	D-Dimer (ng/mL) ($n = 20$)	2,664 (1,469.5–6,510)	<250
	S. Fibrinogen (mg/dL) ($n = 20$)	339 (281–508)	200–400
Cardiac biomarkers	S. Troponin I (pg/mL) ($n = 16$)	53.5 (21.75–367.9)	0–15.6
	CPK (MB) IU/l ($n = 11$)	215 (107–321)	<25

19% ($n = 4/21$) cases were in the form of low voltage QRS, RBBB with ST changes, narrow complex tachycardia, and junctional rhythm; all of these changes resolved during ICU stay. All these patients had high Troponin I levels ranging from 12.7 to 1,406 ng/L.

Dysglycemia was noted in 38% ($n = 8/21$) cases during the PICU stay of which six children had hyperglycemia and five of them needed insulin therapy transiently. Two other children had hypoglycemia, requiring high glucose infusion.

Treatment and Outcome

All children presenting with MIS-C to PICU were managed with stabilization of hemodynamics and immune therapy along with anticoagulation. The mean length of stay in PICU was 5 days (range 4–7 days). Table 3 summarizes the management and outcome of children with MIS-C. Four children who had dilated coronaries were transferred to the ward on low molecular weight heparin and subsequently started on Aspirin.

Three children expired with MIS-C. A 15-year-old boy with aplastic anemia with refractory shock. Another 7-year-old girl with catecholamine resistant shock and cardiac dysfunction, died within 12 hour of admission. Third child was a 9-month-old previously healthy infant, catecholamine-resistant shock with multiorgan dysfunction. He developed severe rhabdomyolysis with maximum serum CPK level of 176,000 IU/L and acute kidney injury. All three children received intravenous immunoglobulin (IVIG) and steroids, and one received Tocilizumab as well.

Statistical analysis of the data with respect to age, PRISM III, absolute lymphocyte count, N:L ratio, multiorgan dysfunction syndrome (MODS) did not show any association with mortality or length of hospital stay. This is probably because of the relatively smaller numbers in our study.

Table 3: Summary of clinical features treatment and outcome of children of MIS-C

	No. of cases = 21
Shock, *n* (%)	20 (95%)
Acute kidney injury, *n* (%)	8 (38%)
Left ventricular ejection fraction <55%, *n* (%)	9 (43%)
Coronary dilatation, *n* (%)	5 (24%)
Fluid boluses (mL/kg), median (IQR)	40 (30–50)
Vasoactive infusion score (VIS), median (IQR)	40 (20–95)
Adrenaline, *n* (%)	18/21 (85.7%)
Noradrenaline, *n* (%)	19/21 (90%)
Vasopressin, *n* (%)	5/21 (23%)
Milrinone ± dobutamine, *n* (%)	3/21 (14%)
Antibiotics, *n* (%)	21/21 (100%)
Anticoagulation low-molecular weight heparin (LMWH), *n* (%)	21/21 (100%)
Steroids (methylprednisolone), *n* (%)	18 (86%)
IV immune globulin, *n* (%)	11 (52%)
Tocilizumab, *n* (%)	4 (10%)
Heated humidified high-flow nasal cannula (HHHFNC), *n* (%)	1 (5%)
Noninvasive ventilation, *n* (%)	6 (29%)
Invasive ventilation, *n* (%)	7 (33%)
Multiorgan dysfunction syndrome (MODS)	13/21 (61%)
Discharged	18 (86%)
Death	3 (14%)

Discussion

Mumbai has become the epicenter of the SARS-CoV-2 pandemic in India. As noted worldwide, we started seeing patients with MIS-C soon after the peak of the COVID-19 cases in Mumbai in May 2020. These children typically presented with fever, gastrointestinal, and mucocutaneous symptoms similar to reports from other centers.[2,3,8]

Our hospital is a tertiary care public hospital catering to children from lower socioeconomic group living in crowded conditions. Studies from Asia are lacking on MIS-C and till date there are no reported cases of MIS-C from China. Genetics, environment, immunity differences, socioeconomic disparity, and country health care matrix remain among many determinants of the outcomes even in presence of protocol-based management.

In the present study, antibody titers to SARS-CoV-2 were present on admission with a coexistent positive RT-PCR in 5/21 of the children. This has been reported by others[9–12] as well and it has been inferred that the infection occurred earlier in children, and the hyperinflammatory state and clinical features were antibody or immune complex mediated.

Laboratory parameters showed a trend toward lower lymphocyte counts and high N:L ratio >3.5. Meta-analysis by Lagunas-Rangel[13] has shown association between high white cell count, low lymphocyte count, low platelet count, elevated CRP, and severity of disease as well as mortality in adults. In our cohort, mild to moderate thrombocytopenia was seen, unlike the severe thrombocytopenia typically seen in dengue and sepsis. CRP and IL-6 were elevated in all our patients. There is increasing evidence in adult studies, that raised levels of CRP and IL-6 are associated with severe disease and mortality.[14] Ferritin levels were high suggesting macrophage activation. As noted in both pediatric and adult patients with COVID-19, D-dimers were typically elevated. While evidence from adult studies suggests that elevated D-dimer levels are associated with poor outcome,[15] the therapeutic implications of the high D-dimer are yet to be understood fully.[16] Two children in our cohort developed thrombosis related to radial artery catheter. Davies et al.[17] reported thrombi in three children (4%) from a cohort of 78 children with PIMS. Increased incidence of thrombosis associated with SARS-CoV-2 has been reported in adults[18] and prophylactic anticoagulation has been suggested in patients with severe COVID.[19,20] A recent pediatric guideline suggests mechanical and/or pharmacological thromboprophylaxis in children with COVID and risk factors for thrombosis such as presence of central venous catheter, postpubertal age, decreased mobility, and past or family history of thromboembolism.[21] Low-molecular weight heparin (LMWH) was used in all the patients in the present study as per the above guidelines. Further evidence for appropriate dose and therapeutic agent for thromboprophylaxis and treatment is awaited.

