# Fellow's Column: Diagnostic and Treatment Challenges in Multisystem Inflammatory Syndrome in Neonates (MIS-N): A Success Story with Anakinra

*Kaydeen Morris-Whyte, MD, Robert Reid, MD*

***"Multisystem inflammatory syndrome in neonates (MIS-N) associated with COVID-19 remains a unique diagnostic challenge as the exact pathogenesis is uncertain. The spectrum of possible manifestations has only been reported in a few cases. There is not yet an expert consensus on a case definition for MIS-N, which adds to the diagnostic difficulty. "***

**Introduction**

Multisystem inflammatory syndrome in neonates (MIS-N) associated with COVID-19 remains a unique diagnostic challenge as the exact pathogenesis is uncertain. The spectrum of possible manifestations has only been reported in a few cases. There is not yet an expert consensus on a case definition for MIS-N, which adds to the diagnostic difficulty. MIS-N management is informed by recommendations for multisystem inflammatory syndrome in children (MIS-C) as outlined by the American College of Rheumatology (ACR) ( 1). The mainstay of treatment is intravenous immunoglobulin (IVIG) and corticosteroid with a role for biologics in refractory disease.

***"We are reporting a case of MIS-N that required treatment intensification with anakinra and had a favorable outcome."***

We are reporting a case of MIS-N that required treatment intensification with anakinra and had a favorable outcome.

**Case Presentation**

A 1-hour-old male neonate born at 39 weeks gestation weighing 4125 grams was admitted to the Neonatal Intensive Care Unit (NICU) for hypoglycemia. The neonate was delivered vaginally to a woman with a history of gestational diabetes, limited antenatal care, unknown GBS status, and incidental positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by reverse transcription polymerase chain reaction (RT-PCR). The mother had no prior SARS-CoV-2 vaccination. The mother's membranes ruptured 8 minutes before delivery, and no intrapartum antibiotics were administered. APGAR scores were 9 and 9 at 1 and 5 minutes, respectively. The patient transitioned to the newborn nursery with the mother, and hypoglycemia protocol was initiated per our institution guidelines for an infant of diabetic mother and large-for-gestational age.

At one hour of age, the neonate developed hypoglycemia (blood glucose 20mg/dl), associated with increased breathing work. He was transferred to the NICU and isolated due to maternal-positive SARS-CoV-2 RT-PCR. Initial vital signs were significant for a respiratory rate of 75 breaths/min with room air oxygen saturation of 89%. Physical examination was remarkable for an active, tremulous male infant with bilateral coarse breath sounds on auscultation. Investigations revealed a C-reactive protein (CRP) of 3.79mg/dl and borderline cardiomegaly on a chest radiograph (Figure 1). He stabilized on a high-flow nasal cannula on 21% oxygen and maintenance intravenous fluid with 10% Dextrose.

***"At 18 hours, the neonate developed grunting respirations, abdominal distension, and decreased urine output. Examination revealed a fever with a temperature of 38.8 (0)C. He had clinical features of hypotensive shock, indicating repeated intravenous crystalloid and albumin boluses and the addition of dopamine and hydrocortisone."***

At 18 hours, the neonate developed grunting respirations, abdominal distension, and decreased urine output. Examination revealed a fever with a temperature of 38.8 (0)C. He had clinical features of hypotensive shock, indicating repeated intravenous crystalloid and albumin boluses and the addition of dopamine and hydrocortisone. Simultaneously, he experienced a rapid decline in respiratory status, requiring intubation. The neonate now required glucose infusion greater than 25 mg/kg/min to maintain euglycemia. Laboratory results were remarkable for white blood cell of 10,000 /uL with 12% bands, platelet 115,000/uL, creatinine 1.30 mg/dl (at birth was 0.81 mg/dl), PTT 49.7s, PT 22.3s, AST 107 U/L, ALT 144 U/L, indirect bilirubin 10.69 mg/dL and ionized calcium 0.95 mmol/L. Babygram showed mild pulmonary interstitial infiltrates and dilated bowel loops (Figure 2). An echocardiogram showed asymmetric septal hypertrophy consistent with hypertrophic cardiomyopathy observed in IDM, moderate RVH, hyperdynamic global LV systolic function, very small PDA and mild TR but normal coronary arteries. Ultrasound of the head was normal. Abdominal ultrasound demonstrated trace bilateral pelviectasis and gall bladder sludge but no sign of primary intraabdominal pathology. He received a second dose of Vitamin K for coagulopathy and was initiated on phototherapy. The respiratory pathogen panel and blood culture performed on admission were negative.

