Abstract
Childhood exanthems are frequently related to recent viral or bacterial infection. Other causes involve medications and inflammatory conditions such as immune-mediated vasculitis. We present a challenging case of an asymptomatic 7-year-old girl with an atypical exanthem and discuss differential diagnoses, focusing on common viral and bacterial causes.

Introduction
Viral and bacterial infections are common causes of generalized rashes in children, and patients may present with systemic signs and symptoms such as pharyngitis, fever or malaise. Common infectious agents include adenovirus, echovirus, coxsackievirus, EBV, HHV6, HHV7, parvovirus B19 and streptococcus pyogenes. Determining the underlying pathogen relies heavily on characteristic skin findings and detailed history gathering of timing, progression and immunization status. The morphology and distribution of cutaneous and mucosal lesions are also essential diagnostic clues that help distinguish between childhood exanthems. We present a challenging exanthem diagnosis in a 7-year-old female, providing insights into diagnostic tools that can help guide diagnosis and treatment in patients who present with atypical physical exam findings. We review characteristic features of several childhood exanthems and discuss appropriate workup and treatment for each condition.

Case Report
A 7-year-old female presented to our dermatology clinic with a two-day history of a generalized erythematous pruritic eruption. She stated the lesions first appeared on her face, and spread to her trunk and extremities after one day. The patient denied cough, fever, chills, sore throat, abdominal pain, arthritis, dysuria, hematuria, diarrhea, bloody stools, sick contacts or recent travel. On physical exam, there were generalized, bright red, erythematous, blanchable macules and confluent patches affecting the malar cheeks, torso, arms, palms and legs, with sparing of the eyelids, chin, axilla and antecubital fossae (Figure 1). Oral exam revealed a white strawberry tongue (Figure 2). There were no lesions on the buccal or palatal mucosa. Pharyngeal erythema, tonsillar enlargement and exudates were also absent. There was no cervical or axillary lymphadenopathy.

Two punch biopsies were performed on the lower back. Histopathology showed polymorphous dermatitis with neutrophils, nuclear dust and red cell extravasation. Fibrinoid necrosis was not observed (Figure 3).

Biopsy and lab findings were consistent with streptococcal toxin-mediated exanthem. Due to a history of penicillin intolerance, the patient was treated with cefadroxil 30 mg/kg for 10 days, hydrocortisone 2.5% cream twice daily as needed for two weeks, and camphor/menthol lotion as needed. On follow-up, 14 days after initiating treatment, the eruption had completely resolved (Figure 4).

Discussion
Exanthematous eruptions occur most commonly in school-aged children. In the early 1900s, six classical infectious childhood exanthems were described. These include measles, scarlet fever, rubella, Duke's disease, erythema infectiosum and roseola infantum. Physicians no longer recognize Duke's disease as a distinct entity, but rather an atypical presentation of another classical exanthem. Overlapping and atypical exanthematous clinical presentations are often encountered. In order to establish a prompt diagnosis, it is important to have a detailed
understanding of the clinical characteristics that help distinguish between various viral, bacterial and inflammatory cutaneous eruptions.

In the following sections, we discuss identifying features such as cutaneous distribution and progression, associated signs and symptoms, and appropriate laboratory workup of common viral and bacterial exanthems.

Streptococcal infection
Scarlet fever (scarlatina) is caused by infection with group A beta-hemolytic streptococcus (GABHS), a microbe responsible for streptococcal pyogenes, which produces pyrogenic exotoxins A, B and C. These exotoxins produce local inflammatory mediators and alterations of the cytokine milieu, leading to dilation of blood vessels and delayed-type skin reactivity. 1 Streptococcal infections are most commonly seen in children between 1 year old and 10 years old. The infection is spread person-to-person via respiratory droplets and is typically easy to contract in close-contact settings, such as schools, daycares, and households. 2

Unlike in our case, once infected, patients typically develop an abrupt onset of fever with sore throat, tonsillar enlargement, headache, nausea, vomiting, abdominal pain, myalgias, and malaise. The rash typically appears 12 hours to 48 hours after the onset of fever and is classically characterized by a sandpaper-like texture. 6,7 Our patient did not develop sandpaper-like skin findings, nor did she experience associated pharyngitis or tonsillar enlargement. Her lesions also lacked the lacy reticular pattern classically observed in parvovirus eruptions. Laboratory testing confirmed diagnosis with a positive throat culture and elevated anti-streptolysin O antibody titer, strongly supporting a streptococcal etiology. In addition, parvovirus B19-specific IgM and IgG antibodies were absent.

