Enteropathogenic *E coli* (EPEC) is an important cause of diarrhea in infants, especially in developing countries. EPEC previously was associated with outbreaks of diarrhea in nurseries in developed countries. EPEC adhere to the mucosal cells of the small bowel. Chromosomally mediated factors promote tight adherence. There is loss of microvilli (effacement), formation of filamentous actin pedestals or cup-like structures, and occasionally, entry of the EPEC into the mucosal cells. Characteristic lesions can be seen on electron micrographs of small bowel biopsy lesions. The result of EPEC infection is watery diarrhea, which is usually self-limited but can be chronic. EPEC diarrhea has been associated with multiple specific serotypes of *E coli;* strains are identified by O antigen and occasionally by H antigen typing. A two-stage infection model using HEp-2 cells also can be performed. Tests to identify EPEC are performed in reference laboratories. The duration of the EPEC diarrhea can be shortened and the chronic diarrhea cured by antibiotic treatment.

bidity rate but a low mortality rate. Typically, 50–60% of cases of acute gastroenteritis of hospitalized children throughout the world are caused by rotaviruses.

Rotavirus infections usually predominate during the winter season. Symptomatic infections are most common in children between ages 6 months and 2 years, and transmission appears to be by the fecal-oral route. Nosocomial infections are frequent.

Rotaviruses are ubiquitous. By age 3 years, 90% of children have serum antibodies to one or more types. This high prevalence of rotavirus antibodies is maintained in adults, suggesting subclinical reinfections by the virus. Both humans and animals can become infected even in the presence of antibodies. Local immune factors, such as secretory IgA or interferon, may be important in protection against rotavirus infection. Alternatively, reinfection in the presence of circulating antibody could reflect the presence of multiple serotypes of virus. Asymptomatic infections are common in infants before age 6 months, the time during which protective maternal antibody acquired passively by newborns should be present. Such neonatal infection does not prevent reinfection, but it may protect against the development of severe disease during reinfection.

Treatment & Control

Treatment of gastroenteritis is supportive, to correct the loss of water and electrolytes that may lead to dehydration, acidosis, shock, and death. Management consists of replacement of fluids and restoration of electrolyte balance either intravenously or orally, as feasible. The infrequent mortality from infantile diarrhea in developed countries is due to routine use of effective replacement therapy.

In view of the fecal-oral route of transmission, [illegible] treatment and sanitation are significant

mal function to be restored.

Clinical Findings & Laboratory Diagnosis

Rotaviruses cause the major portion of diarrheal illness in infants and children worldwide but not in adults (Table 37–2). There is an incubation period of 1–4 days. Typical symptoms include diarrhea, fever, abdominal pain, and vomiting, leading to dehydration.

In infants and children, severe loss of electrolytes and fluids may be fatal unless treated. Patients with milder cases have symptoms for 3–8 days and then recover completely. Asymptomatic infections, with seroconversion, occur.

Adult contacts may be infected, as evidenced by seroconversion, but they rarely exhibit symptoms, and virus is infrequently detected in their stools. A common source of infection is contact with pediatric cases. However, epidemics of severe disease have occurred in adults, especially in closed populations, as in a geriatric ward. Group B rotaviruses have been implicated in large outbreaks of severe gastroenteritis in

mental inoculations, but it is not clear if they occur in nature. In experimental studies, human rotavirus can induce diarrheal illness in newborn colostrum-deprived animals (eg, piglets, calves). Homologous infections may have a wider age range. Swine rotavirus infects both newborn and weanling piglets. Newborns often exhibit subclinical infection due perhaps to the presence of maternal antibody, whereas overt disease is more common in weanling animals.

