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COVID-19 Pediatric Dermatology

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KEYWORDS

• MIS-C • Pediatric dermatology • COVID-19 children • Perniosis • Pernio-like lesions

KEY POINTS

- The robust immune system in younger individuals may be protective from traditional respiratory symptoms of COVID-19 but also may underlie cutaneous responses like those seen in multisystem inflammatory syndrome and pernio-like lesions.
- Cutaneous manifestations reported in children are diverse and include (but are not limited to) macular, papular, morbilliform, vesicular, urticarial, and vascular morphologies.
- The prognosis of pediatric patients who manifest COVID-19 cutaneously is excellent and usually self-limiting.

INTRODUCTION

During the coronavirus disease 2019 (COVID-19) pandemic, people of all ages are susceptive to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Diagnoses in more than 3 million children beginning in the neonatal period have been made as of April 2021.[1,2] When compared with adults, however, pediatric patients manifest with less severe respiratory sequelae and higher frequencies of no, mild, or atypical symptoms.[3–6]

Reasons behind the contrasting presentation of COVID-19 in youth compared with aged individuals are multifactorial.[7] Children are less likely to have predisposing factors for severe disease, such as underlying medical comorbidities[8] or damaged endothelium.[9] Moreover, young people demonstrate differing antibody responses to SARS-CoV-2 infection[10] and possess stronger antiviral innate and adaptive immunity compared with older adults (including more cytokines, increased production of interferons,[11] increased $CD4^+/CD8^+$ T cells, and a more vigorous $CD8^+$ T-cell response to new antigens).[12] Although these inherent protections likely aid in preventing the serious respiratory sequelae of COVID-19 in most children,[13] robust immune mechanisms also might contribute to alternate manifestations observed, such as cutaneous eruptions.

Lack of traditional or severe signs can heighten attention to nontraditional presentations, making dermatologic manifestations particularly relevant in children. Cutaneous signs sometimes are the predominant or only clue toward pediatric COVID-19 infection.[14,15] One of the earliest exemplifications of pediatric dermatoses related to the pandemic is the acral skin eruption, known as COVID toes.[16] Many children and adolescents since have presented with various acral and nonacral skin findings in connection to SARS-CoV-2 infection; cutaneous manifestations are recognized as the seventh most common extrapulmonary COVID-19 association in children.[17] Greater than 8% of hospitalized COVID-19 positive pediatric patients have a cutaneous eruption,[18] and dermatologic manifestations may be a component of a serious, systemic pediatric presentation, such as multisystem inflammatory syndrome in children (MIS-C). Thus, although cutaneous signs of

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COVID-19 infection often are a form of mild disease in children, it also is necessary to consider the possibility of more serious complications.

Herein, the clinical presentation, demographic trends, pathophysiologic theories, implications, and management strategies for dermatologic presentations of COVID-19 are addressed with respect to MIS-C, acral eruptions, and various vascular, inflammatory, and nonspecific skin findings. Through descriptions of COVID-19 pediatric cutaneous manifestations, this article demonstrates the role of the dermatologist and importance of prompt recognition.

MULTISYSTEM INFLAMMATORY SYNDROME

- MIS-C is a serious and sometimes life-threatening response to COVID-19 infection in children, leading to organ dysfunction, shock, and often the need for intensive care and circulatory support.
- Skin and/or mucous membrane changes may be present in more than half of children affected by MIS-C and appear with various morphologies and distributions.
- Although most require intensive care, patients with MIS-C carry a good prognosis, with mortality estimated at 2%.

Definition

To date, one of the most severe pediatric consequences of COVID-19 infection is MIS-C. Initially recognized approximately 1 month after the first COVID-19 pandemic surge,[19] MIS-C is a hyperinflammatory response to SARS-CoV-2 infection in pediatric patients that leads to dysfunction in several organs. The Centers for Disease Control and Prevention (CDC) has defined MIS-C as an individual under 21 years old with current or recent SARS-CoV-2 infection (or exposure), a fever lasting greater than 24 hours, laboratory inflammatory marker evidence, and the presence of severe illness involving greater than 2 organs (cardiac, respiratory, gastrointestinal, dermatologic, renal, hematologic, or neurologic), requiring hospital admission that cannot be explained by other illness (**Fig. 1**).[20,21]

Demographics

Since the earliest reported cases in England,[22] more than 3000 children have been affected by MIS-C, as of April 2021.[23] A majority of children who develop MIS-C previously were healthy.[24] Cases have been reported as young as 1 month old[25] to 20 years old,[26] with median age estimated between 5 years and 11.5 years old.[20] There is a slight male predominance, and minority races/ethnicities are affected by MIS-C more commonly than non-Hispanic white children.[19,24]

