



# The rash with maculopapules and fever in children



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**Abstract** Several medical conditions can cause children to present with fever and a maculopapular rash Although some presentations are benign, others may be medical emergencies, which warrant a prompt diagnosis. We review some of the more common causes of fever and maculopapular dermatitirs, rash including infectious processes (roseola; rubeola; rubella; parvovirus B19; hand, foot, and mouth disease; scarlet fever; meningococcemia; Epstein-Barr virus infection), hypersensitivity reactions (exanthematous drug reactions), and vasculitis syndromes (Kawasaki disease). We have included a diagnostic algorithm to facilitate rapid identification of the etiology of the rash and fever. Those conditions that can occur in children but are seen predominantly in adults are discussed in the contribution "Rash with maculopapules and fever in adults" in this issue.

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## Introduction

A number of conditions may cause children to present with fever and a maculopapular eruption. These include viral and bacterial illnesses, vasculitis syndromes, and drug reactions (Table 1). Many causative conditions are medical emergencies. Prompt recognition and treatment are crucial. The differential diagnosis for maculopapular dermatitis with fever is broad. Eliciting a thorough history and physical examination is important for diagnosis. Factors to consider in any patient presenting with maculopapular dermatitis and fever include the distribution of the patient's dermatitis (central versus peripheral), exposure to sick contacts, new medications, and recent travel. We describe many of the common causes of maculopapular eruptions with fever in children and ways to identify and treat them. In this issue, we also describe those conditions that affect adults with fever and a maculopapular

eruption in "Rash with maculopapules and fever in adults". For many of the diseases discussed, the conditions can present in children as well as in adults.

# Diagnostic algorithm

Because the differential diagnosis for a child presenting with a maculopapular dermatitis and fever is broad, eliciting a thorough history is critical for making a prompt diagnosis. The following questions should be asked of all patients presenting with fever and dermatitis as well as their caregivers<sup>1</sup>:

- 1. Did you have any clinical manifestations before you noticed the dermatitis?
- 2. Have you noticed any associated clinical manifestations with the dermatitis?
- 3. Does anyone else around you have the same clinical manifestations?
- 4. On which part of the body did the dermatitis present? Has it changed over time?

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Disease	Epidemiology in children	Characteristic clinical presentation in children
Rubeola (measles)	Infants and unvaccinated children	Cough, coryza, and conjunctivitis. Punctate white or gray lesions on erythematous base on buccal mucosa (Koplik spots). High fever and blanching maculopapular dermatitis that originates on the forehead and upper neck and descends to cover the trunk and lower extremities.
Rubella (German measles)	Unvaccinated populations, including immigrants	Tender adenopathy in the posterior auricular, posterior cervical and suboccipital lymph nodes. Pink maculopapular dermatitis that starts on the face and spreads to the trunk and extremities. May be associated with petechiae on the soft palate
Roseola (exanthem subitum)	Infants and young children	(Forchheimer's sign).  High fever followed by dermatitis that originates or trunk and spreads to extremities. Dermatitis starts as discrete pale, pink macules and may become confluent. Spares face.
Zika virus	Travelers from endemic regions (Africa, Southeast Asia, South	Maculopapular dermatitis that starts on trunk and
Kawasaki disease	and Central America, Pacific Islands, and Caribbean) Infants and children, with a higher incidence in Japanese populations	descends to lower extremities.  Diffuse maculopapular dermatitis that spares face; bilateral conjunctival infection; cervical adenopathy erythema of palms and soles; oral findings include "strawberry tongue." May precipitate coronary artery aneurysms in children.
Parvovirus B19	School-aged children	High fever followed by a dermatitis that originates on trunk and spreads to extremities. Dermatitis starts as discrete pale, pink macules and may become confluent.
Rocky Mountain spotted fever	Throughout US; especially North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri	Fever, nausea, abdominal pain, and headache. Pink macular dermatitis starts on the ankles and wrists and spreads to the trunk. Children may present with altered mental status.
Meningococcemia	Increased incidence in infants and young adults aged 16-23 y	Fever, nuchal rigidity, photophobia, and altered mental status. Dermatitis on the trunk and extremities and may be maculopapular, petechial, or purpural.
Hand, foot, and mouth disease (cox- sackie virus)	Infants and children younger than age 5 y	Maculopapular or vesicular dermatitis on the hands feet, buttocks, legs, and arms.
Ehrlichiosis	Increased incidence in Southeast and South Central US	Widespread, erythematous maculopapular dermatitis with fever, headache, and malaise.
Exanthematous drug eruption	Typically 4-21 days after initiation of a new drug. Increased risk with antiepileptics (carbamazepine, lamotrigine, and phenytoin) and antibiotics (penicillins, cephalosporins, and sulfonamides)	
Infectious mononucleosis	Adolescents and young adults	Fever, cervical lymphadenopathy, and pharyngeal inflammation. Maculopapular dermatitis on trunk and arms.
West Nile virus	Africa, Europe, Middle East, North America, and West Asia	Fever, headache, myalgias, and maculopapular dermatitis on trunk. Complications include severe central nervous system disease and death.
Scarlet fever	Most common in children aged 5-15 y.	Sudden-onset fever, malaise, pharyngitis, or tonsillitis. Strawberry tongue with enlarged papillae Blanching erythematous dermatitis that starts on the trunk and spreads outward, typically sparing the face, palms, and soles.