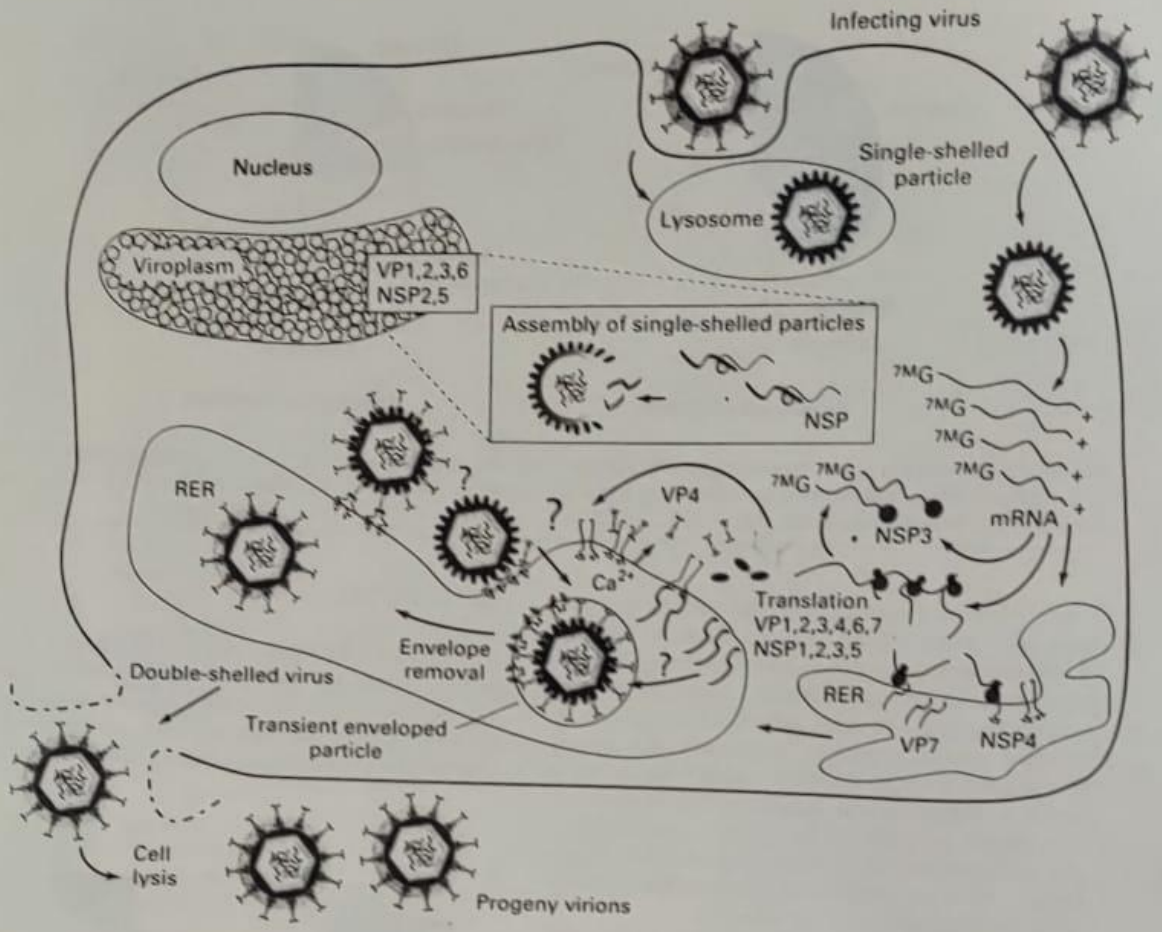

Figure 37–3. Overview of the rotavirus replication cycle. (Reproduced, with permission, from Estes MK: Rotaviruses and their replication. In: *Fields Virology*, 3rd ed. Fields BN et al [editors]. Lippincott-Raven, 1996.)

zootic diarrhea of infant mice, and SA11 virus of monkeys.

Rotaviruses are closely related to reoviruses in terms of morphology and strategy of replication.

Classification & Antigenic Properties

Rotaviruses possess common antigens located on most, if not all, the structural proteins. These can be detected by immunofluorescence, ELISA, and immune electron microscopy (IEM). Three major antigenic subgroups of human rotaviruses have been identified. Type-specific antigens are located on the outer capsid. Both VP4 and VP7 carry epitopes important in neutralizing activity, though VP7 glycoprotein seems to be the predominant antigen. These type-specific antigens differentiate among rotaviruses and are demonstrable by Nt tests. At least nine serotypes have been identified among human rotaviruses, and at least five more serotypes exist among animal isolates. Some animal and human rotaviruses share serotype specificity. For example, monkey virus SA11 is very similar to human serotype 3. The gene-coding assignments responsible for the structural and antigenic specificities of rotavirus proteins are shown in Figure 37–4.

