coronavirus Disease 2019 (COVID-19) or bacterial infections. His biochemical, hematological parameters and acute phase reactants at admission were in the normal reference range. On the 3rd day of admission, he developed tachycardia and became restless and inconsolable. His laboratory results revealed elevated C-reactive protein level [8.75 mg/dl (0–0.5 mg/dl)]. Empirical antimicrobial treatment (ampicillin and cefotaxime) was initiated after sepsis workup was performed. Enterobacter cloacae was isolated from the 2 consecutive blood cultures.

COVID-19 seems to have a favorable clinical course in children; however, knowledge about the course of disease in asymptomatic infants is scarce. 1 A study of pediatric SARS-CoV-2 cases in China reported that 11% of infants had a severe or critical illness. 2 In infants, findings such as fever, lethargy, poor feeding, vomiting, tachypnea and tachycardia attributed to the SARS-CoV-2 can be also seen in bacterial sepsis. Laboratory parameters may not always help distinguish between COVID-19 and bacterial sepsis. Bacterial coinfection has been previously reported in SARS-CoV-2-positive infants. 3 A preterm neonate was reported to develop sepsis caused by Enterobacter species as in our case. 2 It is important that clinicians be aware of the development of bacterial sepsis during SARS-CoV-2 infection, especially in infants.

Elif Böncüoğlu, MD, Elif Kuyvet, MD, Miray Yılmaz Çelebi, MD, Elin Cem, MD, Mustafa Gülderen, MD, Şahika Şahinkaya, MD, Nuri Bayram, MD, and İlke Devrim, MD
From the Department of Pediatric Infectious Diseases, University of Health Sciences Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Izmir, Turkey.

REFERENCES
1. Rozyczki HH, Kotecha S. Covid-19 in pregnant women and babies: what pediatricians need to know. Paediatr Respir Rev. 2020;35:31–37.
2. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145:e20200702.
3. Chen Y, Peng H, Wang L, et al. Infants born to mothers with a new coronavirus (COVID-19). Front Pediatr. 2020;8:104.
4. McLaren SH, Dayan PS, Fenster DB, et al. Novel coronavirus disease 2019 (COVID-2019) was first reported in patients presenting with shock in Europe and North America in mid-April 2020. 1,2 Here, we present 3 pediatric cases with MIS-C who had identical twins (Fig. 1). In all 3 cases, while the twin was infected, they did not develop MIS-C.

CASE 1
A 2-year-old previously healthy boy presented with a 4-day fever, diffuse rash, nausea-vomiting, and diarrhea. Vital signs at the time of examination included a temperature of 39.6°C, heart rate of 146 beats/min, blood pressure of 95/60 mm Hg, respiratory rate of 33 breaths/min, and oxygen saturation of 94% on room air. On admission, physical examination showed a diffuse urticarial rash that localized on bilateral axillary and inguinal regions, bilateral conjunctivitis, and papillitis of the tongue, lip cracking, and fissuring. He was tachycardic with 3/6 systolic murmurs and had clear lungs to auscultation bilaterally. He was admitted to pediatric intensive care unit (PICU) with a diagnosis of MIS-C. His identical twin was asymptomatic, his physical examination was normal. Clinical and laboratory findings were shown in Table 1. Nasopharyngeal swab for SARS-CoV-2 by RT-PCR was negative, but SARS-CoV-2 antibodies were positive. Also, his identical twin and his parents were antibody positive. An echocardiogram revealed ventricular systolic dysfunction and left ventricular ejection fraction (LVEF) 45% with mitral insufficiency. Treatment was initiated with fluid replacement therapy, milrinone (0.5 μg/kg/min) infusion, aspirin 100 mg, and intravenous immunoglobulin. On day 10, the patient was discharged home on prednisone and aspirin 100 mg. Although the identical twin had COVID-19 infection 1 month ago and was positive for antibodies, he developed no symptoms and laboratory values were normal.

