BMJ Best Practice

Roseola

Straight to the point of care

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Summary

Roseola is a common febrile viral illness of early childhood; it is usually caused by human herpesvirus (HHV)-6B and occasionally by HHV-7.

Roseola is characterized by 3 to 7 days of fever, often high grade (>103.0°F [39.5°C]), followed by onset of a diffuse morbilliform rash that appears with defervescence of fever. The lesions are discrete 3- to 5-mm pink-red macules and papules that commonly begin on the neck and trunk and spread to the extremities.

Roseola is usually a benign self-limited illness that has been associated with febrile seizures.

Definition

Roseola (also called exanthem subitum or sixth disease for the sixth classic pediatric exanthem) is a common early childhood febrile illness, characterized by 3 to 7 days of high fever followed by onset of rash that appears with resolution of fever. The rash consists of asymptomatic pink-red macules and papules. Febrile seizures may occur. Roseola is most commonly caused by human herpesvirus (HHV)-6B, but occasionally by HHV-7 and rarely by other viruses. HHV-6A (associated with thyroiditis), HHV-6B (roseola), and HHV-7 (roseola) are lymphotropic viruses within the *Herpesviridae* family and *Betaherpesvirinae* subfamily, and all establish latency. HHV-6A, HHV-6B, and HHV-7 can occasionally integrate into the host chromosome. Reactivation of the roseola viruses may occur with immunosuppression.

THEORY

Epidemiology

Roseola is most prevalent between 6 and 24 months of age and is rarely diagnosed before 3 months or after 4 years of age.

Human herpesvirus (HHV)-6B is found worldwide. Over 90% of children are seropositive for HHV-6B by 24 months of age.[1] Primary infection with HHV-7 occurs at an older age than HHV-6B. About 65% of children are seropositive for HHV-7 by 36 months of age.[2] By adulthood >95% of patients are seropositive for HHV-6 and 85% are seropositive for HHV-7.[3] Contemporary studies show no pattern of seasonal variance.[4] While more than 90% of children with primary HHV-6B infection have fever, only a minority develop classic roseola rash (reported as 23% in one study).[4] Most have an undifferentiated febrile illness without rash.

Etiology

Roseola is caused primarily by human herpesvirus (HHV)-6, sometimes by HHV-7, and rarely by other viruses, including coxsackievirus, echovirus, adenovirus, and parainfluenza virus. The incubation period ranges from 1 to 2 weeks.[4] [5]

There are three species of human herpesvirus in the *Roseolovirus* genus: HHV-6A (associated with thyroiditis), HHV-6B (roseola), and HHV-7 (roseola). These are part of the *Herpesvirinae* family and *Betaherpesvirinae* subfamily.[6] [7]

Pathophysiology

Human herpesvirus (HHV)-6B and HHV-7 are most likely to be spread through respiratory secretions in asymptomatic contacts. HHV-6B and HHV-7 DNA may be found in saliva for extended periods of time following primary infection. These viruses are double-stranded DNA viruses with tropism for CD4+ T lymphocytes.[1] HHV-6B can infect multiple other cell types as well. It downregulates expression of CD3 on T cells, thus acting as a potential immunosuppressant. It is also a powerful TNF-alpha and interleukin-1beta inducer.[8] Following acute infection, HHV-6B remains latent in many tissues and reactivation is noted most commonly during periods of immunosuppression. Possible associations have been made between latent HHV-6B infection and some chronic conditions, however no causal evidence supports these claims.[9]

Case history

Case history #1

A previously healthy 9-month-old infant presents with a 4-day history of irritability and high fever in the range of 102°F to 104°F (39°C to 40°C), peaking in the early evening. On day 4 of illness his fever and irritability resolved, and he then developed a rash consisting of 2- to 5-mm red macules on his trunk that spread to his proximal extremities. The rash faded over a day and he has remained well.

Other presentations

Febrile seizures occur in 10% to 15% of infants with roseola. Other findings include a bulging anterior fontanelle; oropharyngeal inflammation and ulcers; mild posterior cervical, postauricular, or occipital lymphadenopathy; tympanic inflammation; cough; rhinorrhea; and mild diarrhea. Encephalitis can occur, but very rarely. Some polymerase chain reaction viral panels have become available for testing cerebrospinal fluid samples of patients with encephalitis. These panels frequently include HHV-6. In the authors' experience, they have occasionally found HHV-6 positives in infants with very mild encephalitis and, on one occasion, severe encephalitis.