Pathogenesis

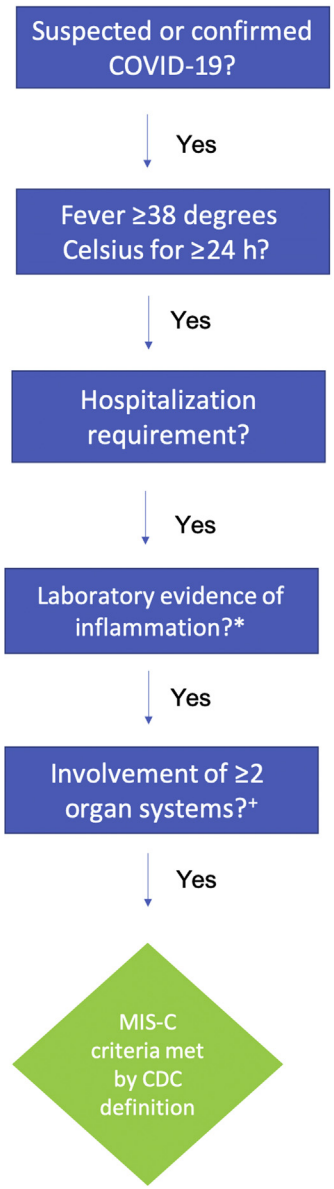
Due to temporal emergence of MIS-C with the pandemic in addition to confirmed laboratory evidence of SARS-Co-V-2 infection in 99% of cases,[23] it is highly suggestive that MIS-C indeed is a consequence of COVID-19 infection. Specifically, it is thought that MIS-C is a late or postviral complication due to trends revealing a higher likelihood of SARS-CoV-2 antibody positivity compared with viral RNA detection.[27–30] Children who report milder viral symptoms before MIS-C onset support the notion of MIS-C being a later sequelae; the median time to onset has been reported at 25 days.[24]

Although the exact mechanisms are not yet understood, MIS-C is described as the result of a cytokine storm in response to COVID-19 infection.[31] Pathogenesis theories include the role of an overly robust pediatric innate and/or cellular immune response,[27] superantigen region on the SARS-CoV-2 spike protein,[32,33] and immune-complex development from viral antigens (type III hypersensitivity)[34] inciting strong cytokine cascade. A pediatric biorepository has been established with one main goal to better understand the complex immunologic mechanisms underpinning MIS-C.[35]

Cutaneous Presentation

MIS-C demonstrates a wide spectrum of cutaneous associations (**Fig. 2**). Mucocutaneous findings are a component of MIS-C in 50% to 83% of children,[19,24,29,36,37] which are variable and polymorphic (**Table 1**). Purpuric, targetoid, erythematous, retiform, reticular, livedoid, urticarial, scarlatiniform, papular, macular, maculopapular, desquamative, erythema multiforme (EM)-like, and morbilliform exanthems have been described.[37–41] Eruptions may be generalized or localized, such as to the trunk, face, periorbital area, extremities, or diaper area.[29,38,40,41] In 1 series of 7 MIS-C patients with cutaneous findings, 57% had lesions described as urticarial-like plaques, all had involvement of the lower extremities, and 29% experienced mild pruritis.[37]

The hands and feet frequently are a site of cutaneous symptoms; findings include erythema, swelling (edema), and desquamation.[28,38–40] Mucositis in the forms of papillitis of the tongue (strawberry tongue),[29,41] cheilitis (lips appearing erythematous, swollen, dry, or cracked/



*Laboratory Inflammatory Evidence
↑ D-dimer
↑ Procalcitonin
↑ Fibrinogen
↑ Ferritin
↑ Neutrophilia
↑ Elevated lactate dehydrogenase
↑ Erythrocyte Sedimentation Rate
↑ C-reactive Protein
↑ Interleukin-6
↓ Lymphopenia
↓ Albumin

+Organ System	Examples of involvement
Gastrointestinal	Abdominal pain, diarrhea, nausea, vomiting, abnormal hepatobiliary markers
Hematologic	Fever, myalgias, lymphadenopathy, fatigue, abnormal blood counts
Neurologic	Headache, irritability, altered mental status, dizziness
Dermatologic	Cutaneous eruption, conjunctivitis, edema, mucositis
Respiratory	Dyspnea, upper respiratory infection-like signs, cough, wheezing, respiratory failure, pulmonary infiltrates
Cardiovascular	Shock, chest pain, myocarditis, coronary artery dilatation/aneurysm, elevated cardiac enzyme markers
Renal	Acute kidney injury

Fig. 1. CDC diagnostic criteria for MIS-C. An individual aged less than 21 with SARS-CoV-2 (confirmed or suspected within prior 4 weeks), a fever for greater than or equal to 24 hours, involvement of at least 2 organ systems (+gastrointestinal, hematologic, neurologic, dermatologic, respiratory, cardiovascular, or renal), laboratory evidence of inflammation, severity requiring hospitalization, and no other explanation must be present.[21] (*Laboratory markers of inflammation include but are not limited to elevations in fibrinogen, ferritin, D-dimer, erythrocyte sedimentation rate, C-reactive protein, procalcitonin, interleukin-6, neutrophils, lactic acid dehydrogenase, and/or low albumin or lymphocytes[21]; examples of hepatobiliary markers: AST/ALT119; examples of hematologic markers: neutrophil, lymphocytes, platelets, hemoglobin[119]; examples of cardiac markers: troponin, brain natriuretic proenzyme[21]; and examples of renal markers: creatinine,[119] blood urea nitrogen, electrolytes.)

fissured),[28,39,40,42] and/or conjunctivitis[29,41] frequently are observed.