- 5. Have you traveled anywhere recently?
- 6. Have you started any new medications recently?

The answers to these questions can help health care providers differentiate between infectious and noninfectious causes of maculopapular dermatitis. They may also help differentiate benign conditions from emergent ones. Figure 1 provides a diagnostic algorithm for evaluating fever and maculopapular dermatitis in a child.

# Selected conditions

## Roseola (exanthem subitum)

# Virology

Roseola is caused by human herpes virus 6 (HHV-6), a double-stranded DNA virus. There are two major groups of HHV-6 (variants A and B),<sup>2</sup> and 97% to 100% of primary infections with HHV-6 are caused by variant B.<sup>3</sup> Primary infection with HHV-7 may also present as typical roseola.<sup>4</sup>

# **Epidemiology and incidence**

Roseola is a common childhood disease that is not seasonal and occurs throughout the year. From birth to the age of 6 months, the disease is rare as newborns are protected by maternal antibodies against HHV-6. After the age of 6 months, infection with HHV-6 is common, with 80% of infants becoming infected by the age of 2 years.<sup>2</sup>

# Clinical findings

The majority of primary infections with HHV-6 are asymptomatic or subclinical, presenting with a nonspecific low-grade fever. The classic presentation of roseola infantum occurs in 20% of children infected with HHV-6.5 Roseola has an incubation period of 9 to 10 days. The disease first presents with a high fever (102°F to 105°F) that lasts for 3 days. Roseola-induced febrile seizures are common in patients and are reported to be the etiology of 33% of febrile seizures and recurrent febrile seizures seen in emergency rooms. The exanthem of roseola may occur concurrently with the fever or after the fever subsides. The dermatitis consists of discrete pale, pink macules 1 to 5 mm in diameter, which commonly originate on the trunk, neck, and behind the ears and spread to the proximal extremities (Figure 2). It commonly spares the face and distal extremities. The dermatitis lasts for 2 to 48 hours, may become confluent, and may be preceded by an enanthem of erythematous macules on the soft palate.2

In immunocompromised patients, HHV-6 may reactivate, causing a number of manifestations, including dermatitis, hepatitis, pneumonia, and encephalitis.<sup>2</sup>

# Diagnosis and treatment

Sera for HHV-6 may be used to diagnose roseola. Anti-HHV-6 IgM is detectable 7 to 14 days after onset of illness and may become undetectable after only a few weeks. Anti-HHV-6 IgG develops 2 to 4 weeks after onset of the clinical illness and can be detected indefinitely. HHV-6 may also be cultured from saliva. Polymerase chain reaction (PCR) can

