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# Morbilliform Eruptions in the Hospitalized Child

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**KEYWORDS**

• Morbilliform eruption • Pediatric • Inpatient dermatology • Diagnosis • Management
• Viral exanthem • Drug eruption

**KEY POINTS**

- Morbilliform eruptions are common in the pediatric inpatient setting.
- Accurate diagnosis relies on a thorough full-body physical examination and complete history.
- Infectious causes, such as measles, arboviridae, and Rocky Mountain spotted fever, should be considered in patients with morbilliform eruption and the appropriate vaccination and travel history.
- Both simple and complex drug eruptions can present with a morbilliform morphology in the hospitalized child and must be differentiated.
- Other inflammatory conditions, such as Kawasaki disease, and in the COVID-19 era, multisystem inflammatory syndrome in children, should be on a differential diagnosis of a child with fever and morbilliform eruption.
- Graft-versus-host disease and engraftment syndrome are 2 causes of morbilliform eruption that should be considered in the child with a transplant.

## MORBILLIFORM ERUPTIONS IN THE HOSPITALIZED CHILD

The ability to accurately diagnose a child with a new-onset eruption in a timely manner is a fundamental skill for the dermatology consultant. Morbilliform eruptions inspire a broad and varied differential spanning across inflammatory and infectious categories. The goal of this article is to help the clinician develop an approach toward the pediatric patient with a morbilliform eruption in the emergency room or hospital setting. The authors review several high-yield clinical scenarios with a focus on recently emerging and reemerging childhood diagnoses.

## THE HISTORY AND DEFINITION OF THE MORBILLIFORM ERUPTION

The term morbilliform originates from *morbilli*, the Italian diminutive of Il Morbo. In the Middle Ages, Il Morbo, or the great plague, referred to smallpox, and *morbilli* described the "small plague" of measles, as both epidemics have cooccurred since the sixth century.[1,2] Over time, the term morbilliform has been adopted to describe any eruption resembling measles. By definition, a morbilliform eruption is generalized and symmetric with involvement of the trunk and some portion of the extremities. The primary morphology is blanching, erythematous pink to red macules and papules that become confluent with time (**Fig. 1**). Today, morbilliform is a descriptor well engrained in the dermatology lexicon, often used synonymously with maculopapular exanthem, and defines eruptions that are distinct from those that are urticarial, eczematous, psoriasiform, pustular, vesicular, or vasculitic.

## EVALUATION OF THE CHILD WITH A MORBILLIFORM ERUPTION

A fever and morbilliform eruption in a child should prompt a thorough evaluation for either an

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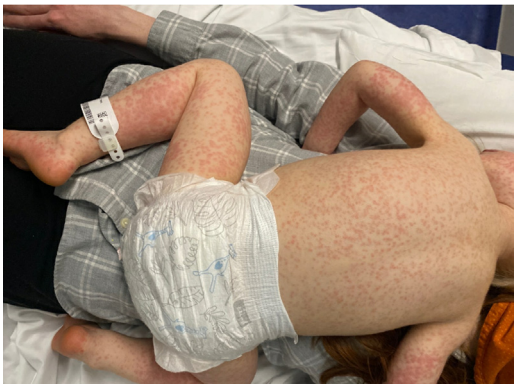

Fig. 1. Morbilliform eruption. A young child with acute Epstein-Barr virus infection with associated morbilliform rash.

infection, a medication allergy, or other systemic illness (eg, Kawasaki disease). Commonly implicated infections include enterovirus, adenovirus, Herpesviridae (Epstein-Barr virus, human cytomegalovirus, and human herpes virus 6 [HHV-6]), and parvovirus. Other respiratory infections, such as influenza B and *Mycoplasma pneumoniae*, may also cause morbilliform eruptions.[3] Because morbilliform eruptions can also be harbingers of more serious illness, the physician's task is to integrate an illness's timeline, a child's past medical history, exposures, and recent public health trends to ensure a comprehensive evaluation.

### History Taking

The history should focus on a child's exposures (relevant sick contacts, a detailed travel history, infections circulating in the community, and medications) and their own host risk factors (vaccination and immune system status). Because morbilliform eruptions indicate a systemic inflammatory response, a complete review of systems should always be obtained.

### Physical Examination

A full-body skin examination is necessary in all cases. Caregiver-provided photographs can be invaluable in illustrating the progression of a rash and in deciphering more subtle clinical findings, such as swelling. The conjunctiva, oral mucosa, genitalia, palms, soles, and lymph nodes should not be overlooked on the physical examination. Attention should also be paid to how an eruption has progressed. Certain eruptions, such as measles and drug rash with eosinophilia and systemic symptoms (DRESS), have facial involvement early in the course. Last, in an ill child with fever and a morbilliform eruption, the findings of petechiae and purpura serve as red flags for potentially life-threatening illnesses, such as Rocky Mountain spotted fever (RMSF), meningococcemia, or evolving disseminated intravascular coagulation.

### Laboratory Evaluation

The laboratory workup is dictated by the differential diagnosis being considered (**Table 1**).

