JAMA Dermatology | Brief Report

# Mucocutaneous Manifestations of Multisystem Inflammatory Syndrome in Children During the COVID-19 Pandemic

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**IMPORTANCE** To date, no study has characterized the mucocutaneous features seen in hospitalized children with multisystem inflammatory syndrome in children (MIS-C) or the temporal association of these findings with the onset of systemic symptoms.

**OBJECTIVE** To describe the mucocutaneous findings seen in children with MIS-C during the height of the coronavirus disease 2019 (COVID-19) pandemic in New York City in 2020.

**DESIGN, SETTING, AND PARTICIPANTS** A retrospective case series was conducted of 35 children admitted to 2 hospitals in New York City between April 1 and July 14, 2020, who met Centers for Disease Control and Prevention and/or epidemiologic criteria for MIS-C.

**MAIN OUTCOMES AND MEASURES** Laboratory and clinical characteristics, with emphasis on mucocutaneous findings, of children who met criteria for MIS-C. The characterization of mucocutaneous features was verified by 2 board-certified pediatric dermatologists.

**RESULTS** Twenty-five children (11 girls [44%]; median age, 3 years [range, 0.7-17 years]) were identified who met definitional criteria for MIS-C; an additional 10 children (5 girls [50%]; median age, 1.7 years [range, 0.2-15 years]) were included as probable MIS-C cases (patients met all criteria with the exception of laboratory test evidence of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection or known exposure). The results of polymerase chain reaction tests for SARS-CoV-2 were positive for 10 patients (29%), and the results of SARS-CoV-2 immunoglobulin G tests were positive for 19 patients (54%). Of the 35 patients, 29 (83%) exhibited mucocutaneous changes, with conjunctival injection (n = 21), palmoplantar erythema (n = 18), lip hyperemia (n = 17), periorbital erythema and edema (n = 7), strawberry tongue (n = 8), and malar erythema (n = 6) being the most common findings. Recognition of mucocutaneous findings occurred a mean of 2.7 days (range, 1-7 days) after the onset of fever. The duration of mucocutaneous findings varied from hours to days (median duration, 5 days [range, 0-11 days]). Neither the presence nor absence of mucocutaneous findings was significantly associated with overall disease severity.

**CONCLUSIONS AND RELEVANCE** In this case series of hospitalized children with suspected MIS-C during the COVID-19 pandemic, a wide spectrum of mucocutaneous findings was identified. Despite their protean and transient nature, these mucocutaneous features serve as important clues in the recognition of MIS-C.

*JAMA Dermatol*. doi:10.1001/jamadermatol.2020.4779
Published online December 9, 2020.

Supplemental content

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Multisystem inflammatory syndrome in children (MIS-C) has emerged as a pediatric consequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] Characterized by fever, multiorgan involvement, and known or suspected exposure to SARS-CoV-2, MIS-C demonstrates clinical overlap with Kawasaki disease (KD), a rare medium-vessel vasculitis that typically occurs in children younger than 5 years.[2] Mucocutaneous findings have been reported in up to 74% of patients with MIS-C,[3] although no studies have detailed the morphologic characteristics, distribution, or evolution of these eruptions, to our knowledge. In this report, we characterize the mucocutaneous manifestations of MIS-C in a cohort of hospitalized children at our institution.

### Key Points

**Question** What were the mucocutaneous findings in hospitalized patients with multisystem inflammatory syndrome in children (MIS-C) during the peak incidence of coronavirus disease 2019 (COVID-19) in New York City in 2020?

**Findings** This case series included 35 hospitalized children who met definitional and/or epidemiologic criteria for MIS-C, 83% of whom exhibited mucocutaneous symptoms that lasted from hours to days. Conjunctival injection, palmoplantar erythema, lip hyperemia, periorbital erythema and edema, strawberry tongue, and malar erythema were the most common findings.

**Meaning** This study suggests that mucocutaneous findings, while polymorphous and transient, may aid in the recognition of MIS-C.

