Rotaviruses, Reoviruses, Coltiviruses, and Orbiviruses

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General Concepts

Rotaviruses

Clinical Manifestations

Rotaviruses cause enteric disease with symptoms characterized by diarrhea, vomiting, abdominal discomfort, and fever, or any combination. The virus affects mainly infants and young children. Diarrhea ranges from mild to severe and can cause fatal dehydration.

Structure

The 70-nm-diameter wheel-shaped particles consist of a double-layered icosahedral capsid enclosing a core particle that contains 11 segments of double-stranded RNA, each segment representing one gene.

Classification and Antigenic Types

Rotavirus is a genus in the family Reoviridae. Rotaviruses have three important antigenic specificities: group, subgroup, and serotype. Group A rotaviruses are major pathogens in humans and animals. Ten serotypes of human group A rotaviruses are defined by neutralization of one (VP7) of the two outer capsid proteins. Of the non-group A rotaviruses (groups B through G), only groups B and C have been detected in humans; they are not an important cause of disease in infants and young children.

Multiplication

The virus enters the cell by endocytosis or by direct membrane penetration if activated by protease. Replication occurs in the cytoplasm. Removal of the outer shell of the
capsid in lysosomes activates the viral RNA polymerase. Newly assembled subviral particles acquire the outer capsid proteins by budding through the endoplasmic reticulum, and are released by cell lysis.

**Pathogenesis**

Transmission is by the fecal-oral route (and possibly the respiratory route). Reversible damage to the proximal small intestine appears as shortened villi and as sparse, irregular microvilli with a patchy, irregular but predominantly intact mucosa and as mononuclear cell infiltration of the lamina propria.

**Host Defenses**

The mechanism of immunity is not firmly established. In animals, antibody in the intestinal lumen is crucial. In humans, studies of the role of serum antibodies with protection have yielded conflicting results.

**Epidemiology**

Group A rotaviruses are ubiquitous and infect most individuals by the third year of life. They are the single most important cause of severe diarrhea in infants and young children worldwide, accounting for about 30 to 50 percent of cases requiring hospitalization or treatment. In temperate climates, incidence peaks in the winter; in the tropics, the disease occurs year-round.

**Diagnosis**

Clinical findings are nonspecific. Diagnosis depends on detecting virus in feces (e.g., by immunoassay) or on demonstrating a serum antibody response.

**Control**

Dehydration is treated by fluid and electrolyte replacement. Vaccine development is under way and appears promising.

**Reoviruses**

Reovirus infections occur frequently, but most are mild or subclinical. The role of these viruses in human disease is not clear, but they are not considered to be important agents of human disease.

**Orbiviruses, and Coltiviruses**

**Clinical Manifestations**

Four human orbiviruses or coltiviruses cause fevers. The most important is Colorado tick fever, a biphasic fever with headache, severe muscle pain, and arthralgia. Children may develop hemorrhage or encephalitis.

**Structure**
The spherical virions (diameter, 60 to 80 nm) are similar to those of rotaviruses except that the genome contains 10 or (in Coltivirus) 12 RNA segments.

**Classification and Antigenic Types**

The genera *Orbivirus* and *Coltivirus* contain 109 serotypes in 13 serogroups; four serotypes cause human disease.

**Multiplication**

Multiplication is as for rotaviruses and takes place in both the arthropod vector and the vertebrate host. Gene segment reassortment occurs among closely related serotypes.

**Pathogenesis**

Colorado tick fever coltivirus chronically infects the tick *Dermacentor andersoni*, which transmits it to humans. The virus infects bone marrow cells, arresting development of several blood cell types and sometimes causing thrombocytopenia. In young children, the virus may invade the central nervous system and cause encephalitis.

**Host Defenses**

Colorado tick fever elicits interferon and humoral antibody; the role of these and other defenses is not known.

**Epidemiology**

The distribution of Colorado tick fever, in the Rocky Mountains and western United States, matches that of its tick vector. The virus propagates in a rodent-tick cycle, with humans as secondary hosts.

