BMJ Best Practice

Rubella

Straight to the point of care

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Summary

Rubella is typically a mild, self-limited, systemic infection caused by the rubella virus. Treatment of symptomatic rubella infection is largely supportive, as the illness is self-limited.

The most important consequence of rubella infection is congenital rubella syndrome, which may result from infection during pregnancy. Specialty consultation is strongly recommended for pregnant women with exposure to rubella.

Rubella immunization programs have eliminated endemic spread of the virus in the Americas; most cases are imported or associated with imported infections.

Definition

This topic focuses on postnatal rubella (German or 3-day measles), a mild, self-limited, systemic infection caused by rubella virus. Up to one half of all cases are asymptomatic. The common manifestations of symptomatic infection include mild fever, a generalized rash, lymphadenopathy, conjunctivitis, and arthralgias or arthritis. Maternal infection in pregnancy, particularly early in gestation, may cause spontaneous abortion, fetal death, or a wide spectrum of anatomic and laboratory anomalies (congenital rubella syndrome).

THEORY

Epidemiology

Before the licensure of rubella vaccine, rubella usually occurred in a seasonal pattern, with epidemics at 5- to 9-year intervals.[2] The incidence of endemic rubella in unimmunized populations was highest in preschool and young school-age children. As part of the Global Vaccine Action Plan, the World Health Organization reports that progress is being made toward rubella elimination.[2] Among 194 WHO Member States, 173 (90%) included rubella-containing vaccine in their immunization schedules in 2022, an increase from 132 (68%) in 2012, and 68% of the world's infants were vaccinated against rubella in 2022.[3] Reported rubella cases declined by 48%, from 94,277 in 2012 to 49,136 in 2019, and decreased further to 10,194 in 2020. The elimination of endemic rubella in the US was announced in 2004.[4] At present, fewer than 10 people per year in the US are reported as having rubella infection, and since 2012, all those with rubella infections had evidence of becoming infected while living or traveling outside the US.[5] [6] Most cases now affect adolescents and young adults.[7] In 2015, the Pan American Health Organization determined that endemic transmission of rubella in the Americas had been eliminated.[8] In the World Health Organization European Region, rubella incidence declined from 234.9 cases per million population in 2005 to 0.7 cases per million by 2019.[9]

Endemic rubella and congenital rubella syndrome, however, remain a global health problem, primarily of South East Asia and Africa. Outbreaks have been reported in countries where vaccination rates are suboptimal.[10] Globally, more than 100,000 infants are born each year with congenital rubella syndrome.[11] The risk to unimmunized travelers to areas where rubella remains endemic may be high.

Etiology

Rubella is caused by rubella virus, which is a togavirus and the only member of the genus *Rubivirus*. Humans are the only natural host. The virus has a positive-stranded RNA genome and a glycolipid envelope. There is only 1 antigenic type. Rubella virus is readily inactivated by chemical agents, low pH, heat, and cold. It can be cultivated in a variety of cell lines. Cell-mediated immunity develops 2 to 4 weeks after infection and hemagglutination inhibition and neutralizing antibodies directed against the virus peak at approximately 4 weeks. Immunity following rubella usually persists for life, although recurrent infection has been reported. Rubella vaccines are reported to be approximately 97% effective in preventing disease after a single dose.[12] Most rubella infections in the US are imported from countries in which rubella is endemic and affects unimmunized people.

Pathophysiology

Rubella is transmitted from human to human only by direct or droplet contact with infected body fluids, most commonly nasopharyngeal secretions.[7] Patients may shed infectious virus from 7 to 30 days after infection (from 1 week before to 2 weeks after the onset of rash). However, infants with congenital rubella syndrome may be contagious for >1 year. The average incubation period is 17 days (range: 12 to 23 days), during which the virus replicates in the nasopharynx and local lymph nodes and then spreads hematogenously throughout the body (including, in pregnant women, to the placenta and fetus).[5] Systemic symptoms are due to viral infection, but some manifestations (rash, thrombocytopenia, arthritis) probably have an immunologic basis.

Case history

Case history #1

A 35-year-old man presents with a 3-day history of low-grade fever, malaise, headache, and aching knees. That morning he developed a rash on his face, which has now spread to his chest and arms. His physical exam is notable for mild conjunctival injection, mild bilateral posterior auricular lymphadenopathy, and a discrete erythematous papular rash on his face, trunk, and upper arms. The patient is a business traveler from Nigeria who arrived in the United States a week prior to the onset of his illness. He is unaware of his immunization status and reports that a coworker with whom he had close contact had a similar rash recently.

Case history #2

A 2820-gram female infant is born to a 22-year old primigravid mother at approximately 38 weeks' gestation following an uncomplicated pregnancy. The baby has mild hepatosplenomegaly, numerous purplish firm nonblanching skin nodules, scattered petechiae, and a grade 3 continuous murmur audible at the left infraclavicular area. The baby's mother immigrated from Vietnam during the sixth month of her pregnancy; she cannot recall having been immunized in childhood.

Other presentations

Postnatal rubella infection may be complicated by overt arthritis. This is more common in adults and females and may persist for weeks to months. Thrombocytopenia occurs in approximately 1 out of 3000 cases, most commonly in children.[1] Serious hemorrhagic complications may occur. Rare complications include neurologic disorders, myocarditis, pericarditis, hepatitis, and bone marrow failure.

Approach

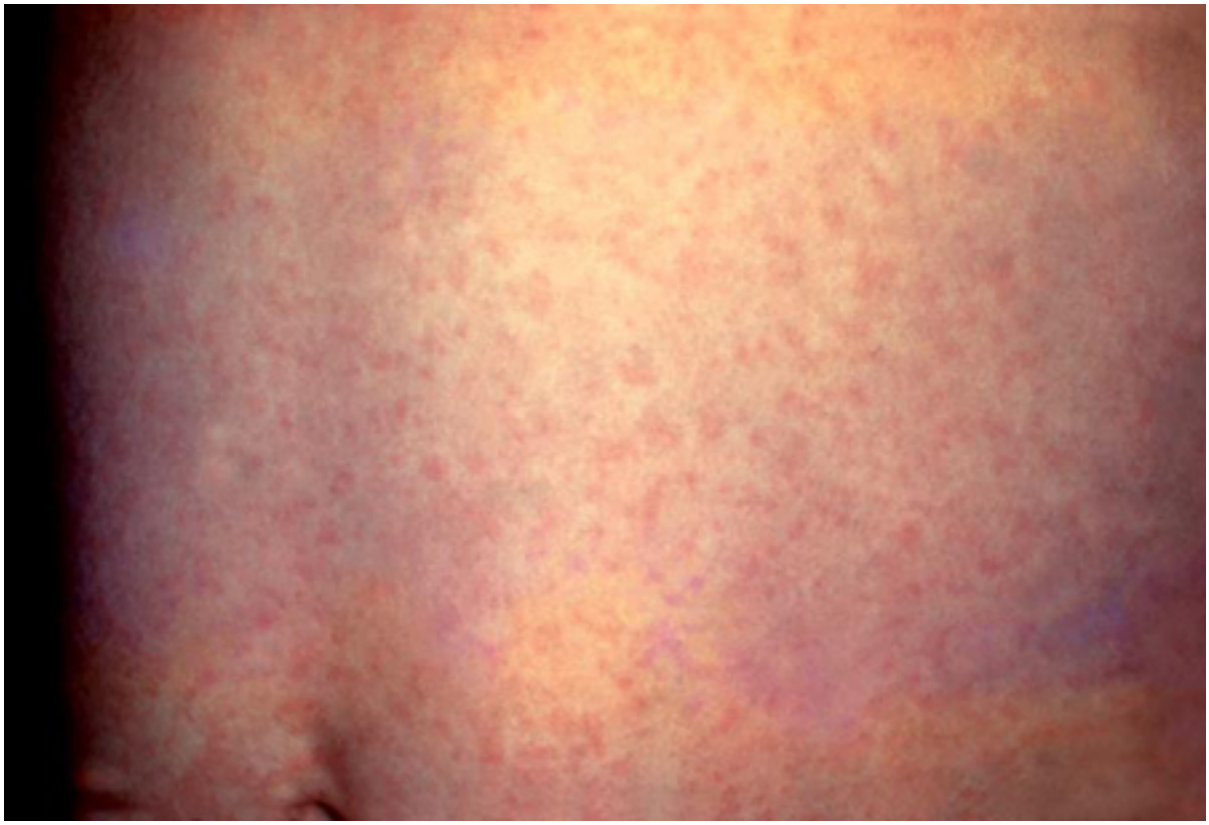
Postnatal rubella is most commonly diagnosed by serologic testing in patients who present with a generalized maculopapular rash, fever >99°F (37.2°C), and arthralgia/arthritis, lymphadenopathy, or conjunctivitis. Diagnostic testing is indicated for people with risk factors for rubella (under-immunization, known contact with a case of rubella, travel to a region of the world where rubella is endemic) and a clinical picture consistent with rubella. Identifying contagious people may prevent the spread of rubella to susceptible contacts, especially pregnant women. Diagnostic testing is also indicated for people who have risk factors for rubella and who have potential complications of the disease, for example, arthritis, thrombocytopenia, or encephalitis.

Clinical features

Rash is often the first manifestation of rubella in young children. The rash of rubella is erythematous, discrete, maculopapular, and sometimes mildly pruritic, and may be accentuated by heat. It usually begins on the face and spreads from the head to the feet. Occasionally there may be a petechial component to the rash or palatal petechiae. The rash persists for an average of 3 to 4 days.

