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A REVIEW ON- ROSEOLA INFANTUM DISEASE

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INTRODUCTION

Roseola infantum was first described by Zahorsky (1910), and since this time cases have been recorded by many writers both in America and Europe but the disease has received little recognition in England. It has been labelled exanthem subitum and sixth disease but Zahorsky (1947) and others have put forward a plea for the retention of the name roseola infantum or the 'rose rash of infancy'.

The infectious nature of the disease was discussed by Barenberg and Greenspan (1939), who report it to be periodically epidemic in an institution for children and describe an epidemic of twentyseven cases occurring over a period of three months, the incidence of infection in the respective wards being 35 per cent. and 45 per cent. The incubation period was five to fifteen days with an average of twelve days. Cushing (1927) describes an epidemic in Montreal with incubation periods between eight and fourteen days.[1]

Roseola infantum is a common disease of childhood caused by a primary infection with human herpesvirus 6 (HHV-6) and less frequently, by human herpesvirus 7 (HHV-7). This disease, also known as exanthema subitum and sixth disease, presents in children ages six to 12 months with90% of cases occurring in children younger than two years. Caused by the B variant of HHV-6,patients with the virus classically present with an acute onset of a high-grade fever up to 40 C(104 F) for three to five days.[2] The child will experience a rapid defer vescence of the fever with accompanying nonpruritic, pink papular rash that begins on the trunk. It is found universally and has been discovered to be the cause of 10% to 45% of febrile illness in infants. Due to the high fever and the ability of the virus to cross the blood-brain barrier, 15% of children will also experience an acute febrile seizure during the febrile phase of the illness. Roseola infantum is clinically diagnosed, self-limited illness that can be treated symptomatically. HHV-6 will like lyremain latent in immune competent patients but can be a major cause of morbid. Roseolo viruses is a linear, double stranded DNA virus belonging to the order Herpes virales, family Herpes viridae and the subfamily Beta herpes virinae. These are of two types named HHV-6 & HHV-7. HHV-6 has further been categorized as HHV-6A & HHV-6B. These viruses were first isolated either from patients suffering from lympho proliferative diseases and AIDS (HHV-6) or from CD4+ T cells taken from peripheral blood lymphocytes (HHV7). Roseolo viruses cause a rash developing disease in human known as Roseola infantum whose entire disease cycle is completed within 3 to 6 days. Once after an infection, the Roseolo viruses remain latent for lifelong. Virus may cause cancer and tumor suppressor genes may be reactivated. Studies have shown that some of these hidden viruses if reactivated in future develop severe complications in human. The present study discusses the Roseolo viruses causing diseases, complications and cancer in human.[3]

Roseola

Other names :- Exanthema subitum roseola infantum, sixth disease, baby measles, rose rash of infants, three-day fever
Specialty :- Infectious diseases
Symptoms :- Fever followed by rash
Complications :- Febrile seizures
Usual onset :- Before the age of three
Duration :- Few days

Causes :- Human herpesvirus 6 (HHV-6) of herpesvirus 7)
Diagnostic method :-Typically based on symptoms
Differential diagnosis:- Measles, rubella, scarlet fever
Treatment :- Supportive care

OBJECTIVES

- Review the etiology of roseola infantum.
- Describe the presentation of a patient with roseola infantum.
- Summarize the management of roseola infantum.
- Explain the importance of enhancing care coordination amongst inter professional team members to improve outcomes for patients affected by roseola infantum.