**Diagnosis**

Diagnosis depends on isolation of virus from erythrocytes or detection of viral antigen on erythrocytes by immunofluorescence. Antibody appears in convalescent-phase serum.

**Control**

Control is by avoidance of tick bites.
INTRODUCTION

The family Reoviridae is composed of eight genera: Orthoreovirus, Orbivirus, Coltivirus, Rotavirus, Aquareovirus, Cypovirus, Phytoreovirus, and Fijivirus. Certain Orthoreovirus, Orbivirus, Coltivirus, and Rotavirus species infect humans; Phytoreovirus and Fijivirus species infect plants and insects; the cypoviruses (the cytoplasmic polyhidrosis viruses) infect insects, and aquareoviruses infect fish. This chapter concerns only the members of the Reoviridae known to infect humans.

Although the orthoreoviruses (referred to commonly as reoviruses), orbiviruses, coltiviruses, and rotaviruses are similar in morphology, diameter (about 70 nm), and possession of a segmented, double-stranded RNA genome, they differ in epidemiology, association with disease, and ability to be cultured. In addition, the four groups are distinct antigenically.

Rotaviruses are major agents of severe diarrhea in infants and young children in developed and developing countries. Such diarrhea can lead to dehydration that may be fatal if rehydration fluids are not available. Reovirus infections are quite common in humans, although they tend to be mild or subclinical. The extent of their role as agents of illness in humans is unclear. Four human orbiviruses or coltiviruses have been
associated with human disease. The most serious of these diseases is Colorado tick fever, characterized by diphasic fever, headache, muscle pain, anorexia, leukopenia, and weakness; some cases are complicated by encephalitis, hemorrhage, thrombocytopenia, or pericarditis; death is rare.

**Rotaviruses**

Diarrheal diseases are a major cause of morbidity in infants and young children in developed countries and a major cause of morbidity and mortality in developing countries. For example, in a family study of some 25,000 illnesses in the United States, infectious gastroenteritis was the second most common disease and accounted for 16 percent of all illnesses. The impact of diarrheal illnesses on infants and young children in developing countries is staggering. An estimate of the number of diarrheal episodes in children younger than 5 years of age in Asia, Africa, and Latin America for a 1-year period indicated that more than 450 million cases of diarrhea occurred and that 1 to 4 percent were fatal, resulting in the deaths of 5 to 18 million children. A later study in the same areas estimated 3 to 5 billion cases of diarrhea and 5 to 10 million diarrhea-associated deaths in 1 year, ranking diarrhea first among infectious diseases in the categories of both frequency and mortality, with the burden greatest in infants and young children. Despite the importance of this disease, the agents of a large proportion of diarrheal illnesses of infants and young children were not known until relatively recently. It was assumed that viruses were important because the bacterial agents known at that time, could be recovered from only a small proportion of cases during nonepidemic periods. In 1973, rotaviruses were discovered in duodenal biopsies obtained from hospitalized infants and young children with acute gastroenteritis. Subsequently, the agent was detected in stools by electron microscopy, and laboratories all over the world soon began to detect the virus in stools of a large proportion of pediatric patients with gastroenteritis. Efficient and practical tests were developed to detect rotavirus from clinical specimens, thus facilitating the study of this agent which replicated inefficiently in cell cultures. Soon, the major role of rotavirus in diarrheal disease was established. The other major pathogens associated with diarrheal disease in infants and young children (predominantly in developing countries), the enterotoxigenic *Escherichia coli* strains, are discussed in Chapter 25. In addition, the 27-nm Norwalk group of viruses that is associated with epidemic gastroenteritis in older children and adults is discussed in Chapter 65.