Low-grade fever of >99°F (37.2°C) occurs in up to 50% of infections. Prodromal malaise and other mild constitutional symptoms are more common in adults than in children. Mild upper respiratory symptoms are common in children of school age and adults, and may precede the onset of rash by several days. Arthralgias and arthritis are frequent in adults (occurring in up to 70% of adult women) but uncommon in children. The most common joints affected are the fingers, wrists, and knees. The onset of joint symptoms usually coincides with the rash, and symptoms may persist for weeks. Rarely, symptoms may be recurrent or chronic.[22]

Mild lymphadenopathy involving the postauricular, posterior cervical, and occipital lymph node groups occurs in almost all patients and may precede the onset of rash by up to 1 week. Nodes are typically nontender and mobile. Nonpurulent conjunctivitis is reported in about 70% of adolescents and adults, but is less common in children.



Rubella rash

Centers for Disease Control and Prevention (CDC) Public Health Image Library

Tests

Antibody testing

Suspected cases of rubella should be confirmed by serologic testing. Anti-rubella IgM can be detected by enzyme immunoassay at the onset of clinical illness in almost all patients and persists for weeks to months. The optimum time-point for collection of serum is 5 days after the onset of symptoms (fever and rash), when >90% of cases will be IgM positive.[5] However, because rubella is a rare disease and the specificity of the test is <100%, false-positives are possible. Rubella IgM assays may produce false-positive results for several reasons, such as cross-reacting IgM resulting from infection with viruses other than rubella (such as parvovirus), the presence of rheumatoid factor, and persistent IgM after infection or vaccination.[23] A positive test, therefore, should always be confirmed by measuring anti-rubella IgG in paired acute and convalescent sera (drawn 2 to 3 weeks apart), or by measuring IgG avidity (the overall strength of binding between the antigen and antibody, which increases with time as the immune response matures). A 4-fold rise in serum rubella IgG or seroconversion between acute and convalescent samples indicates acute infection and is useful as a confirmatory test or if a false-negative rubella IgM is suspected. Low avidity IgG antibodies can be detected for up to 4 months after infection and indicate recent infection, while the presence of high avidity IgG suggests a more distant exposure (which may be from either infection or vaccination). Rubella IgG can last a lifetime. Detection of rubella IgG should be used for assessing rubella immunity, including before, during, and after pregnancy. [CDC: laboratory protocols - rubella] (http://www.cdc.gov/rubella/lab/index.html) [CDC: laboratory support for surveillance of vaccine-preventable diseases] (http://www.cdc.gov/vaccines/pubs/surv-manual/chpt22-lab-support.html)

Rubella IgM can be used to diagnose congenital rubella syndrome cases. Suspected cases should be tested as close to birth as possible, and again at 1 month of age if the initial IgM test is negative. If paired sera are to be collected, the second sample should be collected 14 to 21 days after the acute specimen was collected. At 3 months of age, approximately 50% of cases would still have detectable rubella IgM in their serum. The presence of rubella IgG in an infant after the decline of maternal antibodies (around 9 months of age) and the absence of vaccination or exposure to rubella will also confirm congenital rubella syndrome.[5]

Reverse transcription polymerase chain reaction (RT-PCR)

Detection of rubella RNA in direct clinical specimens or after incubation in tissue culture can also confirm infection. This is available commercially and through several state health departments. Nasopharyngeal swabs are the preferred sample type. The utility of RT-PCR is limited because of the narrow window when the virus can be detected in clinical samples; in respiratory samples, rubella RNA is typically only detectable from 2 days before rash onset to 4 days after. Swabs should be collected as soon after symptom onset as possible, preferably one to 3 days after onset, but no later than 7 days postonset.[5]

RT-PCR assays on throat swabs, nasopharyngeal swabs, and urine specimens from a neonate can be used for confirmation of suspected congenital rubella syndrome cases. Samples should be collected prior to 3 months of age if possible, because by 3 months of age approximately 50% will no longer shed virus.[5]

Viral culture

Rubella virus can be isolated from the nasopharynx, throat, urine, blood, and CSF from about 1 week before to 2 weeks after the onset of rash. Isolation of rubella virus from clinical specimens is diagnostic; however, viral cultures are not routinely obtained because they are labor-intensive and performed only in specialized reference laboratories. Molecular typing of rubella isolates by PCR is invaluable for epidemiologic purposes however, and viral isolation should be attempted in all cases of confirmed or strongly suspected rubella. Testing is especially important for pregnant women who may require expert maternal-fetal management due to the risk of congenital rubella syndrome.

CBC

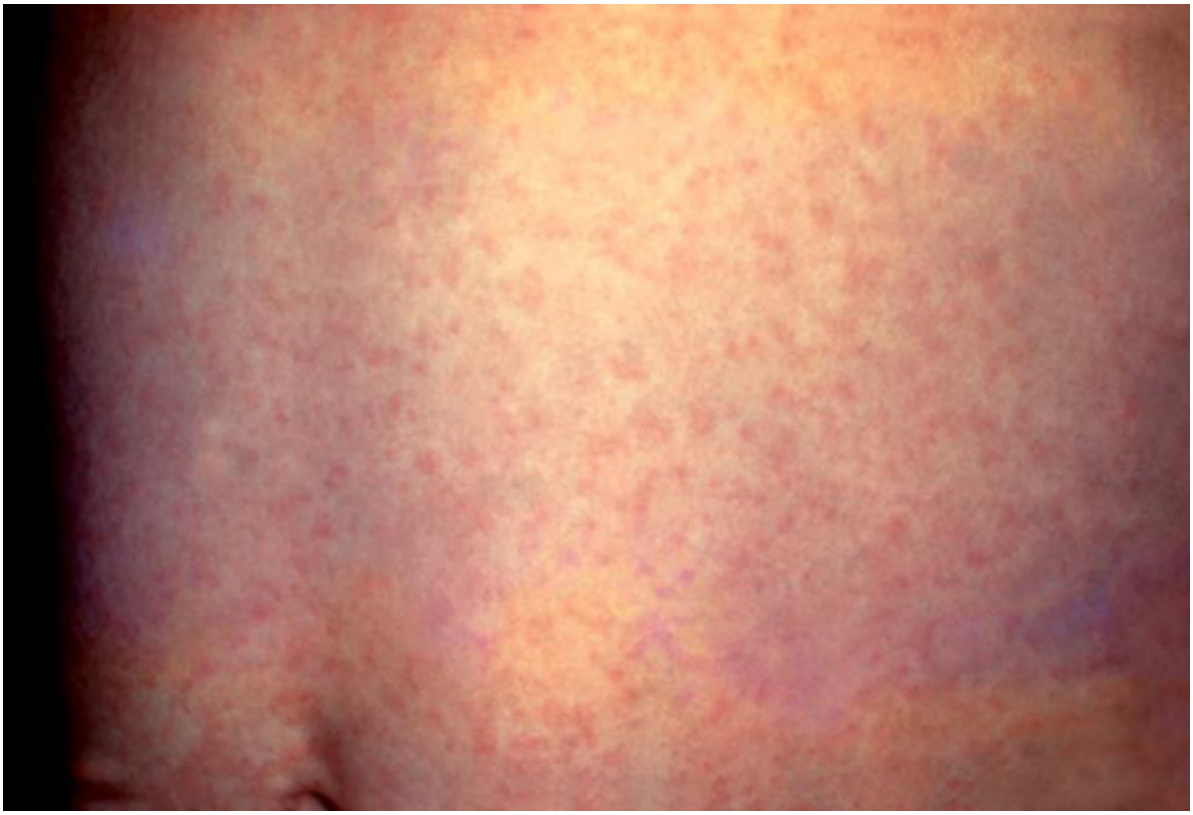
Typically, no other routine labs are needed. A CBC may be obtained if patients develop petechiae due to thrombocytopenia or if other more serious infections are suspected.

History and exam

Key diagnostic factors

maculopapular rash (common)

- Rash is often the first manifestation of rubella in young children. The rash of rubella is erythematous, discrete, maculopapular, and sometimes mildly pruritic, and may be accentuated by heat.



Rubella rash

Centers for Disease Control and Prevention (CDC) Public Health Image Library

- It usually begins on the face and spreads from the head to the feet. Occasionally, there may be a petechial component to the rash or palatal petechiae. The rash persists for an average of 3 to 4 days.

fever (common)

- Low-grade fever >99°F (37.2°C) occurs in up to 50% of infections.

arthralgias (common)

- Arthralgias are common in adults (occurring in up to 70% of adult women) but uncommon in children. The most common joints affected are the fingers, wrists, and knees. The onset of joint symptoms usually coincides with the rash and symptoms may persist for weeks. Rarely, symptoms may be recurrent or chronic.[22]

lymphadenopathy (common)

- Mild lymphadenopathy involving the postauricular, posterior cervical, and occipital lymph node groups occurs in almost all patients and may precede the onset of rash by up to 1 week. Nodes are typically nontender and mobile.

incomplete immunization (common)

- Unimmunized people or those whose immunization status is unknown (e.g., people born in countries where immunization is not carried out or where measles-mumps-rubella [MMR] or measles-rubella [MR] immunization rates are low).