The viruses usually associated with human gastroenteritis are classified as group A rotaviruses, but antigenically and genomically distinct rotaviruses have also caused diarrheal outbreaks, primarily in adults.

Molecular epidemiologic studies have analyzed isolates based on differences in the migration of the 11 genome segments following electrophoresis of the RNA in polyacrylamide gels (Figure 37–5). Extensive genome heterogeneity has been demonstrated in numerous studies. These differences in electropherotypes cannot be used to predict serotypes; however, electropherotyping can be a useful epidemiologic tool to monitor viral transmission.

Animal Susceptibility

Rotaviruses have a wide host range. Most isolates have been recovered from newborn animals with diarrhea. Cross-species infections can occur in experi-

ROTAVIRUSES

Rotaviruses are a major cause of diarrheal illness in human infants and young animals, including calves and piglets. Infections in adult humans and animals are also common. Among rotaviruses are the agents of human infantile diarrhea, Nebraska calf diarrhea, epi-

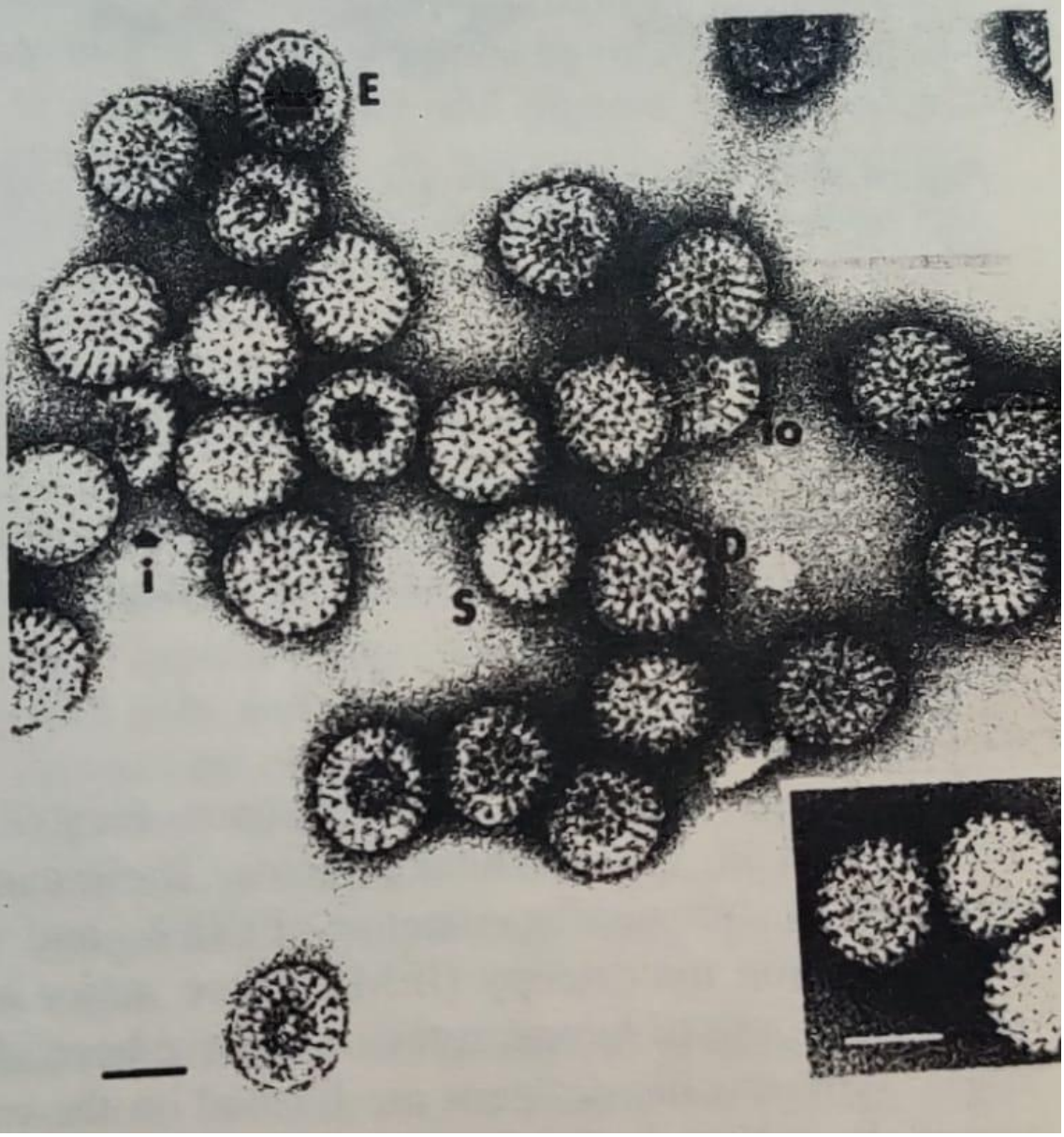

Table 16–4. Representative antigenic formulas of salmonellae.

O Group	Serotype	Antigenic Formula[1]
D	*S typhi*	**9, 12** (Vi):d:—
A	*S paratyphi* A	**1, 2, 12**:a—
C_1	*S choleraesuis*	**6, 7**:c:1,5
B	*S typhimurium*	**1, 4, 5, 12**:i:1, 2
D	*S enteritidis*	**1, 9, 12**:g, m:—

[1] O antigens: boldface numerals.
(Vi): Vi antigen if present.
Phase 1 H antigen: lower-case letter.
Phase 2 H antigen: numeral.

Variation

Organisms may lose H antigens and become nonmotile. Loss of O antigen is associated with a change from smooth to rough colony form. Vi antigen may be lost partially or completely. Antigens may be acquired (or lost) in the process of transduction.

Pathogenesis & Clinical Findings

S typhi, *S choleraesuis*, and perhaps *S paratyphi* A and *S paratyphi* B are primarily infective for humans, and infection with these organisms implies acquisition from a human source. The vast majority of salmonellae, however, are chiefly pathogenic in animals that constitute the reservoir for human infection: poultry, pigs, rodents, cattle, pets (from turtles to parrots), and many others.