## Methods

We performed a retrospective case series of pediatric patients hospitalized with suspected MIS-C or KD from April 1 to July 14, 2020, at New York University (NYU) Langone Health Hassenfeld Children's Hospital and NYU Winthrop Hospital. We screened all patients with suspected MIS-C or KD for whom pediatric rheumatology and/or infectious disease specialists were consulted. Using the Centers for Disease Control and Prevention case definition of MIS-C, patients were included if they met all of the following criteria: (1) aged 21 years or younger presenting with fever, laboratory evidence of inflammation, and severe illness requiring admission; (2) had involvement of at least 2 organ systems; and (3) had no alternative plausible diagnosis.[4] We documented laboratory evidence of SARS-CoV-2 infection and history of suspected SARS-CoV-2 exposure but did not exclude based on this criterion alone because many patients in New York City became infected without known exposures.[5] Cases were classified as either confirmed or probable MIS-C based on positive results of laboratory testing and/or known coronavirus disease 2019 (COVID-19) exposure. Included patients were evaluated for KD using criteria established by the American Heart Association.[6] Data regarding demographic characteristics, clinical and laboratory test features, and treatments were collected. Mucocutaneous findings were characterized by 2 board-certified pediatric dermatologists (S.J.O. and V.S.O.) through a combination of in-person evaluation (24% [7 of 29]), review of photographs (62% [18 of 29]), and review of documentation provided by pediatric rheumatology or infectious disease specialists (14% [4 of 29]). The Wilcoxon test (for continuous age) and the Pearson $\chi^2$ test and the Fisher exact test (for counts <5) were used to examine associations between confirmed vs probable MIS-C cases and independent clinical and demographic variables. All *P* values were from 2-sided tests, and results were deemed statistically significant at $P < .05$. This study was approved by the New York University Grossman School of Medicine Institutional Review Board, which waived parental consent because all data were deidentified and obtained retrospectively.

## Results

Among 56 screened patients, 35 met inclusion criteria (**Table**). Twenty-five children (11 girls [44]; median age, 3 years [range, 0.7-17 years]) met definitional criteria for MIS-C, while the remaining 10 children (5 girls [50%]; median age, 1.7 years [range, 0.2-15 years]) were included as probable MIS-C cases.

The results of polymerase chain reaction tests for SARS-CoV-2 were positive for 10 patients (29%), and the results of SARS-CoV-2 immunoglobulin G tests were positive for 19 patients (54%). Twenty-nine patients (83%) exhibited mucocutaneous findings (eTable 1 in the Supplement). Conjunctival injection (n = 21), palmoplantar erythema (n = 18), lip hyperemia (n = 17), lip cracking (n = 13), periorbital erythema and edema (n = 7), strawberry tongue (n = 8), and malar erythema (n = 6) were the most common findings (**Figure 1**). Additional cutaneous morphologic findings included scarlatiniform eruptions (n = 5), morbilliform eruptions (n = 3), urticarial eruptions (n = 3), and reticulated eruptions (n = 3) (**Figure 2**). There was no statistically significant difference between patients younger than 3 years (n = 17) and those aged 3 years or older (n = 18) with regard to the development of certain mucocutaneous symptoms. Among patients with mucocutaneous changes, 19 of 29 experienced fever a mean of 2.7 days (range, 1-7 days) before recognition of the first mucocutaneous finding. The remainder either developed fever and mucocutaneous symptoms concurrently (4 of 29) or developed mucocutaneous symptoms prior to fever (5 of 29 [mean, 1.4 days; range, 1-2 days]); in 1 patient, it was unclear whether fever or mucocutaneous findings developed first. The duration of mucocutaneous symptoms was highly variable, lasting hours to days (median, 5 days [range, 0-11 days]). By the study end date, 34 patients had been seen for outpatient follow-up, and 9 experienced palmoplantar desquamation (eFigure in the Supplement) up to 1 month after fever onset. One patient underwent a skin biopsy of a morbilliform eruption suspected to be associated with MIS-C, which showed a nonspecific perivascular lymphohistiocytic infiltrate with focal interface changes.