ETIOLOGY

The causative agent of roseola infantum was discovered in 1986. The Roseolovirus genus of the beta herpes virus hominis subfamily contains human herpes virus (HHV)-6 and HHv-7. HHV6 has 2 variants: HHV -6A and HHV-6B. Their major differences are cellular tropism. Debate has existed whether they represent 2 species. HHV-6A infection is rarely associated with roseola infantum. HHV-6A is associated with infection in adults who are immune copromised. HHV-6A infection occurs later in life, and details are lacking. HHV-6B is the cause of roseola in infants. Because sero positivity is nearly 100% in older children, most primary infections with HHV-6B are asymptomatic. HHV-7 has been identified in a few cases of roseola infantum. Recurrences of roseola infantum are not common. A welldocumented case of a 13month-old child who had a second episode of roseola exists. In the acute phase of the second episode, HHV-7 was identified and excreted in the saliva. This was followed by excretion of HHV6. Human herpesvirus 6, a virus found in the Herpesviridae family, causes roseola infantum. HHV-6 is a beta herpesvirus, closely related to human cytomegalovirus (HCMV) and human herpesvirus 7 (HHV-7). This group of beta herpesvirus is known to have less cell tropism than other members of the Herpes viridae family. HHV-6B contains a linear, double-stranded DNA genome and is flanked by direct terminal repeats that contain reiterations of a hexa nucleotide, GGGTTA. These reiterations have been thought to play a role in the maintenance of the viral genome in latently infected cells.[4]

In 1941, Breese reported vigorous attempts to isolate a filterable virus from three children with preeruptive roseola. These studies included extensive animal inoculations, but no viral agents were uncovered. In 1950, Kempe and associates reported the passage of the illness to a 6-month-old susceptible infant by thein travenous injection of serum from an 18-monthold child with preeruptive roseola. Febrile illnesses without exanthem also were produced in monkeys with serum and throat washings from a child with the syndrome. In similar experiments, He llstrom and Vahlquist produced the syndrome in three children aged 6 to 9days after the intramuscular administration of blood from typical roseola cases.

In electron microscopy studies, Reagan and associates observed uniform virus like particles (100 to 110 nm) in the blood of an 18-month-old child with the syndrome. Febrile illness was produced in two monkeys after concentrated virus-containing material was inoculated.

Since the advent of modern diagnostic virology in the early 1950s, numerous viral agents have been recovered from children with roseola. In 1951, Neva and associates studied an epidemic exanthematous illness caused by echovirus 16, in which many of the illnesses were characteristic of roseola. In 1954, Neva observed additional cases of roseola-like illness associated with echovirus 16 infection. In 1974, Hall and colleagues reported four additional echovirus 16 infections with clinical manifestations of roseola. The reporting of roseola in Rochester, New York, nearly doubled during the time of echovirus 16 activity in the area. Roseola-like illnesses that also have been associated with entero viruses are caused by coxsackie virus A6, A9, B1, B2, B4, andB5 and echovirus 9, 11, 25, 27, and 30. Outbreaks of roseola that occur in the summer and fall probably are caused by enteroviral infections.[5]

PATHOPHYSIOLOGY

In the primary infection, replication of the virus occurs in the leukocytes and the salivary glands. HHV-6 is present in saliva. A study monitoring HHV-6 and HHV-7 DNA in saliva samples during the acute and convalescent phases demonstrated a significantly higher rate of detection in children aged 3-9 years versus adults, suggesting that children in the convalescent phase of roseola infantum are the more probable source of infection. Early invasion of the CNS is believed to occurs, thus accounting for seizures and other CNS complications. Evidance suggests that high serum levels of matrix metallo proteinases 1 in infants infected with HHV-6 may may lead to blood-brain barrier dysfuntion, which may result in febril seizures. Study of cerebrospinal fluid levels of interleukin 1 beta and basic fibroblast growth factor may indicate a role in contributing to HHV-6B growth and the onset of encephalitis.[6]

Although rare in the primary disease of infancy, generalized organ involvement has been reported with gastrointestinal, hematopathic syndromes; hepatitis; and hepato splenomegaly. Following the acute primary infection, HHV-6 remains latent in lymphocytes and monocytes and has been found in low levels in many

tissues. Peripheral blood mononuclear cell cultures develop enlarged balloon like cells. Cells supporting virus growth are CD4+T lymphocytes. HHV-6 down-regulates the host immune response through several mechanisms, including molecular mimicry by production of functional chemokine and chemokine receptors. The two variants of HHV-6 are A and B. The genomes of HHV-6A/B have been sequenced. HHV-6B, the main cause of roseola, consists of 97 unique genes. CD46 is the cell receptor for HHV-6, which imparts the virus broad tissue tropism. A possible association of HHV-6 and multiple sclerosis has been suggested but is still inconclusive. HHV-6 has been isolated in Kaposi sarcoma (caused by human herpes virus 8), in which it may contribute to tumor progression. HHV-6 may facilitate oncogenic potential in lymphoma and has been associated with chronic fatigue syndrome.