Other diagnostic factors

malaise (common)

- Prodromal malaise and other mild constitutional symptoms are more common in adults than in children.

coryza or pharyngitis (common)

- Mild upper respiratory symptoms are common in school-age children and adults, and may precede the onset of rash by several days.

arthritis (common)

- Arthritis is common in adults (occurring in up to 70% of adult women) but uncommon in children. The most common joints affected are the fingers, wrists, and knees. The onset of joint symptoms usually coincides with the rash and symptoms may persist for weeks. Rarely, symptoms may be recurrent or chronic.[22]

conjunctivitis (common)

- Nonpurulent conjunctivitis is reported in about 70% of adolescents and adults, but is less common in children.[24]

Risk factors

Strong

incomplete immunization

- In the US, 65% to 80% of rubella infections are reported in unimmunized people or those whose immunization status is unknown (i.e., people born in foreign countries where immunization is not carried out or where measles-mumps-rubella [MMR] or measles-rubella [MR] immunization rates are low).[4] Rubella vaccines are reported to be approximately 97% effective in preventing disease after a single dose.[12]

exposure to infectious contact

- Rubella has been reported among susceptible contacts of people with rubella, often individuals who have been infected abroad.[6] Up to 50% of cases are asymptomatic, so a negative exposure history does not exclude rubella.

international travel

- Rubella remains a global infectious disease concern, but vaccination efforts have decreased reported cases by 97% between 2000 and 2018.[13] By the end of 2022, 175 countries had introduced rubella vaccines and global coverage was around 68%.[3][14] Since 2012, all people in the US with rubella infection had evidence of becoming infected while living or traveling outside the US.[5] The risk to unimmunized travelers to areas where rubella remains endemic or where outbreaks have been reported, particularly in developing regions of Africa and Asia, may be high.[15]

Tests

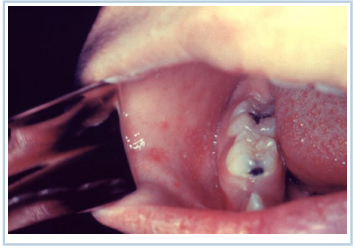
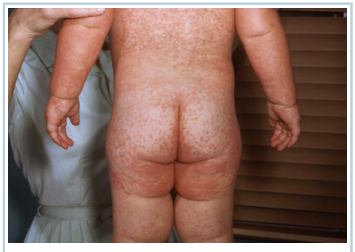
1st test to order

Test	Result
serology • The most common diagnostic test is rubella-specific IgM serum antibody. The preferred test is capture ELISA. The optimum time-point for collection of serum is 5 days after the onset of symptoms (fever and rash), when >90% of cases will be IgM positive.[5] False positive IgM tests are possible, so all positive IgM tests should be confirmed by demonstrating a four-fold rise in rubella-specific IgG serum concentrations between acute and convalescent sera (drawn 2-3 weeks apart), or by measurement of IgG avidity (the overall strength of binding between the antigen and antibody, which increases with time as the immune response matures). Low avidity IgG antibodies can be detected for up to 4 months after infection and indicate recent infection, while the presence of high avidity IgG suggests a more distant exposure (which may be from either infection or vaccination). Rubella IgG can last a lifetime. Detection of rubella IgG should be used for assessing rubella immunity, including before, during, and after pregnancy. [CDC: laboratory protocols - rubella] (http://www.cdc.gov/rubella/lab/index.html) [CDC: laboratory support for surveillance of vaccine-preventable diseases] (http://www.cdc.gov/vaccines/pubs/surv-manual/chpt22-lab-support.html) • Rubella IgM can be used to diagnose congenital rubella syndrome cases. Suspected cases should be tested as close to birth as possible, and again at ages 1 month if the initial IgM test is negative. If paired sera are to be collected, the second sample should be collected 14 to 21 days after the acute specimen was collected. At ages 3 months, approximately 50% of cases would still have detectable rubella IgM in their serum. Additionally, the presence of rubella IgG in an infant after the decline of maternal antibodies (ages 9 months) and the absence of vaccination or exposure to rubella will confirm congenital rubella syndrome.[5]	**IgM: positive in acute serum; IgG: seroconversion or 4-fold rise between acute and convalescent titers**
CBC • Occasionally thrombocytopenia may be present. This is thought to have an immunologic basis.	**usually normal**

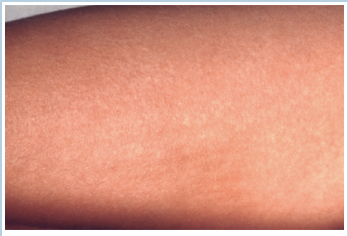
Other tests to consider

Test	Result
viral culture • Rubella virus can be isolated from the nasopharynx, throat, urine, blood, and CSF from about 1 week before to 2 weeks after the onset of rash. Viral cultures are not routinely obtained because they are labor-intensive and performed only in specialized reference laboratories. Viral isolation is important from an epidemiologic perspective and should be attempted if rubella is strongly suspected. Specimens should be obtained as early in the course of the illness as possible. Information is available from the Centers for Disease Control and Prevention laboratory protocols. [CDC: laboratory protocols - rubella] (http://www.cdc.gov/rubella/lab/index.html)	**may be positive**
reverse-transcriptase PCR#(RT-PCR) • Detection of rubella in direct clinical specimens or after incubation in tissue culture can confirm infection. • Available commercially and through several state health departments. Nasopharyngeal swabs are the preferred sample type. The utility of RT-PCR is limited because of the narrow window when the virus can be detected in clinical samples; in respiratory samples, rubella RNA is typically only detectable from 2 days before rash onset to 4 days after. Swabs should be collected as soon after symptom onset as possible, preferably 1 to 3 days after onset, but no later than 7 days post-onset.[5] RT-PCR assays on throat swabs, nasopharyngeal swabs, and urine specimens from a neonate can be used for confirmation of suspected congenital rubella syndrome cases. Samples should be collected prior to ages 3 months if possible, because by ages 3 months approximately 50% will no longer shed virus.[5] • Information is available from the CDC. [CDC: laboratory protocols - rubella] (http://www.cdc.gov/rubella/lab/index.html) [CDC: laboratory support for surveillance of vaccine-preventable diseases] (http://www.cdc.gov/vaccines/pubs/surv-manual/chpt22-lab-support.html)	**may be positive**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Measles (rubeola)	• Measles is a more severe illness. Erythematous or brownish morbilliform rash spreads from the head and neck downward and persists for 3 to 7 days. Coryza, cough, and conjunctivitis are usual. • A pathognomonic enanthem (Koplik spots) occurs early in the disease. Complications are common, particularly in immunocompromised and malnourished people.  *Koplik spots* *CDC Public Health Image Library*  *Child with measles showing the characteristic red blotchy rash on his buttocks and back during the third day of the rash* *CDC Public Health Image Library*	• Positive serum measles anti-IgM antibody is the preferred test (sensitivity 83% to 89%, specificity 87% to 100%).[25] [26] • Significant rise in serum measles anti-IgG antibody in paired acute and convalescent specimens. • Isolation of measles virus from throat, nasopharynx, blood, or urine (usually processed by public health and reference laboratories only).
Roseola infantum (HHV-6, HHV-7, exanthem subitum, sixth disease)	• Typically affects children <2 years of age.[27] Coryza, conjunctivitis, and cervical or occipital lymphadenopathy may precede 3 to 7 days of high fever and irritability. Development of an erythematous or pinkish maculopapular rash coincides with the resolution	• Anti-HHV-6/HHV-7 IgG antibody seroconversion between paired acute and convalescent specimens is the preferred test.[28] Increases in serum-specific antibody occur with viral reactivation. Specific serum IgM testing is not reliable.

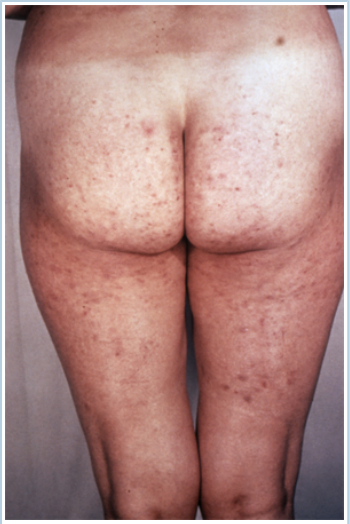
Condition	Differentiating signs / symptoms	Differentiating tests
	of fever and persists for hours to several days. Febrile seizures occur in 10% to 15%.	HHV-6 and HHV-7 are serologically cross-reactive. • Positive HHV-6/HHV-7 nucleic acid amplification from serum or plasma (sensitivity 90% to 100%, specificity 100%). Cannot distinguish acute infection from reactivation.[29] • Isolation of virus from peripheral blood (usually processed by public health and reference laboratories only).
Scarlet fever (group A Streptococcus pyogenes)	• Most common in school-age children. Usually associated with streptococcal pharyngitis, but occasionally complicates skin and soft-tissue infection. • Pharyngitis, anterior cervical adenopathy, and fever precede a confluent erythematous blanching "sandpaper" rash that begins on the trunk and behind the ears and is accentuated in flexural creases. Rash resolves with desquamation in 3 to 8 days. • Other features include an erythematous-coated "strawberry" tongue, circumoral pallor, and Pastia lines (linear erythematous lesions in skinfolds, particularly elbows and axillae).	• Group A streptococcal rapid antigen testing is 60% to 85% sensitive and 90% to 100% specific.[30] Negative results should be confirmed by throat culture. • Isolation of group A streptococcus from throat culture on blood agar is 80% to 98% sensitive and 100% specific.