Although some investigations have found no correlation between mucocutaneous findings and worsened disease severity,[29,41] 1 study reported that mucocutaneous signs were a risk factor for intensive care unit admission, more severe inflammatory marker derangement (C-reactive protein

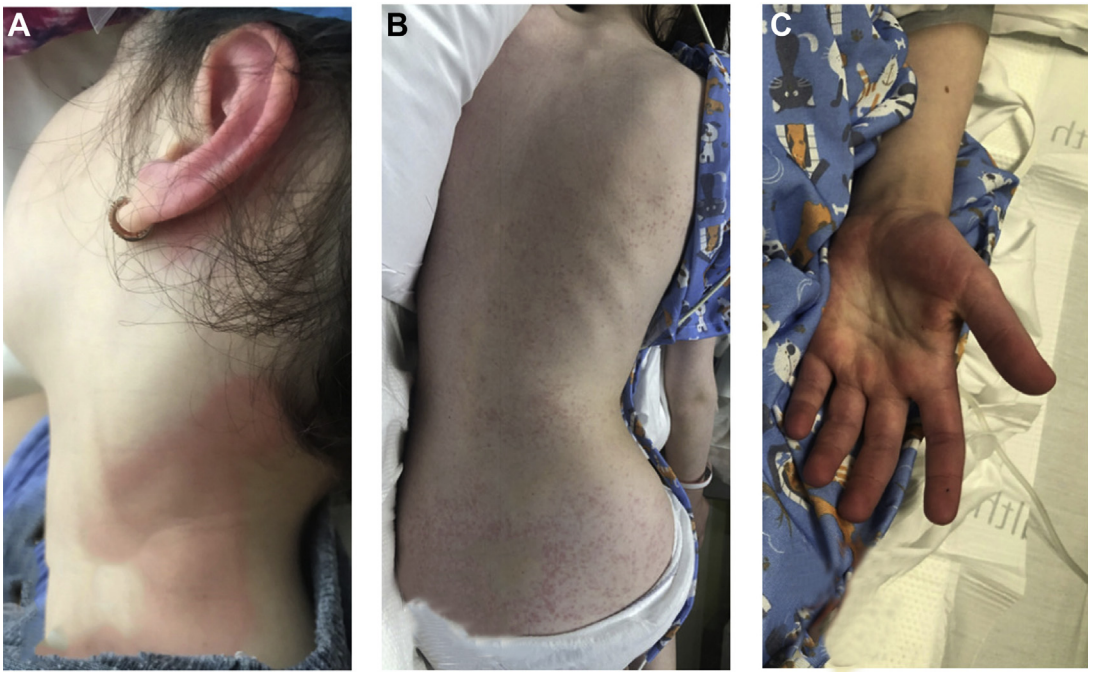


Fig. 2. Cutaneous eruptions in patients with MIS-C. (*A*) An erythematous plaque of the neck on a 7-year-old girl. (*B*) A 12-year-old boy with a maculopapular eruption of the trunk and extremities as well as (*C*) erythema of the palms. (*From* Fludiona Naka, Laura Melnick, Mark Gorelik, Kimberly D. Morel, A dermatologic perspective on multisystem inflammatory syndrome in children, Clinics in Dermatology, 2020.)

[CRP], D-dimer, and lymphopenia), and poor presentation with severe tachycardia.[43] Mucocutaneous manifestations typically resolve with treatment of underlying MIS-C.[37] Importantly, mucocutaneous findings associated with fever in a child are nonspecific, and in the setting of negative COVID-19 testing can pose a diagnostic challenge.

Extracutaneous Presentation

In addition to dermatologic presentation, awareness of the most common extra-mucocutaneous findings of MIS-C is necessary when evaluating a child for skin eruption in the COVID-19 pandemic. Fever, a critical component of the MIS-C diagnosis,[21] usually precedes mucocutaneous findings but can occur after or during acute presentation.[29] Other vital sign changes in the form of tachycardia, tachypnea, and hypotension are presenting signs in more than three-quarters of affected children.[26,36]

The gastrointestinal system is the most common organ system involved in MIS-C, and signs in the form of abdominal pain, vomiting, and/or diarrhea are noted in 80% to 92% of cases.[24,26] Respiratory symptoms, such as dyspnea, upper respiratory infection-like signs, and respiratory insufficiency, are observed in 21% to 70% of cases.[24,26,29] Cardiovascular involvement may present clinically as hypotension, shock, or, less commonly, chest pain.[44,45] Neurologic and hematologic abnormalities manifest with various signs and symptoms, such as headache, dizziness, mental status change, fatigue, lymphadenopathy, lethargy, and myalgias.[26,44]

