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MICROORGANISMS RESPONSIBLE FOR NEONATAL DIARRHEA

Miguel L. O'Ryan • James P. Nataro • Thomas G. Cleary

At the beginning of the 21st century, diarrheal disease continues to be a significant cause of morbidity and mortality worldwide. During the period of 1986 to 2000, an estimated 1.4 billion children younger than 5 years suffered an episode of acute diarrhea every year in developing countries; among these, 123.6 million required outpatient medical care, and 9 million required hospitalization. Approximately 2 million diarrhea-associated deaths occurred in this age group annually, primarily in the most impoverished areas of the world.[1] These estimates are somewhat lower than the more than 3 million annual deaths from diarrhea reported in the prior 10 years,[2] indicating progress in prevention and treatment of acute diarrhea. In the United States, approximately 400 childhood deaths per year were reported during the late 1980s,[3,4] although the actual number may be higher.[4]

Accurate incidence rates for acute diarrhea in neonates from different populations are not readily available. The relative sparing of the newborn probably results from low exposure to enteropathogens and protection associated with breast-feeding.[5-8] After the first few months of life, increasing interaction with other individuals and the environment, including introduction of artificial feeding, increases the risk of exposure to enteropathogens. For most pathogens, the incidence of acute diarrhea peaks in children between 6 months and 4 years old.[9] Neonatal diarrhea is more common in underdeveloped areas, where low educational levels, crowding, and poor standards of medical care, environmental sanitation, and personal hygiene favor early contact with enteropathogens. As the incidence of neonatal gastroenteritis rises, there is a proportional increase in neonatal deaths because medical care for the poor often is inadequate.[10,11] For very low birth

weight infants (<1500 g), the death rate from diarrhea is 100-fold greater than for higher-birth-weight infants.[12]

This chapter discusses the pathogenesis, diagnosis, treatment, and prevention of gastroenteritis based on the available knowledge about pathogens that can cause neonatal diarrhea. Pathogens that rarely or never cause acute diarrhea in neonates are not discussed. After an overview of host defense mechanisms and protective factors in human milk, the remainder of the chapter is devoted to specific pathogens that cause inflammatory or noninflammatory diarrhea.

ENTERIC HOST DEFENSE MECHANISMS

The neonate is a host that is uniquely susceptible to enteric infections. Neonates have not had the opportunity to develop local or systemic immune responses, and in the first few days of life, they have not acquired the highly important enteric flora that protects the normal adult gastrointestinal tract.[13-18] Still less is known about the barrier effect of the neonate's gastric acidity,[19] intestinal mucus,[20] or motility,[21,22] each of which provides protection against gastrointestinal tract infections in older infants, children, and adults.

The gastric acid barrier appears to be least effective during the first months of life. The average gastric pH level of the newborn is high (pH 4 to 7; mean, 6).[23,24] Although the pH falls to low levels by the end of the first day of life (pH 2 to 3),[23] it subsequently rises again; by 7 to 10 days of life, the hydrochloric acid output of the neonatal stomach is far less than that of older infants and children.[24,25] The buffering action of frequent milk feedings and the short gastric emptying time[26-29] interpose additional factors in the neonate that would be expected to permit viable ingested organisms to reach the small intestine.

The intestinal epithelium serves as a nutrient absorptive machine, barrier to pathogen entry, and regulator of inflammation. Intestinal epithelial cells have receptors for bacterial products and produce chemokines (e.g., interleukin [IL]-8, monocyte chemotactic protein type 1 [MCP-1], granulocyte macrophage-cell stimulating factor [GM-CSF]) and pro-inflammatory cytokines (e.g., IL-6, tumor necrosis factor-α [TNF-α], IL-1) in response to invasion by enteropathogens.[30] The gut epithelium orchestrates the immune response. However, in the newborn, phagocytic, chemotactic, and complement functions are immature. B and T lymphocyte functions are impaired, resulting in a preferential IgM production in response to antigenic stimulation. IgG is actively transferred from mother to infant across the placenta at about 32 weeks' gestation and peaks by about 37 weeks; premature neonates, especially those born before 28 weeks' gestation, are deficient in these maternally derived serum antibodies.[31]

PROTECTIVE FACTORS IN HUMAN MILK

The importance of breast-feeding infants for the prevention of diarrheal disease has long been emphasized.[13,32-45] Published studies reporting the association between breast-feeding and diarrhea are extensive and suggest that infants who are breast-fed suffer fewer episodes of diarrhea than those who are not. This protection is greatest during a child's

Table 20-1   Association between Antibodies in Human Milk and Protection against Enteropathogens

Organism	Antibody
Vibrio cholerae	Lipopolysaccharide, enterotoxin
Campylobacter jejuni	Surface proteins
Enteropathogenic Escherichia coli	Adherence proteins
Enterotoxigenic E. coli	Enterotoxin, adherence proteins
Shigatoxin producing E. coli	Adherence proteins
Shigella	Lipopolysaccharide, virulence plasmid–associated antigens
Giardia lamblia	Surface proteins

first 3 months of life and declines with increasing age. During the period of weaning, partial breast-feeding confers protection that is intermediate between that gained by infants who are exclusively breast-fed and that by those who are exclusively bottle-fed.

A striking demonstration of the protection afforded by breast-feeding of newborns has been provided by Mata and Urrutia[13] in their studies of a population of infants born in a rural Guatemalan village. Despite extremely poor sanitation and the demonstration of fecal organisms in the colostrum and milk of almost one third of mothers,[46] diarrheal disease did not occur in any newborns. The incidence of diarrhea rose significantly only after these infants reached 4 to 6 months old, at which time solids and other fluids were used to supplement the human milk feedings. At that time, Escherichia coli and gram-negative anaerobes (e.g., Bacteroides) were found to colonize the intestinal tract.[13] In contrast, urban infants of a similar ethnic background who were partly or totally artificially fed frequently acquired diarrheal disease caused by enteropathogenic E. coli (EPEC).

Multiple mechanisms by which breast-feeding protects against diarrhea have been postulated. Breast-feeding confers protection by active components in milk and by decreased exposure to organisms present on or in contaminated bottles, food, or water. Many protective components have been identified in human milk and generally are classified as belonging to the major categories of cells, antibody, anti-inflammatory factors, and glycoconjugates and other nonantibody factors.[47-50] Examples of milk antibodies are summarized in Table 20-1. For any given pathogen, multiple milk factors may help protect the infant. Human milk typically targets a major pathogenic mechanism using multiple, redundant strategies. Redundancy of milk protective factors and targeting of complex virulence machinery have created a formidable barrier to enteropathogens. Despite the fact that pathogens can rapidly divide and mutate, milk continues to protect infants. For example, human milk has secretory antibodies to Shigella virulence antigens and lipopolysaccharides,[51,52] neutral glycolipid Gb3 to bind Shiga toxin,[53,54] and lactoferrin to disrupt and degrade the surface-expressed virulence antigens.[55-57] In a similar way, milk contains antibodies directed toward the surface expressed virulence antigens of EPEC,[58] oligosaccharides that block cell attachment,[59] and lactoferrin that disrupts and degrades the surface expressed EPEC antigens.[60] Human milk can initiate and

maintain the growth of *Bifidobacterium* and low pH in the feces of newborn infants, creating an environment antagonistic to the growth of *E. coli.*[13,17,18,61]