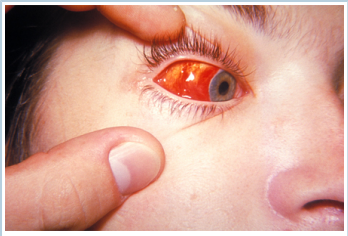
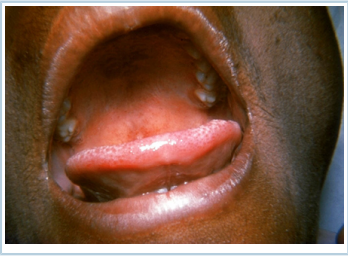
Condition	Differentiating signs / symptoms	Differentiating tests
	 *The scarlet fever rash first appears as tiny red bumps on the chest and abdomen that may spread all over the body; looking like sunburn, it feels like a rough piece of sandpaper, and lasts about 2 to 5 days* *CDC Public Health Image Library*	
Erythema infectiosum (parvovirus B19, fifth disease)	• Most common in children. Mild systemic symptoms and/or fever are followed in 7 to 10 days by a distinctive erythematous facial rash with a "slapped cheek" appearance. • An erythematous lacy maculopapular rash may also appear on the trunk and spread peripherally to the arms and thighs. Occasionally the rash may be atypical and indistinguishable from that of rubella. Arthralgias and arthritis are more common with increasing age.	• Positive serum antiparvovirus B19 IgM is the preferred test in immunocompetent people (90% sensitive, 99% specific).[31] • Nucleic acid amplification of parvovirus B19 DNA from serum or plasma is more sensitive, but may remain positive for up to 9 months after acute infection.[32]
Enteroviral infections (echovirus, coxsackievirus)	• Incidence is highest in infants and young children and in the summer and early fall. Most common presentation is a nonspecific febrile illness. Neurologic and GI symptoms and stomatitis may be prominent.	• Nucleic acid amplification of enteroviral RNA from blood or CSF is the most rapid and sensitive test.[33] • Isolation of enterovirus from stool, rectal swabs, throat, blood, CSF, or urine. • Sensitivity and specificity vary, depending on the type of virus, site of infection, and time at which specimens are obtained.
West Nile virus	• Incidence highest in summer, coinciding with mosquito activity. Fever is generally higher than that observed with rubella, and headache, myalgias,	• Specific IgM by antibody capture ELISA are >95% sensitive and 83% to 99% specific after the first week of illness, but may persist for >1 year.[34]

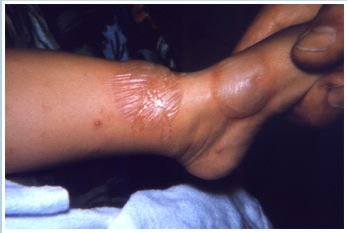
Condition	Differentiating signs / symptoms	Differentiating tests
	and weakness are more prominent. • A diffuse erythematous maculopapular or morbilliform rash, which spares the palms and soles, is more common in children than adults. Neuroinvasive disease occurs in 0.3% to 1.0% of patients.	• Fourfold increase in virus-specific serum antibody titers. Cross-reactivity with other arboviruses may occur. Positive results should be confirmed by virus-specific IgG. • Isolation of virus from CSF or serum. • Virus-specific IgM in CSF or amplification of viral nucleic acid from CSF (neuroinvasive disease).
Dengue virus	• Dengue virus is a flavivirus that is transmitted to humans through the bite of Aedes mosquitos, blood transfusion, organ transplantation, occupational exposure to infected blood, or by in utero or perinatal infection.[35] • Dengue is endemic in many countries in Asia, the Pacific, Africa, the Caribbean, and the Americas, including Puerto Rico, the US Virgin Islands, Samoa, and Guam. Sporadic outbreaks have been reported in Florida, Hawaii, and the Texas-Mexico border, but most cases in the United States are acquired in endemic regions by travelers or immigrants. • Symptomatic patients with mild disease (dengue fever) may present with fever, severe headache, myalgias, arthralgias, and a diffuse erythematous maculopapular rash. Retro-orbital pain and mild hemorrhagic signs are common. More severe forms of disease are characterized by bleeding and shock due to plasma leak and intravascular volume depletion.	• Nucleic acid amplification of dengue virus RNA from serum, plasma, CSF, or tissue specimens is the most rapid and sensitive test in the first week of illness. • Most patients have serum anti-dengue IgM antibodies detectable by ELISA assay by the fifth day of illness. These may remain detectable for 2 to 3 months. IgG antibodies increase more slowly and remain elevated for months to years; comparison of acute and convalescent (with at least 7 days between samples) is useful in differentiating acute from distant infections.
Chikungunya virus	• Chikungunya virus is an alphavirus that is transmitted through the bite of Aedes	• Nucleic acid amplification of chikungunya virus RNA from serum or plasma is the most

Condition	Differentiating signs / symptoms	Differentiating tests
	mosquitos and, rarely, by perinatal infection.[36] • Most patients present with fever and severe joint pain. Headache, myalgias, arthritis, conjunctivitis, or a maculopapular rash may occur. Disease may be more severe in neonates, the elderly, and people with underlying medical conditions. Joint pain or arthritis may persist or recur over months to years. • Chikungunya virus outbreaks have been reported in many countries in Africa, Asia, Europe, the Pacific, the Caribbean, and South America. In the US, most infections have been reported in travelers returning from these areas. Locally-transmitted infections have been reported in Florida, Texas, Puerto Rico and the US Virgin Islands.	rapid and sensitive test in the first week of illness. • Specific anti-chikungunya IgM and neutralizing antibodies may be detectable towards the end of the first week of illness. Comparison of acute and convalescent sera is recommended.
Zika virus	• Zika virus is a flavivirus that is transmitted to humans through the bite of Aedes mosquitoes, by sexual contact with people infected with Zika virus, blood transfusion, or by in utero or perinatal infection.[37] • Zika virus infection should be suspected in returned travelers from endemic areas or those with other epidemiologic risk factors. • Zika virus outbreaks have been reported in many tropical and subtropical regions of the world. Local mosquito-borne transmission has been reported in Puerto Rico, the US Virgin Islands, and American Samoa. There have been no confirmed cases, however, reported from the continental US or US territories since 2019.[38] Most people with Zika virus infection are asymptomatic. Features of	• Currently, Zika virus testing can be obtained through commercial laboratories, the CDC Arboviral Diagnostic Laboratory and several state health departments.[39] • Zika virus can be tested for by PCR during the first week after disease onset. Specific IgM and neutralizing antibodies begin to develop late in the first week of illness. Cross-reactions with other flaviviruses are common, so positive, equivocal, or inconclusive tests should be confirmed by plaque-reduction neutralization assay.

Condition	Differentiating signs / symptoms	Differentiating tests
	symptomatic disease include fever, a maculopapular rash, arthralgia, myalgia, headache, and conjunctivitis. Symptoms are generally mild and persist for days to a week. Rare complications include Guillain-Barre syndrome. Complications of Zika virus infection in pregnant women include fetal loss, microcephaly, and congenital central nervous system and ocular abnormalities.	
Secondary syphilis	• A generalized polymorphous maculopapular rash begins on the trunk and typically involves the palms and soles. Other common manifestations include condyloma lata, mucosal lesions, and generalized lymphadenopathy. • Fever and other constitutional symptoms are not prominent. Clinical manifestations resolve spontaneously or with treatment over several weeks to months.	• Positive VDRL, RPR tests are 100% sensitive and 93% to 99% specific.[40] • Results should be confirmed by a specific treponemal test (FTA-ABS, 100% sensitive and 94% to 100% specific). • Identification of spirochetes by dark-field exam of scrapings from moist mucocutaneous lesions.

Condition	Differentiating signs / symptoms	Differentiating tests
	 *Patient with a syphilitic roseola-like rash, similar to that of viral eczema, which developed on her buttocks and legs during the secondary stage of the disease* *CDC Public Health Image Library; from the collection of J. Pledger, BSS/VD; used with permission*	
Infectious mononucleosis (Epstein-Barr virus)	• High fever, exudative pharyngitis, cervical or generalized lymphadenopathy, hepatosplenomegaly, and an atypical lymphocytosis are common in adolescents and adults. • Periorbital edema is frequently observed early in infection. Children are more likely to be asymptomatic or have a mild form of illness. A polymorphous rash, usually on the trunk and arms, occurs in up to 20% of cases. Rash is more common in patients treated with ampicillin and other penicillins. Sometimes conjunctival hemorrhage may be seen.	• Positive anti-viral capsid antigen (VCA) IgM antibodies are detectable in the second week of illness and disappear over several months. Anti-VCA IgG antibody is also detectable early in infection and persists for life, whereas anti-EBV-associated nuclear antigen (EBNA) antibody develops weeks to months after infection. The presence of anti-VCA Ab and absence of anti-EBNA Ab are diagnostic of acute infection (sensitivity 95% to 100%, specificity 86% to 100%).[41] • Heterophile antibody testing (monospot) is sensitive (81% to 95%) and specific (98% to 100%) in school-age children and adults, but is insensitive in young children.

Condition	Differentiating signs / symptoms	Differentiating tests
	 *A conjunctival hemorrhage of the right eye of this patient with infectious mononucleosis* *CDC Public Health Image Library; from the collection of Thomas F. Sellers, Emory University; used with permission*  *Tongue and palate of patient with infectious mononucleosis* *CDC Public Health Image Library; from the collection of Dr Sellers, Emory University; used with permission*	
Kawasaki syndrome	• Occurs almost exclusively in children <8 years of age. Prominent features are a persistent high fever, bulbar conjunctivitis, erythematous changes of the mouth and pharynx, and dry, cracked lips, swelling and pain of the hands and feet, and cervical lymphadenopathy. • Irritability, abdominal pain, diarrhea, and vomiting are common. Periungual desquamation may be noted in the second week of the illness. Coronary and other arterial aneurysms may develop 1 to 4 weeks after the onset of illness.	• No specific diagnostic test is available. • Suggestive laboratory and diagnostic imaging findings include sterile pyuria, hepatitis, CSF pleocytosis, pericardial effusion, gallbladder hydrops, and coronary artery abnormalities.

Condition	Differentiating signs / symptoms	Differentiating tests
Cutaneous drug reaction	• Medications commonly associated with cutaneous reactions include antibiotics and anticonvulsants. Many drug-induced rashes have characteristic features (erythema multiforme, urticaria).  *Bullous erythema multiforme* *CDC Public Health Image Library; from the collection of Dr John Noble, Jr; used with permission*	• Clinical diagnosis based on exposure history, resolution after withdrawal of the implicated drug, and exclusion of other potential causes. Eosinophilia is suggestive, but not diagnostic, of cutaneous drug reactions.
Juvenile rheumatoid arthritis	• Systemic-onset juvenile rheumatoid arthritis commonly affects children and adolescents. Children are often ill-looking. Typically there are daily high-spiking fevers that, in the absence of therapy, persist for weeks to months. • The rash is evanescent, salmon-colored, and linear and typically involves the trunk and extremities. The presence of the rash often coincides with fever. Mild hepatosplenomegaly and myalgias (or muscle tenderness) are common. Serositis may occur. • Many patients develop a chronic synovitis of ≥1 joints, but the onset of joint involvement may be delayed.	• There is no definitive laboratory test. Leukocytosis, thrombocytosis, anemia, elevated ESR, and elevated serum ferritin concentrations are suggestive.