Scarlatina classically begins in the skin folds and then rapidly expands to cover the trunk and extremities; the palms and soles are usually spared. The skin-fold lesions often exhibit a linear petechial character, known as Pastia’s lines, which was not observed in our case. 7 Desquamation occurs after approximately four to five days in a cephalocaudal progression.

Strawberry tongue is another distinct finding of scarlatina. On day one or two, the tongue has a heavy white coating that overlies edematous red papillae, known as the “white strawberry tongue.” By day four or five, the white coating sloughs off, leaving red, edematous papilla that produce a strawberry tongue appearance. 2

Although our patient had a positive throat culture, we could not rule out the possibility that she was a chronic GABHS carrier. In the U.S. population, 5% to 15% of children are asymptomatic colonized carriers; therefore, ASO titer may be useful for confirmatory purposes. 10 The presence of elevated ASO titer confirmed that our patient had a recent streptococcal infection.

First-line treatment for scarlatina is penicillin (amoxicillin). In the case of an anaphylactic reaction to penicillin, clindamycin or erythromycin may be used. If pruritus is present, oral antihistamines and emollients may be added to the treatment plan. Children may return to school or daycare 24 hours after initiation of antibiotics. 11,12

The prognosis of scarlatina is excellent when caught in a timely manner. Prior to the existence of antibiotics, GABHS infections had a 20% mortality and morbidity rate. Since the introduction of antibiotics, the mortality rate has fallen to less than 1%. 6 The primary goal of treatment is to prevent the long-term nonsuppurative complications of GABHS infections: rheumatic fever and glomerulonephritis. The sequela of rheumatic fever is specifically GABHS pharyngitis, whereas glomerulonephritis may be caused by both pharyngeal and cutaneous GABHS infections, such as perianal streptococcal infection. 13-15

Acute rheumatic fever typically occurs two to four weeks post GABHS infection. The Jones criteria for diagnosis include both major and minor clinical findings. The major criteria include arthritis, pancarditis, Sydenham chorea, subcutaneous nodules and erythema marginatum. The minor signs include arthralgia, fever, elevated acute phase reactants, and prolonged PR intervals. 16 By the Jones criteria, in order to diagnose rheumatic fever, a patient must present with either two major signs or one major plus two minor signs. 17 Prompt diagnosis and treatment is essential in order to prevent the severe long-term complication of rheumatic heart disease.

Acute glomerulonephritis is the leading cause of acute nephritic syndrome. It occurs approximately 10 days after GABHS pharyngitis and two weeks after GABHS skin infection. Most patients present with oliguria, hematuria, flank pain, headache, malaise, nausea, vomiting and anorexia. 18 Diagnosis is based on clinical and serological findings. 19 Acute post-streptococcal nephritis in children generally resolves with a return to normal renal function and carries an excellent prognosis, while adults may experience long-term effects such as hypertension and proteinuria.

Parvovirus B19
Erythema infectiosum, or fifth disease, is a common childhood illness caused by parvovirus B19, a single-stranded DNA virus that causes suppression of erythropoiesis and pancytopenia. Although most patients are asymptomatic, approximately 15% of patients report a prodromal period characterized by fever, headache and flu-like symptoms. Cutaneous features appear in roughly 25% of patients. 20

The exanthem typically begins on the malar cheeks as bright red, macular erythema, known commonly as a “slapped cheek appearance.” Later, a lacy, reticulated macular eruption spreads to the trunk and extremities. 21 In addition, approximately 10% of patients develop transient mild arthralgia that lasts a few weeks. 22

Papular-purpuric gloves and socks syndrome (PPGSS) is another clinical variant of parvovirus B19 infection. Many patients experience non-specific prodromal symptoms including fever, myalgia, arthralgia and fatigue. As the disease progresses, the hands and feet develop bright red erythema and edema, as well as papular and purpuric lesions on the palms and soles. 23