The protective effect of human milk antibodies against enteropathogen-specific disease has been described for *Vibrio cholerae,*[62] *Campylobacter jejuni,*[63] EPEC,[59] enterotoxigenic *E. coli* (ETEC),[64,65] *Shigella,*[66,67] and *Giardia lamblia*[68,69] and for bovine milk concentrate against ETEC,[70] rotavirus,[71] and *Shigella.*[72]

In 1933, the nonlactose carbohydrate fraction of human milk was found to consist mainly of oligosaccharides.[73] In 1960, Montreuil and Mullet[74] determined that up to 2.4% of colostrum and up to 1.3% of mature milk are oligosaccharides. Human milk contains a larger quantity of the oligosaccharides than does milk from other mammals, and its composition is singularly complex.[75] The metabolic fate of the oligosaccharides is of interest. Only water, lactose, and lipids are present in greater amounts than the oligosaccharides. Despite the fact that substantial energy must be expended by the mother to synthesize the many hundreds of different milk oligosaccharides, the infant does not use them as food. Most of the oligosaccharides pass through the gut undigested.[76,77] It is thought that they are present primarily to serve as receptor analogues that misdirect enteropathogen attachment factors away from gut epithelial carbohydrate receptors. Likewise, enteropathogens use the oligosaccharide portion of glycolipids and glycoproteins as targets for attachment of whole bacteria and toxins. Evidence is emerging that these glycoconjugates may have an important role in protection of the breast-fed infant from disease.[48]

Human milk protects suckling mice from the heat-stable enterotoxin (ST) of *E. coli*; on the basis of its chemical stability and physical properties, the protective factor has been deduced to be a neutral fucosyloligosaccharide.[79,80] Experiments have shown that EPEC attachment to HEp-2 cells can be inhibited by purified oligosaccharide fractions from human milk.[59] Oligosaccharides also may be relevant to protection from Norwalk virus and other caliciviruses, because these viruses attach to human ABO, Lewis, and secretor blood group antigens.[80,81] Human milk contains large amounts of these carbohydrates. The ganglioside fraction in human milk has been shown to inhibit the action of heat-labile toxin (LT) and cholera toxin on ileal loops more effectively than secretory IgA.[82,83] Lactadherin in human milk has been shown to bind rotavirus and to inhibit viral replication in vitro and in vivo.[84] A study of infants in Mexico showed that lactadherin in human milk protected infants from symptoms of rotavirus infection.[72]

ESCHERICHIA COLI

E. coli organisms promptly colonize the lower intestinal tracts of healthy infants in their first few days of life[85-88] and constitute the predominant aerobic coliform fecal flora throughout life in humans and in many animals. The concept that this species might cause enteric disease was first suggested in the late 19th and early 20th centuries, when several veterinary workers described the association of diarrhea (i.e., scours) in newborn calves with certain strains of *E. coli.*[89-94]

In 1905, Moro[95] observed that *Bacterium* (now *Escherichia*) *coli* was found more often in the small intestines of children

with diarrhea than in children without diarrhea. Adam[96,97] confirmed these findings and noted the similarity with Asiatic cholera and calf scours. He further extended these observations by suggesting that *E. coli* strains from patients with diarrhea could be distinguished from normal coliform flora by certain sugar fermentation patterns. Although he called these disease-producing organisms *dyspepsicoli* and introduced the important concept that *E. coli* could cause enteric disease, biochemical reactions have not proved to be a reliable means of distinguishing nonpathogenic from pathogenic *E. coli* strains. There are now at least six recognized enteric pathotypes of *E. coli.*[98] The pathotypes can be distinguished clinically, epidemiologically, and pathogenetically (Table 20-2).[98-104]

ETEC organisms are defined by their ability to secrete the LT or the ST enterotoxin, or both. LT is closely related to cholera toxin and similarly acts by means of intestinal adenylate cyclase,[105,106] prostaglandin synthesis,[107,108] and possibly platelet activating factor.[109,110] ST (particularly the variant STa) causes secretion by specifically activating intestinal mucosal guanylate cyclase.[111-113] The STb toxin causes noncyclic, nucleotide-mediated bicarbonate secretion and appears to be important only in animals.[114-116] Enteroinvasive *E. coli* (EIEC) has the capacity to invade the intestinal mucosa, thereby causing an inflammatory enteritis much like shigellosis.[117,118] EPEC elicits diarrhea by a signal transduction mechanism,[98-102,119,120] which is accompanied by a characteristic attaching-and-effacing histopathologic lesion in the small intestine.[121] Enterohemorrhagic *E. coli* (EHEC) also induces an attaching-and-effacing lesion, but in the colon.[98] EHEC also secretes Shiga toxin, which gives rise to the sequela of hemolytic-uremic syndrome (HUS). Diffusely adherent *E. coli*[122] executes a signal transduction effect, which is accompanied by the induction of long cellular processes.[123] Enteroaggregative *E. coli* (EAEC) adheres to the intestinal mucosa and elaborates enterotoxins and cytotoxins.[98,103,125]

A major problem in the recognition of ETEC, EIEC, EPEC, and EHEC strains of *E. coli* is that they are indistinguishable from normal coliform flora of the intestinal tract by the usual bacteriologic methods. Serotyping is of value in recognizing EPEC serotypes[126] and EIEC, because these organisms tend to fall into a limited number of specific serogroups (see Table 20-2).[126,127] EIEC invasiveness is confirmed by inoculating fresh isolates into guinea pig conjunctivae, as described by Sereny.[128] The ability of organisms to produce enterotoxins (LT or ST) is encoded by a transmissible plasmid that can be lost by one strain of *E. coli* or transferred to a previously unrecognized strain.[129-131] Although the enterotoxin plasmids appear to prefer certain serogroups (different from EPEC or invasive serogroups),[132] ETEC is not expected to be strictly limited to a particular set of serogroups. Instead, these strains can be recognized only by examining for the enterotoxin. This is done in ligated animal loops,[133] in tissue culture,[134,135] or by enzyme-linked immunosorbent assay (ELISA)[136] for LT or in suckling mice for ST.[137,138] Specific DNA probes also are available for LT and ST.[98] Whether there are other mechanisms involved in the ability of the versatile *E. coli* species to cause enteric disease, such as by producing other types of enterotoxins[139] or by fimbriate adherence traits alone,[140,141] remains to be elucidated.

Table 20–2   **Predominant Serogroups, Mechanisms, and Gene Codes Associated with Enterotoxigenic, Enteroinvasive, Enteropathogenic, Enterohemorrhagic, and Enteroaggregative *Escherichia coli***

ETEC	EIEC	EPEC	EHEC	EAEC
		Class I Serogroup		
LT	O28ac		O157:H7	O3:H2
O6:K15	O29, O112	O55:K59 (B5)	O26:H11/H-	O44
O8:K40	O115, O124	O111ab:K88 (B4)	O128, O103:H2	O78:H33
	O136, O144	O119K6a (B14)	O39	O15:H11
LT and ST	O147, O152	O125ac:K70 (B15)	O111:K58:H8/H-	O77:H18
O11:H27	O164	O126:K71 (B16)	O113:K75:H7/H21	O51:H11
O15, O20:K79		O127a:K63 (B8)	O121:H-, O145:H-	And many others
O25:K7		O128abc:K67 (B12)	Rough	
O27, O63		O142, O158	And many others	
O80, O85, O139				
		Class II Serogroup		
ST				
O groups 78, 115		O44:K74		
128, 148, 149, 153		O86a:K61 (B7)		
159, 166, 167		O114:H2		
Mechanisms				
Adenylate or guanylate cyclase activation	Colonic invasiveness (e.g., *Shigella*)	Localized attachment and effacement	Shiga toxins block protein synthesis; attachment and effacement	Aggregative adherence and toxins
Gene Codes				
Plasmid	Chromosomal and plasmid	Chromosomal and plasmid	Phage and chromosomal	Plasmid and chromosomal

ETEC, enterotoxigenic *Escherichia coli*; EIEC, enteroinvasive *E. coli*; EPEC, enteropathogenic *E. coli*; EHEC, enterohemorrhagic *E. coli*; EAEC, enteroaggregative *E. coli*; LT, heat-labile toxin; ST, heat-stable toxin.