Criteria

Centers for Disease Control and Prevention 2013 case definition[42]

Suspected

- Any generalized rash illness of acute onset that does not meet the criteria for probable or confirmed rubella or any other illness.

Probable

- Absence of a more likely diagnosis and all of the following:
  - Acute onset of generalized maculopapular rash
  - Fever >99°F (37.2°C), if measured
  - Arthralgia, arthritis, lymphadenopathy, or conjunctivitis
  - Lack of epidemiologic linkage to a laboratory-confirmed case
  - Noncontributory or no serologic or virologic testing.

Confirmed

- A person with or without symptoms who has laboratory evidence of rubella infection confirmed by one or more of the following tests:
  - Isolation of rubella virus
  - Detection of rubella-virus specific nucleic acid by polymerase chain reaction
  - IgG seroconversion or a significant rise in serum rubella IgG antibody titers between acute- and convalescent-phase sera as measured by any standard serologic assay
  - Positive serologic test for rubella IgM antibody (note: false-positives are reported in people with some other acute viral illnesses and in the presence of rheumatoid factor).
- Or, an illness characterized by all of the following:
  - Acute onset of generalized maculopapular rash
  - Fever >99°F (37.2°C), if measured
  - Arthralgia, arthritis, lymphadenopathy, or conjunctivitis
  - Epidemiologic linkage to a laboratory-confirmed case of rubella.

Screening

Postpubertal females should be assessed for rubella susceptibility at annual health examinations, family planning visits, and visits to sexually transmitted infection clinics.[43] If these patients are found to be susceptible by serologic screening or their immunization status is undocumented, they should be immunized with measles-mumps-rubella (MMR) vaccine unless they are known to be pregnant.[43]

People at increased risk of rubella infection (travelers to rubella endemic countries) should be assessed for susceptibility to rubella and, if susceptible, should be immunized with MMR vaccine unless they are known to be pregnant or attempting to become pregnant.

Approach

Postnatal rubella is generally a mild, self-limited condition. In nonpregnant patients, treatment is supportive. No specific antiviral therapy is available. The disease is usually so mild that symptomatic treatment is usually unnecessary, except for those with arthritis who may feel better with a nonsteroidal anti-inflammatory drug for a brief period.

Rubella is a nationally notifiable disease in the US and UK.[11] [44]

Pregnant: susceptible to and exposed to rubella

Pregnant women with known exposure to rubella who are susceptible include those without immunity to rubella or who have uncertain immunity (no or unknown immunization history and no previous serologic testing). Regardless of symptoms, they should be referred to a high-risk perinatal specialist and a pediatric infectious disease specialist to evaluate the likelihood of fetal infection and risk of sequelae.

High dose polyclonal immune globulin may be of benefit for preventing clinical rubella but is not routinely recommended for this purpose because there is insufficient evidence for prevention of congenital rubella in the fetus.[45] This option may be considered for post-exposure prophylaxis.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
pregnant: susceptible to and exposed to rubella		
	1st	**specialist referral**
	adjunct	**intramuscular immune globulin**
nonpregnant: symptomatic rubella		
	1st	**supportive care**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

pregnant: susceptible to and exposed to rubella

1st **specialist referral**

» Pregnant women with known exposure to rubella who are susceptible to rubella or who have uncertain immunity (no or unknown immunization history and no previous serologic testing), whether or not they are symptomatic, should be referred to a high-risk perinatal specialist and a pediatric infectious disease specialist to evaluate the likelihood of fetal infection and risk of sequelae.

adjunct **intramuscular immune globulin**

Treatment recommended for SOME patients in selected patient group

Primary options

» immune globulin (human): 0.55 mL/kg intramuscularly as a single dose

» High dose polyclonal immune globulin may be of benefit for preventing clinical rubella but is not routinely recommended for this purpose because there is insufficient evidence for prevention of congenital rubella in the fetus.[45] This option may be considered for post-exposure prophylaxis.

nonpregnant: symptomatic rubella

1st **supportive care**

» Postnatal rubella is generally a mild, self-limited condition that requires only symptomatic therapy. No specific antiviral therapy is available. A brief course of an NSAID, if no contraindication exists, may be helpful for patients with arthritis.

Primary prevention

Two live attenuated viral vaccines for the prevention of rubella are available in the US: a trivalent measles-mumps-rubella formulation (MMR) and a quadrivalent measles-mumps-rubella-varicella formulation (MMRV; licensed for use in people ages ≤12 years only).[12] [16] [17] [CDC: rubella vaccination] (https://www.cdc.gov/vaccines/vpd/rubella/index.html) Since 1978, there has only been one MMR vaccine used in the US, M-M-R II; however, in June 2022, PRIORIX was licensed as an additional MMR vaccine option.[18] The RA 27/3 strain rubella component of each of these vaccines is identical. Rubella vaccines are reported

to be approximately 97% effective in preventing disease after a single dose.[12] Although 1 dose of rubella vaccine is highly protective, 2 doses of a rubella-containing vaccine are recommended for children and adolescents because of the 2-dose recommendations for measles- and mumps-containing vaccine and to provide additional protection to people who experience primary vaccine failure. Depending on age and risk of exposure, 1 or 2 doses are recommended for susceptible adults.[12] [17] Adverse reactions to MMR vaccines are infrequent. The most common adverse reactions include low-grade fever, transient rash, and lymphadenopathy.[12] Multiple studies have failed to demonstrate a link between MMR vaccines and autism.[19] [20] [21]

As there is a very low incidence of mumps, measles, and rubella in the US, a health provider's clinical diagnosis of rubella should not be considered acceptable evidence of immunity.[12] People at increased risk of rubella infection (healthcare professionals, educators, childcare workers) should be assessed for susceptibility to rubella and, if susceptible, should be immunized with MMR vaccine. [CDC: rubella] (http://www.cdc.gov/rubella) [Pan American Health Organization/WHO: rubella] (http://www3.paho.org/hq/index.php?option=com_topics&view=article&id=48&Itemid=40768&lang=en#gsc.tab=0)

Postpubertal women should be assessed for susceptibility to rubella at all healthcare encounters. If these women are found to be susceptible by serologic screening or their immunization status is undocumented, they should be immunized with MMR vaccine unless they are known to be pregnant. Routine prenatal screening for rubella immunity is recommended. Pregnant people who do not have acceptable evidence of rubella immunity should be advised to avoid travel to countries where rubella is endemic or to areas with known rubella outbreaks, especially during the first 20 weeks of pregnancy.[11] In addition, MMR vaccination should be given to susceptible women in the immediate postpartum period.

Country-specific guidelines should be followed regarding rubella vaccination prior to travel. In the US, unless contraindicated, MMR vaccination should be given to all travelers ages ≥12 months who do not have acceptable evidence of immunity to rubella (documented by ≥1 dose of rubella-containing vaccine on or after the first birthday, laboratory evidence of immunity, or birth before 1957). Before departure from the US, infants ages 6–11 months should receive 1 dose of MMR vaccine (for measles protection), and children ages ≥12 months and adults should receive 2 doses of MMR vaccine ≥28 days apart.[11]

Secondary prevention

Patients with postnatal rubella should be isolated for 7 days after the onset of rash. Droplet and standard precautions are recommended for hospitalized patients.[48]

Contact isolation is recommended for congenitally infected infants until 2 serial nasopharyngeal and urine cultures obtained after 3 months of age are sterile, or for the first year of life.

Patient discussions

Mild analgesics or NSAIDs may be helpful in the management of constitutional and joint symptoms.

Parents should be aware of the importance of immunization. [CDC: rubella - make sure your child gets vaccinated] (http://www.cdc.gov/features/rubella)

FOLLOW UP

Monitoring

Monitoring

In general, no specific follow-up is required. Women who acquire rubella during pregnancy should be managed in consultation with experts in fetal-maternal medicine and infectious diseases.

Complications

Complications	Timeframe	Likelihood
thrombocytopenia	**short term**	**low**
Occurs in approximately 1 in 3000 cases, most commonly in children.[1] Thrombocytopenia is probably immune-mediated. Serious hemorrhagic complications may occur.		
encephalitis	**short term**	**low**
Complicates 1 in 5000 cases of rubella.[46] The overall prognosis is good, but severe disease with permanent neurologic sequelae has been reported.[46] [47] No specific therapy is available for rubella encephalitis. Supportive therapy as needed is indicated.		
congenital rubella syndrome	**long term**	**high**
Maternal infection in pregnancy, particularly early in gestation, may cause spontaneous abortion, fetal death, or a wide spectrum of anatomic and laboratory anomalies. Women who acquire rubella during pregnancy should be managed in consultation with experts in fetal-maternal medicine and infectious diseases.		
neurologic complications	**variable**	**low**
Rare neurologic complications include progressive sclerosing panencephalitis, myelitis, optic neuritis, peripheral neuritis, and Guillain-Barre syndrome. Symptoms typically develop several days after the rash. The overall prognosis is good, but severe disease with permanent neurologic sequelae has been reported.[46] [47]		

Prognosis

Postnatal rubella is generally a mild illness that resolves spontaneously over several days to 1 week. The most important consequence of postnatal rubella infection is congenital rubella syndrome.

Arthritis

Arthralgias and arthritis may persist for weeks or months or recur, particularly in adult women. However, the overall prognosis for joint function is good.

Pregnant women

Maternal infection in nonimmune women during pregnancy, particularly early in gestation, may cause spontaneous abortion, fetal death, or a wide spectrum of anatomic and laboratory anomalies (congenital rubella syndrome).