Both erythema infectiosum and PPGSS are self-limiting and resolve without treatment. In the United States, the seropositive rate of parvovirus reaches 50% in adolescents. 24 Diagnosis primarily relies on clinical findings. IgM and IgG antibodies are elevated in acute infection, with IgM elevation lasting two to three months. The vast majority of cases resolve without serious long-term sequela. Complications may arise when infection occurs during pregnancy, possibly resulting in hydrops fetalis, miscarriage or intrauterine death. These risks are greatest when infection occurs during the first or second trimester. Complications may also occur when patients with hemolytic anemia or sickle-cell disease become infected, imparting the risk of transient aplastic crisis. Lastly, patients who are immunocompromised face the risk of life-threatening chronic anemia. 25

Gianotti-Crosti syndrome
Gianotti-Crosti syndrome (CGS), or papular acrodermatitis of childhood, is a type IV hypersensitivity reaction to viral antigens. The most common viral triggers include hepatitis B and EBV, but other causes include hepatitis A and C, rotavirus, EBV rubella, CMV, coxsackievirus (A16, B4 and B5), adenovirus enterovirus, respiratory syncytial virus, parainfluenza virus (types 1 and 2), parvovirus B19, HHV 6, echovirus, poxvirus, and HIV. 26

CGS is typically an abrupt eruption of erythematous, flat-topped papules affecting the face, extensor extremities and buttocks. These papules may coalesce into hemorrhagic plaques and are either asymptomatic or pruritic. 26 Diagnosis relies exclusively on clinical presentation. Recent studies have proposed diagnostic criteria for GCS, which include the clinical findings described above along with symmetrical distribution, duration of 10 days, and a lack of truncal lesions and scaled lesions. 26 GCS is self-limiting, and treatment is supportive.

Epstein-Barr virus
Epstein-Barr virus (EBV), also known as human herpesvirus 4, is best known as the causative agent of infectious mononucleosis. Transmission occurs via saliva. In the United States, 50% of the population is infected by the age of 5. 27

Cutaneous involvement is usually seen in children and may be the only symptom present. The eruption is described as an erythematous macular rash in a scattered, haphazard distribution. Cutaneous findings are seen in 3% to 15% of those infected with EBV. Additional symptoms include fever, hepatomegaly, splenomegaly, posterior cervical lymphadenopathy and pharyngitis. 27 These symptoms are rare in children but may be seen in adolescents and adults.

Patients with EBV mistakenly diagnosed as streptococcal infection and treated with amoxicillin or ampicillin will also present with a cutaneous eruption. This rash is typically described as a...
bright red, morbilliform eruption that occurs approximately one week after receiving improper treatment. The eruption resolves spontaneously after treatment is discontinued. Infectious mononucleosis is self-limited and only requires supportive care.

**Coxsackie A16 virus**
Coxsackievirus is a single-stranded RNA enterovirus that most commonly affects children and infants. The virus is spread through multiple routes, including fecal-oral and respiratory droplets. Coxsackieviruses are associated with a variety of clinical manifestations including upper respiratory tract infection, meningoencephalitis and non-specific cutaneous eruptions. Coxsackie A16 is responsible for the exanthem hand, foot and mouth disease (HFMD) and the exanthem herpangina.

HFMD begins as vesicular lesions typically on the palms, soles, and oral mucosa but can also present on the extremities, trunk and neck. Herpangina, on the other hand, presents as vesicles in the posterior oropharynx. In HFMD and herpangina, patients often report sore throat, fever and headache.

Diagnosis of HFMD and herpangina relies primarily on clinical exam findings; however, viral culture of vesicular fluid may be performed for confirmatory purposes. Both conditions are self-limited, and treatment consists of supportive care.

**Measles**
Measles, also known as rubeola, is a highly contagious, single-stranded RNA virus most commonly seen in children, though it can occur at any age. Individuals who are susceptible to the virus have a 90% chance of becoming infected upon exposure. Transmission occurs through respiratory droplets, either airborne or on a surface. People immunized with the live-attenuated vaccine are typically protected from contracting the virus upon exposure.

In 2000, the virus was considered to be eliminated in the United States, but due to a decrease in childhood vaccinations, measles has been on an uptrend. Between 2000 and 2014, 288 cases were confirmed by the CDC. Of those infected, patients were either unimmunized or had an unclear vaccination history.