With accumulating cases, an analysis of 570 children reported to the CDC allowed the identification of 3 distinct subgroups based on patient underlying features. Rash and mucocutaneous findings were prominent in a group of "MIS-C overlapping with Kawasaki disease (KD)," that was characterized by younger patients (median age 6 years) and lower frequency of myocardial dysfunction or shock. In contrast, the other groups represented "MIS-C without overlap with acute COVID-19 or KD" (median age 9 years) with prominent cardiovascular and gastrointestinal symptoms, and "MIS-C overlapping with severe acute COVID-19" (median age 10 years) with prominent respiratory symptoms.[30,46]

Work-up

The CDC recommended laboratory work-up for suspected MIS-C includes a SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) test and serologic testing (prior to treatment initiation) when available.[21] Inflammatory marker elevation is a critical component of

Table 1
Mucocutaneous findings in multisystem inflammatory syndrome in children

Location	Descriptors
Generalized[40,109]	Urticarial[41]
Perineal[40]	Papular[38]
Trunk[100]	Maculopapular[38]
Face[29]	Macular[39]
Ears[109]	Morbilliform[39]
Periorbital area[29,109]	Desquamative[40]
	Edematous[39]
Extremities[41]	Erythematous[41]
	Purpuric[38]
	Targetoid[41]
	Retiform[41]
	Reticular[38]
	Scarlatiniform[40]
	Petechiae[28]
	Livedoid[37]
	EM-like[37]
Hands	Edematous[40]
Feet	Erythematous[40]
	Desquamative[40]
	Purpuric[38]
	Petechiae[28]
Tongue	Papillitis[41]
	Strawberry tongue[40]
	De-epithelialized[28]
Lips	Cracked/fissured[39,41]
	Erythematous[29]
Eyes	Injected[29,109]
	Swollen[39]
	Nonpurulent discharge[39]

diagnosis, and markers to test include erythrocyte sedimentation rate, CRP, fibrinogen, procalcitonin, ferritin, lactic acid dehydrogenase, D-dimer, interleukin-6, and albumin.[21] Additionally, a complete blood cell count to look for lymphocytopenia, neutrophilia, and/or thrombocytopenia is warranted, because hematologic abnormalities are present in the majority cases.[24] A comprehensive metabolic panel may reveal end organ impacts, such as acute kidney injury or abnormal hepatobiliary markers.[38,44]

Usually, children receive cardiac work-up, including cardiac enzyme biomarkers, brain natriuretic peptide, echocardiogram, and/or electrocardiogram[21] due to a known relationship between MIS-C and myocarditis, cardiac dysfunction, and/or coronary artery dilatation/aneurysm.[30,47] When clinically warranted, radiologic assessment of the chest or abdomen is performed and may reveal further systemic effects, such as pulmonary infiltrates, lymphadenopathy, pleural effusion, hepatosplenomegaly, ascites, or ileitis.[38,47,48]

Differential Diagnosis

Many features of MIS-C presentation resemble KD in children, making KD a top differential diagnosis. Findings, such as high fever, conjunctivitis, lymphadenopathy, cheilitis, skin rash, myocarditis, and coronary artery aneurysms,[24,36] occur in both KD and MIS-C. Although the features of MIS-C overlap with KD and incomplete KD, many children do not meet the full diagnostic criteria,[24,25,36,41] and distinguishing demographic trends in age and geography are apparent between the 2 diseases (**Table 2**).

A severe COVID-19 infection (without meeting criterion for MIS-C) also is possible. A retrospective comparison of MIS-C versus severe COVID-19 in 1116 hospitalized patients ages 21 and under revealed MIS-C patients presented more frequently with mucocutaneous signs than those with severe COVID-19. MIS-C cases showed greater laboratory inflammation, and complications were more likely to involve the cardiac system.[48]

In addition to KD, the differential for MIS-C includes systemic illnesses, such as macrophage-activation syndrome, toxic-shock syndrome, bacterial sepsis, and scarlet fever.[40,49] Depending on the clinical picture, drug hypersensitivity, vasculitis, or other viral infections may be considered.[38]

Prognosis and Management

MIS-C is a serious complication of COVID-19 in children, requiring intensive care unit admission in up to 80% of cases[24,26] and often supportive care, including vasopressors, fluids, and/or mechanical ventilation.[48,49] Treatment includes intravenous immunoglobulin and corticosteroids; many patients also receive anticoagulants and/or antiplatelet agents.[48] Medications, such as antivirals, cytokine blockers, and various immunomodulatory agents, have been used.[19,48,50] Few children may improve without any immunomodulatory therapy.[25] The median hospital stay is approximately 1 week,[24] and a large majority of MIS-C patients enter remission. There have been reports of death, however, due to MIS-C following COVID-19 infection[24,42]; mortality is estimated at 2%.[24,26]

The post-hospitalization sequelae of MIS-C are just beginning to be appreciated. Coronary artery abnormalities were identified in a notable percentage of patients in all 3 clinical presentations/subgroups of MIS-C, described previously, ranging from 16% to 21%,[46] which has an impact on patient return to baseline activities. It has been observed that a majority of MIS-C patients with severe cardiac complications recover within 1 months to 3 months.[48] Although impacts on hair are not robustly documented in pediatric patients