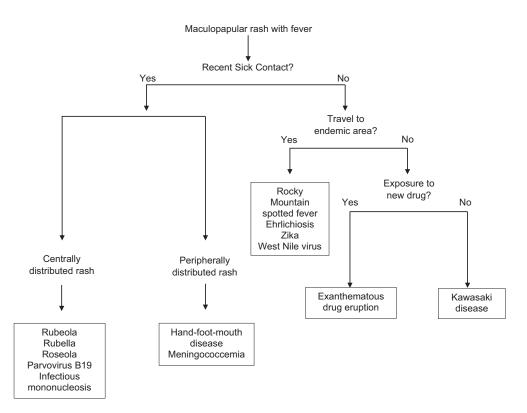


Fig. 1 Diagnostic approach for adults with fever and maculopapular dermatitis.



Fig. 2 Erythematous maculopapular dermatitis of roseola on the trunk of a child. (Image from Wikimedia commons; courtesy: Emiliano Burzagli.)

be used to detect viral DNA in the blood and cerebrospinal fluid.<sup>2</sup>

In immunocompetent patients, roseola is self-limiting, and no treatment is usually required; however, in immunosuppressed patients, ganciclovir, foscarnet, or cidofovir may be used for treatment.<sup>2</sup>

# Rubeola (measles)

## Virology

Rubeola is caused by an RNA virus in the *Morbillivirus* genus in the Paramyxoviridae family.<sup>2</sup>

# **Epidemiology and incidence**

The incidence of rubeola, or measles, has declined substantially in the past few decades due to increased vaccination efforts globally; however, it remains an important public health issue, with 254,928 reported cases of measles in 2015 worldwide. Historically, measles has primarily been a disease of young children. Although the incidence of measles has decreased across all age groups with increased vaccination efforts, the relative incidence of measles has increased in groups that may be less likely to be vaccinated, including older adults, children under the age of 1 year, and social groups that eschew vaccinations.

#### Clinical findings

Measles presents in a relatively characteristic fashion in immunocompetent patients. The incubation period for measles ranges from 10 to 12 days and is followed by a prodrome of malaise, headache, and low-grade fever. This may precede or occur concurrently with cough, coryza, and conjunctivitis. During the prodrome, patients may develop Koplik spots, the

typical enanthem of measles, which appear as punctate white or gray lesions on an erythematous base (Figure 3A). Koplik spots originate on the buccal mucosa and may spread to the hard or soft palate. After approximately 4 days, patients will develop a high fever and an erythematous, blanching maculopapular dermatitis (Figure 3B). The typical dermatitis originates on the patient's hairline, forehead, and upper neck and spreads to the trunk and extremities over the next 3 days. The dermatitis persists for 2 to 4 days. Coryza and conjunctivitis typically clear with the dermatitis, while cough may persist for another 5 days. Immunosuppressed patients may have an atypical presentation, may not develop the characteristic dermatitis of measles, and therefore may be challenging to recognize. 2,8

Respiratory and central nervous system complications may occur as a result of measles infection; 0.1% of children develop acute encephalitis, which commonly causes permanent brain damage; 0.1% to 0.2% of children expire from neurologic or respiratory complications. Seven to 10 years after primary measles infection, children may develop subacute sclerosing panencephalitis, a rare degenerative disease of the central nervous system, which is commonly fatal. This may present with seizures and behavioral changes in a child who was previously infected with measles.<sup>8</sup>

#### Diagnosis and treatment

Although viral cultures can confirm the diagnosis of measles, they may be technically challenging to obtain. Clinically, measles infection may be confirmed through sera for measles antibody. A significant rise in measles IgG is diagnostic. Measles IgM may also be detected 3 to 30 days after dermatitis onset. PCR of viral RNA is also diagnostic but may not be readily available.<sup>2</sup>