CASE 2
A 12-year-old previously healthy boy presented with a 7-day history of fever, vomiting, diarrhea, and abdominal pain. One month ago, our patient, his identical twin, and parents were PCR positive for SARS-CoV-2 from nasopharyngeal swabs. Vital signs at the time of examination included a temperature of 39.1°C, heart rate of 149 beats/min, blood pressure of 88/42 mm Hg, respiratory rate of 36 breaths/min, and oxygen saturation of 92% on room air. On admission, physical examination showed a diffuse erythematous rash that localized on bilateral axillary and inguinal regions, bilateral conjunctivitis, and papillitis of the tongue, lip cracking, and fissuring. He had signs of meningeal irritation, decreased breath sounds at the lung bases. He was tachycardic with 3/6 systolic murmurs and hypotensive, so he was admitted to PICU with a diagnosis of MIS-C. His identical twin was asymptomatic, his physical examination was normal. Clinical and laboratory findings were shown in Table 1. An echocardiogram revealed ventricular systolic dysfunction and LVEF 40% with mitral insufficiency. Brain magnetic resonance imaging (MRI) showed hyperintensity on T2-weighted images in the splenium of the corpus callosum with restricted diffusion. Treatment was initiated with fluid replacement therapy, milrinone (0.5 μg/kg/min) and norepinephrine (0.1 μg/kg/min) infusion, enoxaparin (low molecular weight heparin) 6000 U, IVIG 1 g/kg for 2 days, and methylprednisolone 30 mg/kg/day for 3 days followed by a prednisone taper. The patient experienced a near resolution of symptoms and normalization of vital signs within 4 days. Inflammatory markers improved rapidly over 7 days. Repeated brain MRI on day 7 was normal, indicating the resolution of the lesion in the splenium of the corpus callosum. On day 10, the patient was discharged home on prednisone and aspirin 100 mg. Although the identical twin had COVID-19 infection 1 month ago and was positive for antibodies, he developed no symptoms and laboratory values were normal.

A 10-year-old previously healthy boy presented with a 4-day history of fever, nausea-vomiting, and diarrhea. Vital signs at the time of examination included a temperature of 39.1°C, heart rate of 149 beats/min, blood pressure of 88/42 mm Hg, respiratory rate of 36 breaths/min, and oxygen saturation of 92% on room air. On admission, physical examination showed a diffuse erythematous rash that localized on bilateral axillary and inguinal regions, bilateral conjunctivitis, and papillitis of the tongue, lip cracking, and fissuring. He had signs of meningeal irritation, decreased breath sounds at the lung bases. He was tachycardic with 3/6 systolic murmurs and hypotensive, so he was admitted to PICU with a diagnosis of MIS-C. His identical twin was asymptomatic, his physical examination was normal. Clinical and laboratory findings were shown in Table 1. An echocardiogram revealed ventricular systolic dysfunction and LVEF 40% with mitral insufficiency. Brain magnetic resonance imaging (MRI) showed hyperintensity on T2-weighted images in the splenium of the corpus callosum with restricted diffusion. Treatment was initiated with fluid replacement therapy, milrinone (0.5 μg/kg/min) and norepinephrine (0.1 μg/kg/min) infusion, enoxaparin (low molecular weight heparin) 6000 U, IVIG 1 g/kg for 2 days, and methylprednisolone 1 g/day for 5 days followed by a prednisone taper. The patient experienced a near resolution of symptoms and normalization of vital signs within 4 days. Inflammatory markers improved rapidly over 7 days. Repeated brain MRI on day 7 was normal, indicating the resolution of the lesion in the splenium of the corpus callosum. On day 10, the patient was discharged home on prednisone and aspirin 100 mg. Although the identical twin had COVID-19 infection 1 month ago and was positive for antibodies, he developed no symptoms and laboratory values were normal.
vomiting, diarrhea, and abdominal pain. One month earlier, his mother was positive for PCR for SARS-CoV-2 in the nasopharyngeal swab. Vital signs at the time of examination included a temperature of 38.6°C, heart rate of 159 beats/min, blood pressure of 85/69 mm Hg, respiratory rate of 30 breaths/min, and oxygen saturation of 94% on room air. On admission, physical examination showed nonspecific erythema that localized his trunk and inguinal region. He was tachycardic with 3/6 systolic murmur and had clear lungs to auscultation bilaterally. He was admitted to PICU with a diagnosis of MIS-C. His identical twin was asymptomatic, and his physical examination was normal. Clinical and laboratory findings were shown in Table 1. Nasopharyngeal swab for RT-PCR for SARS-CoV-2 and the SARS-CoV-2 antibodies were positive.