**Clinical Manifestations**

Rotaviruses induce a clinical illness characterized by vomiting, diarrhea, abdominal discomfort, fever, and dehydration (or a combination of some of these symptoms) that occurs primarily in infants and young children and may lead to hospitalization for rehydration therapy. Fever and vomiting frequently precede the onset of diarrhea. Although milder gastroenteric illnesses that do not require hospitalization are also common, most studies of clinical manifestations of rotavirus-induced gastroenteritis rely on data from hospitalized patients. The duration of hospitalization ranges from 2 to 14 days with a mean of 4 days. The highest attack rate is usually among infants and young children 6 to 24 months old, and the next highest in infants less than 6 months old. Normal neonates infected with rotavirus do not usually develop clinical manifestations. Deaths from rotavirus gastroenteritis may occur from dehydration and...
electrolyte imbalance. In older children and adults, rotavirus gastroenteritis occurs infrequently, although subclinical infections are common.

Rotaviruses also induce chronic symptomatic diarrhea in immunodeficient children, with an occasional fatal outcome. In addition, rotavirus infections can be especially severe and sometimes fatal in individuals of any age who are immunosuppressed for bone marrow transplantation. Rotavirus infections have also been associated with necrotizing enterocolitis and hemorrhagic gastroenteritis in neonates in special-care units. Rotaviruses have also been found in stools of patients with a variety of other conditions, but the association appears to be temporal rather than etiologic.

**Structure**

Rotaviruses have a distinctive wheel-like shape (Fig. 63-1). Complete particles have a double-layered capsid and measure about 70 nm in diameter. When the outer layer is absent, they measure about 55 nm. Within the inner capsid is the 37-nm core, which contains the RNA genome. The term rotavirus is derived from the Latin word "rota," meaning wheel, and was suggested because the sharply defined circular outline of the outer capsid resembles the rim of a wheel placed on short spokes radiating from a wide hub. Morphologically, rotaviruses resemble the reoviruses, coltiviruses and orbiviruses. However, the sharply defined circular outline of the outer capsid of rotavirus differs from the amorphous outer capsid of orbiviruses and coltiviruses. Reoviruses also have a distinct outer capsid, although it is not characteristically as sharply defined as that of the rotaviruses.
The rotavirus genome contains 11 segments of double-stranded RNA, in contrast to the reoviruses and orbiviruses, both of which contain 10 segments and the coltiviruses which contain 12 segments of double-stranded RNA. The segmented genome of rotavirus readily undergoes genetic reassortment during coinfection. Rotavirus RNA segments 1, 2, 3, and 6 encode inner capsid polypeptides VP1, VP2, VP3, and VP6, respectively, whereas RNA segments 4 and 7, 8, or 9 encode the major outer capsid polypeptides VP4 and VP7, respectively. The biochemical properties of human rotaviruses have not been studied extensively because these agents were initially difficult to propagate in cell culture. Rotaviruses, coltiviruses and orbiviruses are ether stable, but acid labile, whereas reoviruses are acid and ether stable. Studies of the effect of various disinfectants on simian rotavirus infectivity demonstrated that 95 percent (vol/vol) ethanol was most effective for rotavirus inactivation in the laboratory setting, where disinfection may be necessary.

**Classification and Antigenic Types**

Rotaviruses are distinct serologically from the three reovirus serotypes and from all orbiviruses with which they have been tested. Most human rotaviruses share a common group antigen and are designated group A rotaviruses, but other antigens separate the
group A rotaviruses into serotypes and subgroups. Ten human rotavirus serotypes have been defined by neutralization of one of the outer capsid proteins, VP7. Group A rotaviruses can also be separated into two distinct subgroups by various assays. The neutralization and subgroup specificities are encoded by different genes. Rotaviruses also have been detected in stools of the young of numerous animals with diarrhea. Rotaviruses of humans and animals characteristically share a common group antigen, but strains may differ in serotype specificity by neutralization. However, many animal rotavirus strains (simian, canine, feline, equine, murine, porcine, and lapine strains) share serotype specificity with human rotavirus. In addition, a few human and animal rotavirus strains have been detected (by electron microscopy) that do not share the common group antigen; these have been designated as non-group A rotaviruses. The non-group A viruses are divided into groups B, C, D, E, F, and G on the basis of distinct group antigens. The group A rotaviruses are the most important agents of severe diarrhea in infants and young children and are prevalent worldwide. The group B and C rotaviruses have a more limited distribution and are not considered to be an important cause of infantile diarrhea. Group B rotavirus has been responsible for large outbreaks of severe gastroenteritis in China, which predominantly involved adults, but the importance of the group B rotaviruses outside China has not been defined. Groups D, E, F, and G have not been detected in humans. Unless otherwise noted, the description of rotaviruses in this chapter deals with the group A rotaviruses exclusively.