Treatment for measles is primarily symptomatic. Nonsteroidal anti-inflammatory drugs or acetaminophen may be used to manage pain and fever. Oral vitamin A has been shown to decrease morbidity in patients who are malnourished. The World Health Organization recommends daily supplementation with vitamin A for 2 days for all children with acute measles; however, specific doses of vitamin A vary with age<sup>2</sup>; excess vitamin A supplementation in pregnant women can cause severe fetal malformations.<sup>9</sup>

# Rubella (German measles)

Rubella can cause fever with maculopapular dermatitis in both adults and children. A description of rubella infection can be found in the article "Dermatitis with maculopapules and fever in adults" in this issue. Rubella infection is typically mild in infants and children. Up to 50% of infections in this age group may be asymptomatic.<sup>2</sup>

## Parvovirus B19

#### Virology

Parvovirus B19 is a single-stranded, nonenveloped DNA virus, which is part of the Parvoviridae family in the *Erythrovirus* genus.<sup>10</sup>

# **Epidemiology and incidence**

Parvovirus B19 is a common global infection with seroprevalence increasing with age: 15% of preschool-aged children, 50% of young adults, and 85% of older adults demonstrate sera indicating past infection. B19 infection is most common during the winter and early spring. Epidemics typically strike every 3 to 4 years, with most occurring in children. Adults who work closely with children, such as teachers and daycare workers, are also at risk of infection.<sup>10</sup>

#### **Clinical findings**

Infection with parvovirus B19 in immunocompetent children is typically mild. Patients may develop a low-grade fever. One to 4 days after the onset of fever, the characteristic exanthem induced by B19 may appear. At this time, children are typically afebrile. The exanthem starts as an erythematous facial dermatitis (Figure 4A), also known as a "slapped cheek" dermatitis. After 1 to 4 days, the dermatitis becomes maculopapular and spreads to the trunk and extremities (Figure 3B). Central clearing of the dermatitis may give it a reticular, lacelike appearance. The dermatitis on the trunk and extremities persists for 1 to 6 weeks. During this time, the intensity of the dermatitis may vary with exposure to sunlight or heat. 10,11

Arthralgias after infection with B19 occur in 8% of children but are more common in adolescents and adults. In children, arthralgias characteristically involve the knees and ankles. <sup>11</sup> B19 can precipitate aplastic crises in patients with chronic hemolytic anemias, such as those due to sickle

cell disease or hereditary spherocytosis. These patients less commonly develop a dermatitis but may present with such clinical findings as anemia, pallor, or malaise, after a mild febrile illness. <sup>12</sup>

The most severe complication of B19 infection is fetal loss that can occur in 5% to 10% of infected pregnant women. Fetuses may develop hydrops fetalis as a result of maternal infection.<sup>10</sup>

## Diagnosis and treatment

Diagnosis of parvovirus B19 can be made through serology or PCR. Detection of viral RNA or DNA through PCR is indicative of acute or persistent infection. B19 IgM may be detected 10 days after infection and can persist for up to 4 months. B19 IgG is present shortly after IgM and persists indefinitely.<sup>10</sup>

B19 infection in immunocompetent patients is typically self-limited. In patients with aplastic crises from B19, hospitalization and transfusion may be required. The fetuses of women with B19 infection should be monitored weekly with ultrasonography for the development of hydrops fetalis. In fetuses with hydrops fetalis due to B19, the administration of intrauterine erythrocyte transfusions can reduce fetal mortality. <sup>10</sup>