| Case 1 | Case 2 | Case 3 |
|--------|--------|--------|
| Age/Gender | 2/Male | 12/Male | 10/Male |
| Symptoms | Fever, diffuse rash, diarrhea, vomiting | Fever, diarrhea, vomiting, abdominal pain | No |
| Consanguinity | Yes | Yes | No |
| Vital signs | | | |
| SpO₂ (%) | 94 | 92 | 94 |
| Heart rate (per min) | 146 | 149 | 159 |
| Blood Pressure (mm Hg) | 95/60 | 88/42 | 85/69 |
| Respiratory Rate (per min) | 33 | 36 | 30 |
| Body Temperature (°C) | 39.6 | 39.1 | 38.6 |
| Laboratory findings | | | |
| White blood cell (per μL) | 3290 | 6330 | 8910 |
| Lymphocyte (per μL) | 630 | 260 | 960 |
| Neutrophil (per μL) | 2280 | 5490 | 7760 |
| Platelet (per μL) | 84,000 | 98,000 | 111,000 |
| CRP (mg/L) | 11.4 | 10.9 | 10.5 |
| Procalcitonin (mg/mL) | 123 | 350 | 415 |
| Ferritin (μg/L) | 11.28 | 29.05 | 100.32 |
| Urea (mg/dL) | 251 | 1037 | 1115 |
| Creatinin (mg/dL) | 19 | 30 | 17 |
| AST (U/L) | 45 | 104 | 163 |
| ALT (U/L) | 29 | 43 | 462 |
| Fibrinogen (mg/dL) | 493 | 556 | 528 |
| D-dimer (μg FEU/mL) | 1.22 | 5.44 | 2 |
| Pro-BNP (mg/L) | 13,400 | 6470 | 3720 |
| Troponin (mg/ml) | 24 | 124 | 57 |
| IL-6 (pg/mL) | 256 | 318 | 43 |
| SARS-CoV-2 PCR | Negative | Negative | Positive |
| SARS-CoV-2 Antibody | Positive | Positive | Positive |
| Echocardiography | LV systolic dysfunction | LV systolic dysfunction | LV systolic dysfunction |
| LVEF %45 | LVEF %40 | LVEF %50 |

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; LVEF, left ventricular ejection fraction.

We, herein, describe 3 children with MIS-C who had identical twins who did not develop MIS-C. Although MIS-C is indeed related to infection with SARS-CoV-2, the pathophysiological mechanism of disease is unknown. Researchers suspect that adaptive immune mechanisms have a major role to play in pathogenesis of MIS-C. Since only a small percentage of patients develop MIS-C, it is possible that there are genetic factors that make some children susceptible. Identical twins share a common genotype. On the other hand, monozygotic twin pairs are not identical; due to epigenetic differences. While identical twins are epigenetically indistinguishable during the early years of life, older identical twins exhibited remarkable differences in their epigenetic information. In addition, the timing of the immune response to SARS-CoV-2 infection may vary with viral load and genetic differences in host response. When viral load is high or genetic factors slow antiviral responses, virus replication can delay IFN response and cytokine storm can result before adaptive responses clear the virus, which may result in MIS-C.