Human rotaviruses are rather fastidious agents, and for many years they could not be efficiently cultivated from clinical specimens. However, efficient cell culture propagation of human rotavirus strains directly from clinical material became possible by altering the conditions of propagation.

**Multiplication**

Rotaviruses replicate exclusively in the cytoplasm. The virion enters the cell by endocytosis (or direct membrane penetration if activated by protease), and the outer shell of the double capsid is removed in lysosomes with the liberation of 50-nm subviral particles, thus activating the viral RNA polymerase (transcriptase). RNA positive-sense transcripts induce the production of proteins and are also a template for the production of antisense strands, which remain associated with the positive-sense strand. About 8 hours after infection, viroplasmic inclusions of dense granular material, representing newly synthesized proteins and RNA, accumulate in the cytoplasm. Viral RNA is packaged into core particles, and viral capsid proteins assemble around the cores. These particles accumulate in vesicles of the endoplasmic reticulum and leave the viroplasm by budding through the membrane of the endoplasmic reticulum, where they acquire the outer capsid protein. The budding process (plus transient acquisition of an envelope) is unique to rotaviruses among members of the family Reoviridae. Particles are released by cell lysis.

**Pathogenesis**

Rotaviruses are transmitted by the fecal-oral route (Fig. 63-2). Other routes of transmission, such as water-borne or airborne (respiratory) routes, have also been suggested. From clinical studies, the incubation period of rotavirus diarrheal illness was estimated to be less than 48 hours. Large numbers of virus particles are shed in the stool following multiplication in epithelial cells of the small intestine. Shedding may persist
for 10 days or more after the illness, but peak shedding appears to occur within 8 days of illness. Studies in adult volunteers have demonstrated that oral administration of a rotavirus-containing suspension can induce a diarrheal illness in certain individuals. Also, human rotavirus induces a gastrointestinal illness following administration by the alimentary route in various newborn, colostrum-deprived animal models. Histopathologic studies of tissue from the small intestine of infants and young children with rotavirus infection show shortening and blunting of villi on a patchy, irregular, but predominantly intact mucosa, and mononuclear cell infiltration of the lamina propria. Electron microscopy shows sparse and irregular microvilli with denudation of epithelial cells in some areas, distended cisternae of the endoplasmic reticulum that contain virus particles, and mitochondrial swelling. D-Xylose absorption was impaired, and some patients had depressed disaccharidase levels.

![Figure 63-2 Pathogenesis of rotavirus infection](image)

**FIGURE 63-2 Pathogenesis of rotavirus infection.** Virus entry is via the oral route, with virus replication and pathology in proximal small intestine, resulting in diarrhea and/or vomiting.

**Host Defenses**

The mechanism of immunity is not firmly established. Serum antibody in volunteers was found to correlate with resistance to rotavirus-induced illness, whereas the relationship of intestinal fluid neutralizing activity to resistance was not clear. In animal models, resistance to rotavirus-induced illness correlates with rotavirus antibody present in the intestinal lumen, and not with circulating serum antibody. Serotype-specific immunity may be of importance in protecting against illness with individual serotypes, but this is still under investigation. Little is known about other host defenses during rotavirus infection.
Epidemiology

Despite the frequency of rotavirus diarrhea in developed countries, mortality is low. For example, it was estimated that the under 5-year age group in the United States would experience annually more than 1 million cases of severe diarrhea and up to 150 deaths. In contrast, it was estimated that in developing countries infants and young children under 5 years of age would experience annually more than 18 million moderately severe or severe cases of rotavirus diarrhea and that 873,000 children in the under 5-year group would die from rotavirus diarrhea.