# Hand, foot, and mouth disease

# Virology

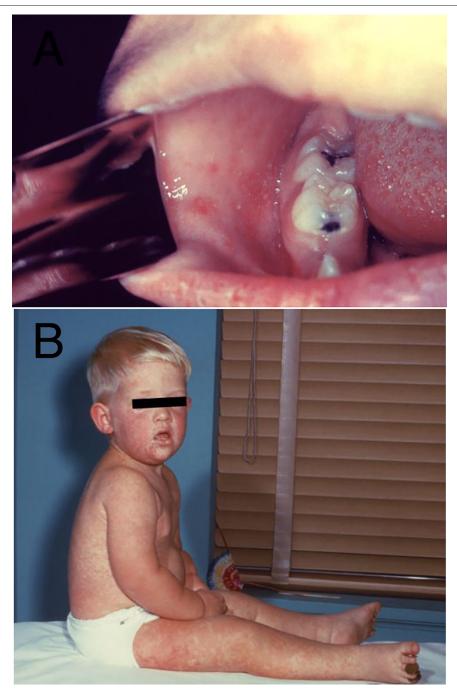
Hand, foot, and mouth disease (HFMD) is caused by serotypes of enterovirus, a single-stranded RNA virus. Coxsackievirus A16 and enterovirus A71 cause the majority of cases of HFMD.<sup>13</sup>

## **Epidemiology and incidence**

Although HFMD can occur in patients of all ages, it typically affects infants and children under the age of 5 years. <sup>14</sup> Cases of HFMD occur worldwide, with an increased incidence in the summer and early fall. <sup>13</sup>

## Clinical findings

HFMD characteristically presents with mouth or throat pain. In young, nonverbal children, this may manifest as refusal to eat. The enanthem of HFMD typically occurs on the tongue and buccal mucosa (Figure 5A). The enanthem starts as erythematous macules and progresses to vesicles and then to superficial ulcers. The exanthem of HFMD usually presents on the hands, feet, buttocks, legs, and arms and may be maculopapular and/or vesicular (Figure 5B). It lasts for 3 to 4 days and is not classically pruritic or painful.<sup>13</sup> Prognosis is generally good. Rarely, patients may develop meningitis or encephalitis.<sup>14</sup> In 2012, the CDC reported a number of atypical HFMD infections, many of which were caused by coxsackievirus A6. Fever and dermatitis associated with atypical HFMD is more severe than that associated with typical HFMD, and hospitalization is more likely. 15 The exanthem of atypical HFMD includes diffuse vesicles, bullae, and erosions. In



**Fig. 3** A, Koplik spots on the buccal mucosa of a patient with rubeola. (Image courtesy: the Public Health Image Library from the CDC.) B, Widespread, erythematous maculopapular exanthem of rubeola. (Image courtesy: the Public Health Image Library from the CDC.)

addition to the classic locations of HFMD (hands, feet, buttocks, oral mucosa), atypical HFMD also occurs on the torso and perioral area.  $^{16}$ 

# Kawasaki disease

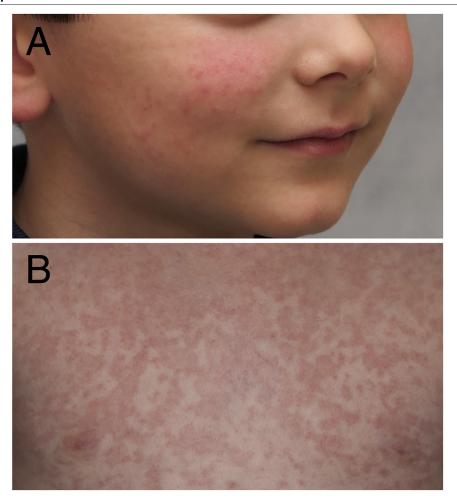
## **Etiology**

Kawasaki disease is an acute vasculitis syndrome. Etiology is unknown; however, it is hypothesized that it is caused by an

immunologic response to an unknown trigger in a genetically susceptible person. 17

# Epidemiology and incidence

Kawasaki disease primarily affects infants and children, with 80% of cases occurring in children under the age of 5 years. Older children and adolescents may also be affected. The highest incidence of Kawasaki disease is found in Japan, with 265 cases per 100,000 children under the age



**Fig. 4** A, Slapped face exanthema secondary to parvovirus. (Image courtesy: Dr. Justin Finch and the UConn Department of Dermatology.) B, Maculopapular eruption on trunk due to parvovirus. (Image courtesy: Dr. Justin Finch and the UConn Department of Dermatology.)