### Management

Treatment should focus on the underlying illness. For patients who have symptoms related to their morbilliform eruption, low- to medium-strength topical corticosteroids can help.

## MORBILLIFORM ERUPTIONS IN THE UNVACCINATED CHILD

Before widespread childhood vaccination, measles and rubella (also known as German measles or 3-day measles) were the primary cause of morbilliform eruptions in children. In the early twentieth century, more than 500,000 cases of measles (rubeola) were reported in the United States each year.[4,5] By 2000, the World Health Organization declared measles eliminated in the US, a historic achievement resulting from the measles vaccine introduced in 1963.[6]

Unfortunately, measles is still a common cause of childhood morbidity and mortality globally, especially within Africa and India, and rates are surging with a 50% increase in mortality since 2016.[7] Over the past decade, multiple outbreaks have occurred in the United States, with the convergence of imported cases from travel, and their spread within undervaccinated or unvaccinated populations. The largest outbreak occurred in 2019 with 1249 cases reported across 31 states.[8] The outbreak's epicenter was close-knit Orthodox Jewish communities within New York City, which accounted for 75% of the cases. Within this outbreak, the median age of patients was 5 year old, and 71% were unvaccinated.[8] The recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19) pandemic has heightened concerns of a measles resurgence because of the disruption of well-child visits and vaccinations. A study in Alabama found overall vaccination rates to have declined by 10% from 2019 to 2020, and a reduction in measles, mumps, and rubella (MMR) vaccination by 54.7% over the same time period.[9]

For the clinician evaluating a child with fever and morbilliform eruption, accurate documentation of a child's vaccine status and travel history is critical. In the setting of an outbreak, children under

**Table 1**
**Confirmatory testing for select infectious causes of morbilliform eruptions in children**

| Diagnosis | Laboratory Workup |
|---|---|
| Measles | Measles-specific IgM and RT-PCR from throat or nasal swab |
| Zika | RT-PCR of serum and urine for Zika RNA if ≤7 d of illness<br>Zika-specific IgM positive if >7 d of illness (IgM can remain positive for months to years and can cross-react with Dengue) |
| Chikungunya | RT-PCR of serum if ≤ 7d of illness<br>Chikungunya-specific IgM if >7 d since onset of illness |
| Dengue | RT-PCR of serum if ≤7 d of illness<br>Dengue-specific IgM if >7 d since onset of illness |
| RMSF | Diagnosis can rarely be established during the early phase so empiric treatment should be started<br>Convalescent antibody titer through indirect immunofluorescence antibody testing for IgG against the *R rickettsii* antigen |

the age of 5 are the most vulnerable because of incomplete vaccination with the MMR vaccine being administered typically at 1 and 4 to 5 years of age.[10] Measles is a highly transmissible, airborne virus with an attack rate of 90% in susceptible, exposed individuals.[11] Therefore, any consideration for measles should immediately prompt isolation and airborne precautions. Children with measles present with a prodrome lasting 2 to 4 days consisting of fever up to 104°F and the classic 3 C's of cough, coryza (rhinitis), and conjunctivitis. The pathognomonic enanthem, Koplik spots, consists of clustered gray-white to pink papules located on the buccal mucosa (**Fig. 2**). Koplik spots may be absent at the time of dermatologic evaluation because their onset precedes the exanthem by 48 hours and only lasts 12 to 72 hours.[12,13] Classically, the exanthem starts 2 to 4 days after the prodrome, lasts 6 to 7 days, and spreads in a cephalocaudal pattern beginning on the face, favoring the forehead, hairline, and posterior auricular area. Many routine childhood exanthems instead start on the trunk and typically spare the face. As the exanthem progresses, it fades in the order that it appeared and can adopt a brownish discoloration in lighter-skinned patients. Measles has an incubation period of 10 days, and patients are contagious 5 days before the onset of the rash and for 4 days after its disappearance.[13] A child suspected of having measles should have both a serum measles-specific immunoglobulin M (IgM) antibody test and a respiratory real-time polymerase chain reaction (RT-PCR) test from a throat or nasopharyngeal swab performed.[14] Children hospitalized for measles should receive supportive care. Administration of vitamin A and ribavirin may have a role in severe cases.[15]

## MORBILLIFORM ERUPTIONS IN THE RETURNING TRAVELER

Travel screening has increasingly become a routine component of triage in pediatric emergency departments because of public health concerns over emerging infections, such as Ebola, Zika, and now

