Triple Threat: COVID-19 with Superimposed Bacterial Sepsis and MIS-C

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ABSTRACT

COVID-19 among the pediatric population most often presents as asymptomatic to moderate infection in the majority of the cases. In rare cases, children can be severely affected, and the condition may progress to life threatening condition. This paper outlines a COVID-19 confirmed child who initially exhibited mild symptoms but subsequently acquired a nosocomial infection caused by a multidrug-resistant bacterium known as Acinetobacter lowffii during their hospitalization. As the hospitalization progressed, the patient also developed pneumonia and prolonged fever, eventually showing symptoms consistent with Multisystem Inflammatory Syndrome in Children (MIS-C). This paper will discuss the importance of early recognition and intervention of co-infection and complications of COVID-19 to ensure the best outcomes for affected children, as the management of sepsis and MIS-C can differ significantly, and prompt, accurate diagnosis can guide appropriate treatment strategies.

Keywords: COVID-19, Sepsis, Nosocomial infection, Acinetobacter lwoffii, MIS-C, Pediatrics

INTRODUCTION

The COVID-19 pandemic has affected individuals of all age groups across the globe, with a vast majority of pediatric cases initially presenting as mild or asymptomatic. While children have generally experienced milder symptoms compared to adults, a concerning subset of cases has demonstrated a unique and perplexing clinical course. Some children with seemingly mild initial presentations of COVID-19 have gone on to develop severe complications during their hospital stay, including sepsis, pneumonia, and multisystem inflammatory syndrome in children (MIS-C). This intriguing phenomenon has raised significant questions about the underlying mechanisms, diagnostic challenges, and the clinical management of pediatric COVID-19.

This report presents a case of a child initially admitted for mild COVID-19, which later progressed to a severe form of the illness, being infected with a multidrug resistant organism (Acinetobacter lowffii) sepsis and pneumonia during the course of hospital stay. The patient then had prolonged fever and eventually exhibited signs and symptoms of MIS-C on the 3rd week of illness. This paper will explore the critical role of timely diagnosis, the evolving understanding of pediatric COVID-19, and the importance of vigilant monitoring for these severe complications in pediatric patients.

CASE PRESENTATION

Patient is a 2-year-old male, born preterm at 32 weeks AOG, third of triplets, admitted upon birth in Neonatal ICU for two months for Respiratory Distress Syndrome, Sepsis, and Prematurity. Patient was discharged stable with no other hospitalization. Patient had exposure to COVID-19 positive mother and developed fever and colds one day prior to admission. On the day of consult, patient had febrile convulsion and upon admission was noted to be COVID-19 RT PCR positive. On physical examination, patient was febrile with no other significant findings, with normal neurologic examination. Patient was initially started on supportive management.

During the first three days of hospital stay, patient had intermittent high grade fever and eventually developed cough, vomiting, and episodes of diarrhea, hence workup was done which revealed elevated Procalcitonin 2.2 ng/mL (high risk) and IL-6 205.6 pg/mL (reference range: 0-7 pg/mL). Chest X-ray was normal at the time. Patient was initially started on Ceftazidime, but blood culture after three days showed multidrug resistant Acinetobacter lwoffii hence antibiotic was shifted to Ampicillin-Sulbactam and Colistin.

On the 12th hospital day, on day five of antibiotics, patient had fever recurrence, with noted progression of cough severity, with episodes of tachypnea and occasional alar flaring, requiring