Table 2
Kawasaki disease compared with multisystemic inflammatory syndrome in children

	Kawasaki Disease	Multisystem Inflammatory Syndrome in Children[44]
Demographics		
Age	Younger children (90% of cases under age 5)[110]	Mean age 9 years old
Geography	More common in Asia (Japan, South Korea, and Taiwan)[111]	Majority of reports from the US and Europe
Race/ethnicity	Most common in Asian and Pacific Islanders[112]	>65% of cases in Hispanic/Latino or non-Hispanic black children
Gender	Male predominance[110]	Slight male predominance
Clinical signs		
Fever	Unexplained fever lasting ≥5 d must be present[112]	Fever lasting >24 h must be present
Conjunctivitis Oral mucosal change Distal extremity changes Skin rash Cervical lymphadenopathy	4 of 5 are part of diagnostic criteria (or 3 of 5 for incomplete KD)[112]	<50% meet criteria for KD
Gastrointestinal involvement	Present in 61%[113]	Present in 87%
Respiratory involvement	Slightly less common Present in 35%[113]	Slightly more common Present in 41%
Cardiovascular shock	Less common Present in <10%[114]	More common Present in 66%

with MIS-C, there are reports of alopecia areata and telogen effluvium, which may be related to the infection, a postinfectious sequelae of disease, or associated stress.[51]

Although skin findings are nonspecific and nondiagnostic, dermatologists must be aware of MIS-C and potential downstream sequalae. Children who present with a new skin eruption, swollen extremities, or mucous membrane changes during the COVID-19 era benefit from a full review of systems, vital signs, and in-person examination. If a presentation is suspicious for MIS-C but the patient otherwise is stable, it is appropriate to obtain laboratory testing to assess for COVID-19 infection and markers of inflammation for signs of multiorgan dysfunction, and/or consult subspecialists.[52] Stable patients with cutaneous eruption of unknown etiology during the pandemic may be counseled to monitor for development of accompanying signs of MIS-C. Severely ill children must be evaluated by emergency/critical care for immediate further work-up and management.

PERNIO (CHILBLAINS)-LIKE LESIONS

- Pernio-like lesions are an inflammatory response to COVID-19 resulting in purpuric and erythematous acral cutaneous surfaces.
- Children and young adults are more likely to manifest with pernio-like lesions than older adults.
- Pernio-like lesions typically are self-limiting with excellent prognosis, although recurrent skin sequelae are being appreciated.

Evolution of COVID-19 Toes

Traditional pernio, also called chilblains, is an inflammatory reaction of the superficial vasculature on acral cutaneous surfaces (fingers, toes, nose, and ears) that often is idiopathic and triggered by cool and/or damp temperatures (primary pernio) or, less commonly, is due to an underlying autoimmune or systemic inflammatory disease (secondary pernio).[53] Outside of the COVID-19 era, pernio is considered a relatively uncommon disease[54]; 1 study reported only 8 pediatric cases in 10 years,[55] although many consider this reaction to be clinically identified and readily managed with supportive care.

Following the start of the COVID-19 pandemic, thousands of children and young adults with no prior history of acral skin changes began to develop asymptomatic, painful, and/or pruritic lesions with striking resemblance to pernio: erythematous, purpuric papules, and macules

affecting the toes, feet, fingers, and hands (**Fig. 3** morphologies are discussed in further detail in Ritesh Agnihothri and Lindy P. Fox's article, "Clinical Patterns and Morphology of COVID-19 Dermatology," in this issue). The temporal relationship of increased pernio-like cases coinciding with the pandemic alluded to a possible relationship. Thus, the terms, COVID toes and COVID fingers, were coined, and pernio-like lesions since have become the cutaneous manifestation in confirmed or suspected COVID-19 infected individuals across the globe reported most frequently.[56]

Why Youth?

Younger, healthy people tend to present with pernio-like lesions at higher frequencies than older adults.[57] The median age of pernio-like lesions is the mid-20s to-late 20s,[56,58] and 29% of those with pernio-like lesions are children or adolescents.[59] Leading theories aid in explaining the demographical trend toward healthy youth. The immune system of younger individuals has higher amounts of interferon compared with older adults,[11] which provides innate immunity against viruses.[60] It is known that constitutive type 1 interferon responses lead to autoinflammatory manifestations, including chilblains.[61] Thus, it is possible that when infected with COVID-19, healthy children and young adults mount a strong interferon response, clearing the virus,[62] and subsequently develop pernio-like lesions as a delayed consequence of inflammation.[63,64]

Supporting this theory, it has been found that individuals with pernio-like lesions respond with significantly higher blood levels of interferon alpha when stimulated with immune ligands compared with patients with acute COVID-19 infection.[65] Higher rates of antibody test positivity compared with rates of RNA detection in individuals with pernio-like lesions,[65] in addition to the tendency for delayed presentation of lesions in relation extracutaneous symptoms (**Table 3**),[56,59] provide additional support of pernio-like lesions as a postviral manifestation of COVID-19 infection. Biopsies of pernio-like lesions offer evidence of a primarily inflammatory process.[66]