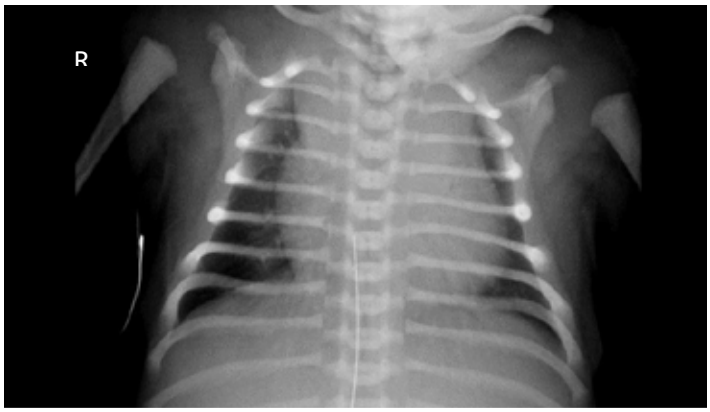


**Figure 1**. Anterior- posterior chest radiograph of patient showing mild cardiomegaly

A repeat blood culture was taken. He was started on ampicillin, gentamicin and cefepime due to the rapid decompensation.

At three days of age, he continued with persistent hypoglycemia, refractory hypotension, and hypotonia. Norepinephrine was added with the resultant stabilization of blood pressure. Laboratory investigations showed a lactate of 1.60mmol/L, platelet 70,000/uL, CRP 15 mg/dl, NT-proBNP 57,700 pg/mL, and troponin I 0.71ng/mL. Additional investigations included negative SARS-CoV-2 RT-PCR and normal ferritin, triglycerides, lymphocyte subset, and gamma globulins. Brain MRI had findings consistent with Grade 1A Neonatal Hypoxic Ischemic Encephalopathy (NIE) and trace intraventricular hemorrhage. Video EEG revealed no epileptiform activity.

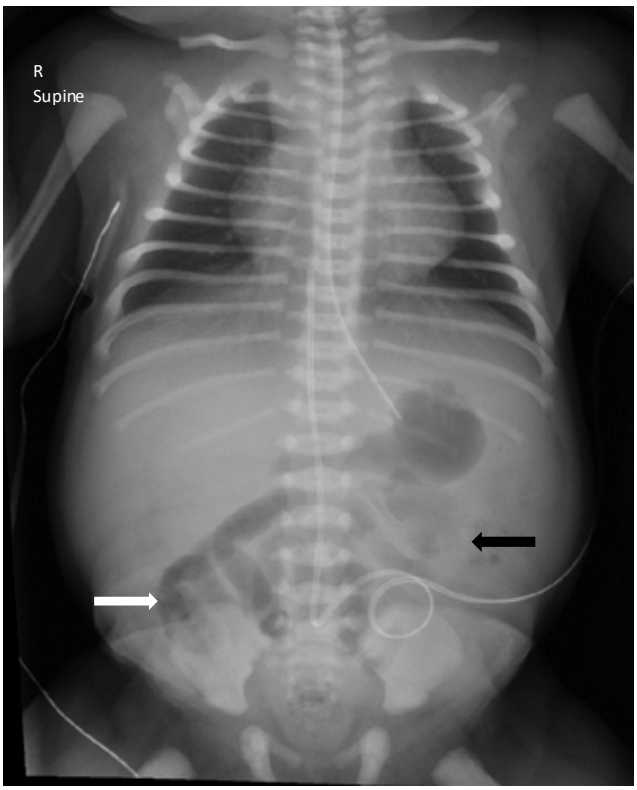


**Figure 2.** Supine chest and abdomen radiograph showing mild pulmonary interstitial infiltrates, paucity of bowel gas in left hemi abdomen (black arrow) and distension of loops of bowel in the right