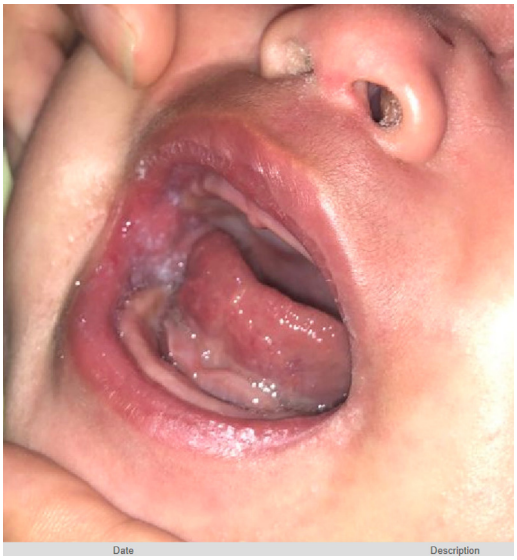


**Fig. 2.** Koplik spots. Pinpoint white macules along the buccal mucosa in an infant with measles infection.

COVID-19.[16] In addition to asking about any travel within the past 21 days, a detailed travel history also includes other relevant information to help narrow the differential. In the child with a fever and rash, important considerations include arboviruses (Zika, Dengue, Chikungunya), Brucellosis, Leptospirosis, Rickettsial diseases, and again, measles, depending on a child's vaccination status. In light of this, a travel history should document purpose of travel (tourist, visiting family and friends), location (urban vs rural), mosquito bites (arboviruses), tick bites (rickettsial diseases), exposure to unpasteurized dairy products (brucellosis), livestock exposure (leptospirosis), and freshwater exposure (leptospirosis). The article focuses on the arboviruses Zika, Dengue, and Chikungunya and the rickettsial infection RMSF, as the incidence of these infections is on the increase.[17,18]

Zika, Dengue, and Chikungunya are endemic in parts of the Caribbean, Central America, and South America.[19] The main vector for these viruses is the *Aedes aegypti* and *Aedes albopictus* mosquitoes. Several factors linked to their continued geographic spread include global warming, travel, and urbanization.[20] All 3 arboviruses have considerable overlap and should be considered when a child presents with fever, rash, conjunctivitis, and/or arthralgia after travel (**Table 2**).

### *Zika (Equatorial Africa and Asia, Pacific Islands, Caribbean, Latin America, North America)*

Zika virus (ZIKV) is a *flavivirus* predominantly transmitted by mosquitos, with less common modes of transmission being sexual, intrauterine, perinatal, and laboratory exposure. From 2015 to 2016, a large outbreak of ZIKV occurred within the Americas, resulting in travel-associated cases in the United States but also local transmission in Florida and Texas.[21] As of 2020, no confirmed cases of ZIKV have been reported in the United States.[22] Eighty percent of cases are asymptomatic. The incubation period of Zika lasts from 3 to 14 days.[19] Acute infection is typically mild with rash, low-grade fever, arthralgia, myalgias, and nonpurulent conjunctivitis. Rash is common and was documented in 90% of patients in 1 cohort with ZIKV.[23] The ZIKV exanthem has been described as "distinct papules" descending from the trunk to the lower body, which can involve the palms and soles.[24] Mucosal involvement includes conjunctivitis and palatal petechiae.[24] Although acute infection is often self-limited, complications can include Guillain-Barre syndrome and congenital Zika syndrome from vertical transmission during pregnancy, leading to cerebral calcifications, severe microcephaly, intrauterine growth restriction, congenital contractures, ophthalmologic disease, and potentially fetal demise.[25,26]

### *Chikungunya (Asia, Africa, Latin America, Caribbean, Florida, Puerto Rico, US Virgin Islands)*

Chikengunya virus (CHIKV) of the Togaviridae family has an expanding geographic spread.[27] Since 2013, CHIKV has expanded to include the Americas, particularly the Dominican Republic, Puerto Rico, and Haiti.[28] The incubation period can vary between 1 and 12 days.[19] Acute infection is

**Table 2**
**Mucocutaneous characteristics of arbovirus infections**

| | Zika | Chikungunya | Dengue |
|---|---|---|---|
| Incubation period, d | 3–14 | 1–12 | 5–8 |
| Cutaneous manifestations in symptomatic individuals | 90% of infections, morbilliform or fine papular eruption, descends from trunk to lower extremities, can be pruritic | ~50% of infections, morbilliform, typically *spares face*, involves trunk and limbs, can be pruritic<br>*Chik sign: centrofacial hyperpigmentation* | ~50% of infections, *facial*, trunk, extremities, white "islands in sea of red," confluent erythema that can progress to morbilliform, typically not pruritic, usually spares palms and soles |
| Mucosal findings | Common, 55%, nonpurulent conjunctivitis | Uncommon | ~15% to 30%, conjunctival or scleral injection, cracked lips, strawberry tongue, vesicles on soft palate |
| Laboratory findings | Nonspecific | Nonspecific | Thrombocytopenia |

characterized by a high fever for 3 to 5 days, arthralgias, myalgias, and rash. As CHIKV can replicate within joint spaces, polyarthralgia is a hallmark feature and can occur before the onset of fever.[29] A maculopapular eruption occurs in 50% of cases, involving the trunk and extremities, occasionally the palms and soles, and appears 2 to 5 days after the fever starts.[8,19,30] It classically spares the face and can have islands of sparing similar to Dengue.[31] The rash resolves within 7 to 10 days of onset, whereas arthritis and arthralgias can persist for up to 3 years.[29] The "Chik sign" refers to postinfectious, centrofacial hyperpigmentation with a predilection for the nose and is well documented in children[31] (**Fig. 3**).