Our case series we did not study the contribution/role of epigenetic modifications.

In conclusion, the occurrence of MIS-C in one of the identical twins may be due to epigenetic differences as well as the difference in exposure to viral load.

CONSENT
The written informed consent to publication has been obtained from the parents.

Nihal Akçay, MD, Mustafa Oğur, MD, Mehmet Emin Menentoğlu, MD, Kübra Boydag Güvenç, MD, Ayse Irem Sofuoğlu, MD, and Esra Sevkoğlu, MD
From the Department of Pediatric Intensive Care Unit, Bakırköy Dr. Sadi Konuk Research and Training Hospital, University of Health Sciences, Istanbul, Turkey.
TABLE 1. Characteristics and Outcome of Children and Adolescents COVID-19 Patients in the Residential Treatment Centers

| Characteristic and outcome | Delta-minor (n = 92) | Delta-dominant (n = 143) | P value |
|----------------------------|---------------------|--------------------------|---------|
| Age (mean ± SD, years)     | 13.8 ± 3.3          | 10.2 ± 4.4               | <0.001  |
| Children (<10 years of age)| 13 (14.1)           | 68 (48.2)                | 0.002   |
| Male                       | 56 (60.9)           | 75 (52.4)                | 0.21    |
| Underlying disease         | 0                   | 0                        | NA      |
| Duration from diagnosis to | 0.7 ± 1.1           | 1.6 ± 1.4                | <0.001  |
| RTC entry (mean ± SD, days)|                     |                          |         |
| Symptom during isolation   |                     |                          |         |
| Fever                     | 5 (5.4)             | 7 (4.9)                  | >0.99   |
| Duration of fever (mean ± SD, days) | 1.4 ± 0.9 | 1.7 ± 1.9               | 0.74    |
| Chill                     | 4 (4.3)             | 2 (1.4)                  | 0.21    |
| Myalgia                   | 7 (7.6)             | 3 (2.1)                  | 0.051   |
| Fatigue                   | 3 (3.3)             | 2 (1.4)                  | 0.38    |
| Anorexia                  | 5 (5.4)             | 3 (2.1)                  | 0.27    |
| Cough                     | 26 (28.3)           | 52 (36.4)                | 0.21    |
| Sputum                    | 24 (26.1)           | 27 (18.9)                | 0.2     |
| Shortness of breath       | 0                   | 1 (0.7)                  | >0.99   |
| Rhinorrhea                | 23 (25)             | 15 (10.5)                | 0.003   |
| Nasal stuffiness          | 32 (34.8)           | 22 (15.4)                | 0.001   |
| Sore throat               | 22 (23.9)           | 18 (12.6)                | 0.02    |
| Chest pain                | 1 (1.1)             | 0                        | 0.39    |
| Nausea/vomiting           | 4 (4.3)             | 4 (2.8)                  | 0.72    |
| Diarrhea                  | 7 (7.6)             | 8 (5.6)                  | 0.54    |
| Abdominal pain            | 2 (2.2)             | 3 (2.1)                  | >0.99   |
| Headache                  | 10 (10.9)           | 20 (14.9)                | 0.49    |
| Parosmia                  | 8 (8.7)             | 14 (9.8)                 | 0.78    |
| Parageusia                | 9 (9.8)             | 12 (8.4)                 | 0.72    |
| Asymptomatic during isolation | 27 (29.5) | 62 (43.4)                | 0.03    |
| Pneumonia during isolation| 2 (2.2)             | 1 (0.7)                  | 0.56    |
| Length of isolation (mean ± SD, days) | 9.3 ± 2.0 | 8.4 ± 1.9 | 0.001 |
| Transfer to hospital      | 5 (5.4)             | 3 (2.1)                  | 0.27    |
| COVID-19 related cause    | 1 (1.1)             | 0                        | 0.39    |
| Non-COVID-19 related cause| 4 (4.3)             | 3 (2.1)                  | 0.44    |
| Oxygen supply             | 0                   | 0                        | NA      |
| ICU admission             | 0                   | 0                        | NA      |
| Length of hospital stay (mean ± SD, days) | 10.8 ± 10.2 | 8.7 ± 8.1 | 0.77 |

SD, standard deviation; NA, not available; RTC, residential treatment center; ICU, intensive care unit.