Enterotoxigenic *Escherichia coli*

Although early work on the recognition of *E. coli* as a potential enteric pathogen focused on biochemical or serologic distinctions, there followed a shift in emphasis to the enterotoxins produced by previously recognized and entirely "new" strains of *E. coli*. Beginning in the mid-1950s with work by De and colleagues[142,143] in Calcutta, *E. coli* strains from patients with diarrhea were found to cause a fluid secretory response in ligated rabbit ileal loops analogous to that seen with *V. cholerae*. Work by Taylor and associates[144,145] showed that the viable *E. coli* strains were not required to produce this secretory response and that this enterotoxin production correlated poorly with classically recognized EPEC serotypes. In São Paulo, Trabulsi[146] made similar observations with *E. coli* isolated from children with diarrhea, and several veterinary workers demonstrated that ETEC was associated with diarrhea in piglets and calves.[147-150] A similar pattern was described in 1971 with acute undifferentiated diarrhea in adults in Bengal from whom *E. coli* could be isolated from the upper small bowel only during acute illness.[151,152] These strains of *E. coli* produced a nondialyzable, LT, ammonium sulfate–precipitable enterotoxin.[153] Analogous to the usually short-lived diarrheal illnesses of *E. coli* reported by several workers, a short-lived course of the secretory response to *E. coli* culture filtrates compared with the secretory response of cholera toxin was described.[154] However, like responses to cholera toxin, secretory responses to *E. coli* were associated with activation of intestinal mucosal adenylate cyclase that paralleled the fluid secretory response.[155,156]

The two types of enterotoxins produced by *E. coli*[157-159] have been found to be plasmid-encoded traits that are potentially separable from each other and from the equally important plasmid-encoded adherence traits for pathogenesis.[129-131,160] ST causes an immediate and reversible secretory response,[133] whereas the effects of LT (e.g., cholera toxin) follow a lag period necessitated by its intracellular site of action.[105,106,134] Only LT appears to cause fluid secretion by activating adenylate cyclase, which is accomplished by toxin-induced ADP-ribosylation of the $G_s\alpha$ signaling protein.[98,105] The activation of adenylate cyclase by LT and by cholera toxin is highly promiscuous, occurring in many cell types and resulting in development of nonintestinal tissue culture assay systems such as the Chinese hamster ovary (CHO) cell assay[134] and Y1 adrenal cell assay.[135] The antigenic similarity of LT and cholera toxin and their apparent binding to the monosialoganglioside GM_1 have enabled development of ELISAs for detection of LT and cholera toxin.[138,161-163]

ST is a much smaller molecule and is distinct antigenically from LT and cholera toxin.[134,137,138] Although it fails to alter cAMP levels, ST increases intracellular intestinal mucosal cyclic guanosine monophosphate (cGMP) concentrations and specifically activates plasma membrane–associated intestinal guanylate cyclase.[111-113] Like cAMP analogues, cGMP analogues cause intestinal secretion that mimics the response to ST.[111] The receptor for STa responds to an endogenous ligand called *guanylin*, of which STa is a structural homologue.[164] Because the capacity to produce an enterotoxin may be transmissible between different organisms by a plasmid or even a bacteriophage,[129-131] interstrain gene transfer

may be expected to be responsible for occasional toxigenic non–E. coli. Enterotoxigenic Klebsiella and Citrobacter strains have been associated with diarrhea in a few reports, often in the same patients with ETEC.[165,166] Likewise, certain strains of Salmonella appear to produce an LT, CHO cell–positive toxin that may play a similar role in the pathogenesis of the watery, noninflammatory diarrhea sometimes seen with Salmonella enteritidis infection.[167,168] At least equally important as enterotoxigenicity for E. coli to cause disease is the ability of these organisms to colonize the upper small bowel, where the enterotoxin produced has its greatest effect. A separable, plasmid-encoded colonization trait was first recognized in porcine E. coli. Veterinary workers demonstrated that the fimbriate K-88 surface antigen was necessary for ETEC to cause disease in piglets.[160] An autosomal dominant allele appears to be responsible for the specific intestinal receptor in piglets. In elegant studies by Gibbons and co-workers,[169] the homozygous recessive piglets lacked the receptor for K-88 and were resistant to scours caused by ETEC. At least 15 analogous colonization factors have been described for human E. coli isolates[98,170,171] against which local IgA antibody may be produced. These antigens potentially may be useful in vaccine development.

Epidemiology and Transmission

Data on the epidemiology and transmission of ETEC remain scanty for the neonatal period. In the past 2 decades, these strains have been recognized among adults with endemic, cholera-like diarrhea in Calcutta, India, and in Dacca, Bangladesh,[105,151] and among travelers to areas such as Mexico and Central Africa.[173-175]

The isolation of ETEC is uncommon in sporadic diarrheal illnesses in temperate climates where sanitation facilities are good and where winter viral patterns of diarrhea predominate. ETEC is commonly isolated from infants and children with acute watery summer diarrhea in areas where sanitary facilities are less than optimal.[35,165,175-187] These include areas such as Africa,[165] Brazil,[35,175,181,186,187] Argentina,[177] Bengal,[178,179] Mexico,[180] and Native American reservations in the southwestern United States.[182,183] In a multicenter study of acute diarrhea in 3640 infants and children in China, India, Mexico, Myanmar, and Pakistan, 16% of cases (versus 5% of 3279 controls) had ETEC.[184] A case-control study from northwestern Spain showed a highly significant association of ETEC with 26.5% of neonatal diarrhea, often acquired in the hospital.[185] Although all types of ETEC (LT and/or ST producers) are associated with cholera-like, non inflammatory, watery diarrhea in adults in these areas, they probably constitute the major cause (along with rotaviruses) of dehydrating diarrhea in infants and young children in these areas. In this setting, peaks of illnesses tend to occur in the summer or rainy season, and dehydrating illnesses may be life threatening, especially in infants and young children.[35,181,186] Humans are probably the major reservoirs for the human strains of ETEC, and contaminated food and water probably constitute the principal vectors.[188,189] Although antitoxic immunity to LT and asymptomatic infection with LT-producing E. coli tends to increase with age, ST is poorly immunogenic, and ST-producing E. coli continues to be associated with symptomatic illnesses into adulthood in endemic areas.[183,187]

The association of ETEC with outbreaks of diarrhea in newborn nurseries is well documented. Ryder and colleagues[190] isolated an ST-producing E. coli from 72% of infants with diarrhea, from the environment, and in one instance, from an infant's formula during a 7-month period in a prolonged outbreak in a special care nursery in Texas. Another ST-producing E. coli outbreak was reported in 1976 by Gross and associates[191] from a maternity hospital in Scotland. ETEC and EPEC were significantly associated with diarrhea among infants younger than 1 year in Bangladesh.[192]

An outbreak of diarrhea in a newborn special care nursery that was associated with enterotoxigenic organisms that were not limited to the same serotype or even the same species has been reported.[193] The short-lived ETEC, Klebsiella, and Citrobacter species in this outbreak raised the possibility that each infant's indigenous bowel flora might become transiently toxigenic, possibly by receiving the LT genome from a plasmid or even a bacteriophage.