Table. Demographic and Clinical Characteristics of Patients With Multisystem Inflammatory Syndrome in Children

| Characteristic | Patients, No. (%) (N = 35)[a] |
|---|---|
| Age, median (range), y | 2 (0.2-17) |
| Female | 16 (46) |
| Race/ethnicity[b] | |
| Hispanic | 12 (34) |
| Black | 10 (29) |
| White | 6 (17) |
| Asian | 4 (11) |
| Pacific Islander or Native Hawaiian | 1 (3) |
| Unknown or not reported | 2 (6) |
| COVID-19 diagnosis or exposure | |
| Positive laboratory test result (PCR and/or IgG) | 21 (60) |
| SARS-CoV-2 | |
| Nasopharyngeal PCR and IgG positive | 8 (23) |
| Nasopharyngeal PCR positive only[c] | 2 (6) |
| IgG positive only | 11 (31) |
| Known exposure to a contact with COVID-19 | 17 (49) |
| Negative laboratory test results | |
| Known COVID-19 contact | 4 (11) |
| Unknown COVID-19 contact | 10 (29) |
| Mucosal findings | |
| Conjunctivitis | 21 (60) |
| Any oral mucosal change | 20 (57) |
| Strawberry tongue | 8 (23) |
| Lip | |
| Hyperemia | 17 (49) |
| Cracking | 13 (37) |
| Cutaneous findings (rash) | 28 (80) |
| Patients in whom fever developed before rash | 19/28 (68) |
| Days of fever before rash onset, mean (SD) | 2.7 (1.6) |
| Patients in whom rash developed before fever | 5/28 (18) |
| Days of rash before fever, mean (SD) | 1.4 (0.6) |
| Duration of cutaneous symptoms, median (range), d | 5 (0-11) |
| Palmoplantar | |
| Erythema | 18 (51) |
| Edema | 14 (40) |
| Periorbital erythema and edema | 7 (20) |
| Morbilliform eruption | 3 (9) |
| Erythema | |
| Malar | 6 (17) |
| Lacy or reticular | 3 (9) |
| Macular | 4 (11) |
| Eruption | |
| Scarlatiniform | 5 (14) |
| Urticarial | 3 (9) |
| Other[d] | 4 (11) |
| Patients who met criteria for Kawasaki disease[e] | |
| Kawasaki disease | |
| Typical | 14 (40) |
| Incomplete | 7 (20) |
| Kawasaki shock syndrome | 4 (11) |
| Treatments[f] | |
| Intravenous immunoglobulin | 27 (77) |
| Systemic corticosteroids[g] | 24 (69) |
| Aspirin | 22 (63) |
| Remdesivir | 3 (9) |
| Anakinra | 3 (9) |
| Hospitalization | |
| Admitted to ICU | 10 (29) |
| ICU length of stay, median (range), d | 6 (3-28) |
| Hospital length of stay, median (range), d | 5 (2-55) |

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IgG, immunoglobulin G; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Unless otherwise indicated.

[b] Race/ethnicity was classified by parent or self-report as documented in the electronic medical record.

[c] Both patients who tested positive by PCR only did not undergo antibody testing.

[d] Other morphologic findings observed in individual patients were annular plaques, marked desquamation of the diaper area, helical erythema, and acute generalized exanthematous pustulosis. Acute generalized exanthematous pustulosis was identified in 1 patient who had received vancomycin 2 days prior; as such, the cause of this eruption (multisystem inflammatory syndrome in children vs drug-induced) remains unclear.

[e] Based on published criteria from the American Heart Association.