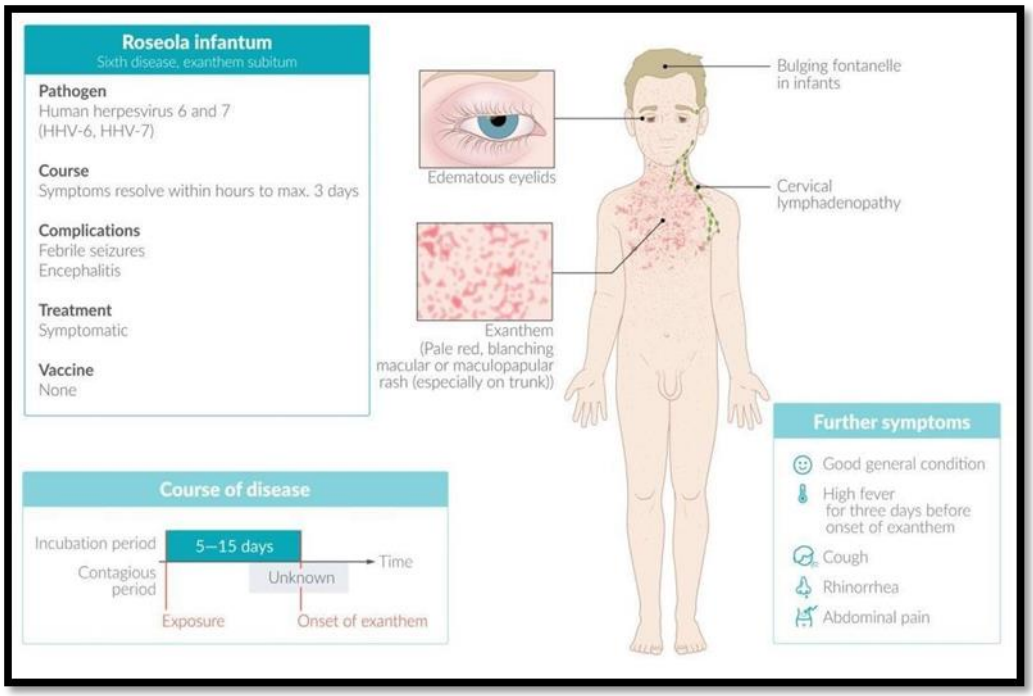


Diagram Of Roseola Infantum

The pathophysiology of roseola is unknown. Watson, in the pre–HHV-6 era, suggested that roseola is not an infection caused by one particular pathogen but is instead the result of an immunizing reaction against many different viruses. He also suggested that the rash is caused by the neutralization of virus in the skin atthe end of the period of viremia.

Viremia is common in HHV-6, HHV-7, entero viral, and adenoviral infections; thus a reasonable conclusion (as originally suggested by Watson) is that the rashin roseola is related to an immunologic event resulting from the virus that is localized in the skin. Why the pattern of fever and then rash with defervescence isso clearly age dependent is unknown. Most of the viruses that in the past have been associated with roseola cause other exanthematous manifestations in older patients.[7]

ONCOLOGY

Roseolo viruses have got their own distinguishing ability to be integrated in human chromosomes. They are covalently integrated into subtelomeric region of human chromosomes in about 1% of the general population. Further, the process of gametogenesis and the fusion of gametes transfer the same integration to the next generation increasing the risk of developing three times angina in humans. Some of other ailments and diseases including cancer caused by these viruses are briefly summarized as under.[8]