Clinical Manifestations

The clinical manifestations of ETEC diarrhea tend to be mild and self-limited, except in small or undernourished infants, in whom dehydration may constitute a major threat to life. In many parts of the developing world, acute diarrheal illnesses are the leading recognized causes of death. There is some suggestion that the diarrheal illnesses associated with ST-producing ETEC may be particularly severe.[179] Most probably the best definition of the clinical manifestations of ETEC infection comes from volunteer studies with adults. Ingestion of 10^8 to 10^{10} human ETEC isolates that produce LT and ST or ST alone resulted in a 30% to 80% attack rate of mild to moderate diarrheal illnesses within 12 to 56 hours that lasted 1 to 3 days.[117] These illnesses, typical for traveler's diarrhea, were manifested by malaise, anorexia, abdominal cramps, and sometimes explosive diarrhea. Nausea and vomiting occur relatively infrequently, and up to one third of patients may have a low-grade fever. Although illnesses usually resolve spontaneously within 1 to 5 days, they occasionally may persist for 1 week or longer. The diarrhea is noninflammatory, without fecal leukocytes or blood. In outbreaks in infants and neonates, the duration has been in the same range (1 to 11 days), with a mean of approximately 4 days.

Pathology

As in cholera, the pathologic changes associated with ETEC infection are minimal. From animal experiments in which Thiry-Vella loops were infected with these organisms and at a time when the secretory and adenylate cyclase responses were present, there was only a mild discharge of mucus from goblet cells and otherwise no significant pathologic change in the intestinal tract.[106] Unless terminal complications of severe hypotension ensue, ETEC organisms rarely disseminate beyond the intestinal tract. Like cholera, ETEC diarrhea is typically limited to being an intraluminal infection.

Diagnosis

The preliminary diagnosis of ETEC diarrhea can be suspected by the epidemiologic setting and the noninflammatory nature of stool specimens, which reveal few or no leukocytes. Although the ability of E. coli to produce enterotoxins may be lost or transmitted to other strains, there is a tendency for the enterotoxin plasmids to occur among certain predominant

serotypes, as shown in Table 20-2.[132] These serotypes differ from EPEC or invasive serotypes, but their demonstration does not prove that they are enterotoxigenic. The only definitive way to identify ETEC is to demonstrate the enterotoxin itself by a specific gene probe for the toxin codon, by a bioassay such as tissue culture or ileal loop assays for LT or the suckling mouse assay for ST, or in the case of LT, by immunoassay such as ELISA. However, even these sensitive bioassays are limited by the unavailability of any selective media for detecting ETEC by culture. Even though substantial improvements have been made in enterotoxin assay (particularly for LT), the necessary random selection of E. coli from a relatively nonselective stool culture plate resulted in a sensitivity of only 43% of epidemiologically incriminated cases in an outbreak when 5 to 10 isolates were randomly picked and tested for enterotoxigenicity.[189] By also examining paired serum samples for antibody against LT, only 36% demonstrated significant serum antibody titer rises, for a total sensitivity of ETEC isolation or serum antibody titer rises of only 64%. Some have suggested that isolates may be pooled for LT or ST assay. The capacity to prove with radiolabeled or enzyme-tagged oligonucleotide gene sequences for the enterotoxins (LT or ST) further facilitates the identification of enterotoxigenic organisms.[194,195] A novel method of combining immunomagnetic separation (using antibody-coated magnetic beads) followed by DNA or polymerase chain reaction (PCR) probing may enhance the sensitivity of screening fecal or food specimens for ETEC or other pathogens.[196,197]

Therapy and Prevention

The mainstay of treatment of any diarrheal illness is rehydration.[198] This principle especially pertains to ETEC diarrhea, which is an intraluminal infection. The glucose absorptive mechanism remains intact in E. coli enterotoxin-induced secretion, much as it does in cholera, a concept that has resulted in the major advance of oral glucose-electrolyte therapy. This regimen can usually provide fully adequate rehydration in infants and children able to tolerate oral fluids, replacing the need for parenteral rehydration in most cases.[199,200] Its use is particularly critical in rural areas and developing nations, where early application before dehydration becomes severe may be lifesaving.

The standard World Health Organization solution contains 3.5 g NaCl, 2.5 g NaHCO$_3$, 1.5 g KCl, and 20 g glucose per liter of clean or boiled drinking water.[198] This corresponds to the following concentrations: 90 mmol/L of sodium, 20 mmol/L of potassium, 30 mmol/L of bicarbonate, 80 mmol/L of chloride, and 110 mmol/L of glucose. A variety of recipes for homemade preparations have been described,[201] but unless the cost is prohibitive, the premade standard solution is preferred. Each 4 ounces of this solution should be followed by 2 ounces of plain water. If there is concern about hypertonicity, especially in small infants in whom a high intake and constant direct supervision of feeding cannot be ensured, the concentration of salt can be reduced.[202] A reduced osmolality solution with 60 mmol/L of sodium and 84 mmol/L of glucose and a total osmolality of 224 (instead of 311) mOsm/kg has been found to reduce stool output by 28% and illness duration by 18% in a multicenter trial involving 447 children in four countries.[203] Commercially available rehydration solutions are increasingly available worldwide.[198]

The role of antimicrobial agents in the treatment or prevention of ETEC is controversial. This infection usually resolves within 3 to 5 days in the absence of antibacterial therapy.[198] Moreover, there is concern about the potential for coexistence of enterotoxigenicity and antibiotic resistance on the same plasmid, and co-transfer of multiple antibiotic resistance and enterotoxigenicity has been well documented.[204] Widespread use of prophylactic antibiotics in areas where antimicrobial resistance is common has the potential for selecting for rather than against enterotoxigenic organisms. The prevention and control of ETEC infections would be similar to those discussed under EPEC serotypes. The use of breast-feeding should be encouraged.

Enteroinvasive *Escherichia coli*

EIEC causes diarrhea by means of *Shigella*-like intestinal epithelial invasion (discussed later).[117,118] The somatic antigens of these invasive strains have been identified and seem to fall into 1 of 10 recognized O groups (see Table 20-2). Most, if not all, of these bacteria share cell wall antigens with one or another of the various *Shigella* serotypes and produce positive reactions with antisera against the cross-reacting antigen.[118] However, not all strains of *E. coli* belonging to the 10 serogroups associated with dysentery-like illness are pathogenic, because a large (140 MDa) invasive plasmid is also required.[205] Additional biologic tests, including the guinea pig conjunctivitis (Sereny) test or a gene probe for the plasmid, are used to confirm the property of invasiveness.[117]

Although an outbreak of foodborne EIEC diarrhea has been well documented among adults who ate an imported cheese,[118] little is known about the epidemiology and transmission of this organism, especially in newborns and infants. Whether the infectious dose may be as low as it is for *Shigella* is unknown; however, studies of adult volunteers suggest that attack rates may be somewhat lower after ingestion of even large numbers of EIEC than would be expected with *Shigella*. The outbreak of EIEC diarrhea resulted in a dysentery-like syndrome with an inflammatory exudate in stool and invasion and disruption of colonic mucosa.[118] Descriptions of extensive and severe ileocolitis in infants dying with *E. coli* diarrhea indicate that neonatal disease also can be caused by invasive strains capable of mimicking the pathologic features of shigellosis.[206] The immunofluorescent demonstration of *E. coli* together with an acute inflammatory infiltrate[207] in the intestinal tissue of infants tends to support this impression, although it has been suggested that the organisms may have invaded the bowel wall in the postmortem period.[117] There is still little direct evidence concerning the role of invasive strains of *E. coli* in the cause of neonatal diarrhea.[175] The infrequency with which newborns manifest a dysentery-like syndrome makes it unlikely that this pathogen is responsible for a very large proportion of the diarrheal disease that occurs during the first month of life.