Data are number (%) of patients, unless otherwise indicated.

**Features of COVID-19 Among Children and Adolescents Without Risk Factors Before and After the Delta Variant Outbreak in South Korea**

**To the Editors:**

As the Delta variant of coronavirus disease 2019 (COVID-19) pandemic spreads, the number of children and adolescents infected with this lineage is increasing. However, the relationship between the prognosis of pediatric patients and the Delta variant has not been fully elucidated. In this regard, two studies using the national big data reported a similar incidence of intensive care unit (ICU) admission and mechanical ventilation in the age group of 0–17 years before and after the Delta variant outbreak in the USA.1,2 However, additional data reflecting various races and regions are still needed. In South Korea, mild-to-moderate COVID-19 patients without risk factors are isolated in residential treatment centers (RTCs). We retrospectively compared the clinical features of unvaccinated children and adolescents admitted to RTCs before and after the Delta variant outbreak in South Korea.

We collected demographics, COVID-19 symptoms, chest radiograph findings and hospital transfer of patients <18 years of age who were admitted to two RTCs in Gyeongsangnam-do, South Korea from December 2020 to August 2021. Based on the nationwide surveillance data of SARS-CoV-2 variants, we divided the patients into the following two groups: (1) the Delta-minor group (diagnosed from December 2020 to June 2021, detection rate <10%) and (2) the Delta-dominant group (diagnosed during August 2021, detection rate >90%). Patients diagnosed during July 2021 were excluded because of inconclusive detection rates of the Delta variant (53.7%). The collected medical information was compared between the two groups. This study was approved by the Institutional Review Board of Gyeongsang National University Changwon Hospital (No.2021-09-023). Descriptive/inferential statistics and regression analysis were used.

Among the 235 patients, 92 (39.1%) were in the Delta-minor group and 143 (60.9%) were in the Delta-dominant group. The Delta-dominant group patients were younger (mean age 13.8 vs. 10.2 years, P < 0.001). Neither group had any underlying diseases considered as risk factors for severe COVID-19, such as hypertension or diabetes. There was no significant difference between the two groups.

The authors have no funding or conflicts of interest to disclose.

Address for Correspondence: Oh-Hyun Cho, MD, PhD, Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Gyeongsang National University College of Medicine, 11 Samjongja-ro, Seosugun-gu, Changwon, Gyeongsangnam-do 51472, South Korea. E-mail: zenmd@naver.com

**REFERENCES**

1. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ* 2020;369:m2094.

2. DeBiasi RL, Song X, Delaney M, et al. Severe coronavirus disease-2019 in children and young adults in the Washington, DC, metropolitan region. *J Pediatr* 2020;223:199–203.e1.

3. World Health Organization. Case report form for suspected cases of multisystem inflammatory syndrome (MIS) in children and adolescents temporally related to COVID-19. WHO-2019-nCoV/MIS_Children_CRF-2020.2. Available at: <https://www.who.int/publications/i/item/WHO-2019-nCoV-MIS_Children_CRF-2020.2>. Accessed May 15, 2021.

4. Kabeerdoss J, Pilania RK, Karkhele R, et al. Understanding SARS-CoV-2 related multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. *Rheumatol Int* 2021;41:19–32.

5. Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nat Rev Immunol*. 2020;97:371–373.

6. Ebina-Shibuya R, Namkoong H, Shibuya Y, et al. Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic in South Korea. *Eur J Pediatr*. 2020;179:1021–1026.

7. Fraga MF, Ballestar E, Paz MF, et al. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci U S A*. 2005;102:10604–10609.