### *Dengue (Tropics and Subtropics)*

Dengue is a mosquito-borne *flavivirus* endemic in popular tourist destinations in the Caribbean, Central and South America, Southeast Asia, Africa, and the Pacific Islands. Dengue ranges from being asymptomatic (75% of cases) to a life-threatening disease.[32] The incubation period ranges from 5 to 8 days following a bite from a mosquito with a high viral load. Classic dengue consists of fevers lasting 2 to 5 days, retro-orbital pain, nausea, vomiting, myalgia, arthralgias, and a morbilliform rash.[33] The rash of Dengue occurs in approximately 50% of symptomatic infections and within the first 24 to 48 hours of the illness.[19,34] Often referred to as "white islands in a sea of red," the Dengue exanthem has unaffected skin interspersed among broad patches of erythema[34] (**Fig. 4**). The febrile phase can be followed by either a defervescence phase, whereby the patient recovers, or Dengue hemorrhagic fever (DHF), characterized by increased vascular permeability, plasma leakage, and subsequent volume depletion.[33] DHF typically occurs in patients who have been previously infected and are then reinfected with a different viral strain. DHF more often affects children less than 15 years of age and has a more severe course, including facial flushing, vomiting, circumoral pallor, and cyanosis.[35] Petechiae, purpura, or ecchymoses can also be seen because of hemorrhage and are typically a sign of more severe forms of the disease, such as DHF or Dengue septic shock.[19,34] Mucosal involvement is also more common with DHF than with dengue fever, occurring in 15% to 30%, and can include conjunctival and scleral injection, cracked lips, strawberry tongue, and vesicles on the soft palate.[34] Most individuals develop thrombocytopenia, which can result in severe bleeding.[19] Diagnosis can be confirmed by viral serologic testing and by both PCR and enzyme-

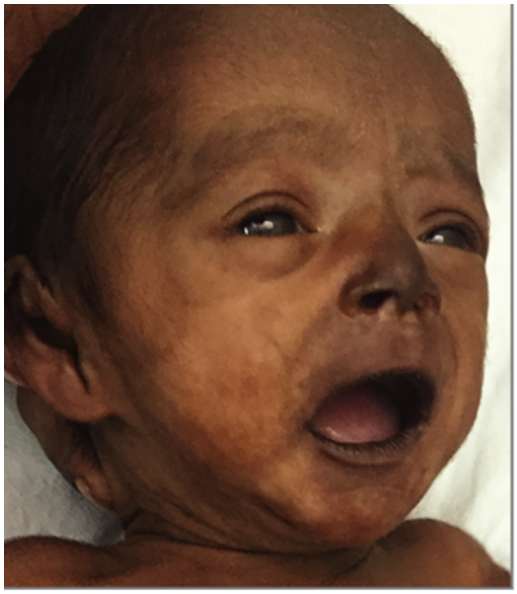

**Fig. 3.** Chik sign. Clinical photograph of an infant's face demonstrates a positive chik sign. (*From* Dabas G, Vinay K, Mahajan R. Diffuse Hyperpigmentation in Infants During Monsoon Season. JAMA Dermatol. 2020 Jan 1;156(1):99-101.)

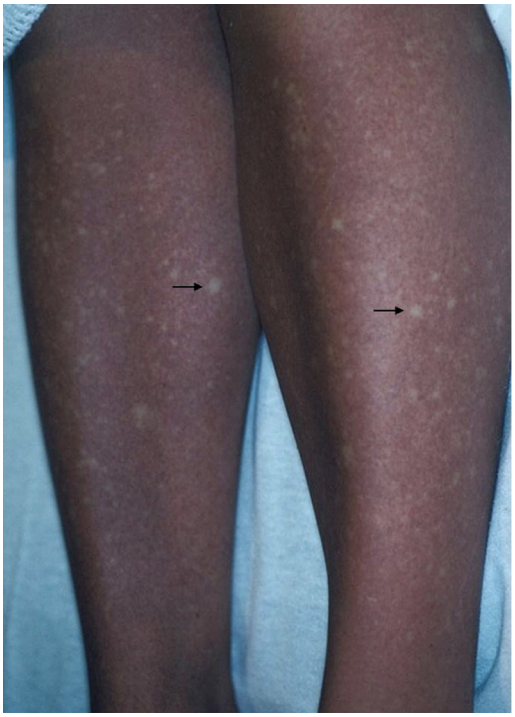

**Fig. 4.** Dengue virus. Pinpoint petechiae and islands of sparing (*arrows*) on a background of erythema. (*From* Pincus LB, Grossman ME, Fox LP. The exanthem of dengue fever: Clinical features of two US tourists traveling abroad. J Am Acad Dermatol. 2008 Feb;58(2):308-16.)

linked immunosorbent assay for RNA and dengue viral protein, respectively.[36]