Rotaviruses are recognized as the major agents of severe gastroenteritis of infants and young children in most areas of the world. These agents also have been associated with milder episodes of gastroenteritis that do not require hospitalization. The efficient transmission of rotavirus is evident by the presence of rotavirus antibody in most children by the age of 3 years. This high prevalence of antibody is maintained into adulthood, probably a result of frequent reinfection. Important sources of rotavirus infection for infants are individuals of any age who shed this virus. Community outbreaks of rotavirus infection occur infrequently, probably because previous rotavirus exposure leads to protective immunity. Although rotavirus gastroenteritis occurs infrequently in adults, large outbreaks of severe gastroenteritis in adults have been associated with a group B rotavirus in China. The importance of non-group A rotaviruses outside China has not been defined.

Rotaviruses have been associated with about 30 to 50 percent of hospitalized cases of diarrheal illness in infants and young children in various countries in the temperate climates. A striking feature of rotaviral illness in these climates is its seasonal distribution. It usually occurs in the cooler months of the year when, cumulatively, more than 50 percent of diarrheal illnesses in the cooler months are associated with rotaviruses (Fig. 63-3). The reason for this temporal distribution is not known. This striking seasonal pattern has not been observed uniformly in all settings. In tropical climates, rotavirus infections have been detected throughout most of the year, although less pronounced peaks can occur. In studies of newborns in nurseries, most neonates with rotavirus infections are asymptomatic. A mechanism for this relative lack of susceptibility to illness in neonates in nurseries has yet to be explained satisfactorily. However, a 3-year study showed that such neonatal infections induced significant protection against postneonatal rotavirus diarrheal illness (but not infection) throughout the study period.
Rotaviruses also cause diarrhea in many newborn animals, such as calves, mice, piglets, foals, lambs, rabbits, deer, antelopes, apes, turkeys, chickens, goats, kittens, and puppy dogs. Human rotavirus has been shown to induce a diarrheal illness in certain animals under experimental conditions. Certain animal rotavirus strains may infect humans, but this appears to be a rare event.

**Diagnosis**

Because the clinical manifestations of rotavirus gastroenteritis are not distinct enough to permit a specific diagnosis, specimens must be examined in the laboratory. This is necessary even in temperate climates during the cooler months of the year, when more than 50 percent of hospitalizations due to diarrhea may be associated with rotavirus.

Laboratory diagnosis of rotavirus infections requires identifying the virus in feces or rectal swab specimens or demonstrating a fourfold or greater increase in antibody to a rotavirus antigen between acute- and convalescent-phase sera. Numerous methods to detect rotavirus in stool and rectal swab specimens have been described. These include electron microscopy, radioimmunoassay, counterimmunoelectro-osmophoresis, centrifuging of clinical material onto tissue culture cells followed by
immunofluorescence, inoculation of tissue cultures, latex agglutination, reverse passive hemagglutination assay, polyacrylamide gel electrophoresis, dot hybridization, polymerase chain reaction, and enzyme-linked immunosorbent assay (ELISA). ELISA has now become the mainstay in most laboratories, because it is practical, rapid, and efficient and does not require sophisticated laboratory equipment. Commercial ELISA kits are now available: certain ones should be used with caution if confirmatory reagents (i.e., positive and negative controls) are not included in the kit, since nonspecific reactions may yield false-positive results. When the number of specimens is limited, the most rapid method of rotavirus diagnosis in a hospital setting is by examination of a stool specimen by negative-stain electron microscopy. This can be accomplished in a few minutes. Non-group A human rotaviruses that do not share the common group antigen cannot be detected by conventional serologic assays; however, they can be detected by electron microscopy because they are morphologically identical to conventional rotaviruses.