The organisms almost always enter via the oral route, usually with contaminated food or drink. The mean infective dose to produce clinical or subclinical infection in humans is 10^5–10^8 salmonellae (but perhaps as few as 10^3 *S typhi* organisms). Among the host factors that contribute to resistance to salmonella infection are gastric acidity, normal intestinal microbial flora, and local intestinal immunity (see below).

Salmonellae produce three main types of disease in humans, but mixed forms are frequent (Table 16–5).

A. The "Enteric Fevers" (Typhoid Fever): This syndrome is produced by only a few of the salmonellae, of which *S typhi* (typhoid fever) is the most important. The ingested salmonellae reach the small intestine, from which they enter the lymphatics and then the bloodstream. They are carried by the blood to many organs, including the intestine. The organisms multiply in intestinal lymphoid tissue and are excreted in stools.

After an incubation period of 10–14 days, fever, malaise, headache, constipation, bradycardia, and myalgia occur. The fever rises to a high plateau, and the spleen and liver become enlarged. Rose spots, usually on the skin of the abdomen or chest, are seen briefly in rare cases. The white blood cell count is normal or low. In the preantibiotic era, the chief complications of enteric fever were intestinal hemorrhage and perforation, and the mortality rate was 10–15%. Treatment with antibiotics has reduced the mortality rate to less than 1%.

The principal lesions are hyperplasia and necrosis of lymphoid tissue (eg, Peyer's patches), hepatitis, focal necrosis of the liver, and inflammation of the gallbladder, periosteum, lungs, and other organs.

B. Bacteremia With Focal Lesions: This is associated commonly with *S choleraesuis* but may be caused by any salmonella serotype. Following oral infection, there is early invasion of the bloodstream (with possible focal lesions in lungs, bones, meninges, etc), but intestinal manifestations are often absent. Blood cultures are positive.