The diagnosis should be suspected in infants who have an inflammatory diarrhea as evidenced by fecal polymorphonuclear neutrophils or even bloody dysenteric syndromes from whom no other invasive pathogens, such as *Campylobacter, Shigella, Salmonella, Vibrio,* or *Yersinia,* can be isolated. In this instance, it may be appropriate to have the fecal *E. coli* isolated and serotyped or tested for invasiveness in the Sereny test. Plasmid pattern analysis and chromosomal restriction

endonuclease digestion pattern analysis by pulsed-field gel electrophoresis have been used to evaluate strains involved in outbreaks.[208] The management and prevention of EIEC diarrhea should be similar to those for acute *Shigella* or other *E. coli* enteric infections.

Enteropathogenic *Escherichia coli*: Classic Serotypes

The serologic distinction of *E. coli* strains associated with epidemic and sporadic infantile diarrhea was first suggested by Goldschmidt in 1933[209] and confirmed by Dulaney and Michelson in 1935.[205] These researchers found that certain strains of *E. coli* associated with institutional outbreaks of diarrhea would agglutinate with antisera on slides. In 1943, Bray[211] isolated a serologically homogeneous strain of *E. coli* (subsequently identified as serogroup O111) from 95% of infants with summer diarrhea in England. He subsequently summarized a larger experience with this organism isolated from only 4% of asymptomatic controls but from 88% of infants with diarrhea, one half of which was hospital acquired.[212] This strain (initially called *E. coli-gomez* by Varela in 1946) also was associated with infantile diarrhea in Mexico.[213] A second type of *E. coli* (called *beta* by Giles in 1948 and subsequently identified as O55) was associated with an outbreak of infantile diarrhea in Aberdeen, Scotland.[214,215]

From this early work primarily with epidemic diarrhea in infants has developed an elaborate serotyping system for certain *E. coli* strains that were clearly associated with infantile diarrhea.[216-218] These strains first were called enteropathogenic *E. coli* by Neter and colleagues[219] in 1955, and the association with particular serotypes can still be observed.[220] As shown in Table 20-1, these organisms are distinct from the enterotoxigenic or enteroinvasive organisms or those that inhabit the normal gastrointestinal tract. They exhibit localized adherence to HEp-2 cells, a phenotype that has been suggested to be useful for diagnosis and pathogenesis research.[119]

Epidemiology and Transmission

EPEC is an important cause of diarrhea in infants in developing or transitional countries.[98,221-223] Outbreaks have become rare in the United States and other industrialized countries, but they still occur.[224] Some have attributed the rarity of this recognition of illness in part to the declining severity of diarrheal disease caused by EPEC within the past 30 years, resulting in fewer cultures being obtained from infants with relatively mild symptoms.[98,225] However, several other variables influence the apparent incidence of this disease in the community. A problem arises with false-positive EPEC on the basis of the nonspecific cross-reactions seen with improper shortening of the serotyping procedure.[226,227] Because of their complexity and relatively low yield, neither slide agglutination nor HEp-2 cell adherence or DNA probe tests are provided as part of the routine identification of enteric pathogens by most clinical bacteriology laboratories. Failure to recognize the presence of EPEC in fecal specimens is the inevitable consequence.

The apparent incidence of EPEC gastroenteritis also varies with the epidemiologic circumstances under which stool cultures are obtained. The prevalence of enteropathogenic strains is higher among infants from whom cultures are obtained during a community epidemic compared with those obtained during sporadic diarrheal disease. Neither reflects the incidence of EPEC infection among infants involved in a nursery outbreak or hospital epidemic.

EPEC gastroenteritis is a worldwide problem, and socioeconomic conditions play a significant role in determining the incidence of this disease in different populations.[228] For instance, it is unusual for newborn infants born in a rural environment to manifest diarrheal disease caused by EPEC; most infections of the gastrointestinal tract in these infants occur after the first 6 months of life.[5,229] Conversely, among infants born in large cities, the attack rate of EPEC is high during the first 3 months of life. This age distribution reflects in large part the frequency with which EPEC causes cross-infection outbreaks among nursery populations[191,230-237]; however, a predominance of EPEC in infants in the first 3 months of life also has been described in community epidemics[238-240] and among sporadic cases of diarrhea acquired outside the hospital.[241-247] The disparity in the incidence of neonatal EPEC infection between rural and urban populations has been ascribed to two factors: the trend away from breast-feeding among mothers in industrialized societies and the crowding together of susceptible newborns in nurseries in countries in which hospital deliveries predominate over home deliveries.[5,229,248] Although the predominant serogroup can vary from year to year,[239,242,243,246,249,250] the same strains have been prevalent during the past 40 years in Great Britain,[251] Puerto Rico,[252] Guatemala,[5] Panama,[205] Israel,[247] Newfoundland,[240] Indonesia,[244] Thailand,[254] Uganda,[255] and South Africa.[256]

When living conditions are poor and overcrowding of susceptible infants exists, there is a rise in the incidence of neonatal diarrhea in general[257] and EPEC gastroenteritis in particular.[215,238,258] A higher incidence of asymptomatic family carriers is found in such situations.[238,239]

Newborn infants can acquire EPEC during the first days of life by one of several routes: (1) organisms from the mother ingested at the time of birth; (2) bacteria from other infants or toddlers with diarrheal disease or from asymptomatic adults colonized with the organism, commonly transmitted on the hands of nursery personnel or parents; (3) airborne or droplet infection; (4) fomites; or (5) organisms present in formulas or solid food supplements.[259] Only the first two routes have been shown conclusively to be of any real significance in the transmission of disease or the propagation of epidemics.

Most neonates acquire EPEC at the time of delivery through ingestion of organisms residing in the maternal birth canal or rectum. Stool cultures taken from women before, during, or shortly after delivery have shown that 10% to 15% carry EPEC at some time during this period.[85,86,88,260,261] Use of fluorescent antibody techniques[261] or cultures during a community outbreak of EPEC gastroenteritis[88] revealed twice this number of persons excreting the organism. Virtually none of the women carrying pathogenic strains of *E. coli* had symptoms referable to the gastrointestinal tract.

Many of the mothers whose stools contain EPEC transmit these organisms to their infants,[85,88] resulting in an asymptomatic infection rate of 2% to 5% among newborns cultured at random in nursery surveys.[85,86,191,262] These results must be considered conservative and are probably an artifact of the sampling technique. One study using 150 O antisera to identify as many *E. coli* as possible in fecal cultures showed a

correlation between the coliform flora in 66% of mother-infant pairs.[263] Of particular interest was the observation that the O groups of E. coli isolated from the infants' mucus immediately after delivery correlated with those subsequently recovered from their stools, supporting the contention that these organisms were acquired orally at the time of birth. In mothers whose stools contained the same O group as their offspring, the mean time from rupture of membranes to delivery was about 2 hours longer than in those whose infants did not acquire the same serogroups, suggesting that ascending colonization before birth also can play a role in determining the newborn's fecal flora.