## RICKETTSIAL DISEASES: ROCKY MOUNTAIN SPOTTED FEVER

Paralleling the increase in arboviruses, tick-borne illnesses within the United States have also seen an increase in incidence and geographic spread.[37] RMSF is one of the most lethal tick-borne illnesses, and clinicians must maintain a high index of suspicion when evaluating a child with a fever and rash whether they practice in an endemic area or not. RMSF is caused by *Rickettsia rickettsii*, an obligate, intracellular bacteria transmitted by the dog tick (*Dermacentor variabilis*) in the Eastern United States and wood tick (*Dermacentor andersoni*) in the Western United States and Canada.[38] RMSF has also been documented in central Mexico, Panama, Costa Rica, northwestern Argentina, Brazil, and Columbia.[39] More than half of the cases in the United States originate from North Carolina, South Carolina, Tennessee, Oklahoma, and Arkansas; however, cases have been found in all 48 contiguous states except for Maine and Vermont.[40] The incidence of RMSF has increased in recent years with a peak of 6248 cases reported in 2017.[41] RMSF preferentially afflicts children less than 10 years old and adults 40 to 64 years of age.[42] Transmission is highest during the spring and summer months of April to August.[38]

Classically, RMSF presents with fever, headache, and rash, but the complete triad is uncommon.[38] An exanthem is seen in 97% of pediatric patients typically starting within the first 2 days of illness onset.[43] Small, 1- to 5-mm blanching macules typically begin on the wrists and ankles and progress to involve the palms and soles, arms and legs, and then trunk (**Fig. 5**). By the end of the first week, a morbilliform eruption often admixed with petechiae is seen.[44] However, it is crucial not to anchor the diagnosis on the finding of petechiae. In a case series of 92 children, 32% never developed a petechial component.[43] Other clinical and laboratory findings supportive of a diagnosis of RMSF and found in greater 50% of children include nausea and vomiting, thrombocytopenia (platelets <150,000/mm$^3$), hyponatremia (<135 mEq/dL), and transaminitis (median alanine transaminase [ALT] 55 U/L, median aspartate transaminase [AST] 83 U/L).[43]

Because RMSF can be fatal if treatment is delayed beyond the first 5 days of illness, treatment should be started as soon as the diagnosis is entertained.[45,46] Doxycycline is the first-line treatment irrespective of a child's age, as advised by both the Centers for Disease Control and Prevention and the American Academy of Pediatrics. Recent studies indicate that short courses of doxycycline have negligible risk for tooth staining in young children.[47,48] Skin biopsy of the RMSF eruption may be of diagnostic assistance, as it can demonstrate endothelial damage that progresses into a leukocytoclastic vasculitis, and immunofluorescence may indicate the bacteria in the vessel walls. However, confirmation of a diagnosis is typically achieved during the convalescent stage by documenting a fourfold increase in the IgG on indirect immunofluorescence serologic assay (IFA). IFA has a lower sensitivity during the acute phase of illness, but increases to 94% during the convalescent stage.[49,50] PCR can be performed on skin tissue from biopsy or whole blood but has low sensitivity.[50]

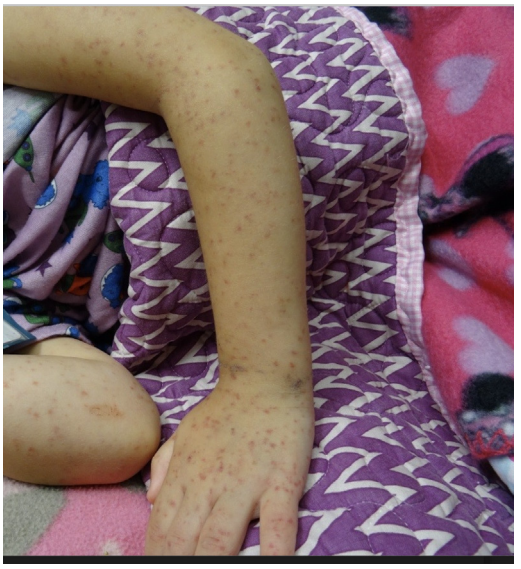

**Fig. 5.** Petechiae and purpuric macules in a child with RMSF.

## MORBILLIFORM ERUPTION IN THE COVID-19 ERA

Starting in the city of Wuhan, China in December 2019, the novel coronavirus SARS-CoV-2 quickly spread to become a global pandemic, the likes of which had not been seen in more than 100 years. The often-cited "saving grace" of this pandemic has been the low morbidity and mortality documented in children. However, as of the writing of this article, a new inflammatory syndrome termed multisystem inflammatory syndrome in children (MIS-C) is on the increase and an important diagnosis to consider when evaluating a child with new-onset fever and rash. The exact cause of

MIS-C is unknown, but it often occurs 2 to 6 weeks after COVID-19 infection, raising the hypothesis of convalescent immune dysregulation.[51] MIS-C was first described in April 2020 in children within the United Kingdom as an inflammatory syndrome similar to atypical Kawasaki disease (KD) and toxic shock syndrome.[52] One year later, as of April 1, 2021, in the United States, 3185 patients have met the criteria for MIS-C, and 36 patients have died of this disease.[53]