At four days of age, the neonate's SARS-CoV-2 antibodies were detected for spike and nucleocapsid proteins. Repeat echocardiogram was significant for prominent coronary arteries, diffuse ectasia of LAD measuring 1.75mm (Z score +2.6), and trivial lateral pericardial effusion. Due to concern for MIS-N, he was managed with IVIG at 2mg/kg and methylprednisolone at 2 mg/kg once daily for three days. He had a transient response, was weaned off inotropes, and extubated to N-CPAP, with resolving abdominal distension, recovering thrombocytopenia, and improved CRP. At day 6 of age, on day 3 of methylprednisolone at 2mg/kg/day, fever recurred, and CRP rebounded. Cerebrospinal fluid and blood cultures were obtained. Methylprednisolone was increased to 10mg/kg/day for two doses; then, a slow taper was started. He responded well with improved activity level, decreasing CRP and cardiac enzymes. At day 14 of age, on corticosteroid taper at 2mg/kg/day, he had a breakthrough fever and an upward trend in the CRP level. Anakinra was started at 2mg/kg/day and discontinued after six doses. At day 38 of age, after corticosteroid taper, the patient remained afebrile with normal CRP, cardiac enzymes, and resolution of all abnormalities seen on the previous echocardiogram.

The patient was discharged home at nine weeks of age.

***"SARS-CoV-2 in neonates and children, although frequently asymptomatic or manifesting with only mild symptoms (2), a severe Coronavirus disease 2019 (COVID-19) complication may occur in children called MIS-C. MIS-C presents within 2-6 weeks following COVID-19 infection. MIS-C is theorized to result from post-infectious antibody-mediated immune dysregulation, manifesting predominantly with cardiac involvement, and has a reported mortality rate of 1-2% (3). "***

**Discussion**

SARS-CoV-2 in neonates and children, although frequently asymptomatic or manifesting with only mild symptoms (2), a severe Coronavirus disease 2019 (COVID-19) complication may occur in children called MIS-C. MIS-C presents within 2-6 weeks following COVID-19 infection. MIS-C is theorized to result from post-infectious antibody-mediated immune dysregulation, manifesting predominantly with cardiac involvement, and has a reported mortality rate of 1-2% (3). There have been published cases of a similar disease entity in neonates born to mothers with a history of COVID-19 infection. It is being termed MIS-N by the medical community, though it is not yet characterized by the Centers for Disease Control and Prevention (CDC) or World Health Organization. MIS-N manifests mainly with cardiovascular involvement (hypotensive shock with or without cardiac dysfunction, coronary abnormalities, and arrhythmias), respiratory distress (requiring re-

**Figure 3. Proposed inclusion criteria for neonatal multisystem inflammatory syndrome (MIS-N) secondary to maternal SARS-CoV-2 exposure or infection**

| |
|---|
| (1) A neonate aged <28 days at the time of presentation |
| (2) Laboratory or epidemiologic evidence of SARS-CoV-2 infection in the mother |
| • Positive SARS-CoV-2 testing by RT-PCR, serology (IgG or IgM—and not secondary to immunization), or antigen during pregnancy OR<br>• Symptoms consistent with SARS-CoV-2 infection during pregnancy OR<br>• COVID-19 exposure during pregnancy with a confirmed case of SARS-CoV-2 infection<br>• Serological evidence (positive IgG specific to SARS-CoV-2 but not IgM) in the neonate (and not secondary to maternal immunization) |
| (3) Clinical criteria |
| • Meet clinical criteria in MIS-C[9](except for fever) |
| (4) Laboratory evidence of inflammation |
| • Meet inflammatory marker criteria in MIS-C[9] |
| (5) No alternative diagnosis (viral or bacterial sepsis; birth asphyxia; maternal lupus etc.) that can explain the clinical features |

Molloy et al. Modified from Pawar et al.

spiratory support), and fever (4-8). It has a reported mortality rate of 11% (4), significantly higher than MIS-C. The CDC case definition informs the diagnosis of MIS-N for MIS-C (9 )with well-cited inclusion criteria specific for MIS-N proposed by Pawar et al. and modified by Molloy et al. (Fig. 3) (2).