of 5 years. In the United States, the incidence of Kawasaki disease is 19 cases per 100,000 children under the age of 5 years.<sup>17</sup>

# **Clinical findings**

Early detection of Kawasaki disease is crucial to prevent complications in otherwise healthy children. The diagnostic criteria include a fever for at least 5 days and at least four of the following criteria in the absence of another illness to account for the clinical manifestations:

- Bilateral conjunctival injection: typically occurs shortly after fever onset and is usually painless and without an exudate.<sup>18</sup>
- 2. Distinct oral findings: red, cracked lips; an erythematous, "strawberry" tongue with prominent fungiform papillae; and erythema of the mucosa of the oropharynx (Figure 6A).<sup>18</sup>
- 3. Cervical lymphadenopathy: typically unilateral and located in the anterior cervical triangle. <sup>18</sup>
- 4. Dermatitis: erythematous dermatitis that appears within 5 days of the onset of fever and has multiple appearances,

- with the most common being a diffuse, maculopapular dermatitis that spares the face (Figure 6B).<sup>18</sup>
- 5. Distinct findings of the extremities: in the acute phase, patients may present with erythema and/or induration of the palms and soles; 2 to 3 weeks after the onset of fever, desquamation of the fingers and toes may occur.<sup>18</sup>

In children aged less than 6 months or greater than 5 years, Kawasaki disease may present atypically with a high fever and at least two of the criteria enumerated above. <sup>19</sup> All clinical manifestations of Kawasaki disease may not present simultaneously, and children may present with only a few of the clinical manifestations listed above at a given time. <sup>18</sup>

The most severe complication from Kawasaki disease is coronary artery aneurysm. It is estimated that 20% of children who are not treated with intravenous immunoglobulin in the acute phase of Kawasaki disease may develop coronary artery aneurysms.<sup>17</sup>

### Diagnosis and treatment

Kawasaki disease is diagnosed clinically. Intravenous immunoglobulin (IVIG) may be used to treat acute Kawasaki



**Fig. 5** A, Enanthem of hand, foot, and mouth disease. (Image courtesy: Dr. Justin Finch and the UConn Department of Dermatology.) B, Exanthem of hand, foot, and mouth disease. (Image courtesy: Dr. Justin Finch and the UConn Department of Dermatology.)

disease. Standard therapy in the United States is 2 g/kg IVIG infused over a period of 10 to 12 hours. <sup>19</sup> High-dose aspirin is given while children are febrile; once fever resolves, patients are switched to low-dose aspirin. Systemic corticosteroids can be used in cases of Kawasaki disease, which are refractory to IVIG. After the resolution of clinical manifestations, children should be monitored at regular intervals with echocardiograms to screen for the development of coronary artery aneurysms. <sup>20</sup>

## Scarlet fever

#### Microbiology

Pyrogenic exotoxin-producing *Streptococcus pyogenes* (Lancefield group A streptococci) causes scarlet fever. *S pyogenes* is a gram-positive, beta-hemolytic cocci.<sup>21</sup>

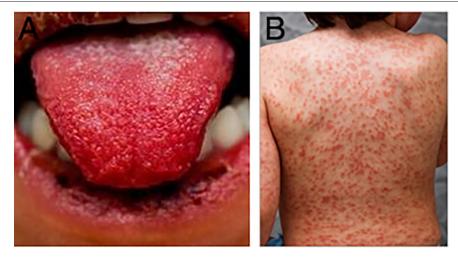
## **Epidemiology and incidence**

Although scarlet fever affects all age groups, it most commonly occurs in children aged 5 to 15 years. Children in close

contact with infected persons (as those at school or daycare) are at risk of infection.<sup>21</sup>