Treatment guidelines

International

Recommended child and adolescent immunization schedule for ages 18 years or younger, United States, 2025 (https://www.cdc.gov/vaccines/hcp/imz-schedules/child-adolescent-age.html) [16]

Published by: Centers for Disease Control and Prevention **Last published:** 2024

Recommended adult immunization schedule for ages 19 years or older, United States, 2025 (https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-age.html) [17]

Published by: Centers for Disease Control and Prevention **Last published:** 2024

CDC Yellow Book: health information for international travel - rubella (https://wwwnc.cdc.gov/travel/page/yellowbook-home) [11]

Published by: Centers for Disease Control and Prevention **Last published:** 2023

Prevention of measles, rubella, congenital rubella syndrome, and mumps (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mmr.html) [12]

Published by: Centers for Disease Control and Prevention **Last published:** 2013

Online resources

1. CDC: rubella vaccination (https://www.cdc.gov/vaccines/vpd/rubella/index.html) *(external link)*
2. CDC: rubella (http://www.cdc.gov/rubella) *(external link)*
3. Pan American Health Organization/WHO: rubella (http://www3.paho.org/hq/index.php?option=com_topics&view=article&id=48&Itemid=40768&lang=en#gsc.tab=0) *(external link)*
4. CDC: laboratory protocols - rubella (http://www.cdc.gov/rubella/lab/index.html) *(external link)*
5. CDC: laboratory support for surveillance of vaccine-preventable diseases (http://www.cdc.gov/vaccines/pubs/surv-manual/chpt22-lab-support.html) *(external link)*
6. CDC: rubella - make sure your child gets vaccinated (http://www.cdc.gov/features/rubella) *(external link)*

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Images

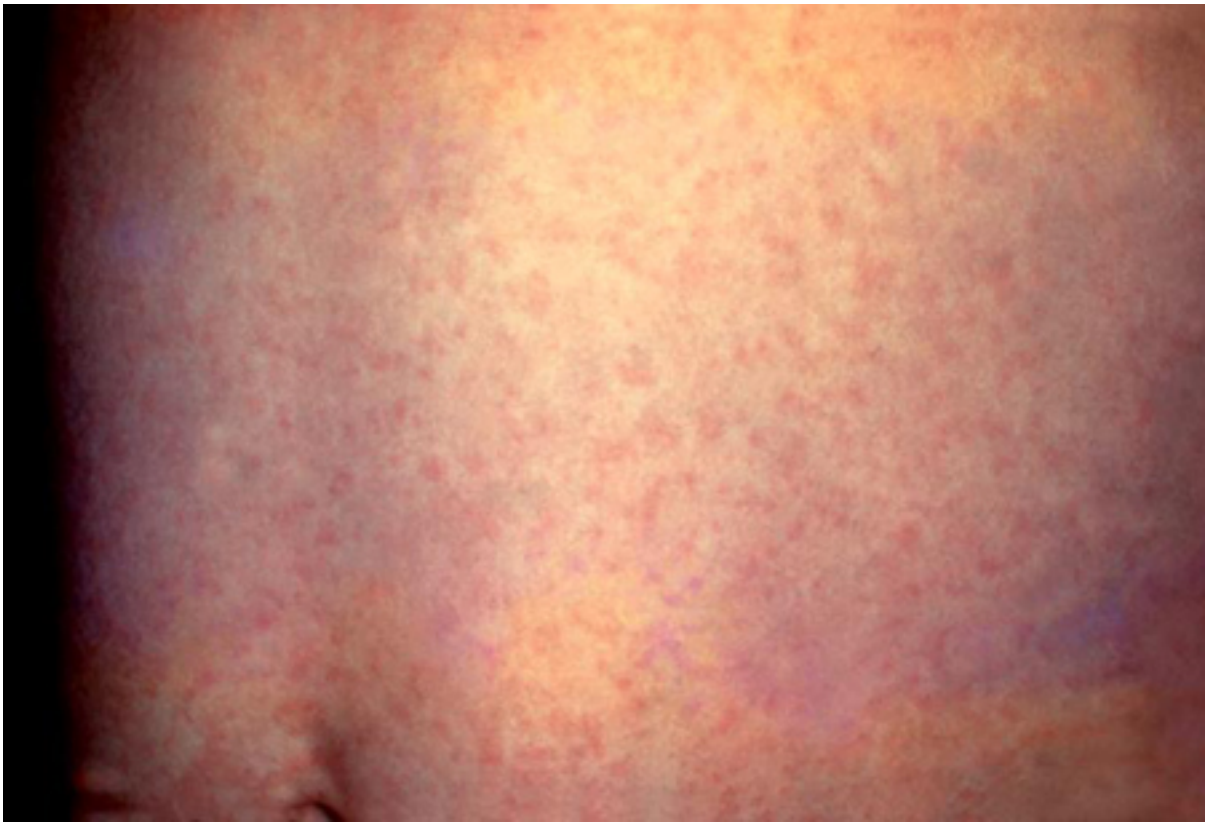

Figure 1: Rubella rash

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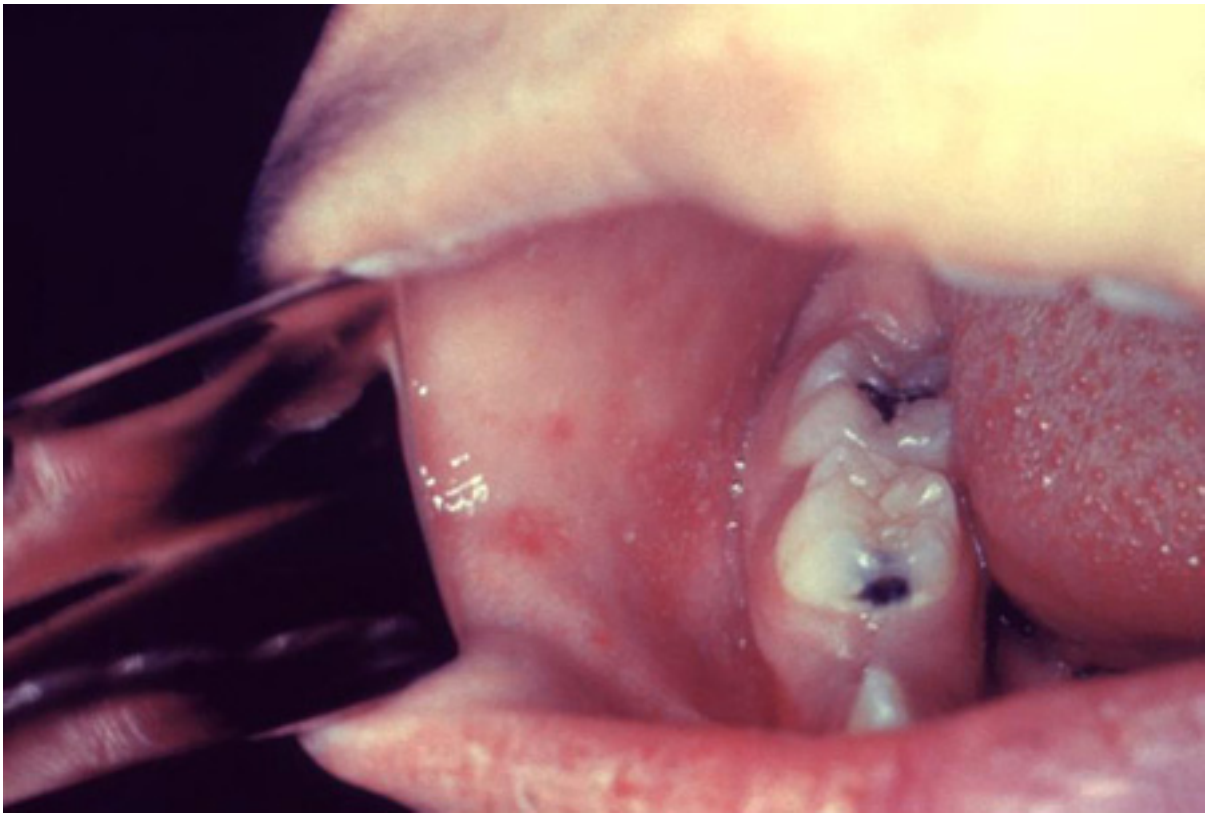

Figure 2: Koplik spots

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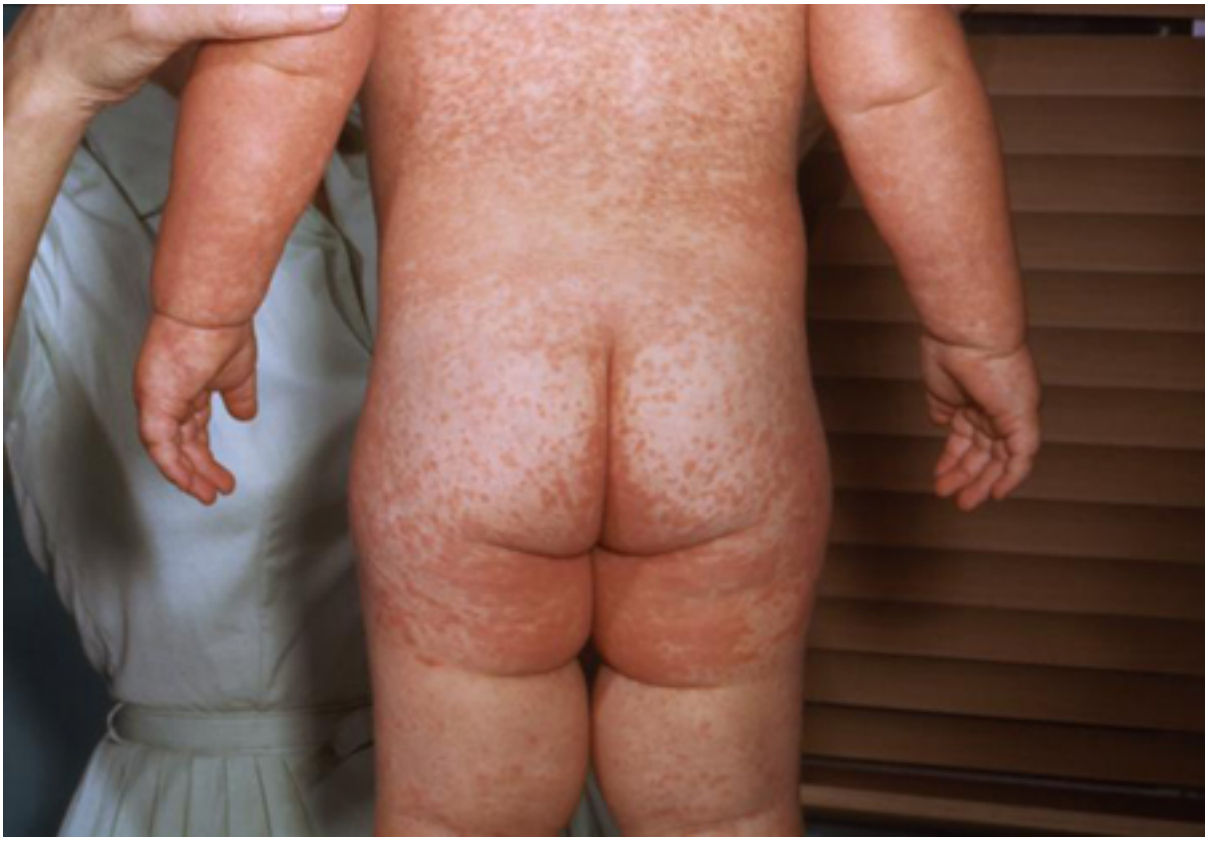