1. HHV-6 has been found to be associated with the patients suffering from multiple sclerosis, a neuro inflammatory disease, causing demyelination in brain. Further, it has been detected in some kind. The human p53 protein functions as a tumor suppressor. The persons not having this protein experience a higher incidence of cancer, a phenomenon known as “LiFraumeni syndrome”. Deregulation of p53 protein factor is associated with cancer. For example, two of the HHV-6 viral gene products named U14 and ORF-1 proteins bind with p53 protein and inactivating it to cause cancer.
2. HHV-6 has also been implicated as a cofactor in chronic fatigue syndrome (CFS). CFS is a debilitating disease of unknown etiology showing neurological, immunological and metabolic findings. Scientists have shown an association between CFS and HHV-6. But, largely, it remains found to be unproven.
3. Similarly, the cells infected with the roseolo viruses are comprehensively being engaged in complete

replication cycle to cause disturbed apoptosis and necrosis developing cancer and death of cells respectively.
4. In addition, HHV-6 develops fibromyalgia in AIDS patient.
5. Researchers have shown that T-cells are highly infectable by HHV-6 virus.
6. Further, Roseoloviruses has been found to be associated with the pathogenesis of a common neurological disorder as epilepsy. HHV-6 has some connection with temporal lobe epilepsy. Further, it has also been reported that the virus enters the brain via olefactory pathways. But, it still requires more researches to prove the link. These viruses have also been found to be linked with Alzheimers.
7. Roseolo viruses can also cause encephalitis and brain dysfunction in both immune ocompetent and immune compromised individuals.
8. HHV-6 has also been found as an important factor for female infertility.
9. Hoshimoto thyroiditis disease has been found to be linked with HHV-6. This is a kind of thyroid ailment where increased lymphocytes are found.
10. Finally, there are reports that Roseolo viruses have frequently been reactivated in transplant recipients.

EPIDEMIOLOGY

Human herpes virus 6 has been found to be the cause of febrile illness in 10% to 45% of in fantsin the United States. A 2005 population-based study indicated that 40% of HHV-6 infection is seen by age twelve months and 77% is seen by age 24 months. This study also reported that the virus is seen in both males and females, but was more common in females and children with older siblings. The peak incidence of the virus is in the spring and fall seasons. Transmission occurs primarily through saliva via respiratory droplets.

Primary infection with HHV-6 is acquired rapidly by essentially all children following the loss of maternal antibodies in the first few months of infancy, 95% of children being infected with HHV-6 by 2 yr of age. The peak age of primary HHV-6 infection is 6-9 mo of life, with infections occurring sporadically and with out seasonal predilection. Infection with HHV-7 is also widespread but occurs later in childhood and at a slower rate; only 50% of children have evidence of prior infection with HHV-7 by 3 yr of age. Sero prevalence reaches 75% at 3-6 yr of age. In a small study of children with primary HHV-7 infection, the mean age of the patients was 26 mo, significantly older than that of children with acute HHV-6 infection.[9]

Although it is presumed that children acquire primary infection with HHV-6 and HHV-7 from the saliva of asymptomatic adults, congenital infection with HHV-6occurs in 1% of newborns. Two mechanisms of vertical transmission of HHV-6 have been identified, trans placental infection and chromosomal integration (CI-HHV6). HHV-6 is unique among the human herpes viruses in that it is integrated at the telomere end of human chromosomes at a frequency of 0.2-2.2% of the population and is passed from parent to child via the germline. Chromosomal integration has been identified as the major mechanism by which HHV-6 is vertically transmitted, accounting for 86% of congenital infections, with one third due to HHV-6 variant A. The clinical consequences of chromosomal integration or transplacental infection with HHV6 have yet to be determined. In one series of infants identified with HHV-6 congenital infection, no evidence of disease was present in the early neonatal period. Congenital infection with HHV-7 has not been demonstrated. DNA of both HHV-6 and HHV-7 has been identified in the cervical secretions of pregnant women, suggesting an additional role for sexual or perinatal transmission of these viruses. Breast milk does not appear to play arole in transmission of either HHV-6 or HHV-7.[10]

DIAGNOSIS

The diagnosis of roseola is made clinically based on the presence of the two phases: fever and rash. Laboratory testing is seldom used as the results do not alter management of the disease. An exception is in people who are immune compromised in who serologic tests with viral identification can be used to confirm the diagnosis. Roseola should be differentiated from other similarappearing illnesses, such as rubella, measles, fifth disease, scarlet fever, and drug reactions. This differentiation may be determined based on symptoms.