In this series, cardiac dysfunction was seen in nearly half of the patients similar to other studies where it was reported in 40–50% of cases.[2,9,12,22] Coronary dilatation was seen in one-fourth of our cohort and seen in 9–23% of children with MISC.[2,9,12,17,22–27] This important finding should be kept in mind while planning fluid resuscitation and IVIG therapy. As the long-term outcomes are unclear, these children will need long-term monitoring of coronary

artery size and other cardiac functions. Neurological manifestations of SARS-CoV-2 are increasingly being reported. Our series had one patient with neurological manifestations and PIMS. A study from the United Kingdom reported four children with PIMS and neurological manifestations and MRI showing white matter changes in the splenium.[25]

The majority of cases in our cohort were critically ill needing vasoactive drugs and respiratory support. Table 4 compares the treatment modalities used in various studies and our study. Steroid use was higher in our study (86%) compared to studies in the west (49–73%).[17,22–24] Due to cost issues, IVIG was our second line agent and additionally administered in half the patients in view of cardiac dysfunction, coronary dilatation or worsening multiorgan dysfunction, and diagnosis of hemophagocytic lymphohistiocytosis. IVIG is the first line immunomodulator for MISC in most centers in the west and used in 71–77% of cases. Tocilizumab (IL-6 inhibitor) was reserved for the most severe cases (10%) who had worsening MODS on steroids and IVIG in absence of sepsis. There is currently insufficient evidence to support one specific agent over another.

Mortality in our study was much higher at 14% (3/21) compared to 1.8–3% from western literature.[9,12,19–21] This could possibly be due to our cohort of ICU patients, possibly presenting late to hospital with shock MODS and 90% needing vasoactive medication. Although cardiac function normalizes prior to discharge in majority of cases, long-term outcome is unknown and follow-up and monitoring of cardiac function is important.

Limitations of Our Study

As this is a new disease, we were handicapped by absence of standard guidelines for management of such patients. More research needs to come from resource limited centers, so as to make unified guidelines which can be accepted and applied uniformly. In the present study, our focus was on the sickest and most critical children, there is a possibility of having milder varieties of this disease spectrum which need to be actively watched for. As all the MIS-C in the present study were in the severe end of the spectrum hence data from this study may not be generalized to milder cases. There is a scope for long-term follow-up studies with larger number of cases to understand the natural course of the disease.

In conclusion, we would like to bring out that the rapidity with which this syndrome has progressed during the COVID-19 pandemic, makes it imperative that pediatricians and critical care providers familiarize themselves with the presenting features of fever and gastrointestinal symptoms and vasoplegic shock with cardiac dysfunction as the predominant finding. Though immunomodulatory therapy remains the cornerstone of management in MIS-C, the choice of immunomodulatory therapy and duration of immune modulation are not known which can only be understood with further research.

Highlight of the Study

MIS-C is now increasingly being seen in the COVID-19 high incidence areas. We present the clinical and laboratory findings in detail to improve recognition of the condition. All children required intensive care support which warranted prompt diagnosis and treatment. In resource limited setting, such as ours, we used steroids as first line immune modulator therapy in these children.

Table 4: Comparison of treatment modalities used in MIS-C with present study

Author, (Ref) no. of patients	*ICU*	*NIV*	*IMV, ECMO*	*RRT*	*Vasopressor*	*Steroid*	*IVIG*	*Both IVIG and steroid*	*Biologics*
This study, *N* = 21	All	29%	IMV 33%	4%	90%	86%	52%	14%	Tocilizumab 10%
Dufort,[9] *N* = 99	80%	NIV 7% HHHFNC 16%	IMV 10%, ECMO 4%	—	62%	64%	70%	48%	
Davies,[17] *N*=78	All	HHHFNC 17% NIV 6%	IMV-46%,`ECMO 4%	1%	83% (fluid bolus 92%)	73%	76%		22% (anakinra, infliximab, tocilizumab, rituximab)
Feldstein,[23] *N* = 186	80%	17%	IMV 32%, ECMO 8%	—	48%	49%	77%		20% (IL-6 or IL-1RA inhibitors)
Whittaker,[24] *N* = 58	All		IMV-43%, ECMO 5%	—	47%	64%	71%		19% (5% anakinra, 14% infliximab)

NIV, noninvasive ventilation; IMV, invasive mechanical ventilation; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation; IL, interleukin; HHHFNC, heated humidified high-flow oxygen; IL-1RA, interleukin-1 receptor antagonist

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