The clinical manifestation of measles occurs in four stages: incubation, prodromal, exanthematosus and recovery. In the incubation period, which lasts for up to three weeks post exposure, patients are typically asymptomatic or may begin to show signs of fever, respiratory symptoms and rash. The prodromal period usually lasts for two to four days and marks the stage of characteristic symptoms including cough, coryza and conjunctivitis. Fever, malaise, and anorexia are also seen in this stage. The cutaneous outbreak occurs two to four days after the fever begins, whether in the incubation or prodromal phase. The rash is described as blanchable, erythematous, maculopapular lesions that begin on the face and spread downward to the trunk and extremities. The soles and palms are typically spared. The rash usually lasts for two days and then begins to improve, indicating the recovery phase. Although the description, distribution and time frame of the rash fits our case, the prodromal characteristic findings were absent.

There are also two variants of the measles: modified and atypical. Modified measles is a milder presentation with a longer incubation period, and it occurs in patients who have preexisting measles immunity. Atypical measles, on the other hand, occurs in patients who received the previous killed-virus vaccine rather than the live-attenuated vaccine. Because the killed-virus vaccine was distributed between 1963 and 1967, the atypical variant occurs in the current adult population.

Measles can be diagnosed by clinical presentation alone, but confirmation by laboratory testing is required due to the necessity of reporting any measles case to public health officials. Tests should include a complete blood count, liver enzymes, serological markers (IgG and IgM antibodies), viral cultures, and reverse transcriptase polymerase chain reaction testing. The measles virus is self-limited, but patients should be given supportive care and vitamin A supplementation. Vitamin A has been shown to reduce mortality in up to 50% of cases, as well as prevent ocular damage and blindness.

**Kawasaki disease**
Kawasaki disease is a febrile vasculitis affecting small- and medium-sized vessels. It is the leading cause of acquired cardiac disease in children. Although the cause of Kawasaki is unknown, it is theorized to be an infectious process worsened by genetic components.

Patients with Kawasaki disease go through three clinical phases: acute, subacute and convalescent. In the acute phase, patients initially present with an abrupt onset of fever that does not subside with antibiotic or antipyretic treatment. This phase may last for up to four weeks. The cutaneous findings of perianal, palm and sole erythema and desquamation present in the acute phase, as well. The rash begins to evolve into a macular, morbilliform eruption on the trunk and extremities. Bilateral nonexudative conjunctivitis, anterior uveitis, strawberry tongue, lip fissures, secondary organ dysfunction and lymphadenopathy may also present in the acute phase. When the fever begins to subside, the patient has entered the subacute phase. The hallmarks of this phase are desquamation on the digits and a risk of coronary aneurysm that may lead to sudden death. Once the clinical signs and symptoms have cleared, with the exception of Beau's lines, the patient is considered to be in the convalescent phase.

The diagnosis of Kawasaki disease is clinical; laboratory tests and imaging are confirmatory. The diagnostic criteria, created by Tomisaku Kawasaki, include a fever that lasts for at least five days and at least four out of the five following signs: bilateral conjunctival injection, mucosal changes (erythematous or fissured lips, erythematous pharynx, or strawberry tongue), extremity changes (erythematous or edematous palms or soles, or desquamation), polymorphous cutaneous eruption, and cervical lymphadenopathy (measuring greater than 1.5 cm). Patients who do not meet the criteria but prompt high suspicion for the diagnosis are considered to have incomplete Kawasaki disease.

Appropriate laboratory testing includes complete blood count, liver enzymes, C-reactive proteins, erythrocyte sedimentation rate and urine analysis. In studies, urine proteins filamin C and meprin A have shown promise as confirmatory biomarkers.

The gold standard of treatment includes the full dose of intramuscular immunoglobulin (IVIG) and high-dose aspirin. It is also imperative to screen for coronary artery aneurysms with EKG at the time of diagnosis, at two weeks, again at six to eight weeks, and finally at one year after the onset of symptoms.