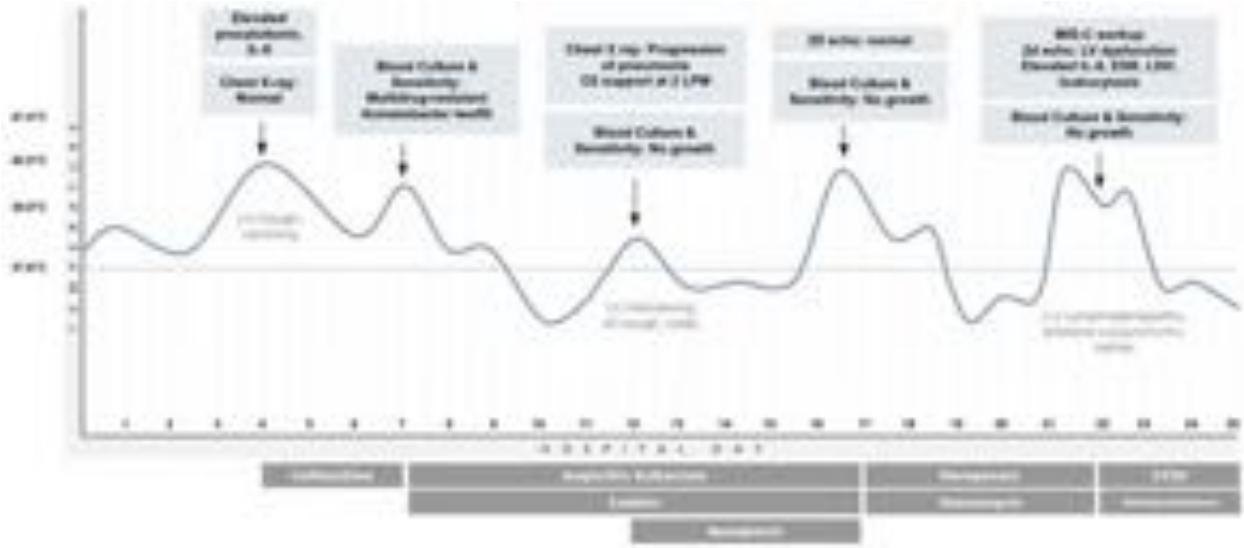


Image 1. Graphic representation of hospital course of the patient

low flow oxygen support at 2 LPM. Repeat chest X-ray revealed pneumonia. Repeat procalcitonin showed elevated result at 24.39 ng/mL (high risk), IL-6 showed 17.0 pg/mL (reference range: 0-7 pg/mL) . Assessment at the time was Moderate COVID-19, hence Remdesivir was started, with noted clinical improvement after 24 hours. Patient was weaned off from oxygen then became afebrile until the 16th hospital day (day nine of Ampicillin and Sulbactam and Colistin, day four of Remdesivir), when patient had fever recurrence. Workup was done which showed elevated leukocytosis at 14,300 mm^3, CRP 6 mg/dL (equivocal), and elevated Procalcitonin 5.28 ng/mL (high risk). 2d echo was done to rule out cardiac pathology which showed normal result. Antibiotics were then shifted to Meropenem and Vancomycin, to which the patient responded clinically.

However, on the 21st hospital day, patient had recurrence of fever, associated with vomiting and diarrhea, with no respiratory symptoms but with fair oral intake. Patient then developed maculopapular rashes, bilateral conjunctivitis, and subcentimeter unilateral cervical lymphadenopathy. Blood culture showed negative result, but due to persistence of fever, workup for MIS-C was done which showed elevated IL-6 56.2 pg/mL (reference range: 0-7 pg/mL), ESR 47 mm/hr (0-10), LDH 285 U/L (reference range: 120-246 U/L), leukocytosis (WBC 14,800 mm^3) with neutrophilia, normal Ferritin levels. Repeat 2D echo showed left ventricular diastolic dysfunction, with normal cardiac markers. Patient was then treated as a case of MIS-C and was started on IVIG and Methylprednisolone. Patient was also referred to rheumatology service to rule out rheumatologic cause with noted negative Rheumatoid factor.

Post-IVIG, patient had clinical improvement then became afebrile for 48 hours and was subsequently discharged stable. Upon follow up, patient was referred to immunology service, with noted normal Immunodeficiency Panel.