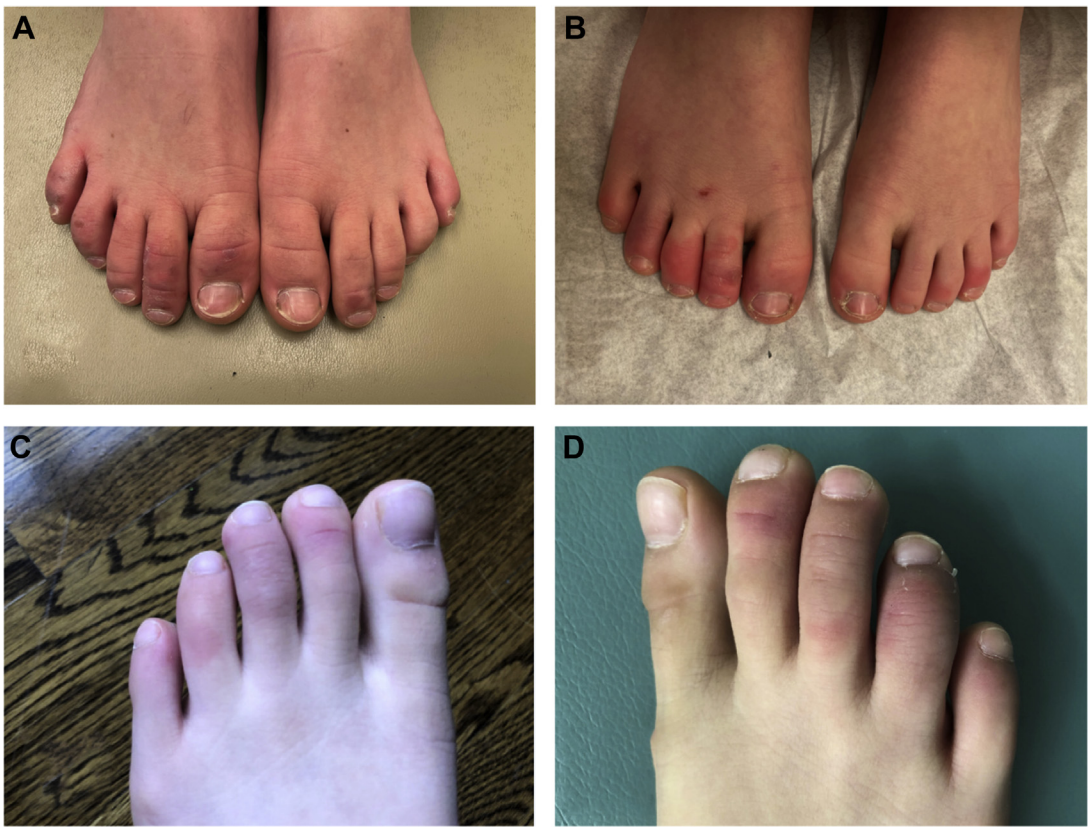


Fig. 3. Pernio-like lesions in children. (A) A child with purpuric papules on the 1st, 2nd, 4th, and 5th right digits and 2nd proximal left digit and (B) Digits on the same child appearing with increased erythema. (C) Right toes of a child appearing with pink and dusky papules and plaques, also involving (D) the child's left digits.

Table 3
Clinical presentation of pernio-like lesions in children[66,67,80,115–117]

Lesion Location	Lesion Color	Primary Lesion Morphology	Secondary Lesion Features	Associated Symptoms	Extracutaneous Symptoms[b]
Toes[a]	Red	Papules	Edema	None	Fever
Feet	Purple	Macules	Erosion	Pruritis	Cough
Ankles	Brown	Vesicles	Crust	Pain	Sore throat
Fingers	Red-bluish	Bullae			Nasal congestion
Hands	Gray	Patches			Rhinorrhea
		Plaques			Chills
					Diarrhea
					Abdominal pain
					Dyspnea
					Myalgia
					Weakness

[a] Including nail involvement.
[b] If extracutaneous signs are present, they precede cutaneous findings more than half the time[59,80,117].

Relationship to COVID-19

SARS-CoV-2 nasopharyngeal RNA and/or serologic results often fail to demonstrate COVID-19 infection in many cohorts of individuals with pernio-like lesions,[58,67–69] leading to theories that the increase in cases may be coincidental, due to patient/provider/media awareness (confirmation bias),[70] or a result of pandemic lifestyle changes (such as walking barefoot at home more often).[71] Lack of laboratory positivity, however, may speak more to testing nuances rather than lack of true infection.[72] Cleared infections[59]; failure to look for IgG, IgM, and/or IgA antibodies in serologic testing[73]; and improper timing of testing in relation to disease (ie, the window between cleared infection and detectable antibodies)[74] are potential reasons why viral testing may read negative following COVID-19 infection. For example, given the theory that pernio-like lesions are a postviral manifestation, for a child presenting with pernio-like lesions 10 days after a mild cough, RNA testing would be negative if the infection was cleared (the median time to undetectable RNA is 14 days, meaning 50% of individuals test negative before then),[75] and antibodies may not yet be detectable (average length to mount response is 1–3 weeks),[76] thus, possible that neither test would be positive. In separate analysis of 906 reported cases of confirmed or suspected COVID-19-associated skin manifestations, COVID-19 tests were more likely to be positive if performed earlier in the disease course, and some negative tests were resulted from patients whose skin biopsies demonstrated SARS-CoV-2 RNA.[72] Mounting evidence supports that a negative test does not necessarily rule out an association of pernio skin lesions with COVID-19,[77] and optimal testing times remain an area of ongoing research.

