

# Case Report of An Extreme Premature Infant with Multisystem Inflammatory Syndrome in Neonates (MIS-N)

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## Abstract

COVID-19 pandemic hit the world hard affecting more than 500 million people. In the SARS-CoV-2 pandemic era, there has been various information on the effect of COVID-19 infected or exposed pregnant women on their neonates. SARS-CoV-2 virus causes a hyperinflammatory syndrome in neonates similar to what may be seen in multisystem inflammatory syndrome in children (MIS-C) but due to transplacental transfer of antibodies rather than a neonatal infection with COVID-19. Case reports about a new pattern of disease, called multisystem inflammatory syndrome of neonate (MIS-N), have been recently appearing. We reviewed the perinatal history, clinical features, and outcomes of a preterm neonate with features consistent with MIS-N related to maternal SARS-CoV-2 infection that was managed in Texas, United States, in 2022. The infant presented with multisystem organ failure at 12 to 15 days of life. All extensive work up for infectious causes on the neonate were negative. Her inflammatory biomarkers were elevated, and she improved with steroids and supportive treatment. The neonate's anti-SARS-CoV-2 IgG was positive and the IgM was negative. Though rare, we speculate that maternal SARS-CoV-2 and other autoantibodies crossing the placenta caused MIS-N. Further studies and reviews are needed to evaluate pathophysiology and to further evaluate the available treatments.

**Keywords:** Premature neonate; multisystem inflammatory syndrome in Neonate (MIS-N); anti-SARS-CoV-2 antibodies; Maternal COVID-19 infection; Intrauterine COVID-19 exposure.

## Introduction

COVID-19 disease is a global public health crisis that affected children and adults. In 2020, case reports of children experiencing multisystem inflammatory syndrome (MIS-C) associated with SARS-CoV-2 were published. In 2021, articles of multisystem inflammatory syndrome in neonate (MIS-N) started to surface worldwide but reports in the United States are still limited, though maybe underreported (1, 2).

Reports suggest that MIS-N is secondary to maternal SARS-CoV-2 infection with maternal autoantibody transfer causing neonatal hyperinflammatory response. The first description of MIS-N was a case series in India. Researchers found an increase in cardiac conduction abnormality cases among newborns with evidence of maternal COVID-19 infection. These neonates had unusual presentations like prolonged QTc, atrioventricular block, thrombosis, or cardiogenic shock (3). Similar cases are reported in India, Germany, and Saudi Arabia, expanding knowledge about MIS-N (4-7).

Symptoms of MIS-N appear to be broad, including thrombotic and neurologic events, respiratory distress, gastrointestinal symptoms, kidney failure, and septic features. The most reported feature is cardiac dysfunction (78% of cases), including arrhythmias, aneurysms, and pericardial effusions (2, 5-10). Fever is less common, reported in one third of patients only (2, 8, 9). Inflammatory markers (ferritin, C-reactive protein, and procalcitonin) and cardiac markers (troponin and brain natriuretic peptide) are often elevated (5, 7, 9). In this paper, we aim to raise awareness about MIS-N by presenting an extremely preterm neonate with MIS-N and systemic inflammatory response syndrome (SIRS).

## Case Presentation

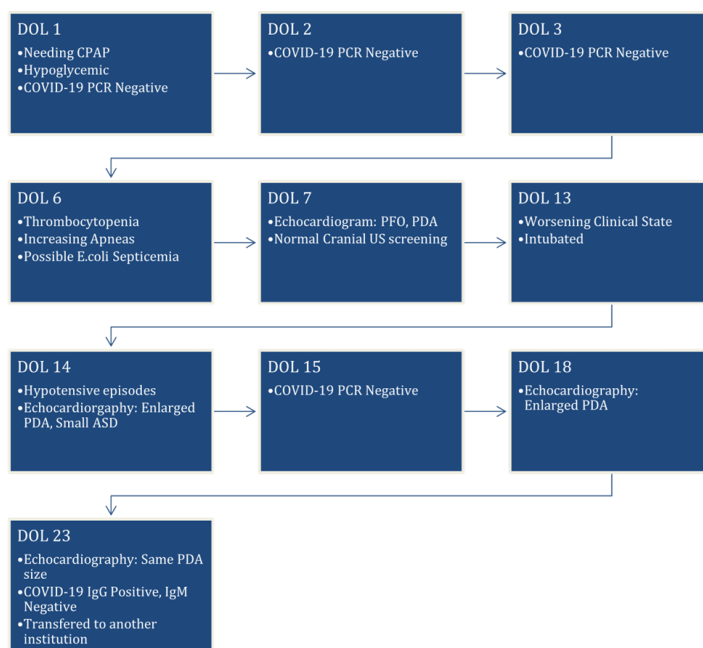
An extremely premature 25.6 weeks gestation female infant was delivered vaginally to a 33-year-old Gravida 1 Para 1 mother. The mother had a positive SARS-COV-2 Antigen and pharyngitis 9 days before delivery. Pregnancy was complicated by chronic hypertension, prolonged preterm premature rupture of membrane, and chorioamnionitis. The infant weighed 740 grams (appropriate weight for gestational age) with APGAR scores of 5 and 7 at 1 and 5 minutes, respectively. She was started on continuous positive airway pressure (CPAP) and was admitted to Neonatal Intensive Care Unit (NICU) for the following indications: extreme premature with respiratory distress and suspected sepsis.