The criteria of MIS-C include age 21 years or younger, fever greater than 38°C, laboratory evidence of inflammation, multisystem organ involvement, and laboratory-confirmed COVID-19 infection (positive RT-PCR testing or antibody test) or epidemiologic link to a person with COVID-19 (**Box 1**).[51] More than half of patients in a targeted surveillance study (n = 186) by Feldstein and colleagues[51] were between 1 and 9 years old with a median age of 8.3 years, although cases in infants and young adults have also been reported. MIS-C disproportionately impacts children of African and Hispanic descent, and obesity has been identified as a risk factor.[54–56] MIS-C commonly presents with fever for 3 to 4 days, gastrointestinal symptoms, mucocutaneous features often seen in KD, and shock. Multisystem organ involvement is a sentinel feature, with 71% of patients having 4 or more systems involved.[51] Gastrointestinal involvement (abdominal pain, vomiting, diarrhea) is the most common organ system (91%–93% of patients) affected. Myocardial dysfunction indicated by either echocardiography or elevated troponin or brain natriuretic peptide is seen in more than 50% of reported cases. Unlike KD, shock is a common feature of MIS-C with 48% of patients requiring vasopressor or vasoactive support throughout their hospital course. Children who present with shock have several distinguishing features, including older age, black race, lack of full criteria for typical or atypical KD, neurologic symptoms, respiratory symptoms, and higher inflammatory markers (specifically, ferritin, C-reactive protein [CRP], and D-dimer).[57]

MIS-C can present with mucocutaneous features that closely resemble those seen in KD. In fact, 40% and 7% of patients with MIS-C meet criteria for typical and atypical KD, respectively.[54] Like KD, conjunctivitis, lip hyperemia/cracking, strawberry tongue, and polymorphic eruptions (urticarial, scarlatiniform, morbilliform) are common features of MIS-C[54] (**Fig. 6**). Periorbital erythema and edema are not characteristically seen in patients with KD, but did occur in 20% of patients with MIS-C, pointing to the possibility of more specific cutaneous findings in this condition.[54] Because of this considerable clinical overlap, distinguishing between KD and MIS-C can be challenging, but, in general, children with MIS-C tend to be older, more likely to have gastrointestinal involvement, myocardial dysfunction, shock, higher inflammatory markers (D-dimer, ferritin, CRP), and tendency toward cytopenia (lymphopenia and thrombocytopenia). Approximately 84% to 90% of patients with MIS-C have positive serologic testing for SARS-CoV-2.[58] The optimal treatment of MIS-C beyond supportive therapy is an area of active investigation.

**Box 1**
**Criteria for diagnosis of multisystem inflammatory syndrome in children**

Age <21 y

Fever >38°C

Multisystem organ involvement (≥2 organ systems)

Laboratory evidence of inflammation

COVID-19 PCR-positive/antibody test–positive, OR epidemiologic link to a COVID-19 infected person

Adapted from Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in US Children and Adolescents. New Engl J Med. 2020;383(4):334 to -46.

## MORBILLIFORM ERUPTION WITH A RECENT DRUG HISTORY

A drug history is important to obtain in any patient with a morbilliform eruption. A comprehensive list

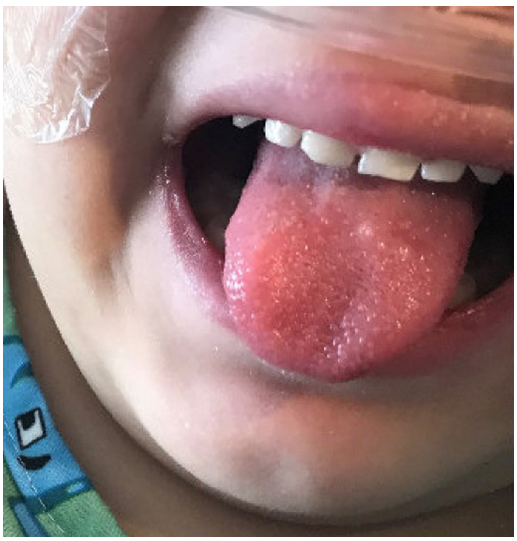

**Fig. 6.** Mucosal findings in MIS-C. Strawberry tongue and cheilitis in a young child with MIS-C.

of all medications, including over-the-counter medications and supplements, taken with start dates of each is needed to determine probable culprit drugs.

Drug eruptions can be thought of as falling into one of 2 categories: "simple" or "complex." Simple drug eruptions most often occur within 4 days to 2 weeks of starting the medication, and constitutional symptoms or laboratory abnormalities are typically absent. Complex drug eruptions include DRESS, also called drug-induced hypersensitivity disorder, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Both simple drug eruptions and DRESS syndrome can present with morbilliform rash. The timing and associated systemic symptoms help differentiate these 2 medication reactions. DRESS syndrome usually develops later after exposure to culprit medication, typically 2 to 6 weeks (**Table 3**). The 2 most common features of DRESS are fever and rash. The cutaneous eruption of DRESS is characterized by confluent, erythematous macules and papules.[59] Facial edema serves as an important clue to the diagnosis, seen in around half of patients[60] (**Fig. 7**). Mucous membrane involvement should not be used to rule out the diagnosis. Mucosal involvement (erythema, edema, and erosions) is in fact common (>50%) in both adults and pediatric patients with DRESS, although it rarely progresses to the level of mucosal sloughing seen in Stevens-Johnson syndrome.[59,61] Lymphadenopathy and periorbital edema are common clinical findings in pediatric patients.[61] In most cases, pruritus is common, whereas skin pain is more rare.[60]