**Henoch-Schönlein purpura**
Henoch-Schönlein purpura (HSP), a vasculitis mediated by immunoglobulin A (IgA), affects small vessels mainly of the skin, kidneys, joints and gastrointestinal tract. Although there is a confirmed role for IgA in HSP, infectious, genetic, antigenic and environmental factors are all thought to play a role in the disease. HSP is the most common vasculitis in children, with 90% of cases presenting between the ages of 3 years and 10 years, but it can also occur in adults.

The cutaneous eruption is usually the complaint upon presentation. It typically occurs symmetrically and in crops, with new crops occurring for up to three weeks. The rash usually begins as a macular or urticarial eruption on the lower extremities and buttocks. The initial lesions coalesce and form petechiae and palpable purpura, marking the hallmark finding of HSP.

The American College of Rheumatology has developed clinical diagnostic criteria for HSP, which include: palpable purpura, presentation before age 20, abdominal pain, and a cutaneous biopsy showing granulocytes in the walls of arterioles or venules.

If suspicion is present, the vasculitis workup should also be completed as a confirmatory measure. In our patient, the maculopapular rash distribution and absence of abdominal pain made the diagnosis of HSP unlikely. Furthermore, our biopsy did not show granulocytes on the walls of the vasculature.

Because HSP is self-limiting, treatment is supportive. If gastrointestinal and renal complaints are present, hospitalization is required to monitor patients to prevent further complications. Those who do not require hospitalization need close follow-up with urine studies to confirm the disease has run its course without further systemic complications.

**Erythema multiforme**
Erythema multiforme (EM) is considered a type IV hypersensitivity reaction to infection, drugs, radiation, autoimmune diseases, malignancies and various other factors. Of reported cases, 90% were caused by an infectious process, and of those, HSV was the most common. Mycoplasma pneumoniae is also a common cause, mainly in children.

As the name implies, erythema multiforme has a wide range of cutaneous presentations; however, the hallmark of EM is a target lesion. This may be the initial presentation, or it may start as an erythematous macule, papule or urticarial plaque that later morphs into a target lesion. A target lesion has a central clearing and/or blistering, along with an erythematous halo.

The diagnosis is based on clinical findings; however, a skin biopsy is warranted in the case of uncertainty due to atypical presentation or suspicion of underlying autoimmune disease. Due to the high incidence of HSV and mycoplasma pneumoniae, serological testing for both is also warranted.
The diagnostic workup should further assist in finding the cause, which will drive the treatment plan for EM. This may entail antibiotics, antivirals, or withdrawal of a causative drug. Additionally, supportive treatment is necessary and includes antihistamines, topical corticosteroids, and wound care.51

Rocky Mountain spotted fever
Rocky Mountain spotted fever (RMSF) is a tick-borne disease caused by *Rickettsia rickettsii*. It is commonly found in the south-central and southeastern United States. Patients usually present with prodromal symptoms, which may include fever, headache, nausea, abdominal pain, myalgia and arthralgia, approximately three days prior to cutaneous involvement. The rash typically occurs on the third to fifth day post exposure. Ninety percent of patients have the rash, which is classically described as a maculopapular eruption starting at the extremities and moving toward the trunk, with the palms and soles affected last. The macules evolve into petechiae; at times, they may present only as petechiae.52

The initial diagnosis is clinical, based on the patient's symptoms and risk of exposure. Without immediate treatment, the disease is lethal; therefore, treatment should be started immediately if the clinical picture fits RMSF. Confirmatory testing can also be done, but will take time to return, so treatment should not be based on these tests. The standard for confirmatory testing involves serologic testing with the indirect fluorescent antibody.53 Skin biopsy is an option for a more time-sensitive response, with a 90% sensitivity rate.54

Doxycycline is the standard of treatment for both children and adults. If antibiotics are started within the first five days of exposure, mortality rates drop from 20% to 5%, and complications may be prevented.55

Conclusion
Exanthematous eruptions can be difficult to diagnose when classic clinical findings are absent or when features of several conditions overlap. A detailed understanding of commonly encountered exanths is necessary in order to establish a comprehensive differential diagnosis and appropriate diagnostic tests. This case illustrates how the use of simple and inexpensive laboratory tests can help narrow differential diagnoses and guide appropriate treatment to prevent complications and long-term sequela.

References
17. Jones TD. The Diagnosis of Rickettsial Fever. JAMA. 1944;126(8):481.