C. Enterocolitis (Formerly "Gastroenteritis"): This is the most common manifestation of salmonella infection. In the USA, *S typhimurium* is prominent, but enterocolitis can be caused by any of the 1500–2000 types of salmonellae. Eight to 48 hours after ingestion of salmonellae, there is nausea, headache, vomiting, and profuse diarrhea, with few leukocytes in the stools. Low-grade fever is common, but the episode usually resolves in 2–3 days.

Inflammatory lesions of the small and large intestine are present. Bacteremia is rare (2–4%) except in immunodeficient persons. Blood cultures are usually negative, but stool cultures are positive for salmonellae and may remain positive for several weeks after clinical recovery.

Table 16–5. Clinical diseases induced by salmonellae.

	Enteric Fevers	Septicemias	Enterocolitis
Incubation period	7–20 days	Variable	8–48 hours
Onset	Insidious	Abrupt	Abrupt
Fever	Gradual, then high plateau, with "typhoidal" state	Rapid rise, then spiking "septic" temperature	Usually low
Duration of disease	Several weeks	Variable	2–5 days
Gastrointestinal symptoms	Often early constipation; later, bloody diarrhea	Often none	Nausea, vomiting, diarrhea at onset
Blood cultures	Positive in 1st–2nd weeks of disease	Positive during high fever	Negative
Stool cultures	Positive from 2nd week on; negative earlier in disease	Infrequently positive	Positive soon after onset

lae are resistant to certain chemicals (eg, brilliant green, sodium tetrathionate, sodium deoxycholate) that inhibit other enteric bacteria; such compounds are therefore useful for inclusion in media to isolate salmonellae from feces.

Antigenic Structure

While salmonellae are initially detected by their biochemical characteristics, groups and species are identified by antigenic analysis. Like other Enterobacteriaceae, salmonellae possess several O antigens (from a total of more than 60) and different H antigens in one or both of two phases. Some salmonellae have capsular (K) antigens, referred to as Vi, which may interfere with agglutination by O antisera and are associated with invasiveness. Agglutination tests with absorbed antisera for different O and H antigens form the basis for serologic classification of the salmonellae.

Classification

The classification of the salmonella-arizona group is complex because the organisms are a continuum rather than defined species. One classification system had three primary species: *Salmonella typhi* (one serotype), *Salmonella choleraesuis* (one serotype), and *Salmonella enteritidis* (over 1500 serotypes). Serotyping is based on the reactivity of the O antigens and the biphasic H antigens. On the basis of DNA hybridization studies, the formal taxonomic classification includes the genus *Salmonella* with seven subgroups, each with its own phenotypic characteristics and history. Almost all (> 99%) of the salmonellae that cause disease in humans are in subgroup 1 and can be isolated from warm-blooded animals; the other groups are predominantly isolated from cold-blooded animals and the environment. In practice, the formal species and subspecies names are not used. The simplified nomenclature considers the serotype names as species names. Laboratory reports typically list a specific serogroup, eg, *Salmonella* serogroup C1 (a serogroup may have many serotypes). Reports from reference laboratories that serotype isolates include the genus name, eg, *Salmonella,* and the serotype, eg, Typhimurium, which is turned into *Salmonella typhimurium* as if it were a genus and species designation.

THE SALMONELLA-ARIZONA GROUP

Salmonellae are often pathogenic for humans or animals when acquired by the oral route. They are transmitted from animals and animal products to humans, where they cause enteritis, systemic infection, and enteric fever.

Morphology & Identification

Salmonellae vary in length. Most species except *Salmonella pullorum-gallinarum* are motile with peritrichous flagella. Salmonellae grow readily on simple media, but they almost never ferment lactose or sucrose. They form acid and sometimes gas from glucose and mannose. They usually produce H_2S. They survive freezing in water for long periods. Salmonel-

Table 16–3. Pathogenic species of *Shigella*.