Roseola is diagnosed clinically based on the characteristic features: fever for three to five days followed by abrupt defervescence and development of a rash in a young childe.

Laboratory evaluation is seldom necessary. In most patients with roseola caused by human herpes virus 6 (HHV-6), by the time the rash appears, viremia has resolved. (See 'Pathogenesis' above.)[11] Virologic studies may be warranted in immune compromised patients and those with an atypical presentation or complications. The diagnostic approach for potential pathogens is discussed separately

- HHV-6 (see "Human herpesvirus 6 infection in children: Clinical manifestations; diagnosis; and treatment", section on 'Diagnosis').
- HHV-7 (see "Human herpes virus 7 infection", section on Diagnosis').
- Enterovirus (see "Clinical manifestations and diagnosis of enterovirus and parechovirus infections", section on Laboratory diagnosis').
- Adenovirus (see "Diagnosis, treatment, and prevention of adenovirus infection") .
- Parainfluenza virus type 1 (see "Parainfluenza viruses in children", section on 'Diagnosis').

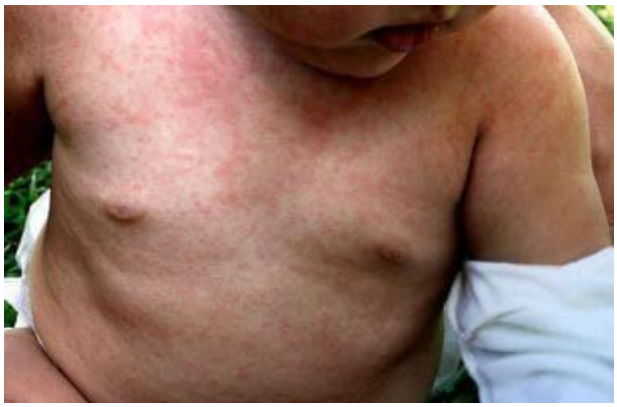
Differntial Dignosis: The differential diagnosis of the roseola rash includes several other infectious exanthems and drug allergy. Roseola generally can be distinguished

from these conditions by epidemiologic or clinical features (eg, age group, temporal relation between fever and rash). Roseola also must be distinguished from urinary tract infection (UTI) in children who present with fever before the onset of rash and are found to have pyuria on during the evaluation of fever.[20]

Infectious exanthems — The infectious exanthems to be considered in the differential diagnosis of roseola include

- Rubella is characterized by simultaneous occurrence of lowgrade fever and rash. The rash classically begins on the face and spreads down the body. Rubella occurs in children who are unimmunized or under immunized. (See "Rubella").
- Rubeola (measles), which is distinguished by a prodrome of coryza, cough, and Koplik spots. The rash classically begins on the face and spreads down the body; it begins as small lesions that enlarge and coalesce. Rubeola occurs in children who are unimmunized or under immunized. (See "Measles: Clinical manifestations, diagnosis, treatment, and prevention").
- Enteroviral infections, which usually occur in epidemics in the spring, summer, and fall (typically with a peak in mid- to late summer) and occur in children of all ages, not just young children. Hand, foot, and mouth syndrome is the classic entero viral rash. (See "Clinical manifestations and diagnosis of entero virus and parecho virus infections", section on 'Laboratory diagnosis' and "Hand, foot, and mouth disease and herpangina: An overview").[12]

SYMPTOMS

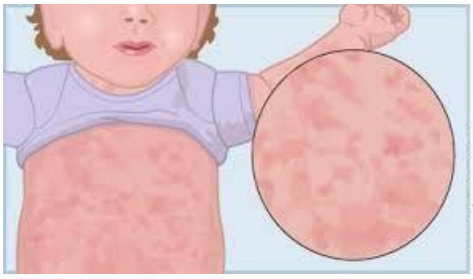


• Fever

Symptoms begin with a three to six day febrile illness. During this time, temperatures can peak above 40 °C and children can experience increased irritability with general malaise.[5] However, many children in the febrile phase feel well, engaged, and alert. For these patients, fever is usually diagnosed incidentally. The most common complication (10-15%of children between 6 and 18 months) and most common cause of hospitalization in Signs and symptom s children with primary infection of HHV-6Bis febrile seizures which can precipitate status epilepticus due to the sudden rise in body temperature.