In children, hematologic and hepatic disturbances are present in greater than 90% of patients.[61] Although peripheral eosinophilia (>700/μL) is the hallmark laboratory abnormality in DRESS, atypical lymphocytes, thrombocytopenia, thrombocytosis, and anemia can also be documented. Hepatic involvement is reported (elevated AST and ALT) in 80% of children, splenomegaly in 21.5%, and renal involvement in 15.4%.[60] Inflammation of other organ systems, including cardiac, gastrointestinal, musculoskeletal, pulmonary, and the central nervous system, have also been reported.[61] Human herpes virus 6 (HHV-6) reactivation is well documented in DRESS, having been implicated in its pathogenesis, used in clinical criteria, and associated with a more severe disease course in children.[62,63] There are clinical criteria available to aid the clinician in evaluating and diagnosing DRESS.[64]

Antiepileptics are the most common culprit medication (50%), attributed to pediatric DRESS cases, with aromatic antiepileptics accounting for 86.2% of cases owing to this class.[60] Antibiotics are the second most common cause, with vancomycin and trimethoprim-sulfamethoxazole number 1 and 2, respectively.[60] The prompt removal of the offending medication is the gold-standard management of DRESS, and systemic steroids typically tapered over 2 to 6 months are recommended for severe cases.[65,66]

## MORBILLIFORM ERUPTIONS IN A BONE MARROW TRANSPLANT PATIENT

A morbilliform eruption in a child with a bone marrow transplant should always be approached with a sense of urgency given the higher risk of acute infection, viral reactivation (cytomegalovirus, Epstein-Barr virus, HHV-6, adenovirus), drug eruption owing to polypharmacy, chemotherapy-induced reactions, and transplant-related rashes, such as acute graft-versus-host disease (GVHD) and engraftment syndrome (ES). GVHD and ES are discussed later, given their uniqueness to this population.

## ACUTE GRAFT-VERSUS-HOST DISEASE

Acute GVHD occurs when activated donor immune cells stimulate an inflammatory cascade that leads to host tissue destruction. Acute GVHD is most common in children with

**Table 3**
**Features of simple versus complex morbilliform drug eruptions**

| | Exanthematous Drug Eruption | DRESS |
|---|---|---|
| Timing after medication exposure | 4–14 d | 2–6 wk |
| Fever | Uncommon | Common |
| Facial edema | No | Common |
| Lymphadenopathy | No | Common |
| Systemic involvement | No | Yes |
| Mucosal involvement | Uncommon | Common |

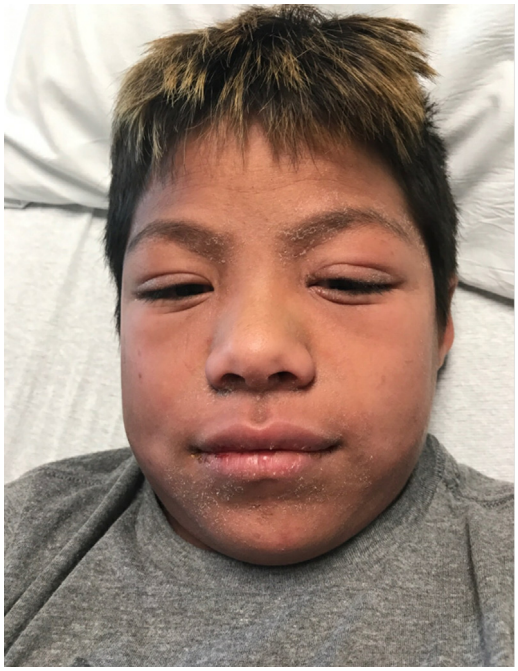

Fig. 7. Erythema, seborrheic scale, and facial edema in a boy with DRESS from ethosuximide.

hematologic malignancies after hematopoietic stem-cell transplantation. According to National Institutes of Health consensus criteria, acute GVHD can be divided into "classic acute GVHD" and "late acute GVHD." "Classic acute GVHD" refers to the development of acute GVHD in the first 100 days following a transplantation. "Late acute GVHD" refers to symptoms of acute GVHD beyond 100 days without features of chronic GVHD. "Late acute GVHD" may be described as "persistent," whereby symptoms of acute GVHD extend beyond 100 days, "recurrent" when a case of classic acute GVHD resolves but then recurs after 100 days, or "de novo" for cases whereby symptoms of acute GVHD only occur for the first time after 100 days.[67] Overall, most cases of acute GVHD coincide with the timing of white blood cell engraftment, occurring around 30 days after transplantation.[68] Organs most commonly affected are the skin, gastrointestinal tract, and the liver, with the skin commonly being first involved.[68] Compared with adults, children have a higher incidence of isolated skin involvement.[52] Mortality in pediatric acute GVHD is highest in recipients of HLA partially matched or mismatched unrelated donor grafts.[68]