The infant's hospital course was eventful (figure 1). At Day of Life (DOL) 1, she had hypoglycemia, respiratory distress syndrome, and apnea of prematurity. Thrombocytopenia was first noted on DOL 6 (platelets of 101,000/mcL). Also, on DOL 6, her apnea events increased. E. Coli septicemia was diagnosed. Thrombocytopenia resolved with sepsis treatment, but she continued to have anemia of prematurity that needed multiple blood transfusions.

Between DOL 7 and 13, the patient was relatively stable. An echocardiogram done on DOL 7 reported a large Patent Ductus Arteriosus (PDA) with low velocity flow and left to right shunting and Patent Foramen Ovale, with no intervention needed per the Pediatric Cardiologist. On DOL 13, the patient was intubated due to hypoxic respiratory failure.

She had hypotensive episodes on DOL 14 (mean arterial pressure 16-24). Echocardiogram on DOL 14 showed a hemodynamically significant enlarged PDA (3 mm) and a small secundum atrial septal defect. The patient also had transaminitis and acute kidney injury (AKI) (Table). She was managed for SIRS and cardiogenic shock, gastrointestinal failure, kidney failure, respiratory distress, and hematologic system failures. Her COVID-19 PCR at 24 hours, 48 hours, and DOL 15 was negative. Her COVID IgG was positive, and IgM was negative at DOL 23. In the absence of any other etiologies, the clinical picture was suggestive of MIS-N due to maternal antibody transfer to the neonate.

Echocardiogram on DOL 23 showed no change in PDA size. She was stabilized with supportive care. By DOL 23, her clinical status improved except for worsening kidney and GI failure despite medical treatment of the hemodynamically significant PDA. She was transferred to level 4 NICU for PDA surgical management.



**Figure 1:** The infant's major events in the NICU stay.

## Investigations

On admission to the NICU, a partial septic work-up that included blood culture, complete blood count (CBC), complete metabolic panel (CMP) and inflammatory markers (CRP and procalcitonin) was not indicative of an infection. Cranial ultrasound, done on DOL 7 to screen for intraventricular hemorrhage, was negative.

Repetitive echocardiograms were done to follow up the PDA which was clinically stable but worsened with time. On DOL 13, the infant's clinical status worsened. Full sepsis work-up on DOL 13 resulted in negative blood, urine, and Cerebral Spinal Fluid (CSF) cultures. Blood and CSF Herpes Simplex Virus (HSV) DNA PCR, HSV Surface culture, respiratory viral and bacterial panels, and fungal cultures were negative. She was empirically treated for bacterial, viral, and fungal sepsis until these results were reported negative. CBC, CMP, and Inflammatory markers were continuously followed throughout the patient's NICU stay. A snapshot of her laboratory results that reflect the patient's clinical status is presented in the table below (Table 1).