• Rash

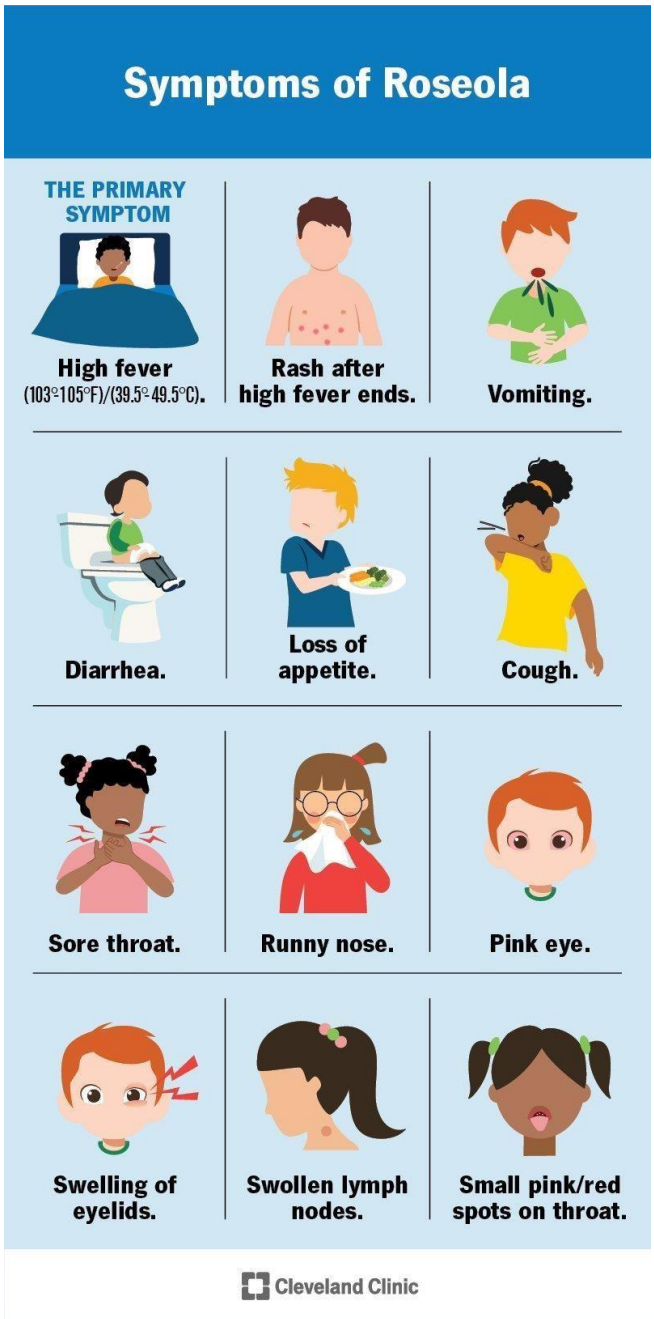
Once the febrile phase subsides, a rash develops. In some cases, the rash can present after one or two days after the fever resolves. The rash is classically described as an erythematous. Morbilli form exanthem and presents as a distribution of soft pink, discrete, and slightly raised lesions each with a 2-5mm diameter. It classically begins on the trunk (torso) and spreads outward to the neck, extremities, and face. This pattern is referred to as a centrifugal spread. Usually, peeling and itching are not characteristic of this rash. This phase can last anywhere from several hours to 2 days.