Figure 3: Child with measles showing the characteristic red blotchy rash on his buttocks and back during the third day of the rash

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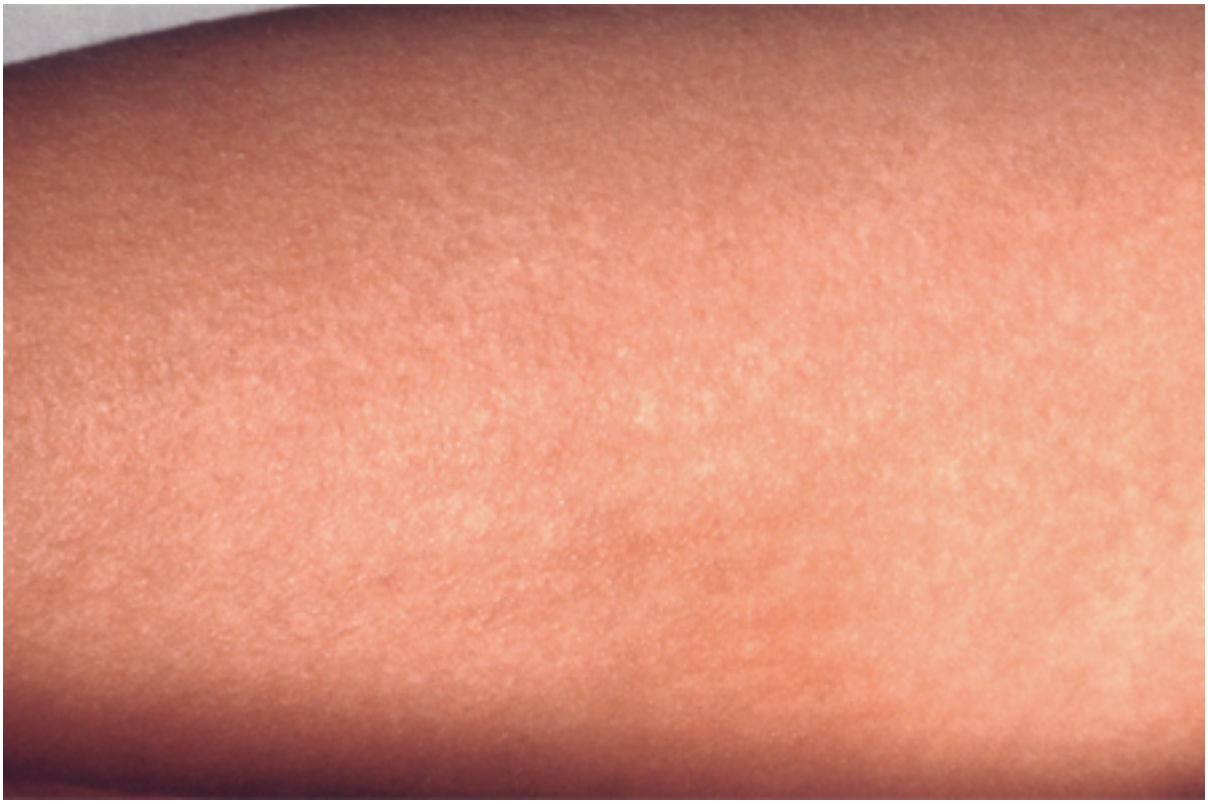

Figure 4: The scarlet fever rash first appears as tiny red bumps on the chest and abdomen that may spread all over the body; looking like sunburn, it feels like a rough piece of sandpaper, and lasts about 2 to 5 days

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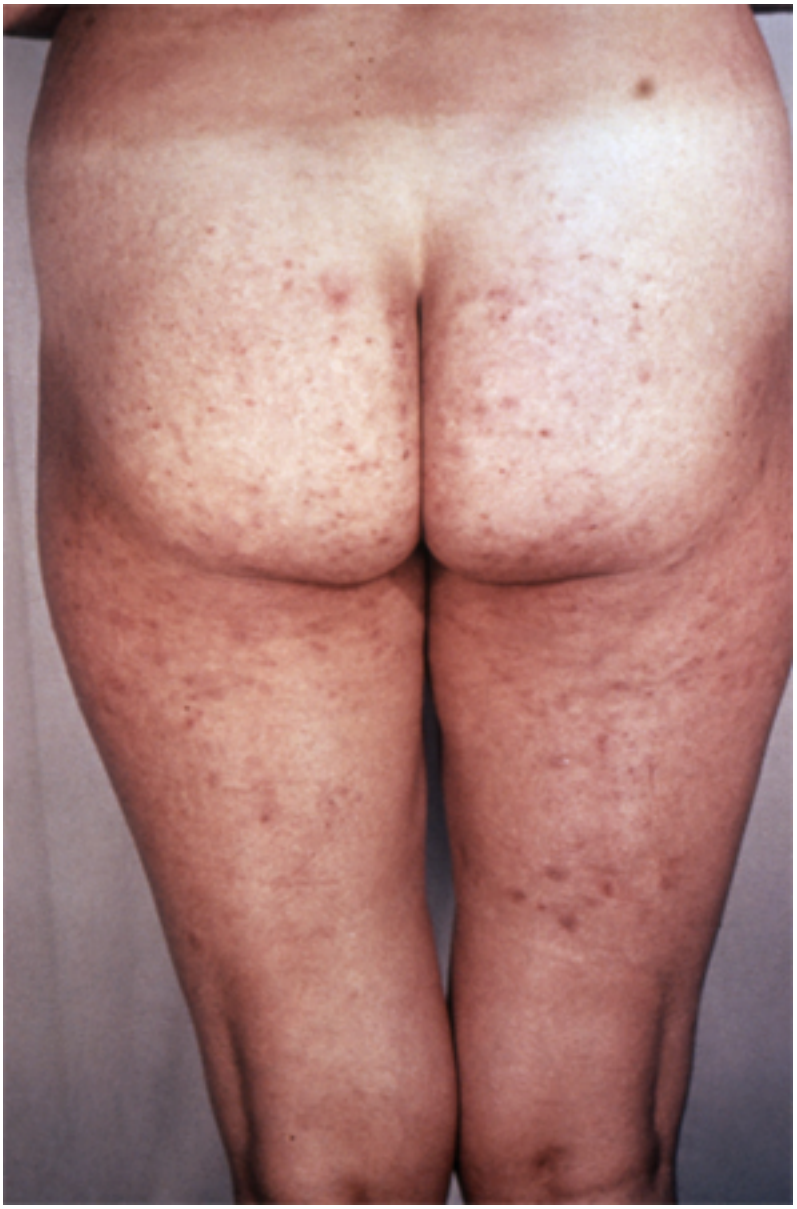

Figure 5: Patient with a syphilitic roseola-like rash, similar to that of viral eczema, which developed on her buttocks and legs during the secondary stage of the disease