#### **Clinical findings**

Scarlet fever presents with sudden onset of fever and malaise 2 to 3 days after infection. Patients may have pharyngitis or tonsillitis. The tongue develops enlarged papillae, which initially appear furry and then become erythematous, resulting in a strawberry tongue appearance. The characteristic dermatitis of scarlet fever is typically seen 2 days after the onset of infection.<sup>22</sup> It is a blanching, erythematous dermatitis, which starts on the trunk and spreads outward (Figure 7). The dermatitis typically spares the face, palms, and soles. It can last for up to a week and result in desquamation. Other cutaneous findings include Pastia's lines, linear accentuations of the dermatitis in flexor creases. Complications from scarlet fever include acute rheumatic fever and poststreptococcal glomerulonephritis.<sup>21</sup> Prompt antibiotic treatment may decrease the risk of developing rheumatic fever as well as peritonsillar and retropharyngeal abscesses. Antibiotics also



**Fig. 6** A, Erythematous, "strawberry" tongue of Kawasaki disease. (Image courtesy: the Kawasaki Disease Foundation.) B, Erythematous, maculopapular exanthem of Kawasaki disease on the back of a child. (Image courtesy: the Kawasaki Disease Foundation.)

shorten the duration of clinical manifestations by approximately 16 hours.<sup>23</sup>.

# Diagnosis and treatment

The gold-standard for diagnosis of scarlet fever is a throat culture. Rapid antigen detection test may also be used. Scarlet fever should be treated with antibiotics. Penicillin and amoxicillin are the first-line antibiotics for treatment. In patients with penicillin allergy, narrow-spectrum cephalosporins, azithromycin, clarithromycin, or clindamycin are recommended.<sup>21</sup>

# Meningococcemia

Meningococcemia commonly causes fever and maculopapular dermatitis in infants and young adults. The characteristic



**Fig. 7** Blanching, erythematous dermatitis of scarlet fever. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

clinical presentation of meningococcal infection is described in the article "Dermatitis with maculopapules and fever in adults" in this issue. Infants with meningococcal infection may present differently from adults. Infants typically have nonspecific clinical manifestations early in disease, including fever, irritability, nausea, vomiting, and poor feeding. Focal seizures have also been reported. Septic shock is more common in children than in adults and is characterized by cold extremities, leg pain, and abnormal skin color. A rapidly progressive hemorrhagic dermatitis, which begins on the lower extremities in children, is usually indicative of sepsis.<sup>24</sup>

# Diagnosis and treatment

Early diagnosis and treatment of meningococcal infection is crucial. Lumbar puncture should be performed in patients with suspected infection. Contraindications to lumbar puncture include prolonged seizures, space-occupying lesions, and severe shock. Gram stain and PCR of cerebrospinal fluid are accomplished to confirm meningococcal infection. Ceftriaxone (100 mg/kg/day) or cefotaxime (100 mg/kg/day divided into 3 doses) are the first-line antibiotics for treatment. Intravenous penicillin is the second-choice treatment. Treatment is recommended for 7 to 10 days. Rifampicin or ciprofloxacin may be used for prophylaxis of close contacts.<sup>24</sup>

#### Infectious mononucleosis

Infectious mononucleosis can cause fever and a maculopapular dermatitis. Although it is more common in adolescents and young adults, Epstein-Barr virus infection may also occur in children. The characteristics of infectious mononucleosis are described in the article "Dermatitis with maculopapules and fever in adults" in this issue. In children, Epstein-Barr virus infection may present differently compared with that in young adults. It is typically mild or asymptomatic and may present with mild pharyngitis or tonsillitis.<sup>25</sup>

# **Exanthematous drug reactions**

Exanthematous drug reactions are common in both adults and children. Please refer to the article "Dermatitis with maculopapules and fever in adults" in this issue for a detailed description.

# **Conclusions**

A number of conditions can cause fever and maculopapular dermatitis in children. Because some conditions are medical emergencies and highly contagious, prompt diagnosis is crucial. Causative factors to consider in all patients include recent sick contacts, travel to endemic regions, drugs that may recently have been started, and the distribution of the dermatitis. We have presented some of the more common causes of childhood fever and maculopapular dermatitis and ways to identify and treat them.

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