• Other symptoms

A small percentage of children acquire HHV-6 with few signs or symptoms of the disease. Children with HHV-6 infection can also present with myringitis (inflammation of the tympanic membranes), upper respiratory symptoms, diarrhea, and a bulging fontanelle. In addition, children can experience pharyngitis with lymphoid hyperplasia seen on the soft palate and

swelling of the eyelids. These symptoms usually present during the febrile phase of roseola. Cervical and post occiptal lymphadenopathy can also 2–4 days after the onset of the febrile phase. In rare cases, HHV6 6 childhood and can show signs of nonnucleosis.[13] be seen, but this generally presents.



PREVENTION

Hygiene: Roseola may be caused by several viruses. Transmission of human herpes virus 6 (HHV-6), the most common cause, probably results from asymptomatic shedding of virus in secretions of close contacts, which is difficult to prevent. The other viruses that cause roseola typically are spread through respiratory secretions or the fecal-oral route. Simple hygienic measures, such as hand washing, may help to prevent spread. (See "Epidemiology, pathogenesis, treatment, and prevention of enterovirus and parecho virus infections" and "Diagnosis, treatment, and prevention of adenovirus infection", section on 'Prevention').[14]

Child care: There is no recommended period of exclusion from out-of-home child care for children with roseola. Children with sporadic cases of roseola are not considered to be contagious. Since most roseola infections occur in young children, it can help to

- Keep your child home if they are not feeling well.
- Wash your and your child's hands frequently.
- Teach your child to use tissues and then wash their hands, or cough and sneeze into their elbow.

- Avoid sharing cups or utensils with others, and encourage your child to do the same.
- Clean and disinfect high touch surfaces regularly (like doorknobs or railings).
- Clean and disinfect toys.[18]

Information for Patients

Up to date offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.[15]

TREATMENT

Roseola infantum is a common paediatric disease caused by the Roseoloviruses. Though, the primary infections of the Roseolo viruses do not require any treatment, other complications arising after reactivation of the viruses are being treated with the help of an antiviral ganciclovir. It can also reduce the risk of reactivation in high risk transplant patients [Joshua and Danielle 2014]. Currently, an effective vaccine is utmost needed for the prevention and treatment of Roseolo viruses and Roseola infantum respectively.

There is no specific treatment for roseola infantum. The majority of cases of roseola infantum aremild and selflimited. Treatment is supportive with rest, maintaining fluid intake and anti pyretics such as acetaminophen or ibuprofen to control the fever. Due to the rash likely being nonpruritic, treatment is unnecessary. There is currently no vaccination or antiviral therapy for the acute phase of this virus.

Adequate hand washing is very important to prevent the spread of the diseasead of the disease.[16]

Most cases of HHV-6 infection improve on their own. Because of this, supportive care is the mainstay treatment. The febrile phase can be managed using acetaminophen to control fever and prevent spikes in temperature which can lead to febrile seizures. In the case of febrile seizures, medical advice should be Treatment sought, and treatment aggressively pursued. Antiepileptic drugs are not recommended for patients who develop seizures from Roseola.[17]

Once children have entered the rash phase, reassurance is important as this indicates resolution of the infection. If encephalitis occurs in immune compromised children, ganciclovir or foscarnet have inconsistently shown usefulness in treatment. Treatment of children who are immune compromised centers around decreasing their levels of immune suppression as much as possible.

CONCLUSION

Roseoloviruses cause a disease in children known as Roseola infantum. Almost, all children of the world have been infected with the same virus at least once in their lifetime with lifelong latencies in the same individuals. Further, the extra quality being acquired by this virus to be integrated with the human chromosomes enlarges the risk of reactivation causing complications developing several diseases including cancer in future course of time.

Unfortunately, no vaccines have so far been discovered for the prevention and treatment of Roseolo viruses. However, some antivirals have been tried to control the disease complications. Last but not the least, as cancer often takes years, even decades to develop after a person gets an infection, there is nothing more to worry about it except to be alert. Similarly, since there is no way to know which people who have cancer causing pathogens will develop cancer, it arises from his bad luck.[19]

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