***"The pathophysiology of MIS-N remains unclear, but experts have made postulations based on the presentation in the early or late neonatal period (2, 5, 7). The proposed pathogenesis for neonates who present within the first week of life is due to the transplacental transfer of maternal antibodies that target neonatal autoantigens. "***

The pathophysiology of MIS-N remains unclear, but experts have made postulations based on the presentation in the early or late neonatal period (2, 5, 7). The proposed pathogenesis for neonates who present within the first week of life is due to the transplacental transfer of maternal antibodies that target neonatal autoantigens. This process triggers the release of inflammatory cytokines that mediate organ dysfunction (2,5,7). Diagnosing MIS-N secondary to this proposed mechanism requires laboratory or epidemiologic evidence of COVID-19 infection in the mother (2). Importantly, it has to be differentiated from an acute COVID-19 infection in the neonate. The other theory is a post-infectious inflammatory cascade induced by neonatal antibodies. These antibodies are produced 2-3 weeks after seroconversion in response to an acute COVID-19 infection and are observed in the later neonatal period.

This case highlights both the diagnostic and treatment challenges in MIS-N. Using the proposed criteria for MIS-N (2), the patient satisfied the case criteria on day 4 of age. Though time sensitive, establishing the diagnosis of MIS-N has to be differentiated from alternative diagnoses (9).

The mother has a history of gestational diabetes, which was believed to contribute to the neonate's initial hypoglycemia and respiratory distress. However, septicemia became the working diagnosis with the onset of multiorgan failure on the background of maternal history of limited prenatal care and unknown GBS status. Multiple repeat cultures were negative, and the patient remained critically ill despite broad-spectrum antibiotics.

***"The differential diagnosis broadened to include immunodeficiencies such as Severe Combined Immunodeficiency Deficiency which was less likely given the normal lymphocyte subset and gamma globulin. Given the neonate's hyperinflammatory state, hemophagocytic lymphohistiocytosis (HLH) was also entertained. "***

The differential diagnosis broadened to include immunodeficiencies such as Severe Combined Immunodeficiency Deficiency which was less likely given the normal lymphocyte subset and gamma globulin. Given the neonate's hyperinflammatory state, hemophagocytic lymphohistiocytosis (HLH) was also entertained. The patient had fever and thrombocytopenia but lacked other cardinal features of HLH, such as organomegaly, hyperfibrinogenemia, and hypertriglyceridemia (10). It was later discovered that the febrile episodes and concomitant uptrend in CRP were associated with corticosteroid taper (Fig. 4). The brain MRI had findings consistent with Grade 1 NIE- which may explain perinatal depres-