Approach

Roseola is usually diagnosed based on the classic presentation of a previously healthy infant, 6 to 24 months of age, with a sudden onset of high fever for 3 to 7 days. Resolution of fever is associated with the onset of discrete red macules and papules on the trunk and extremities. For patients with this classic presentation, a clinical diagnosis can be made based on physical examination findings and history (usually at the time of resolution of fever). Diarrhea and upper respiratory symptoms are also reported though not diagnostic. Laboratory investigation is seldom necessary. A CBC with differential may initially show an elevated WBC, which may evolve into a low WBC with relative neutropenia and atypical lymphocytosis.[10] There may be sterile pyuria in some infants with roseola.[13]

Physical examination

Physical examination findings are limited early in the disease course, though up to 15% of children will present with an episode of febrile seizure. An enanthem (intra-oral eruption) composed of red papules on the soft palate and uvula (Nagayama spots) has been described.[10] [14] The typical exanthem, which occurs 3 to 5 days after the onset of the illness, consists of pink-red macules and papules on the trunk, neck, and proximal extremities, and occasionally on the face. The exanthem fades within a few hours to days. Other signs associated with roseola include tympanic inflammation, periorbital edema, bulging anterior fontanelle, lymphadenopathy (cervical, postauricular, and/or occipital), and abdominal pain.[15]

Laboratory investigations

Serology is rarely performed and may be needed only in children with complicating medical factors (e.g., encephalitis). Measuring IgM levels is not reliable in the diagnosis of human herpesvirus (HHV)-6 or HHV-7 infection. IgG is of diagnostic value for HHV-6/HHV-7 primary infections when it goes from undetectable to positive.[9] Polymerase chain reaction detection of viral DNA may be of use, especially in those who are immunosuppressed (e.g., post bone marrow transplant), and is an adjunct to serology. However, distinguishing between active and latent infection can be problematic; nevertheless, special polymerase chain reaction assays are available to distinguish between latent (chromosomally integrated [ciHHV-6]) versus active infection. Other diagnostic tools include viral culture and electron microscopy, though these are used infrequently in the acute clinical setting. Viral culture is not often used because, in isolation, it cannot accurately distinguish acute primary HHV-6/HHV-7 infection from latent or persistent infection. Also, it is not commercially available.[16]

Skin biopsy

This is rarely performed. Biopsy of the affected skin shows findings of nonspecific viral exanthema with a sparse, lymphocytic perivascular and dermal infiltrate.

History and exam

Key diagnostic factors

age under 2 years (common)

- Human herpesvirus (HHV)-6 is found worldwide and 90% of children are seropositive by the age of 24 months.[1]
- Primary infection by HHV-7 occurs in approximately 50% of children by the age of 2 years.[10]

immunosuppression (common)

- Reactivation of the HHV-6 latent virus is most commonly seen in patients who are immunosuppressed or in the weeks to months following bone marrow or organ transplantation.[12]

high fever (common)

- A sudden onset of high fever >103.0°F (39.5°C).[3]
- Typically peaks in early evening and persists for 3 to 7 days.

exanthem (common)

- The typical exanthem presents with the resolution of fever and consists of 3- to 5-mm pink-red macules and papules on the trunk, neck, and proximal extremities, and occasionally on the face.

Other diagnostic factors

diarrhea (common)

- Seen in up to 65% of children.[12]

abdominal pain (common)

- Abdominal pain is common.[15]

Nagayama spots (common)

- An enanthem composed of red papules on the soft palate and uvula has been described.
- Junctional uvulo-palatoglossal ulcers have also been described.

tympanic membrane inflammation (common)

- Historically noted in the large majority of children with roseola.

upper respiratory symptoms (common)

- Mild cough and rhinorrhea.

seizures (uncommon)

- Up to 15% of children will present with a seizure episode, and primary HHV-6 infection has been associated with approximately one third of first-time childhood febrile seizures.[12] [17]
- Other focal neurologic signs including encephalopathy and altered level of consciousness have been reported.

periorbital edema (uncommon)

- Most common during the febrile phase.

bulging anterior fontanelle (uncommon)

- Present in up to 25% of infants (in whom the skull hasn't already fused).[14]

cervical, occipital, or postauricular lymphadenopathy (uncommon)

- Cervical, occipital, and postauricular lymphadenopathy has been described.