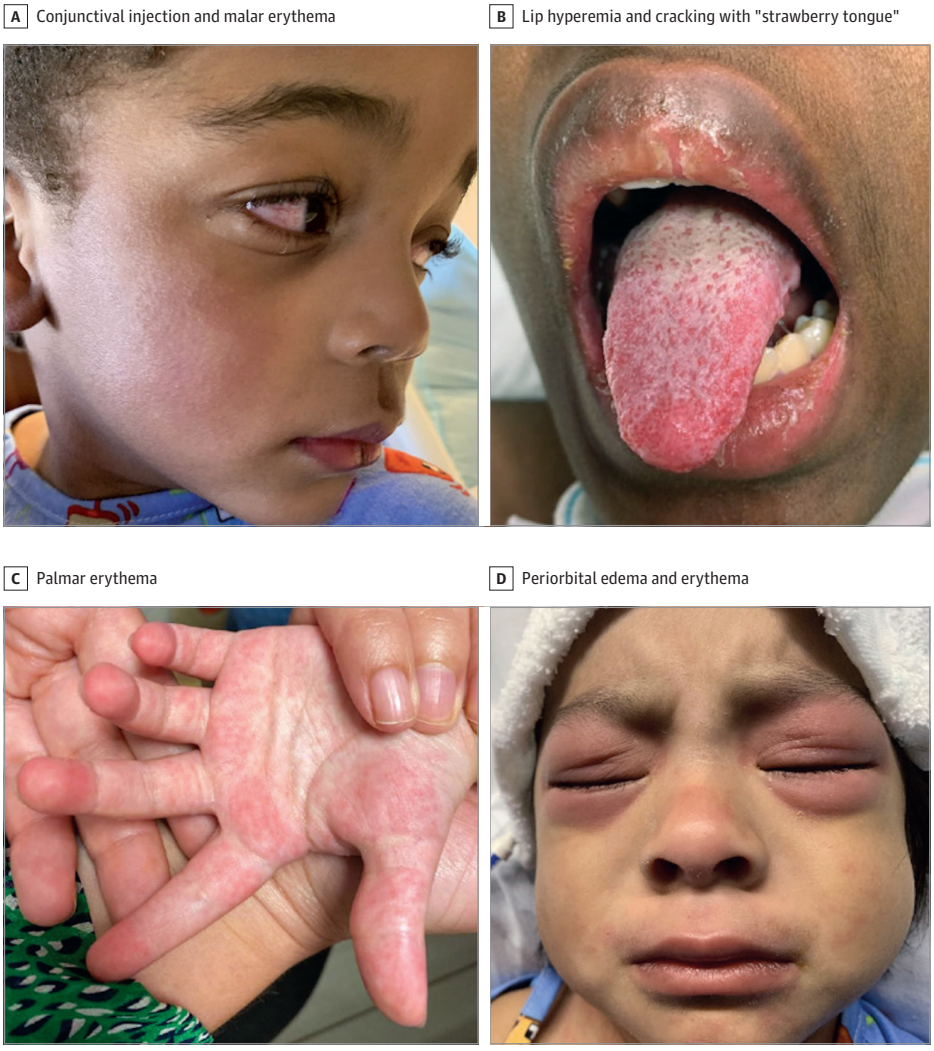
[f] Some patients received more than 1 of these treatments.

[g] Methylprednisolone or prednisolone.

The most commonly involved organ system was gastrointestinal (31 of 35). Five patients reported mild upper respiratory tract symptoms (cough and/or rhinorrhea). All but 1 patient had an elevated D-dimer level, although no patients developed thromboembolic phenomena. A total of 19 patients had cardiac involvement as evidenced by elevated troponin and/or brain natriuretic peptide levels, and 10 patients had abnormal echocardiogram findings. Five patients with cardiac involvement required inotropic support. Treatments are summarized in the Table and fully reported in eTable 2 in the Supplement. All patients recovered and were discharged home.