Although it is possible that select patients manifest idiopathic pernio, the dramatic surge in cases (including in temperate climates),[65] and clustering in families and close contacts,[66] in addition to emerging evidence from larger cohorts,[59] support a connection between pernio-like lesions cases and COVID-19. Of patients with pernio-like lesions during the pandemic, 72% have a suspected COVID-19 infection,[59] and up to 30% of those with serologic testing have antibodies to SARS-CoV-2[59,65] (compared with <10% in the general US population.)[78] In a series of 7 pediatric cases, COVID-19 viral particles were observed in endothelial cells using electron microscopy of biopsied pernio-like lesions.[79] With time, more readily available COVID-19 tests, and emerging data, it is anticipated that the relationship between the pandemic and pernio-like lesions will become more clear.

Pediatric Outcomes and Management

It is overall reassuring that regardless of etiology, pernio-like lesions usually are self-limited.[65] The lesions and associated symptoms often last 1 week to 3 weeks,[59,80,81] although, in some patients, persistence or recurrence may occur.[82] First-line management is observation[83]; topical corticosteroids, topical antibiotics, and nonsteroidal anti-inflammatory agents may be useful for acute inflammation.[67,84] Some patients with increased pain and symptoms require additional pain management, and topical anesthetics and

analgesics, such as topical gabapentin, diclofenac, ketamine, JAK inhibitors, lidocaine patches, and ointment are reasonable choices. The long-term outcomes and recurrence rate of lesions will become apparent with time. With the temporal second wave of COVID-19 cases, there has been another increase in reported cases of pernio-like lesions.[85]

Clinical judgment should be used in the decision to test children for SARS-CoV-2 with consideration to timing from symptoms and pretest probability. Previously healthy children with no history of acral cutaneous disease and lack of overt risk factors for traditional pernio may benefit from RT-PCR testing if they are presenting during the COVID-19 era, particularly if they are evaluated promptly upon lesion onset.

NONSPECIFIC COVID-19 DERMATOSES

- Cutaneous eruptions can be a sole presenting sign of COVID-19, be accompanied by mild extracutaneous disease, or be seen in hospitalized COVID-19 children.
- Various inflammatory, vascular, and nonspecific cutaneous morphologies have been described.

In addition to the well-reported cases of MIS-C and pernio-like lesions in children, various other cutaneous eruptions have been reported. **Table 4** summarizes the different skin findings by etiology that may be related to COVID-19 infection in pediatric patients.

Nonperniotic Acral Cutaneous Eruptions

Some acral manifestations overlap or coexist with pernio-like lesions and are a matter of subtle and/or subjective classification. For example, EM-like lesions have been found on the acral surfaces of children with pernio-like lesions[86] and may present with purpuric morphology.[87] The EM-like pattern of acral eruptions are distinguished from pernio-like lesions as round, coalescing erythematous macules and vesicles, observed more frequently in younger children.[88] Similarly, ecchymotic eruptions of the toes and feet are reported with a distinct description from pernio-like lesions in children: petechial lesions on the sole, plantar singular toes, and/or heels.[89]

In addition to ecchymotic patterns, other vascular morphologies on the acral surfaces, like reticulated purpura of the soles of an infant[90] and acrocyanosis/livedo reticularis of the extremities in children and adolescents,[91] are thought to be late SARS-CoV-2 manifestations. Immunohistochemical positivity for SARS-CoV-2 has been found in EM-like, reticulated purpura, and perniotic-like acral lesions.[86,90] Young individuals with such acral manifestations tend to have an uncomplicated disease course and excellent outcomes.

Nonacral Cutaneous Eruptions

Nonacral surfaces also are involved in cutaneous eruptions related to COVID-19 infection in children. Some manifestations that are observed in COVID-positive adults, such as erythematous, vesicular, or urticarial exanthems,[92] also can present in infants and children with suspected or confirmed SARS-CoV-2 infection.[15,93–95] Petechiae, which are associated with several other viral illness in children,[96] have been observed in 1% to 2% of hospitalized COVID-19 positive children and may be widespread or localized.[14] Case reports of children with COVID-19 further demonstrate the various forms of potential mucocutaneous changes, such as erythematous and purpuric macules on the face,[97] swelling and papillitis of the tongue,[98] vesicular oral eruption,[99] a roseola-like rash,[100] and a pruritic maculopapular rash.[100] These case reports do not support causality between COVID-19 and cutaneous eruptions, because there are many potential causes for exanthems in children. The virus has been further implicated, however, by its demonstration in biopsy tissue from various eruptions, including patients with EM[86] and purpuric and livedoid eruptions.[90]