Risk factors

Strong

age under 2 years

- Human herpesvirus (HHV)-6 is found worldwide and 90% of children are seropositive by the age of 24 months.[1]
- Primary infection by HHV-7 occurs in approximately 50% of children by the age of 2 years.[10]

immunosuppression

- Reactivation of the HHV-6 latent virus is commonly seen in patients who are immunosuppressed or in the weeks to months following bone marrow or organ transplantation.[11] [12]

Investigations

1st test to order

Test	Result
no initial test • Roseola can almost always be diagnosed based on the classic presentation of a previously healthy infant, 6 to 24 months of age, with a sudden onset of high fever for 3 to 7 days, followed by development of discrete red macules and papules on the trunk. For patients with this classic presentation, a clinical diagnosis can be made based on physical examination findings and history (usually at the time of loss of fever). Laboratory investigation is seldom necessary.[10]	**clinical diagnosis**

Other tests to consider

Test	Result
viral culture • Not often employed in clinical diagnosis, because, in isolation, it cannot accurately distinguish acute primary human herpesvirus (HHV)-6 infection from latent or persistent infection. Also, not commercially available.[16] • Viral culture is performed on isolated peripheral blood mononuclear cells with a high sensitivity and specificity.	**positive culture**
antibody detection • Seroconversion in paired serum specimens via enzyme immunoassay indicates recent infection. • Measuring IgM levels is not reliable in the diagnosis of HHV-6 or HHV-7 infection. • A significant increase in titer with enzyme immunoassay with a positive PCR result in a young infant is also highly suggestive of recent infection. • Indirect immunofluorescence and complement fixation immunofluorescence are infrequently used, and results depend on the skill of the interpreter.[2] [18] IgG antibody avidity testing by immunofluorescence may also help to identify recent infection with HHV-6 or HHV-7. This test is rarely needed, though it may be useful in children with complicating medical factors (e.g., encephalitis) where diagnosis is uncertain.	**high HHV-6- or HHV-7-specific IgG levels**

Emerging tests

Test	Result
polymerase chain reaction (PCR) • Viral DNA amplification (PCR) may be useful in conjunction with a single negative serum serology specimen in detecting acute infection.[2] PCR viral panels, which may include HHV-6, are available at some institutions for testing cerebrospinal fluid in patients with encephalitis. Comparison of viral copy number over time can be helpful in diagnosis of reactivation in people who are immunosuppressed.	**may be positive for HHV-6**
immunohistochemistry • Cells with an active infection will stain positively when immunohistochemistry is performed on tissues with monoclonal antibodies to HHV-6. • This test is rarely needed, though it may be useful in children with complicating medical factors (e.g., encephalitis) where diagnosis is uncertain.	**positive**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Measles	• Typically accompanied by a prodrome of significant cough, coryza, and conjunctivitis and an enanthem consisting of gray-white papules on the buccal mucosa (Koplik spots). • The exanthem is an erythematous maculopapular eruption that spreads cephalocaudally and usually persists for 1 week before it begins to clear.[19]	• Diagnosis is usually clinical, based on physical examination and history. • Virus isolation can be obtained from a nasopharyngeal swab, or diagnosis can be confirmed by a serologic assay for measles-specific antibodies.[19]
Enterovirus	• The exanthem associated with enterovirus (especially echovirus) is a nonspecific, maculopapular, erythematous eruption. • Enterovirus often presents as aseptic meningitis. • Other enteroviruses may present with herpangina or vesicular lesions. • Primary differentiation is made based on history, but can be difficult.[20]	• Polymerase chain reaction or rising serologic titers may be used for enterovirus identification in serious cases. • In many uncomplicated cases, history and physical examination are sufficient.[20]
Epstein-Barr virus	• The exanthem is nonspecific erythematous macules and papules and occasionally urticaria. • The primary differentiation is made based on history. • The eruption of Epstein-Barr virus (EBV) often presents after administration of ampicillin or other antibiotic therapy.[21]	• Acute EBV is usually diagnosed with a positive heterophile test (or a rapid Monospot), or with specific serology in the child under 4 years of age. • Atypical lymphocytes are common on examination of a peripheral smear. • EBV-specific antibodies are used in patients with a negative Monospot or in cases with atypical symptoms.[21]
Rubella	• Presents with a nonspecific exanthem of rose-pink macules that spread from the face to the trunk. • Tender cervical, occipital, and/or postauricular lymphadenopathy is common. Joint involvement	• Serology will detect antirubella IgM or a 4-fold increase in antirubella IgG antibodies.[19]

Condition	Differentiating signs / symptoms	Differentiating tests
	is seen in older adolescents and adults.[19]	
Meningococcemia	• Seizures, fever, and signs of encephalopathy can mimic roseola. • Usually associated with a rapidly progressing purpuric eruption and meningeal signs or sepsis.	• Cultures of cerebrospinal fluid and blood yield meningococcus.

Approach

In general, symptomatic control is the mainstay of therapy for roseola and includes antipyretics and maintenance of oral hydration. Acetaminophen or ibuprofen can be given as needed.