DISCUSSION

World Health Organization (WHO) has classified COVID-19 Disease in children as critical, severe, and non severe with the criteria and clinical indicators as follows:

Critical COVID-19
Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life- sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
Severe COVID-19

• Oxygen saturation < 90% on room air • Respiratory rate > 30 breaths/min in adults and children > 5 years old; ≥ 60 breaths/min in children < 2 months old; ≥ 50 in children 2–11 months old; and ≥ 40 in children 1–5 years old • Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).
Non-severe COVID-19
Defined as absence of any criteria for severe or critical COVID-19.

Infants and young children infected with SARS-CoV-2 usually have mild or even asymptomatic cases. However, some may exhibit symptoms consistent with respiratory infections, and in rare cases, severe illness may occur. The Philippine Surveillance and Analysis of COVID-19 in Children Nationwide (SALVACION) database observed comparable patterns in COVID-19 cases among the pediatric population. Around 83.9% of hospitalized children experienced mild to moderate COVID-19 infections, with 8.2% severe cases and 7.9% critical cases reported. The most prevalent symptoms in Filipino children included fever (57.9%) and cough (42.7%). Common underlying health conditions were related to hematology/oncology (7.4%) and neurological/developmental (7.2%) issues, with prematurity accounting to 2.2%. Among the cohort, co-infection with sepsis occured in 6.1% of the patients, and 2.1% had healthcare associated pneumonia.

COVID-19 and Sepsis

Sepsis is a life-threatening condition characterized by a dysregulated immune response to infection, leading to systemic inflammation and organ dysfunction. COVID-19 can lead to sepsis through a complex interplay of immunological and physiological mechanisms. In order to classify a pediatric patient as septic, the following criteria must be met: Pediatric systemic inflammatory response syndrome (SIRS) Criteria as shown in Table 1 where ≥1 of the criteria from Column 1 AND Column 2 in the presence of infection. The patient presented with COVID-19 as the initial infection, with highest temperature of 39.9C and respiratory rate of 25-30 breaths/minute, qualifying the patient in the Pediatric Sepsis Criteria.

SARS-CoV-2, the virus responsible for COVID-19, enters the host via the ACE2 receptor in the respiratory tract. Upon entry, the virus undergoes replication within respiratory epithelial cells. As the virus replicates, the host's immune system is activated. An immune response is initiated, leading to the release of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). In severe COVID-19 cases, a hyperinflammatory state can occur, characterized by an exaggerated release of proinflammatory cytokines. This cytokine storm can lead to systemic inflammation, with potential endothelial damage and coagulation abnormalities. The inflammatory response can cause dysfunction of the endothelium. This endothelial damage may result in increased vascular permeability, causing fluid to leak into tissues, including the alveoli of the lungs, contributing to acute respiratory distress syndrome (ARDS). Endothelial dysfunction also results in increased vascular permeability, microthrombi formation, and impaired blood flow regulation. This can contribute to a hypercoagulable state and impaired tissue perfusion. Subsequently, COVID-19 can weaken the immune system and compromise the body's ability to fight off other infections, such as bacterial or fungal infections. These secondary infections can further contribute to the septic response. As sepsis progresses, the combination of widespread inflammation, fluid imbalance, and secondary infections can lead to organ dysfunction, which may affect multiple organs, such as the heart, liver, and kidneys, and can become compromised, leading to organ dysfunction. The culmination of these factors, including dysregulated inflammation, endothelial damage, coagulation disturbances, secondary infections, and organ dysfunction, can lead to the development of sepsis in children with severe COVID-19. The presented case initially presented with febrile convulsion, eventually leading to respiratory symptoms of cough and colds. Patient then succumbed to nosocomial infection of sepsis and pneumonia, which may be explained by the