The contours of the epidemiologic curves in nursery[238,264-269] and community[238-240] outbreaks are in keeping with a contact mode of spread. Transmission of organisms from infant to infant takes place by way of the fecal-oral route in almost all cases, most likely on the hands of persons attending to their care.[86,267,269,270] Ill infants represent the greatest risk to those around them because of the large numbers of organisms found in their stools[271-274] and vomitus.[275-277] Cross-infection also has been initiated by infants who were healthy at the time of their admission to the nursery.[264,272,278-280]

A newborn exposed to EPEC is likely to acquire enteric infection if contact with a person excreting the organism is intimate and prolonged, as in a hospital or family setting. Stool culture surveys taken during outbreaks have shown that between 20% and 50% of term neonates residing in the nursery carry EPEC in their intestinal tracts.[102,230,231,234] Despite descriptions of nursery outbreaks in which virtually every neonate or low-birth-weight infant became infected,[262,264,281] there is ample evidence that exposure to pathogenic strains of E. coli does not necessarily result in greater likelihood of illness for premature infants than for term infants.[261,272,279,282] Any increased prevalence of cross-infections that may exist among premature infants can be explained more readily by the prolonged hospital stays, their increased handling, and the clustering of infants born in different institutions than by a particular susceptibility to EPEC based on immature defense mechanisms.

The most extensive studies on the epidemiology of gastro-enteritis related to E. coli have dealt with events that took place during outbreaks in newborn nurseries. Unfortunately, investigations of this sort frequently regard the epidemic as an isolated phenomenon and ignore the strong interdependence that exists between community- and hospital-acquired illness.[280,283,284] Not surprisingly, the direction of spread is most often from the reservoir of disease within the community to the hospital. When the original source of a nursery outbreak can be established, frequently it is an infant born of a carrier mother who recently acquired her EPEC infection from a toddler living in the home. Cross-infection epidemics also can be initiated by infected newborns who have been admitted directly into a clean nursery unit from the surrounding district[270,272,285] or have been transferred from a nearby hospital.[278,280,286]

After a nursery epidemic has begun, it generally follows one of two major patterns. Some are explosive, with rapid involvement of all susceptible infants and a duration that seldom exceeds 2 or 3 months.[264,265,276,287] The case-fatality rate in these epidemics may be very high. Other nursery outbreaks have an insidious onset with a few mild, unrecognized cases; the patients may not even develop illness until after discharge from the hospital. During the next few days to weeks, neonates with an increased number of loose stools are reported by the nurses; shortly thereafter, the appearance of the first severely ill infants makes it apparent that an epidemic has begun. Unless oral antimicrobial therapy is instituted (see "Therapy"), nursery outbreaks like these may continue for months[266-269] or years,[270] with cycles of illness followed by periods of relative quiescence. This pattern can be caused by multiple strains (of different phage or antibiogram types) sequentially introduced into the nursery.[278,288,289]

The nursery can be a source of infection for the community. The release of infants who are in the incubation stages of their illness or are convalescent carriers about to relapse may lead to secondary cases of diarrheal disease among young siblings living in widely scattered areas.[238,239,243] These children further disseminate infection to neighboring households, involving playmates of their own age, young infants, and mothers.[238,239,242] As the sickest of these contact cases are admitted to different hospitals, they contaminate new susceptible persons, completing the cycle and compounding the outbreak. This feedback mechanism has proved to be a means of spreading infantile gastroenteritis through entire cities,[238,239,242] counties,[239,285,290] and even provinces.[240] One major epidemic of diarrhea related to EPEC O111:B4 that occurred in the metropolitan Chicago and northwestern Indiana region during the winter of 1961 involved more than 1300 children and 29 community hospitals during a period of 9 months.[240,291] Almost all of the patients were younger than 2 years old, and 10% were younger than 1 month, producing an age-specific attack rate of nearly 4% of neonates in the community. The importance of the hospital as a source of cross-infection in this epidemic was demonstrated through interviews with patients' families, indicating that a minimum of 40% of infants had direct or indirect contact with a hospital shortly before the onset of their illness.

It has been suggested, but not proved, that asymptomatic carriers of EPEC in close contact with a newborn infant, such as nursery personnel or family members, might play an important role in its transmission.[280,284,292] Stool culture surveys have shown that at any one time about 1% of adults[242,293] and 1% to 5% of young children[230,238,243] who are free of illness harbor EPEC strains. Higher percentages have been recorded during community epidemics.[238,239,243] Because this intestinal carriage is transitory,[238,280] the number of individuals who excrete EPEC at one time or another during the year is far higher than the 1% figure recorded for single specimens.[280,293]

Nursery personnel feed, bathe, and diaper a constantly changing population of newborns, about 2% to 5% of whom excrete EPEC.[238,280] Despite this constant exposure, intestinal carriage among nursery workers is surprisingly low. Even during outbreaks of diarrheal illness, when dissemination of organisms is most intense, less than 5% of the hospital personnel in direct contact with infected neonates are themselves excreting pathogenic strains of E. coli.[291,294,295]

Although adult asymptomatic carriers generally excrete fewer organisms than patients with acute illness do,[272] large numbers of pathogenic bacteria may nevertheless exist in their stools.[242,274] However, no nursery outbreak and few family cases[240] have been traced to a symptomless carrier. Instead, passive transfer of bacteria from infant to infant by the hands of personnel appears to be of primary importance in these outbreaks.

EPEC can be recovered from the throat or nose of 5% to 80% of infants with diarrheal illness[275,294,295] and from about 1% of asymptomatic infants.[232,243] The throat and nasal mucosa may represent a portal of entry or a source of transmission for EPEC. Environmental studies have shown that EPEC is distributed readily and widely in the vicinity of an infant with active diarrheal disease, often within 1 day of admission to the ward.[232,296] Massive numbers of organisms are shed in the diarrheal stool or vomitus of infected infants.[249,296] E. coli organisms may survive 2 to 4 weeks in dust[243,296] and can be found in the nursery air when the bedding or diapers of infected infants are disturbed during routine nursing procedures[243,296] or on floors, walls, cupboards, and nursery equipment such as scales, hand towels, bassinets, incubators, and oxygen tents of other infants.[88,243,267] Documentation of the presence of EPEC in nursery air and dust does not establish the importance of this route as a source of cross-infection. One study presented evidence of the respiratory transmission of EPEC; however, even in the cases described, the investigators pointed out that fecal-oral transmission could not be completely ruled out.[238] Additional clinical and experimental data are required to clarify the significance of droplet and environmental infection.