Serologic evidence of rotavirus infection can be detected by various techniques, such as ELISA immunofluorescence, neutralization, and complement fixation.

**Control**

The primary aim of treatment of rotavirus gastroenteritis is the replacement by the intravenous or oral route of fluids and electrolytes lost by vomiting or diarrhea. Oral rehydration is more readily available and has gained widespread use worldwide as a life-saving treatment. In patients with severe dehydration and shock, intravenous rehydration is indicated for efficient replacement of fluid loss. Virus-specific chemotherapy is not available. Ribavirin was found to inhibit animal rotaviruses in vitro, but was not effective against murine rotavirus in the mouse model. Human milk that contains rotavirus antibody is effective when given orally to treat immunodeficient patients with chronic rotavirus infection. Human immune serum globulin (g-globulin) that contains rotavirus antibody was given prophylactically (orally) to low-birthweight infants in a nursery in which recurrent rotavirus infections occurred. Treatment resulted in delayed rotavirus excretion and milder symptoms. In addition, cow colostrum that contains rotavirus antibody was given prophylactically to infants and young children daily, as a single or divided dose orally, and was shown to induce significant protection against rotavirus diarrhea. Oral administration of preparations, which contained rotavirus antibody, has yielded conflicting conclusions with regard to their effectiveness as a method of treatment for children with rotavirus gastroenteritis.

Oral bismuth subsalicylate (BSS) as an adjunct to rehydration therapy was reported to shorten the course of rotavirus diarrhea in a pediatric study. It should be noted that because of the reported association of salicylates with Reye's syndrome, a literature review was carried out by the authors of the report with regard to such an association with BSS and other nonacetylsalicylic acid salicylates, and they failed to find any such reported association.

The importance of rotavirus as a cause of diarrheal illness in infants and young children throughout the world indicates that an effective vaccine is needed to prevent rotavirus-induced illness. An attenuated monovalent bovine rotavirus strain (serotype 6) or an attenuated monovalent rhesus rotavirus strain (serotype 3) has been administered orally to infants and young children as experimental vaccines. Their efficacy has been
variable. Thus, other candidate vaccines are being evaluated with the aim of achieving serotype-specific immunity by combining the VP7 specificity of serotypes 1, 2, 3, and 4 into a single vaccine with promising results.

Because rotaviruses are highly contagious and can spread by the fecal-oral route, careful attention to hand washing, disinfection, and disposal of contaminated material may limit its spread, especially in nurseries and hospitals where nosocomial infections occur frequently.

Reoviruses

The family name Reoviridae is derived from the prototype "reovirus" strain of the genus Orthoreovirus, the first genus of this family to be identified. The name reovirus was proposed in 1959 to describe a group of viruses previously classified as enteric cytopathic human orphan (ECHO) virus type 10, but which was found to differ from the other echoviruses in several important aspects (e.g., size). In addition, the acronym "reo" was suggested to denote that these agents were isolated from the respiratory and enteric tracts and had not been associated with any disease (orphan virus). Important features of the orthoreoviruses (or "reoviruses") include a diameter of 70 nm; a double capsid; ether and acid stability; a genome of 10 segments of double-stranded RNA; three serotypes designated types 1, 2, and 3; and the ability to infect humans as well as various other animals. The three serotypes share a common complement fixation antigen but can be distinguished by hemagglutination inhibition and neutralization techniques. Reoviruses grow efficiently from clinical specimens in various cell cultures, including monkey kidney cells.

Reoviruses are ubiquitous agents. Strains identical serologically to the human reovirus serotypes have been recovered from a wide variety of animals, including mice, chimpanzees, dogs, cats, cattle, sheep, swine, horses, and monkeys. Avian reoviruses also have been isolated; however, with one possible exception, these are antigenically distinct from the three reovirus serotypes described previously. In addition, a reovirus possessing certain characteristics of the mammalian and avian reoviruses has been recovered from a bat.