	Group and Type	Mannitol	Ornithine Decarboxylase
	A	–	–
	B	+	–
	C	+	–
	D	+	+

gas. They may also be divided into those that mannitol and those that do not (Table 16–3).

ic Structure

ae have a complex antigenic pattern. There verlapping in the serologic behavior of dif- cies, and most of them share O antigens enteric bacilli.

matic O antigens of shigellae are lipopoly- s. Their serologic specificity depends on ccharide. There are more than 40 serotypes. fication of shigellae relies on biochemical nic characteristics. The pathogenic species in Table 16–3.

nesis & Pathology

infections are almost always limited to the tinal tract; bloodstream invasion is quite llae are highly communicable; the infective the order of 10^3 organisms (whereas it usu- -10^8 for salmonellae and vibrios). The es- hologic process is invasion of the mucosal ells (eg, M cells) by induced phagocytosis. m the phagocytic vacuole, multiplication within the epithelial cell cytoplasm, and adjacent cells. Microabscesses in the wall intestine and terminal ileum lead to necro- mucous membrane, superficial ulceration, nd formation of a "pseudomembrane" on d area. This consists of fibrin, leukocytes, a necrotic mucous membrane, and bacte- process subsides, granulation tissue fills nd scar tissue forms.

toxin: Upon autolysis, all shigellae re- toxic lipopolysaccharide. This endotoxin ntributes to the irritation of the bowel

***ella dysenteriae* Exotoxin:** *S dysente-* Shiga bacillus) produces a heat-labile ex- fects both the gut and the central ner- toxin," this material may contribute to the extreme severity and fatal nature of *S dysenteriae* infections and to the central nervous system reactions observed in them (ie, meningismus, coma). Patients with *Shigella flexneri* or *Shigella sonnei* infections develop antitoxin that neutralizes *S dysenteriae* exotoxin in vitro. The toxic activity is distinct from the invasive property of shigellae in dysentery. The two may act in sequence, the toxin producing an early nonbloody, voluminous diarrhea and the invasion of the large intestine resulting in later dysentery with blood and pus in stools.

Clinical Findings

After a short incubation period (1–2 days), there is a sudden onset of abdominal pain, fever, and wa diarrhea. The diarrhea has been attributed to an toxin acting in the small intestine (see above). A or so later, as the infection involves the ileum colon, the number of stools increase; they are less liquid but often contain mucus and blood. Each bowel movement is accompanied by straining and tenesmus (rectal spasms), with resulting lower abdominal pain. In more than half of adult cases, fever and diarrh subside spontaneously in 2–5 days. However, in children and the elderly, loss of water and electrolyte may lead to dehydration, acidosis, and even death. The illness due to *S dysenteriae* may be particularly severe.

On recovery, most persons shed dysentery bacill for only a short period, but a few remain chronic intestinal carriers and may have recurrent bouts of the disease. Upon recovery from the infection, most persons develop circulating antibodies to shigellae, bu these do not protect against reinfection.

Diagnostic Laboratory Tests

A. Specimens: Fresh stool, mucus flecks, an rectal swabs for culture. Large numbers of fec leukocytes and some red blood cells often are see microscopically. Serum specimens, if desired, mu be taken 10 days apart to demonstrate a rise in titer agglutinating antibodies.

B. Culture: The materials are streaked on diffe ential media (eg, MacConkey's or EMB agar) and selective media (Hektoen enteric agar or salmonell shigella agar), which suppress other Enterobacte aceae and gram-positive organisms. Colorless (la tose-negative) colonies are inoculated into triple sug iron agar. Organisms that fail to produce H_2S, th produce acid but not gas in the butt and an alkali slant in triple sugar iron agar medium, and that

THE SHIGELLAE

The natural habitat of shigellae is limited to the intestinal tracts of humans and other primates, where they produce bacillary dysentery.

Morphology & Identification

A. Typical Organisms: Shigellae are slender gram-negative rods; coccobacillary forms occur in young cultures.

B. Culture: Shigellae are facultative anaerobes but grow best aerobically. Convex, circular, transparent colonies with intact edges reach a diameter of about 2 mm in 24 hours.

C. Growth Characteristics: All shigellae ferment glucose. With the exception of *Shigella sonnei,* they do not ferment lactose. The inability to ferment lactose distinguishes shigellae on differential media. Shigellae form acid from carbohydrates but rarely