Coliform organisms have also been isolated in significant numbers from human milk,[46,297,298] prebottled infant formulas,[299] and formulas prepared in the home.[292] EPEC in particular has been found in stool cultures obtained from donors of human milk and workers in a nursery formula room.[260] In one instance, EPEC O111:B4 was isolated from a donor, and subsequently, the same serogroup was recovered in massive amounts in almost pure culture from her milk.[260] Pathogenic strains of E. coli have also been isolated from raw cow's milk[300] and from drinking water.[301] Likewise, EPEC has been isolated from flies during an epidemic, but this fact has not been shown to be of epidemiologic significance.[211,220]

Pathogenesis

Infection of the newborn infant with EPEC takes place exclusively by the oral route. Attempts to induce disease in adult volunteers by rectal instillation of infected material have been unsuccessful.[98] There are no reports of disease occurring after transplacental invasion of the fetal bloodstream by enteropathogenic or nonenteropathogenic strains of E. coli. Ascending intrauterine infection after prolonged rupture of the membranes has been reported only once; the neonate in this case suffered only from mild diarrhea.[86]

Bacterial cultures of the meconium and feces of newborns indicate that enteropathogenic strains of E. coli can colonize effectively the intestinal tract in the first days of life.[85-88] Although E. coli may disappear completely from stools of breast-fed children during the ensuing weeks, this disappearance is believed to be related to factors present in the human milk rather than the gastric secretions.[5,302,303] The use of breast-feeding or expressed human milk has even been effective in terminating nursery epidemics caused by EPEC O111:B4, probably by reducing the incidence of cross-infections among infants.[303,304] Although dose-effect studies have not been performed among newborns, severe diarrhea has occurred after ingestion of 10^8 EPEC organisms by very young infants.[305,306] The high incidence of cross-infection outbreaks in newborn nurseries suggests that a far lower inoculum can often effect spread in this setting.

The role of circulating immunity in the prevention of gastrointestinal tract disease related to EPEC has not been clearly established. Virtually 100% of maternal sera have been found to contain hemagglutinating,[219,307,308] bactericidal,[305,310] or bacteriostatic[280,312] antibodies against EPEC. The passive transfer of these antibodies across the placenta is extremely inefficient. Titers in blood of newborn infants are, on average, 4 to 100 times lower than those in the corresponding maternal sera. Group-specific hemagglutinating antibodies against the O antigen of EPEC are present in 10% to 20% of cord blood samples,[219,307,308] whereas bactericidal[307,311] or bacteriostatic[311] activity against these organisms can be found much more frequently. Tests for bacterial agglutination, which are relatively insensitive, are positive in only a small percentage of neonates.[219,311]

The importance of circulating antibodies in the susceptibility of infants to EPEC infection is unknown. Experiments with suckling mice have failed to demonstrate any effect of humoral immunity on the establishment or course of duration of intestinal colonization with E. coli O127 in mothers or their infants.[313] Similar observations have been made in epidemiologic studies among premature human infants using enteropathogenic (O127:B8)[310] and nonenteropathogenic (O4:H5)[269] strains of E. coli as the indicator organisms. In a cohort of 63 mothers and their infants followed from birth to 3 months old, Cooper and associates[85] were able to show a far higher incidence of clinical EPEC disease in infants of EPEC-negative mothers than in infants born of mothers with EPEC isolated from stool cultures. This finding suggested to the investigators the possibility that mothers harboring EPEC in their gastrointestinal tracts transfer specific antibodies to their infants that confer some protection during the first weeks of life.

Protection against enteric infections in humans often correlates more closely with levels of local secretory than serum antibodies. Although it is known that colonization of newborns with E. coli leads to the production of coproantibodies against the ingested organisms,[314,315] the clinical significance of this intestinal immunity is uncertain. The previously mentioned experiment with mice showed no effect of active intestinal immunity on enteric colonization.[313] In human infants, the frequency of bacteriologic and clinical relapse related to EPEC of the same serotype[264,265,279] and the capacity of one strain of EPEC to superinfect a patient already harboring a different strain[247,258,268] also cast some doubt on the ability of mucosal antibodies to inhibit or alter the course of intestinal infection. Studies of the protective effects of orally administered EPEC vaccines could help to resolve these questions.[248]

The mechanism by which EPEC causes diarrhea involves a complex array of plasmid and chromosomally encoded traits. EPEC serotypes usually do not make one of the recognized enterotoxins (LT or ST) as usually measured in tissue culture or animal models,[316-320] nor do these serotypes cause a typical invasive colitis or produce a positive Sereny test result.[315,316] Only uncommonly do EPEC strains invade the bloodstream or disseminate.[288] Nevertheless, EPEC strains that test negative in these tests are capable of causing diarrhea; inocula of 10^{10} E. coli O142 or O127 organisms caused diarrhea in 8 of 10 adult volunteers.[320]

Some EPEC strains may secrete weak enterotoxins,[321,322] but the consensus opinion is that the attaching and effacing

lesion constitutes the critical secretory virulence pheno-type.[98,121] Clinical pathologic reports reveal the characteristic attaching and effacing lesion in the small intestine of infected infants.[324] The lesion is manifested by intimate (about 10 nm) apposition of the EPEC to the enterocytes plasma membrane, with dissolution of the normal brush border and rearrangement of the cytoskeleton.[121,324] In some instances, the bacteria are observed to rise up on pedestal-like structures, which are diagnostic of the infection.[121] Villus blunting, crypt hypertrophy, histiocytic infiltration in the lamina propria, and a reduction in the brush border enzymes may also be observed.[324,325]

Two major EPEC virulence factors have been described; strains with both factors are designated as typical EPEC.[98,99,323] One such factor is the locus of enterocyte effacement (LEE), a type III secretion system encoded by the LEE chromosomal pathogenicity island.[326-328] The LEE secretion apparatus injects proteins directly from the cytoplasm of the infecting bacterium into the cytoplasm of the target enterocytes.[327] The injected proteins constitute cytoskeletal toxins, which together elicit the close apposition of the bacterium to the cell, cause the effacement of microvilli, and most likely give rise to the net secretory state.[98,99,121] One critical secreted protein, called Toll/interleukin-1 receptor (Tir),[120] inserts into the plasma membrane of the epithelial cell, where it serves as the receptor for a LEE-encoded EPEC outer membrane protein called intimin.[121] Animals infected with attaching and effacing pathogens mount antibody responses to intimin and Tir,[329] and both are considered potential immunogens. The lack of protection from EPEC reinfection suggests that natural antibody responses to Tir and intimin are not protective.

The second major virulence factor of typical EPEC is the bundle-forming pilus (BFP),[330] which is encoded on a partially conserved 60 MDa virulence plasmid called EPEC adherence factor (EAF).[331] BFP, a member of the type IV pilus family, mediates aggregation of the bacteria to each other and probably to enterocytes themselves, thereby facilitating mucosal colonization.[332] A BFP mutant was shown to be attenuated in adult volunteers.[333]

Pathology

The principal pathologic lesion with EPEC is the focal destructive adherence of the organism, effacing the microvillous brush border with villus blunting, crypt hypertrophy, histiocytic infiltration of the lamina propria, and reduced brush border enzymes. Rothbaum and colleagues[324] described similar findings with dissolution of the glycocalyx and flattened microvilli with the nontoxigenic EPEC strain O119:B14. There has been a wide range of pathologic findings reported in infants dying of EPEC gastroenteritis. Most newborns dying with diarrheal disease caused by EPEC show no morphologic changes of the gastrointestinal tract by gross or microscopic examination of tissues.[209,210] Bray[211] described such "meager" changes in the intestinal tract that "the impression received was that the term gastroenteritis is incorrect." At the other extreme, extensive and severe involvement of the intestinal tract, although distinctly unusual among neonates with EPEC diarrhea, has been discussed in several reviews of the pathologic anatomy of this disease.[247,319,334] Changes virtually identical to those found in infants dying with necrotizing enterocolitis have been

reported.[334] Drucker and co-workers[319] found that among 17 infants who were dying of EPEC diarrhea, "intestinal gangrene, and/or perforation, and/or peritonitis were present in five, and intestinal pneumatosis in five."