Age Group	Pediatric SIRS Criteria (≥1 of the criteria from Column 1 AND Column 2)							
	Column 1 (≥1 of the below criteria)				Column 2 (≥1 of the below criteria)			Cardiovascular Dysfunction
	Core Temperature (°C)		Leukocyte Count (Leukocytes x10^3/mm^3)		Heart Rate (Beats/Min)		Respiratory Rate	Systolic Blood Pressure (mmHg)
	Hypothermia	Hyperthermia	Leukopenia	Leukocytosis	Bradycardia	Tachycardia	(Breaths/Min)	
0 days to 1 wk	<36	>38.5	NA	>34	<100	>180	>50	<65
1 wk to 1 mo	<36	>38.5	<5	>19.5	<100	>180	>40	<75
1 mo to 1 yr	<36	>38.5	<5	>17.5	<90	>180	>34	<100
2-5 yrs	<36	>38.5	<5	>15.5	NA	>140	>22	<94
6-12 yrs	<36	>38.5	<4.5	>13.5	NA	>130	>18	<104
13 to <18 yrs	<36	>38.5	<4.5	>11	NA	>110	>14	<117

Table 1. Age-specific vital signs and laboratory variables

weakened immune system brought about by the COVID-19 infection.

COVID-19 and MIS-C

Multisystem Inflammatory Syndrome in Children (MIS-C), which can fulfill the criteria for Systemic Inflammatory Response Syndrome (SIRS) and resemble sepsis, is a rare but serious condition that primarily affects children and adolescents. This condition arises following a prior COVID-19 infection or exposure. MIS-C is characterized by symptoms reminiscent of Kawasaki disease or toxic shock syndrome in children who have had previous contact with COVID-19. While there is some overlap in the clinical manifestations of acute severe COVID-19 and MIS-C, these conditions exhibit distinct patterns in terms of how they present clinically and the organs they affect

The exact mechanism of how MIS-C develops is not fully understood, but it appears to be an abnormal and delayed immune response to the viral infection. MIS-C is characterized by significant inflammation in multiple organ systems, including the heart, lungs, kidneys, gastrointestinal tract, skin, and more. It typically presents with symptoms like persistent fever, abdominal pain, vomiting, skin rashes, and swollen lymph nodes.

Centers for Disease Control and Prevention (CDC) developed a new standardized surveillance case definition for MIS-C in December 2022 as follows: An individual aged <21 years and in the absence of a more likely alternative diagnosis:

- Fever (T>38.0°C)
- Clinical severity requiring hospitalization or resulting in death
- C-reactive protein (CRP) >3.0 mg/dL
- New onset manifestations of >2 of the following categories:
  - Shock
  - Cardiac: coronary artery dilatation/aneurysm, left ventricular ejection fraction <55%, or troponin elevated above normal
  - Mucocutaneous:rash,

conjunctivitis/conjunctival injection or extremity findings (erythema, edema) oral mucosal inflammation
- Gastrointestinal: abdominal pain, vomiting or diarrhea
- Hematologic: platelet count <150,000/µL, absolute lymphocyte count <1000/µL

- Detection of SARS-CoV-2 nucleic acid/antigen up to 60 days prior to or during hospitalization or in a postmortem specimen, OR detection of antibody associated with current illness, OR close contact with a confirmed/probable COVID-19 case in the 60 days prior to hospitalization.

Many children with MIS-C receive anti-inflammatory treatments to reduce the excessive inflammation associated with the condition. Patients are usually treated with IVIG, 2 g/kg (max 100 g); patient cardiac function and fluid status influence the duration of the infusion of IVIG therapy. IVIG exerts anti-inflammatory effects by inhibiting the activation and function of immune cells, such as B cells and T cells. It can also reduce the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α), which are often elevated in MIS-C. IVIG can also promote immune tolerance and regulatory pathways, helping to control the excessive immune response seen in MIS-C. This immunomodulatory effect may contribute to a reduction in tissue damage and systemic inflammation.

Those who do not improve clinically, or whose laboratory values do not improve, or who are admitted to intensive care from the outset have also been treated with steroid therapy (ranging from 2 to 30 mg/kg/day of methylprednisolone, depending on severity of illness) to further control inflammation In specific cases, other medications, such as anti-coagulants (blood thinners), may be administered if there is a risk of clot formation.