**Table 1:** Laboratory values reflective of the neonate's clinical status.

	DOL 1	DOL 6	DOL 13	DOL 14	DOL 15	DOL 18	DOL 21	DOL 23
<b>Procalcitonin (ng/ml)</b>	0.33	0.54	2.93†	NA	NA	NA	NA	NA
<b>White Blood Cell Count (WBC in mCL)</b>	10,200	10,900	30,800	40,000	33,300	43,400†	21,700	25,900
<b>Neutrophils (%)</b>	74.6	38.4	NA	71.9	69.3	79.8 †	NA	NA
<b>Lymphocytes (%)</b>	20.9	33.3	NA	17.6	21.8	14.5*	NA	NA
<b>Platelets (x 10<sup>3</sup>/mCL)</b>	222	101	139	97*	110	124	133	135
<b>Albumin (gm/dl)</b>	2.2	2.4	2.5	2.5	1.9	1.8	1.6*	1.6*
<b>Alkaline Phosphatase (ALKP in units/L)</b>	186	563	986	>2,330†	>2,330 †	>2,330†	1,938	981
<b>Aspartate Transferase (AST in units/L)</b>	58	16	200	619†	503	259	42	34
<b>Alanine Transferase (ALT in units/L)</b>	9	<6	42	109†	93	74	9	<6
<b>Creatinine (mg/dl)</b>	1.1	1.0	0.4	2.5†	2.1	1.3	1.8	2.2
<b>Sodium (mmol/L)</b>	146	140	NA	132	124	140	139	137
<b>Potassium (mmol/L)</b>	5.9	3.5	NA	5.2	8.3†	3.6	5.3	4.7
<b>pH‡</b>	7.31	7.23	7.04*	7.33	7.29	7.33	7.39	7.24
<b>Bicarbonate‡, (mmol/L)</b>	23	17	23	16*	18	28	25	20
<b>pCO<sub>2</sub>‡ (mmHg)</b>	44.7	41.7	83.9†	30.8	38.2	53	41.9	47.1

\*Lowest recorded values.

†Highest recorded values.

‡Taken through a capillary blood gas.

## Discussions

We report an extremely preterm neonate born to a mother with a SARS-CoV-2 infection presenting with MIS-N. To our knowledge, this would be the first MIS-N case reported in the United States.

The patient had multiorgan failure (Cardiac, renal, respiratory, gastrointestinal and hematologic failure) with elevated procalcitonin, neutrophilia, and lymphopenia with negative blood, urine, and CSF cultures and negative respiratory panel. Her COVID-19 IgG was positive and IgM was negative, satisfying the diagnostic criteria suggested by Pawar et al (3).

Her PDA started as a benign finding but worsened with time until it became hemodynamically significant. Sepsis and RDS are known contributing factors to the worsening of a PDA (11). In our case, inflammation caused by MIS-N as well as RDS could be the reason for the PDA deterioration.

MIS-N is suspected to occur due to the transfer of maternal antibodies to the fetus causing an inflammatory response or due to the neonate's immune response to SARS-CoV-2 exposure (8, 9). Since maternal vaccination against COVID-19 provides immunity to the neonate through IgG antibodies passing through the placenta and IgA antibodies through breast-milk, it is likely that maternal COVID-19 infection would have a similar effect, giving neonates a protective immunity (3, 5, 9). In some genetically susceptible children, however, SARS-CoV-2 virus triggers auto-antibodies that activate neutrophils and macrophages, increasing inflammatory cytokines leading to MIS-N (3, 5). Other autoantibodies might attack different cell lines (Endothelial, gastrointestinal, and immune cells among others) causing MIS-N's symptoms (3). This is extrapolated from MIS-C patients, as researchers have found that these patients have high levels of certain autoantibodies (such as anti-La and anti-Jo-1) (12).

MIS-C can still occur in neonates due to early-onset SARS-CoV-2 infection. One should differentiate between 'MIS-C in the neonatal period' and MIS-N where the infection occurs in the mother and not in the neonate.

Transferring the SARS-COV-2 virus to the neonate is commonly through horizontal transmission with rare vertical transmission (4, 8, 9, 13). However, maternal antibodies transfer via the placenta (9), with multiple studies reporting transplacental passage of anti-SARS-CoV-2 IgG antibodies to neonates (8, 13). Most infants born to mothers infected with COVID-19 have detectable IgG antibody against it at birth (3, 8, 13).

Treatment is still based on expert opinion, usually supportive or using IVIG and steroids with a possible use of biologic agents (2, 9). Further studies are required to evaluate the risks and benefits of these interventions (2, 8).

Premature Neonates are not immune to MIS-N. MIS-N also adds to the existing complications of prematurity. Based on our case report, we recommend that MIS-N should be considered in the differential diagnosis to explain unusual signs of multisystem inflammation, after excluding common causes.

## Conclusion

Multisystem Inflammatory Disease in Neonates (MIS-N) is a distinct entity thought to be caused by placental autoantibody transfer to the fetus following a COVID-19 infection affecting the mother. Providers should have a high suspicion for MIS-N when the patient presents with multiorgan failure, elevated inflammatory markers, and negative infectious cause with a positive COVID-19 IgG in a neonate born to a COVID-19 infected mother. MIS-N treatment is still under investigation.

## Conflict of Interest

The authors declare no conflict of interest.

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