Compared with those with confirmed MIS-C, patients with probable MIS-C were more likely to exhibit conjunctival injection (9 of 10 [90%] vs 12 of 25 [48%]; $P = .02$) and meet criteria for KD or incomplete KD (9 of 10 [90%] vs 12 of 25 [48%]; $P = .02$) (eTable 3 in the Supplement). No other statistically significant differences in age, demographic characteristics, clinical variables, or disease severity were noted between the 2 groups. There were no statistically significant associations between the presence of mucocutane-

Figure 1. Notable Acrofacial Findings Observed in Hospitalized Children With Multisystem Inflammatory Syndrome




A, Nonexudative, limbic-sparing conjunctival injection and malar erythema. B, Lip hyperemia and cracking with prominent papillae noted on the dorsal surface of the tongue, consistent with a "strawberry tongue." C, Palmar erythema. D, Periorbital edema and erythema.

ous changes and cardiac dysfunction, the need for inotropic support, or intensive care unit admission (eTable 4 in the Supplement).

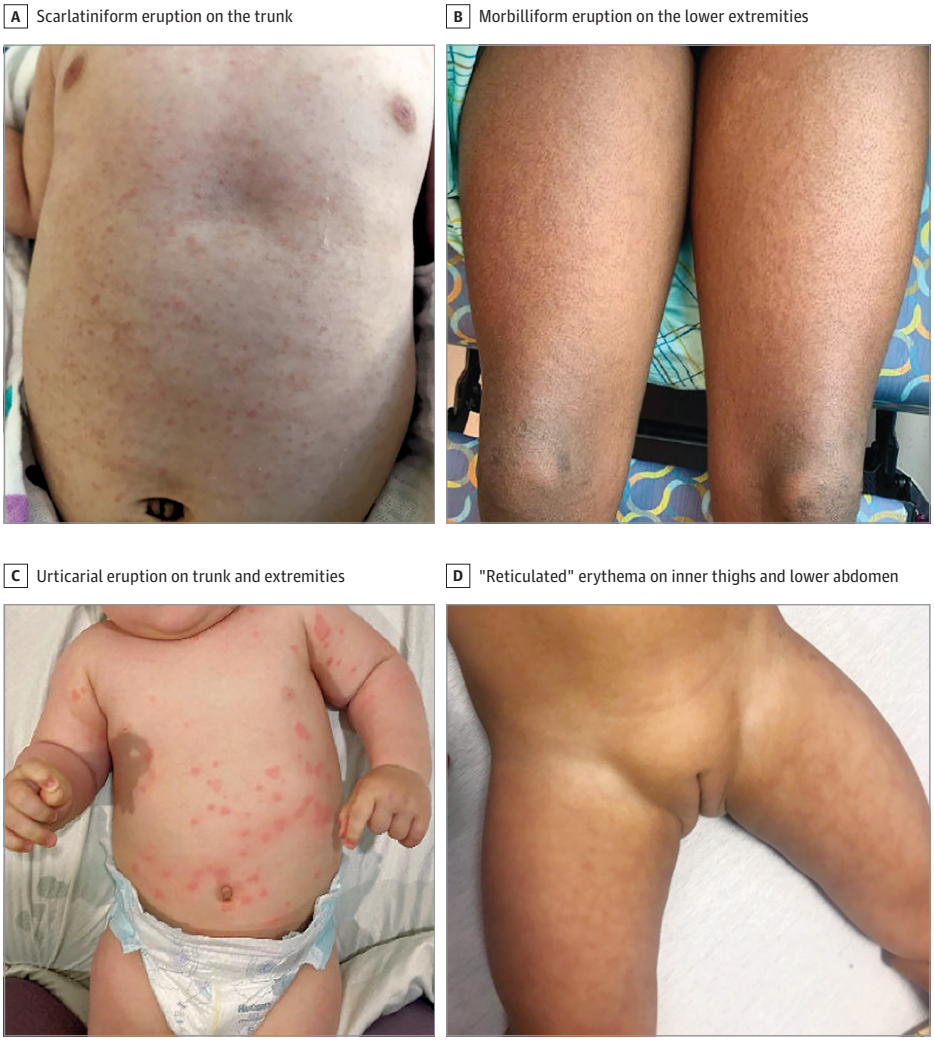
## Discussion

Although most children experience mild illness or no illness from SARS-CoV-2, some develop MIS-C after symptomatic or asymptomatic infection.[2,3] Timely recognition of this syndrome is critical so that appropriate therapeutic options can be clarified. As in patients with KD, mucocutaneous findings have been recognized in up to 74% of hospitalized patients with MIS-C.[3]