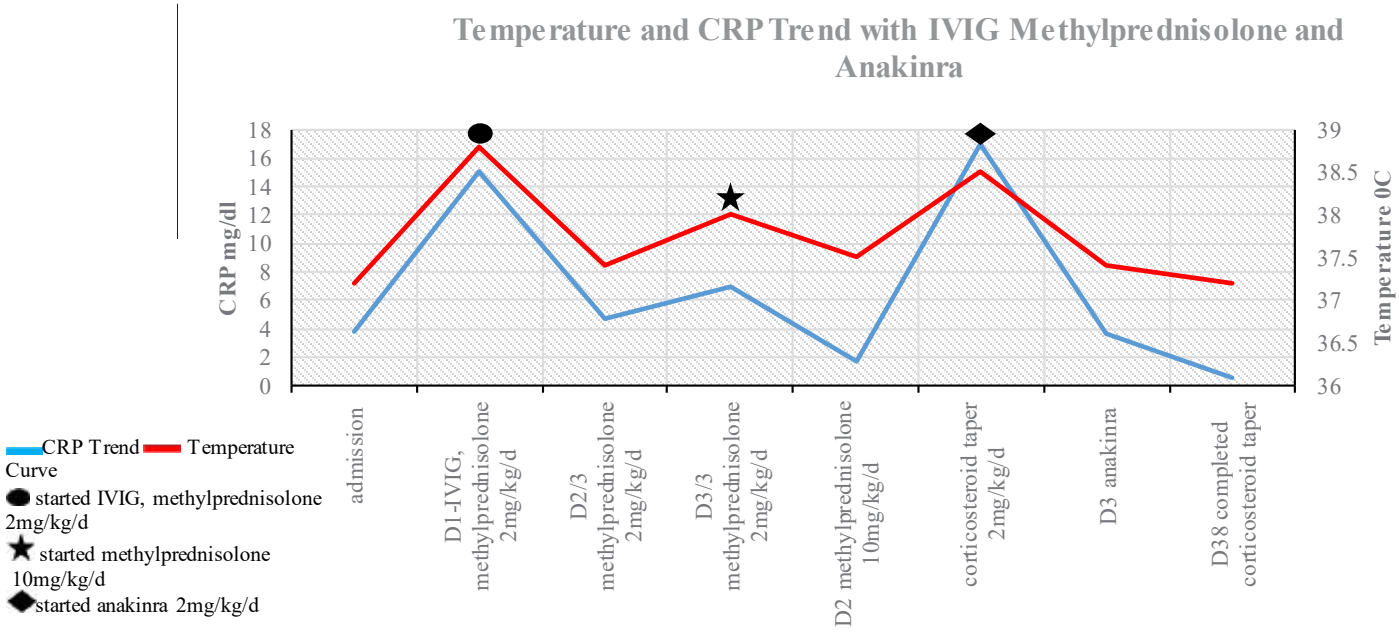


**Figure 4**. Temperature and CRP Trend with IVIG, methylprednisolone at 2mg/kg/day, methylprednisolone at 10mg/kg/day and anakinra 2mg/kg/day
Abbreviations: IVIG, intravenous immunoglobulin; D, day

sion and multiorgan injury but does not account for the coronary artery dilation. The review of placenta pathology (which became available on day 4 of age) identified no features of vascular insults contributing to perinatal asphyxia. Additionally, the placenta had no viral pathogenic changes or other histologic features of infectious villitis to suggest congenital infection.

MIS-N is a diagnosis of exclusion, but it mimics several disease states making it difficult to diagnose. According to the CDC, 225,656 pregnant women in the United States tested positive for COVID-19 from January 22, 2020 – July 25, 2022 (11). Re-infection is possible, and the high rate of maternal SARS-CoV-2 vaccination during pregnancy adds complexity to the interpretation of antibody tests in neonates.

Specific treatment of MIS-N follows a tiered approach starting with IVIG and methylprednisolone at 1-2mg/kg/day for three days with slow tapering over 14 days. Most cases report favorable responses with IVIG and corticosteroids (4-6). Our patient had a transient response to IVIG and methylprednisolone at 2mg/kg/day. Using the ACR recommendations for refractory disease in MIS-C (1,) we added high-dose IV pulse methylprednisolone at 10mg/kg/day, with relapse during tapering; we then escalated to anakinra, IL-1 receptor antagonist. On anakinra, the neonate experienced sustained clinical and biochemical response, likely due to the inhibition of pro-inflammatory cytokines that potentiate multiorgan injury. In a case series published by Kumar et al. of three neonates meeting the proposed classification criteria for MIS-N, anakinra was used in two patients with favorable outcomes in one case. The other succumbed to the illness (12). The use of high-dose corticosteroids and biologics in MIS-N is based on clinical evidence and information extrapolated from Kawasaki Disease (KD), given similar pathogenesis of immune dysregulation (1). Postnatal corticosteroid use is not benign. Therefore, further studies are warranted on the pharmacodynamics of high-dose corticosteroids in MIS-N.

***"In this case, it is difficult to determine the additional benefit of anakinra to pulse corticosteroids. However, it allowed us to taper steroid use quickly (Fig. 4). MIS-N is a new disease, and the immune response of neonates to this syndrome is still unknown, and clinical trials are needed to determine optimal treatment and long-term safety data for potential sequelae. "***

In this case, it is difficult to determine the additional benefit of anakinra to pulse corticosteroids. However, it allowed us to taper steroid use quickly (Fig. 4). MIS-N is a new disease, and the immune response of neonates to this syndrome is still unknown, and clinical trials are needed to determine optimal treatment and long-term safety data for potential sequelae.

## Conclusion

MIS-N is a life-threatening disease requiring a high suspicion index in neonates with SARS-CoV-2 exposure. It is anticipated that as new variants of SARS-CoV-2 emerge and cases of COVID-19 rise, we may see more cases of MIS-N. This report is meant to disseminate information about the clinical and laboratory features of MIS-N and contribute to clinical evidence to guide future studies.

We successfully managed our patient using high-dose corticosteroids and anakinra; however, long-term evidence regarding the safety of the above medications is lacking.