Reovirus infections occur often in humans, but most are mild or subclinical. The virus is detected efficiently in feces. It may also be recovered from nasal or pharyngeal secretions, urine, blood, cerebrospinal fluid, and various organs obtained at autopsy. Despite the ease with which reoviruses are detected in clinical specimens, their role in human disease remains uncertain. Reovirus infections have been observed in patients with various conditions such as fever, exanthema, upper and lower respiratory tract illnesses, gastrointestinal illness (including steatorrhea), hepatitis, pneumonitis, keratoconjunctivitis, neonatal cholestasis, meningitis, encephalitis, myocarditis, and Burkitt's lymphoma. Their role as agents of such illnesses remains unclear since convincing evidence of an etiologic association remains elusive. Thus, it is generally considered that although reoviruses can readily infect humans, they are not important agents of human disease.

Coltiviruses and Orbiviruses

Clinical Manifestations
Coltiviruses and orbiviruses cause fever. Table 63-1 shows the four human pathogens, their diseases, vectors, and geographic distribution. The most serious of these is Colorado tick fever virus, which will be emphasized in the rest of this chapter. Colorado tick fever virus causes diphasic fever in about half the infected individuals. Colorado tick fever is manifested by headache, chills, muscle pain (especially in the back and legs), and photophobia. Children may have hemorrhagic illness or encephalitic signs (including disorientation and stiff neck). Pericarditis has been reported. The case fatality rate is estimated at 0.2 percent. Most patients recover within 2 weeks, but occasionally convalescence is prolonged.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease in Humans</th>
<th>Vector</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorado tick fever</td>
<td>Fever, rarely pericarditis, encephalitis, or hemorrhage</td>
<td>Tick</td>
<td>Western North America</td>
</tr>
<tr>
<td>Kemerovo</td>
<td>Fever, meningitis</td>
<td>Tick</td>
<td>Western Siberia</td>
</tr>
<tr>
<td>Orungo</td>
<td>Fever</td>
<td>Mosquito</td>
<td>Nigeria, Uganda, Senegal, Central African Republic</td>
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<tr>
<td>Changuinola</td>
<td>Fever</td>
<td>Phlebotomine sandfly</td>
<td>Panama, northern South America</td>
</tr>
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Kemerovo virus is a tick-borne virus that was isolated from cerebrospinal fluid of two patients in western Siberia in 1962 during a small outbreak of febrile disease. Orungo virus was found in the blood of febrile patients in tropical Africa and is believed to cause small epidemics. Changuinola virus was isolated from a patient with fever in Panama. Little more is known about the disease potential of these three orbiviruses.

**Structure**

Orbiviruses contain 10 segments of double-stranded RNA, exhibit icosahedral symmetry, and are spherical with a diameter of 60 to 80 nm. The total molecular weight is about 12 X 10^6. Their infectivity is destroyed at pH 3.0. Orbiviruses have at least seven structural and two nonstructural polypeptides.

**Classification and Antigenic Types**

The genera *Orbivirus* and *Coltivirus* consist of at least 109 serotypes of arthropod-borne viruses. They form 13 serogroups and at least 6 ungrouped viruses. The major group-reactive polypeptide is P7, which reacts broadly by the complement fixation test. The major type-specific polypeptide is P2, a surface component principally responsible for the neutralization reaction.

**Multiplication**

Orbiviruses and Coltivirus replicate in the cytoplasm. They replicate in arthropods as well as in vertebrates and are transmitted by arthropods, thus differing from rotaviruses and reoviruses. The virion outer shell must be removed to activate the RNA-dependent RNA polymerase. RNA segment reassortment between closely related orbiviruses accounts for genetic diversity and may lead to rapid changes in properties of viruses.
Pathogenesis

Colorado tick fever virus replicates in *Dermacentor andersoni* ticks that are infected in the larval stage when they feed on blood of the golden-mantled ground squirrel or other rodents (Fig. 63-4). After a period of days or weeks, the virus appears in the tick's saliva. The tick, which remains infectious for life, feeds on humans during its adult stage. The virus does not pass transovarially in the tick.