Severe COVID-19 vs MIS-C

The clinical features of MIS-C and severe acute COVID-19 overlap. However, differing patterns of clinical presentation and organ system involvement may help differentiate MIS-C from severe acute COVID-19. Severe pulmonary involvement (ie, pneumonia, acute respiratory distress syndrome) is a prominent feature in severe acute COVID-19. While respiratory symptoms are common in patients with MIS-C, they are more often secondary to shock and/or impaired cardiac function. On the other hand, myocardial dysfunction and shock, gastrointestinal symptoms (particularly abdominal pain), mucocutaneous findings, are more common in MIS-C than in severe acute COVID-19. Inflammatory markers (CRP, ferritin, and D-dimer) tend to be more elevated in MIS-C compared with severe acute COVID-19. In addition, lymphopenia and thrombocytopenia are more common in MIS-C.

The presented patient initially developed respiratory distress and sepsis, showing signs of severe COVID-19 infection. After three weeks of hospitalization, patient then developed signs of MIS-C such as rash and conjunctivitis, along with elevated inflammatory markers, following the course of MIS-C.

Remdesivir in COVID-19 Among Children

There are no randomized controlled trials (RCTs) to evaluate the use of remdesivir in the treatment of COVID-19 in the pediatric population. One observational study among pediatric patients described the compassionate use of Remdesivir for all 77 patients. It showed 83% of cases recovered after 28 days of follow-up. On subgroup analysis, those on invasive ventilation took a significantly longer time to recover and time to discharge than those without, with 32% of patients presenting at least one adverse event. Pooled results of ten RCTs evaluating the use of remdesivir in adults outpatients with mild to moderate COVID-19 with risk factors has shown significant benefit in terms of reducing risk for hospitalizations and death. For hospitalized/in-patients, remdesivir decreased the risk only for clinical deterioration as measured by the WHO progression scale but did not show benefit in other outcomes: all-cause mortality, need for mechanical ventilation and time to clinical improvement. No increased risk of adverse events and serious adverse events.

Despite the very low certainty of evidence for hospitalized children, the Pediatrics Infectious Disease Society of the Philippines (PIDSP) panel recommends the use of remdesivir. This is due to the significant benefit in decreasing the risk for clinical deterioration (based on WHO progression

scale) and the risk reduction in mechanical ventilation use, although this was not statistically significant. The panel also agreed that because there are very limited treatment options for pediatric patients with COVID-19, this would give better guidance to clinicians. The panel emphasized though that remdesivir should be used for pediatric patients with severe COVID-19 following the classification of PIDSP (on low flow oxygen support).

The Role of COVID Vaccine in Children

Vaccination among the pediatric population has had a significant impact on COVID-19 infection and its clinical presentation. Vaccinated children who do contract COVID-19 generally experience milder symptoms compared to unvaccinated children. Vaccination modulates the pathogenesis of MIS-C, making vaccinated pediatric populations are at a reduced risk of developing severe complications such as multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. With lower infection rates and milder symptoms, vaccinated children are more likely to attend school regularly and safely. This has a positive impact on their education and overall well-being. It is important, however, to note that vaccine effectiveness can vary depending on the specific vaccine, the age of the child, and the level of community vaccination. Additionally, the emergence of new variants and changes in vaccine recommendations may affect the overall impact of vaccination on pediatric COVID-19 cases. Therefore, continued research and vigilance in vaccination efforts are essential to provide the best protection for children and the community as a whole.

CONCLUSION

Both MIS-C and sepsis can lead to severe inflammation and affect multiple organ systems, making early diagnosis and treatment critical. While MIS-C is often associated with previous SARS-CoV-2 infection, sepsis can be triggered by various infections. Sepsis can be a life-threatening condition that requires immediate medical attention, while MIS-C, when identified and treated early, often leads to recovery.

Prompt diagnosis of COVID-19 in children with sepsis and multisystem inflammatory syndrome in children (MIS-C) is crucial for timely and effective medical management. While COVID-19 may present with a wide range of symptoms in children, including respiratory and gastrointestinal symptoms, sepsis, and MIS-C, it is essential for healthcare providers to maintain a high index of suspicion when assessing pediatric patients with unexplained fever, systemic inflammation, and organ dysfunction.

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