Our cohort of patients with MIS-C included children of many racial/ethnic backgrounds, with a high percentage of Black and Hispanic patients.[7,8] The median age of our cohort (2 years [range, 0.2-17 years]) is younger than that of the largest MIS-C case series published to date (median age, 8 years [range, 2 weeks to 20 years]).[9]

Within our cohort, mucocutaneous findings were polymorphous. Exanthems exhibited a broad range of morphologic characteristics, including morbilliform, scarlatiniform, urticarial, and reticulated patterns. The site of involvement varied as well, with some patients demonstrating localized, acrofacial involvement, while others manifested more widespread eruptions. Findings such as conjunctivitis, lip hyperemia or cracking, and palmoplantar erythema were evenly distributed across all ages, while other findings featured a more pronounced age predilection. Urticarial eruptions were seen in those younger than 2 years, and periorbital and palmoplantar edema were seen in those younger than 6 years. Other age-related associations were not observed when the cohort was evaluated by group (those <3 years vs those ≥3 years). Mucocutaneous involvement was not associated with cardiac dysfunction, need for inotropic support, or intensive care unit admission, suggesting that mucocutaneous changes are not associated with disease severity in MIS-C.

Figure 2. Notable Cutaneous Findings Observed on the Trunk and Extremities of Hospitalized Children With Multisystem Inflammatory Syndrome




A, Scarlatiniform eruption on the trunk. B, Morbilliform eruption on the lower extremities. C, Urticarial eruption on trunk and extremities. D, Lacy "reticulated" erythema on the bilateral inner thighs and lower abdomen.

A total of 60% of our patient cohort met criteria for KD or incomplete KD.[4] Although significant clinical overlap exists between KD and MIS-C, MIS-C has been characterized by more widespread systemic inflammation and higher rates of acute complications, including cardiogenic shock.[10] Although mucocutaneous findings classically seen in patients with KD were observed in various combinations in our patients with MIS-C,[11] we also noted unique findings not typically seen in patients with KD. These findings included marked periorbital edema and erythema reminiscent of a heliotrope rash, as well as prominent malar erythema and reticulated erythematous eruptions reminiscent of erythema infectiosum (Figure 1 and Figure 2). Whether specific mucocutaneous findings are unique to one syndrome or the other remains unclear.

## Limitations

Our study has some limitations, including its retrospective nature, which potentially limited our ability to capture all mucocutaneous changes. Because we relied on infectious disease and rheumatology specialists to make the diagnosis of MIS-C, it is possible that patients for whom these services were not consulted were missed. However, we believe this risk to be small because our institutional protocol was for all children with fever of unknown origin to be evaluated by these specialty teams during the study period. Ten patients who met all diagnostic criteria except for positive SARS-CoV-2 laboratory testing results or known COVID-19 exposure were included in this cohort. These patients were thought to have MIS-C clinically and were managed as such. This proportion is not different from previously published case series of MIS-C, in which 30% of patients demonstrated negative polymerase chain reaction SARS-CoV-2 and antibody test results.[3] These "false negatives" have been ascribed to imperfect sensitivity of polymerase chain reaction and antibody testing, particularly in patients presenting at different times during their disease course.[12,13]

## Conclusions

Multisystem inflammatory syndrome in children should be considered in children with unexplained fevers during the ongoing COVID-19 pandemic. Identification of the aforementioned mucocutaneous findings, many of which have significant overlap with KD, may aid in the recognition of MIS-C but are not specific to its diagnosis.