***References:***


1. *Henderson, L. A., Canna, S. W., Friedman, K. G., Gorelik, M., Lapidus, S. K., Bassiri, H., Behrens, E. M., Kernan, K. F., Schulert, G. S., Seo, P., Son, M. B. F., Tremoulet, A. H., VanderPluym, C., Yeung, R. S. M., Mudano, A. S., Turner, A. S., Karp, D. R., & Mehta, J. J. (2022). American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 3. Arthritis & rheumatology (Hoboken, N.J.), 74(4), e1–e20. https://doi.org/10.1002/art.42062*
2. *Molloy, E. J., Nakra, N., Gale, C., Dimitriades, V. R., & Lakshminrusimha, S. (2022). Multisystem inflammatory syndrome in children (MIS-C) and neonates (MIS-N) associated with COVID-19: optimizing definition and management. Pediatric research, 1–10. Advance online publication. https://doi.org/10.1038/s41390-022-02263-w*
3. *Son, MB., et al. COVID-19: Multisystem inflammatory syndrome in children (MIS-C) management and outcome. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on January 28, 2023.)*
4. *Shaiba, L. A., More, K., Hadid, A., Almaghrabi, R., Al Marri, M., Alnamnakani, M., & Shah, P. (2022). Multisystemic Inflammatory Syndrome in Neonates: A Systematic Review. Neonatology, 119(4), 405–417. https://doi.org/10.1159/000524202*
5. *Pawar, R., et al. (2021). "Neonatal Multisystem Inflammatory Syndrome (MIS-N) Associated with Prenatal Maternal SARS-CoV-2: A Case Series." Children 8(7): 572.*
6. *Shaiba, L. A., Hadid, A., Altirkawi, K. A., Bakheet, H. M., Alherz, A. M., Hussain, S. A., Sobaih, B. H., Alnemri, A. M., Almaghrabi, R., Ahmed, M., Arafah, M. A., Jarallah, A., Bukhari, E. E., & Alzamil, F. A. (2021). Case Report: Neonatal Multisystem Inflammatory Syndrome Associated With SARS-CoV-2 Exposure in Two Cases From Saudi Arabia. Frontiers in pediatrics, 9, 652857. https://doi.org/10.3389/fped.2021.652857*
7. *Lakshminrusimha, S., Hudak, M. L., Dimitriades, V. R., & Higgins, R. D. (2022). Multisystem Inflammatory Syndrome in Neonates following Maternal SARS-CoV-2 COVID-19 Infection. American journal of perinatology, 39(11), 1166–1171. https://doi.org/10.1055/a-1682-3075*
8. *De Rose, D. U., Pugnaloni, F., Calì, M., Ronci, S., Caoci, S., Maddaloni, C., Martini, L., Santisi, A., Dotta, A., & Auriti, C. (2022). Multisystem Inflammatory Syndrome in Neonates Born to Mothers with SARS-CoV-2 Infection (MIS-N) and in Neonates and Infants Younger Than 6 Months with Acquired COVID-19 (MIS-C): A Systematic Review. Viruses, 14(4), 750. https://doi.org/10.3390/v14040750*
9. *Centers for Disease Control and Prevention. Covid-19 Information for Pediatric Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C) https://www.cdc.gov/mis/mis-c/hcp/index.html. Assessed January 28, 2023*
10. *Paolino, J., Berliner, N., & Degar, B. (2022). Hemophagocytic lymphohistiocytosis as an etiology of bone marrow failure. Frontiers in oncology, 12, 1016318. https://doi.org/10.3389/fonc.2022.1016318*
11. *Centers for Disease Control and Prevention. Data on COVID-19 during pregnancy: severity of maternal illness. https://stacks.cdc.gov/view/cdc/119588 . Assessed January 28, 2023*
12. *Kumar, C., Anjani, G., Deshmukh, N.N. et al. Multisystem Inflammatory Syndrome in Neonates (MIS-N) Related to Maternal SARS-CoV-2 Exposure. Indian J Pediatr 90, 98 (2023). https://doi.org/10.1007/s12098-022-04407-6*


**NT**


***Corresponding Author***

*Kaydeen Morris-Whyte, MD*
*Pediatrics Resident, PGY-2*
*Joe DiMaggio Children's Hospital*
*Hollywood, Florida*
*305 879 6781*
*Email:* kmorriswhyte@mhs.net

*Robert Reid, MD*
*Pediatrics Infectious Disease Specialist*
*Joe DiMaggio Children's Hospital*
*Hollywood, Florida*
*Email:* roreid@mhs.net