Early skin findings of acute GVHD include pink papules on the scalp, pinna of the ears, face, neck, palms, and soles, which may coalesce into larger plaques or become more generalized throughout the body[69] (**Fig. 8**). This morphology

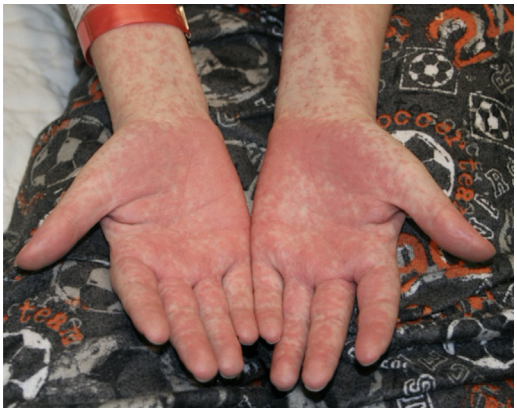

Fig. 8. Acute GVHD. A morbilliform eruption and erythema accentuated on the palms in a child with acute GVHD.

accompanied by diarrhea and/or cholestatic hepatopathy would be the classic presentation for multiorgan involvement of acute GVHD. Histopathological examination of skin biopsies can show changes classic for acute GVHD; however, oftentimes they are more helpful in ruling out alternative diagnoses.[70] One study found that in pediatric patients with concern for acute GVHD, skin biopsies yielded a definitive diagnosis in only 15% of cases, but dermatologic consultation still changed clinical management in 78% of cases.[71]

## ENGRAFTMENT SYNDROME

ES can lead to a clinical picture closely resembling acute GVHD. ES is a self-limited, inflammatory syndrome characterized by noninfectious fever, maculopapular exanthem without histologic features of GVHD, and a vascular leak phenomenon leading to weight gain and noncardiogenic pulmonary edema.[72] The pathogenesis of ES is not fully understood but is linked to neutrophil engraftment irrespective of the form of hematologic stem cell transplantation (autologous, allogeneic). Upon engraftment, a proinflammatory cytokine response ensues. ES most commonly occurs 7 to 14 days after transplant, typically 4 days before and 1 day after neutrophil engraftment with autologous or allogeneic stem cells and 7 to 14 days before neutrophil engraftment from umbilical cord stem cell transplantation.

ES cannot be reliably diagnosed based on any histopathologic change or serologic marker. Spitzer[72] has proposed diagnostic criteria for ES (**Box 2**). In the setting of allogeneic transplantation, distinguishing between acute GVHD and ES can be challenging. Onset with days of neutrophil engraftment, responsive to short course of corticosteroids, and pulmonary involvement can be useful clues for diagnosing ES. Whether children

**Box 2**
**Spitzer's criteria for engraftment syndrome**

Major criteria

Temperature ≥38.3°C with no identifiable infectious cause

Erythrodermatous rash involving more than 25% of body surface area and not attributable to a medication

Noncardiogenic pulmonary edema, manifested by diffuse pulmonary infiltrates consistent with this diagnosis, and hypoxia

Minor criteria

Hepatic dysfunction with either total bilirubin ≥2 mg/dL or transaminase levels ≥ 2 times normal

Renal insufficiency (serum creatinine of ≥2 times baseline)

Weight gain ≥2.5% of baseline body weight

Transient encephalopathy unexplainable by other causes

Must fulfill all 3 major criteria, or 2 major criteria and 1 or more minor criteria within 96 h of engraftment.

Adapted from Spitzer TR. Engraftment syndrome following hematopoietic stem cell transplantation. Bone Marrow Transplant. 2001 May;27(9):893-8.

with ES are at higher risk for GVHD is controversial and area of active investigation.

## SUMMARY

There are many important inflammatory and infectious diagnoses to consider in the hospitalized patient with a morbilliform eruption. The critical goal when evaluating a child with a new-onset morbilliform eruption is to make an accurate diagnosis in a timely manner. Full-body examination and careful history-taking can help to narrow the differential diagnosis and guide the workup.

## CLINICS CARE POINTS

- The Koplik spots of measles start 48 hours prior to the onset of the exanthem and last only 12 to 72 hours so maybe absent later in the disease course.
- Doxycycline should be initiated as soon as a diagnosis of Rocky Mountain Spotted fever is being considered independent of the patient's age.
- Compared to Kawasaki disease, Multisystem inflammatory syndrome in children (MIS-C) generally impacts older children who often present with gastrointestinal symptoms, myocardial dysfunction, shock, high inflammatory markes and cytopenias.
- Facial edema is seen in around half of patients with DRESS.
- The eruption of GVHD Often starts on the scalp, ears, face, neck, palms and soles.

## DISCLOSURE

V. S. Oza, MD is an editor for Visual Dx regarding Multisystem Inflammatory Syndrome content. Drs S. D. Cipriano and J. S. Haber have nothing to disclose.

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