Although most cases of young individuals with cutaneous manifestations have a mild and uncomplicated disease course, some case reports demonstrate more serious forms of disease. MIS-C, as discussed previously, is one such

Table 4
Acral and non-acral potential cutaneous manifestations of pediatric COVID-19

Acral	Nonacral
Pernio-like lesions[59]	Urticaria[95]
EM-like lesions[88]	Erythematous patches[118]
Plantar papules[14]	EM-like lesions[86]
Retiform purpura[41]	Vesicles/papulovesicles[15]
Ecchymotic-like lesions[89]	Herpetiform oral eruption[99]
Livedo reticularis[91]	Roseola-like rash[100]
MIS-C findings (see **Table 1**)	Maculopapular rash[100]
	Macular eruption[14,98]
	Lingual papillitis[97]
	Eccrine hidradenitis[93]
	Erythema nodosum[93]
	Petechiae[14]
	Purpura[97]
	MIS-C findings (see **Table 1**)

example. Other examples in previously healthy COVID-positive children include that of a neonate with mottling skin rash and respiratory distress requiring neonatal intensive care[101] and a 12-year-old girl with nonspecific skin rash, fever, and headache who went on to develop respiratory failure and was found to have encephalomyelitis.[102] Despite acute systemic presentations, both of these patients improved by hospital discharge.

SUMMARY

The COVID-19 era has brought many advances to the understanding of interplay between viral disease, the pediatric immune system, and the skin. Evolving understanding of the mechanisms of MIS-C and pernio demonstrate the unique ways the young immune system operates; although likely protective from the traditional COVID-19 consequences like severe respiratory deterioration, the immune profile of younger individuals may holster a role in delayed inflammatory cutaneous presentations.

Although many cutaneous eruptions in children during the COVID-19 pandemic may not be related directly to infection, the possibility is an important consideration, particularly for patients with risk factors and/or highly impacted communities. Because children often present with no or mild symptoms, dermatologic manifestations of COVID-19 may be presenting signs,[14] serving as a subtle clue toward the highly contagious infection. Even in the absence of more classic signs of COVID-19 like respiratory symptoms, children with COVID-19 still may spread the virus and infect others who are susceptible to a more severe disease course.[103] Thus, dermatologists have an important role in containing the pandemic by appropriately counseling patients and testing for acute infection if indicated. Appropriate social distancing, mask-wearing, and hand-washing should be encouraged in children during the pandemic, especially those with risk factors, regardless of the presence or absence of extracutaneous symptoms.

Whereas some pediatric dermatologic manifestations of SARS-CoV-2, such as the polymorphous rash, mucositis, and conjunctivitis seen in MIS-C, may serve a clue toward serious sequalae, a majority of cutaneous eruptions in relation to the pandemic are benign. Despite the continually evolving understanding of COVID-19 and its potential manifestations, cutaneous eruptions fortunately most often are self-limited and not associated with poor outcomes; some studies even report children with skin rashes have a better prognosis than children with COVID-19 and no rash.[41] With ongoing cases and data reports, the interaction between COVID-19 and the skin in pediatric patients will become better understood. Beyond the dermatologic manifestations of COVID-19 in the pediatric population, children and adolescents face numerous consequences of the pandemic and some are only starting to be appreciated, ranging from physical impacts, such as obesity associated with changes in diet and activity or progression of myopia during home confinement to a wide range of psychosocial consequences of school closures and home/health stressors.[104]

As new, potentially more contagious, strains of COVID-19 arise, such as the B.1.1.7 variant, there has been concern for how this has an impact on the pediatric population. From February 2021 to April 2021, there was more than double the frequency of pediatric cases (all age groups) in Michigan,[105] with several other states following similar trends.[106] Although these rises coincide with the emergence of new variants, there is no evidence that new variants preferentially infect children.[107] It is likely that such increases in pediatric cases reflect vaccination and social trends. Currently (as of April 2021), the 2-dose mRNA Pfizer-BioNTech vaccine is approved in children 16 years and older, and clinical trials are under way for younger populations.[108] As schools open and sporting activities resume, it is important to counsel pediatric patients on appropriate social distancing measures, regardless of vaccination status.

CLINICS CARE POINTS

- A thorough skin exam in children suspected to have COVID-19 may be useful in identifying cutaneous manifestations.
- Clinical judgment must be used when deciding to test a child with new cutaneous findings for COVID-19 based on pre-test probability and test availability.
- It can be challenging to ascertain causality between cutaneous eruptions and COVID-19 infection, thus children should be encouraged to practice social distancing and good hygiene.
- The skin and mucous membranes can provide clues and/or be part of the diagnostic criteria for the serious pediatric complication of MIS-C.

- Children suspected to have MIS-C should seek emergency care.
- Most cutaneous manifestations of COVID-19, such as pernio-like lesions and non-specific eruptions limited to the skin, are self-limited.

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