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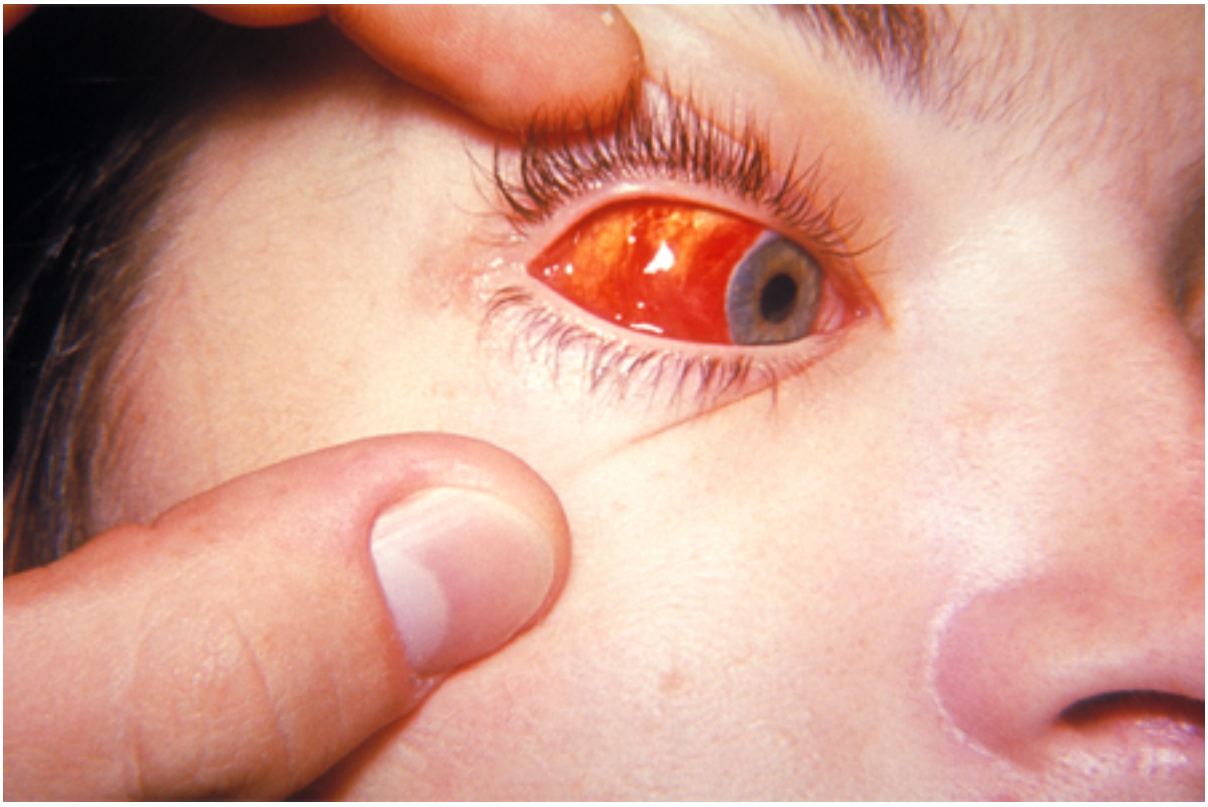

Figure 6: A conjunctival hemorrhage of the right eye of this patient with infectious mononucleosis

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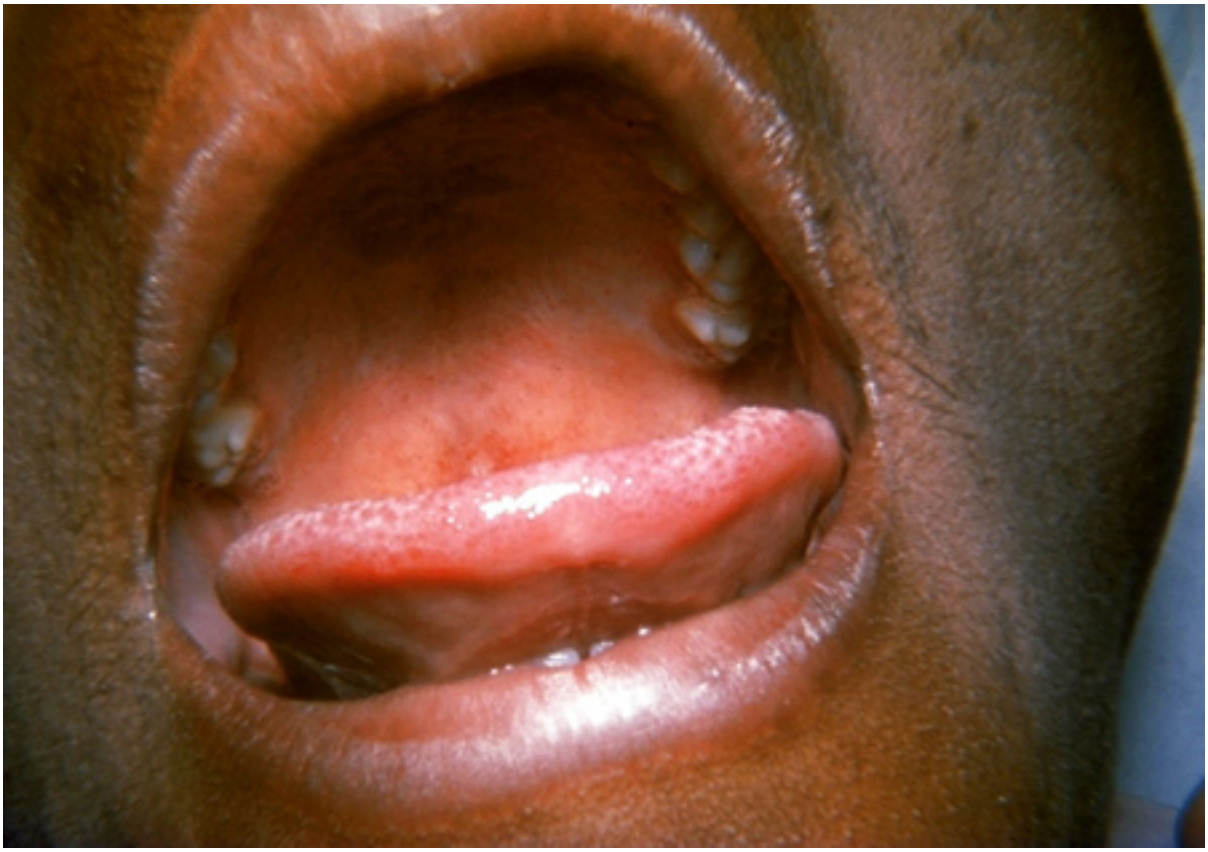

Figure 7: Tongue and palate of patient with infectious mononucleosis

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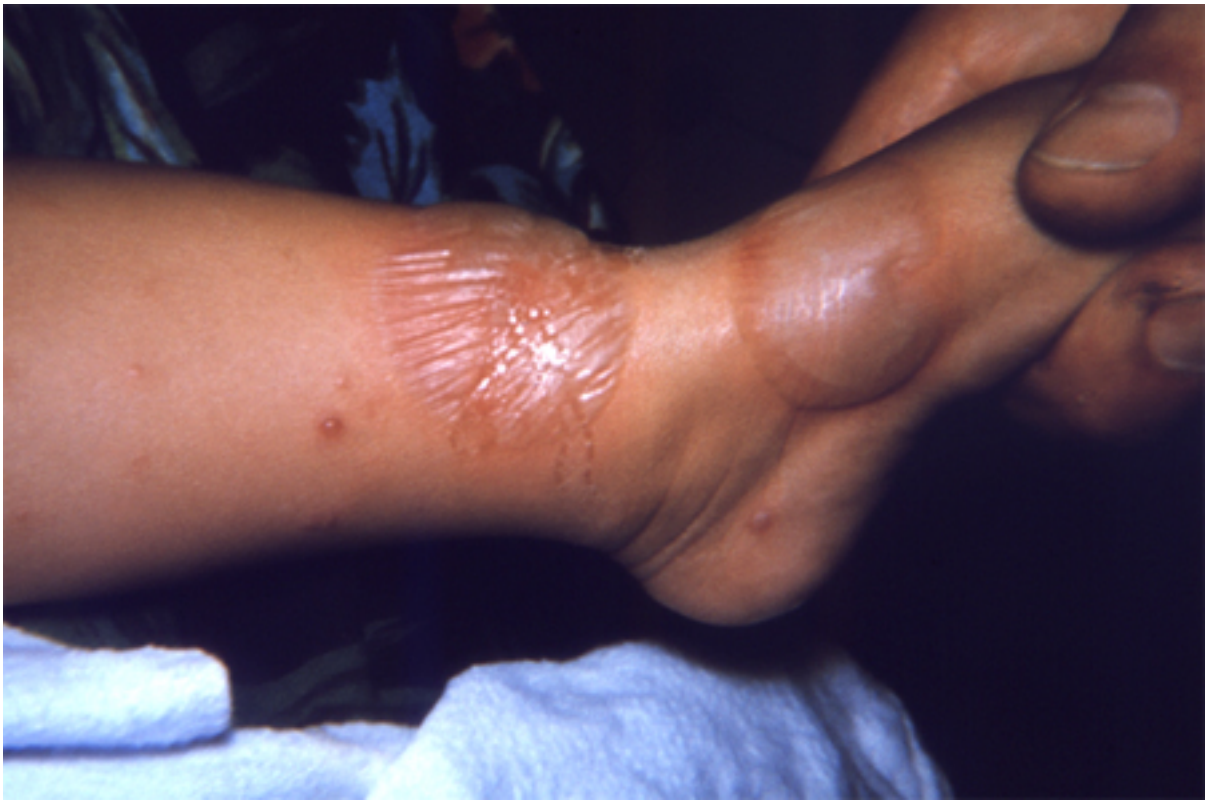

Figure 8: Bullous erythema multiforme

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Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

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Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

Contributors:

// Authors:

Elisabeth Adderson, MD

Associate Member
St. Jude Children's Research Hospital, Associate Professor of Pediatrics, University of Tennessee Health Sciences Center, Memphis, TN
DISCLOSURES: EA declares that she has no competing interests.

// Peer Reviewers:

Elizabeth Barnett, MD, FAAP

Director of International Clinical Maxwell Finland Laboratory for Infectious Diseases
Boston Medical Center, Associate Professor of Pediatrics, Boston University School of Medicine, Boston, MA
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Suzanne M. Garland, MBBS, MD, FRCPAm FAChSHM, FRANZCOG ad eundem

Director of Microbiological Research
Head of Clinical Microbiology and Infectious Diseases, Royal Women's Hospital, Senior Consultant of Microbiology, Royal Children's Hospital, Professor, Faculty of Medicine, Dentistry and Health, Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Australia
DISCLOSURES: SMG has received advisory board fees and grant support from Commonwealth Serum Laboratories and GlaxoSmithKline, and lecture fees from Merck and GSK. SMG has received funding through her institution to conduct HPV vaccine studies for MSD and GSK.

Robert S. Duszak, OD, FAAO

Co-Director of Residency Program and Consulting Staff
Philadelphia Veterans Affairs Medical Center, Consulting Staff, Nemours Health Clinic & Mayfair Eye Associates, Adjunct Clinical Faculty, Pennsylvania College of Optometry, Salus University, Philadelphia, PA
DISCLOSURES: RSD declares that he has no competing interests.