Immunocompromised patients

Herpesvirus antiviral drugs, such as ganciclovir, valganciclovir, and foscarnet, have been used to treat human herpesvirus (HHV)-6 infection in patients who are immunocompromised and in infants with severe encephalitis; however, their efficacy has not been evaluated in clinical trials.[3] [5] These antivirals are most commonly used in the solid organ and hematopoietic stem cell transplant patient population, due to morbidity from HHV-6 reactivation, including hepatitis, encephalitis, and graft rejection.[22] [23]

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)
all patients		
	1st	**antipyretics + oral hydration**

MANAGEMENT

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

all patients

1st **antipyretics + oral hydration**

Primary options

» acetaminophen: infants and children: 10-15 mg/kg orally every 4-6 hours when required, maximum 75 mg/kg/day; children >12 years of age: 325-650 mg every 4-6 hours when required, maximum 4000 mg/day

OR

» ibuprofen: children >6 months of age: 5-10 mg/kg orally every 6-8 hours when required, maximum 40 mg/kg/day; children >12 years of age: 200-400 mg every 4-6 hours when required, maximum 1200 mg/day

» Symptomatic treatment during the febrile phase of the illness.

» Aspirin is avoided because of risk of Reye syndrome.

» Oral hydration is encouraged.

Emerging

Antiviral T-cell transfer

One study has reported proof-of-concept treatment of reactivated HHV-6 (and other viruses) in patients who are severely immunocompromised, using adoptive transfer of antiviral allogeneic cytotoxic T cells.[24] This approach relies upon having local expertise and resources to perform the ex-vivo stimulation and selection of antiviral-specific T-cell clones, and is a not particularly quick approach to the treatment of severely ill patients, with the clonal expansion step taking 9 to 11 days. It may, however, work well in those situations where antiviral drug therapy can provide some degree of effective therapy while the adoptive transfer is prepared. A risk of this approach is graft-versus-host disease (GVHD). One patient in this small study of 11 did develop mild, easily controlled cutaneous GVHD. Studies are currently ongoing regarding this approach.

Primary prevention

Human herpesvirus (HHV)-6B and HHV-7 are both found worldwide and are extremely common; no effective preventive strategies have been identified.

Secondary prevention

No specific secondary prevention measures are likely to be effective, but hand washing and general hygiene are encouraged as with any other viral illness.

Patient discussions

As in any viral illness, it is important for parents to help affected children rest and maintain adequate oral hydration. Reassurance that this is a self-limited condition should be provided. There are no recommended follow-up guidelines for uncomplicated roseola.

Monitoring

Monitoring

In uncomplicated roseola, no monitoring guidelines are recommended.

Complications

Complications	Timeframe	Likelihood
seizures	**short term**	**medium**
In one study conducted in the US, 13% of children with primary human herpesvirus (HHV)-6 infection experienced seizures, which sometimes were prolonged or recurrent.[12] It is undetermined if these seizures are purely febrile seizure episodes or if there is another causative factor related to the infection itself. Up to approximately one third of first-time childhood febrile seizures may be attributed to primary HHV-6 infection.[12] [17] The majority of isolated febrile seizures in otherwise healthy children do not require treatment or further workup, but consultation with a pediatrician is recommended in each case. Emergency evaluation is recommended in the setting of more than one seizure episode, seizure episodes lasting >15 minutes, or seizures in conjunction with any other complicating factors.[27]		
reactivation of latent virus	**long term**	**medium**
Reactivation occurs frequently in solid organ and bone marrow transplant recipients, most commonly in the first month after transplantation. HHV-6 is also associated with encephalitis and related central nervous system disease in patients who are immunocompromised.[11] [28] The most common presentation of HHV-6 reactivation is either an asymptomatic or mild febrile illness, often with rash, in patients who are immunocompromised.		
progression of HIV disease	**long term**	**medium**
HHV-6 reactivation is more common in patients with advanced AIDS. There is controversy regarding whether HHV-6 infection is a factor in HIV disease progression.[5]		

Prognosis

The large majority of patients experience an acute febrile illness that generally resolves without sequelae. There is very little risk of recurrence in healthy individuals. However, up to 15% of children with roseola experience seizures. For example, in one series, 13% of children with roseola experienced seizures, which may be prolonged or recurrent.[25]

FOLLOW UP

Following a primary infection, the virus becomes latent in peripheral blood mononuclear cells, and reactivation after solid-organ or bone marrow transplantation has been associated with morbidity.[26]

Diagnostic guidelines

International

Viral exanthems (http://www.pcds.org.uk/clinical-guidance/viral-exanthems) [15]

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Human herpesvirus 6 (including roseola) and 7 (https://publications.aap.org/redbook) [3]

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Treatment guidelines

International

Human herpesvirus 6 (including roseola) and 7 (https://publications.aap.org/redbook) [3]

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Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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