![Diagram of pathogenesis](image)

**FIGURE 63-4 Pathogenesis of Colorado tick fever.**

In humans, Colorado tick fever virus, possibly after infecting the regional lymph nodes, replicates in the bone marrow cells, arresting the maturation of the polymorphonuclear leukocytes, eosinophils, and basophils and sometimes causing severe thrombocytopenia. Erythrocytes presumably are infected as erythroblasts and are later detected in large numbers as antigen-containing red blood cells in the peripheral blood. The virus is found only briefly in serum. Antibody appears about 2 weeks after the onset of symptoms, but virus can still be isolated from peripheral blood cells for up to 6 weeks.

In 3 to 15 percent of infected children under 10 years of age, Colorado tick fever virus invades the central nervous system and causes encephalitis. Virus has been isolated from the cerebrospinal fluid of some of these patients.

Host Defenses

There have been very few studies of the host defenses against Colorado tick fever virus. Nonimmune persons appear to be uniformly susceptible. Symptoms subside when humoral antibody appears, although exacerbations are reported; the role of cell-
mediated immunity is not known. The virus induces interferon, but it is not known whether interferon is important in host defense.

Epidemiology

The distribution of Colorado tick fever is the same as that of its principal tick vector, *D. andersoni*. The disease is found in California, Colorado, Idaho, Montana, Nevada, Oregon, Utah, Washington, Wyoming, British Columbia, and Alberta; 200 to 400 cases are reported each year. Campers, hikers, and foresters are commonly infected. Infections occur mainly in April, May, and June, when adult ticks are abundant. The virus overwinters in nymphal ticks, which feed on and infect small rodents in the spring. The rodents become viremic and in turn infect larval ticks. The larvae metamorphose during the summer; they overwinter as infected nymphs and do not transmit virus to humans until reaching the adult stage, which may be 1 or 2 years after infection. Foci of infected ticks occur primarily in ecologic zones favorable to large populations of ground squirrels and other small rodents.

Diagnosis

Colorado tick fever should be suspected in individuals in western North America with diphasic fever, leukopenia, and a history of exposure to ticks 3 to 6 days before onset of disease. Diagnosis depends on isolation of the virus, demonstration of antigen in the red blood cells, or demonstration of a fourfold rise or fall in antibody titer from the acute to the convalescent phase. Virus is readily isolated from erythrocytes by inoculating them into tissue culture or intracerebrally into baby mice. Antibody is washed from red cells or removed by trypsin treatment to enhance the chance of isolation. Red cells may still be positive up to 6 weeks after infection. Antigen also can be detected in red cells by the immunofluorescence technique. Within 1 week of onset of symptoms, antibody appears in the serum as determined by indirect immunofluorescence. Neutralizing antibody appears somewhat later. The complement fixation test does not become positive until about 3 weeks after onset of illness. A travel history can aid the physician and the laboratory in diagnosis. Because of the long duration of viremia, definitive diagnosis of Colorado tick fever has been made in persons returning home far from the endemic area where the infection was acquired.

Control

Colorado tick fever can be prevented by avoiding tick-infested areas, by wearing long-sleeved tightfitting clothing, by checking the body for ticks every 3 hours while camping or hiking and removing them, and by using tick repellents such as diethyltoluamide. Theoretically, campgrounds should be located away from the habitat of the golden-mantled ground squirrel and other rodents; however, these creatures are favorites of campers, and such a measure would not be popular. No vaccine or specific treatment for the disease is available, although the nucleoside analog, 3'-fluors-3'-deoxyadanosine, inhibits replication in vitro.

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