### ARTICLE INFORMATION

**Accepted for Publication:** October 16, 2020.

**Published Online:** December 9, 2020. doi:10.1001/jamadermatol.2020.4779

**Author Contributions:** Dr Oza had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Mr Young and Dr Shaw contributed equally to this manuscript.
*Concept and design:* Young, Shaw, Alperin, Orlow, Kahn, Oza.
*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* Young, Shaw, Betensky, Kahn.
*Critical revision of the manuscript for important intellectual content:* All authors.
*Statistical analysis:* Young, Shaw, Shah, Betensky.
*Administrative, technical, or material support:* Shaw, Noor, Alperin, Ratner, Orlow.
*Supervision:* Noor, Alperin, Ratner, Orlow, Betensky, Shust, Kahn, Oza.

**Conflict of Interest Disclosures:** Dr Ratner reported receiving personal fees from and serving as a consultant for Pfizer outside the submitted work. Dr Orlow reported serving on the board of directors for Almirall S.A. Dr Oza reported receiving personal fees from Pfizer Consulting in the field of atopic dermatitis education and from Regeneron-Sanofi Pediatric Advisory Board dupilumab and a grant from Pfizer Grant: Educational Support for Primary Care Provider Management of Pediatric Atopic Dermatitis: A Health Literacy-Informed Approach outside the submitted work. No other disclosures were reported.

**Additional Contributions:** We thank the parents for granting permission to publish photographs of their children in the figures.


### REFERENCES


1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;20(5):533-534. doi:10.1016/S1473-3099(20)30120-1

2. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395(10237):1607-1608. doi:10.1016/S0140-6736(20)31094-1

3. Feldstein LR, Rose EB, Horwitz SM, et al; Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383(4):334-346. doi:10.1056/NEJMoa2021680

4. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Published May 14, 2020. Accessed July 20, 2020. https://emergency.cdc.gov/han/2020/han00432.asp

5. Zachariah P, Johnson CL, Halabi KC, et al; Columbia Pediatric COVID-19 Management Group. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. *JAMA Pediatr*. 2020;174(10):e202430. doi:10.1001/jamapediatrics.2020.2430

6. McCrindle BW, Rowley AH, Newburger JW, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927-e999. doi:10.1161/CIR.0000000000000484

7. Holmes L Jr, Enwere M, Williams J, et al. Black-White risk differentials in COVID-19 (SARS-COV2) transmission, mortality and case fatality in the United States: translational epidemiologic perspective and challenges. *Int J Environ Res Public Health*. 2020;17(12):E4322. doi:10.3390/ijerph17124322

8. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among Black patients and White patients with Covid-19. *N Engl J Med*. 2020;382(26):2534-2543. doi:10.1056/NEJMsa2011686

9. Godfred-Cato S, Bryant B, Leung J, et al; California MIS-C Response Team. COVID-19–associated multisystem inflammatory syndrome in children—United States, March-July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1074-1080. doi:10.15585/mmwr.mm6932e2

10. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. *Children (Basel)*. 2020;7(7):E69. doi:10.3390/children7070069

11. Chasset F, Francès C. Cutaneous manifestations of medium- and large-vessel vasculitis. *Clin Rev Allergy Immunol*. 2017;53(3):452-468. doi:10.1007/s12016-017-8612-9

12. Woloshin S, Patel N, Kesselheim AS. False negative tests for SARS-CoV-2 infection—challenges and implications. *N Engl J Med*. 2020;383(6):e38. doi:10.1056/NEJMp2015897

13. Miller TE, Garcia Beltran WF, Bard AZ, et al. Clinical sensitivity and interpretation of PCR and serological COVID-19 diagnostics for patients presenting to the hospital. *FASEB J*. Published online August 28, 2020. doi:10.1096/fj.202001700RR