The reasons for such wide discrepancies in EPEC disease pathology are not clear. The severity of intestinal lesions at the time of death does not correlate with the birth weight of the patient, the age of onset of illness, the serogroup of the infecting strain, or the prior administration of oral or systemic antimicrobial agents. The suggestion that the intensity of inflammatory changes may depend on the duration of the diarrhea[319] cannot be corroborated in autopsy studies[215,264,335] or small intestinal biopsies.[336,337] It is difficult to reconcile such a thesis with the observation that a wide range of intestinal findings can be seen at autopsy among newborns infected by a single serotype of EPEC during an epidemic. The nonspecific pathologic picture described by some researchers includes capillary congestion and edema of the bowel wall and an increase in the number of eosinophils, plasma cells, macrophages, and mononuclear cells in the mucosa and submucosa.[262,319,335] Villous patterns are generally well preserved, although some flattening and broadening of the villi are seen in the more severe cases. Almost complete absence of villi and failure of regeneration of small bowel mucosa have been reported in an extreme case.[338] Edema in and around the myenteric plexuses of Auerbach, a common associated finding, has been suggested as a cause of the gastrointestinal tract dilatation often seen at autopsy in infants with EPEC infections.[247,335,339] In general, the distal small intestine shows the most marked alterations; however, the reported pathologic findings may be found at all levels of the intestinal tract.

Several complications of EPEC infection have been reported. Candidal esophagitis accounted for significant morbidity in two series collected before[210] and during[247] the antibiotic era. Oral thrush has been seen in 50% of EPEC-infected infants treated with oral or systemic antibiotics.[245,264,335] Some degree of fatty metamorphosis of the liver has been reported by several investigators[210,215 335]; however, these changes are nonspecific and probably result from the poor caloric intake associated with persistent diarrhea or vomiting. Some degree of bronchopneumonia, probably a terminal event in most cases, exists in a large proportion of newborns dying of EPEC infection.[210,215,339] In one reported series of infant cases, EPEC was demonstrated by immunofluorescent staining in the bronchi, alveoli, and interalveolar septa.

Mesenteric lymph nodes are often swollen and congested with reactive germinal centers in the lymphoid follicles.[215,262,293] Severe lymphoid depletion, unrelated to the duration or severity of the antecedent illness, also has been described.[285] The kidneys frequently show tubular epithelial toxic changes. Various degrees of tubular degeneration and cloudy swelling of convoluted tubules are common findings.[215,285,335] Renal vein thrombosis or cortical necrosis may be observed in infants with disseminated intravascular coagulation in the terminal phases of the illness. The heart is grossly normal in most instances but may show minimal vacuolar changes of nonspecific toxic myocarditis on microscopic examination.[335,339] Candidal abscesses of the heart[339] and kidneys[285,335,339] have been described. With the exception of mild congestion of the pia arachnoid vessels and some edema of the meninges,

examination of the central nervous system reveals few changes.[215,262] Despite the observation of Bray[211] that "inflammation of the middle ear [is] exceptional," strains of EPEC have been isolated from a significant number of specimens of the middle ear in case series in which dissection of the temporal bone has been performed.[209,215]

Clinical Manifestations

Exposure of newborns to EPEC may be followed by one of several possible consequences: no infection, infection without illness, illness with gastroenteritis of variable severity and duration, and rarely, septicemia with or without metastatic foci of infection accompanying gastroenteritis.

When infants are exposed to EPEC, a significant number become colonized as temporary stool[85,88,231] or pharyngeal[238] carriers with no signs of clinical disease. Although Laurell[340] showed that the percentage of asymptomatic infections rises steadily as age increases, this observation has not been confirmed by other investigators.[214,341] Similarly, the suggestion that prematurity per se is associated with a low incidence of inapparent EPEC infection has been documented in several clinical studies[262,264,265] but refuted in others.[252,279] Most neonates who acquire infection with EPEC eventually show some clinical evidence of gastroenteritis. The incubation period is quite variable. Its duration has been calculated mostly from evidence in outbreaks in newborn nurseries, where the time of first exposure can be clearly defined in terms of birth or admission dates. In these circumstances, almost all infants show signs of illness between 2 and 12 days after exposure, and most cases show signs within the first 7 days.[215,231,264] In some naturally acquired[85,86] and experimental[306] infections with heavy exposure, the incubation period may be as short as 24 hours; the stated upper limit is 20 days.[232,343] The first positive stool culture and the earliest recognizable clinical signs of disease occur simultaneously in most infants,[264,266] although colonization may precede symptoms by 7 to 14 days.[265,266,344] The gastroenteritis associated with EPEC infection in the newborn is notable for its marked variation in clinical pattern. Clinical manifestations vary from mild illness manifest only by transient anorexia and failure to gain weight to a sudden explosive fulminating diarrhea causing death within 12 hours of onset. Prematurity, underlying disease, and congenital anomalies often are associated with the more severe forms of illness.[214,233,345,346] Experienced clinicians have observed that the severity of EPEC gastroenteritis has declined markedly during the past 3 decades.[225] The onset of illness usually is insidious, with vague signs of reluctance to feed, lethargy, spitting up of formula, mild abdominal distention, or even weight loss that may occur for 1 or 2 days before the first loose stool is passed. Diarrhea usually begins abruptly. It may be continuous and violent, or in milder infections, it may run an intermittent course with 1 or more days of normal stools followed by 1 or more days of diarrhea. Emesis sometimes is a prominent and persistent early finding. Stools are loose and bright yellow initially, later becoming watery, mucoid, and green. Flecks or streaks of blood, which are commonly seen with enterocolitis caused by Salmonella, Campylobacter, or Shigella, are rarely a feature of EPEC diarrheal disease. A characteristic seminal smell may pervade the environment of infants infected with EPEC O111:B34,[232,262,347] and an odor variously described as "pungent," "musty," or "fetid" often surrounds

patients excreting other strains in their stools.[231,256] Because the buttocks are repeatedly covered with liquid stools, excoriation of the perianal skin can be an early and persistent problem. Fever is an inconstant feature, and when it occurs, the patient's temperature rarely rises above 39° C. Convulsions occur infrequently; their occurrence should alert the clinician to the possible presence of electrolyte disturbances, particularly hypernatremia. Prolonged hematochezia, distention, edema, and jaundice are ominous signs and suggest an unfavorable prognosis.[215,240,285] Most infants receiving antimicrobial agents orally show a cessation of diarrhea, tolerate oral feedings, and resume weight gain within 3 to 7 days after therapy has been started.[242,245] Those with mild illness who receive no treatment can continue to have intermittent loose stools for 1 to 3 weeks. In one outbreak related to EPEC O142:K86, more than one third of the untreated or inappropriately treated infants had diarrhea for more than 14 days in the absence of a recognized enteric pathogen on repeated culturing.[267] Recurrence of diarrhea and vomiting after a period of initial improvement is characteristic of EPEC enteritis.[191,239,240] Although seen most often in newborns who have been treated inadequately or not treated at all, clinical relapses also occur after appropriate therapy. Occasionally, the signs of illness during a relapse can be more severe than those accompanying the initial attack of illness.[215,232,285] Not all clinical relapses result from persistent infection. A significant number of relapses, particularly those that consistently follow attempts at reinstitution of formula feedings,[262,265] are caused by disaccharide intolerance rather than bacterial proliferation. Intestinal superinfections, caused by another serotype of EPEC[283,347,348] or by completely different enteric pathogens, such as Salmonella or Shigella,[245] also can delay the resolution of symptoms. Rarely, infants suffer a "relapse" caused by an organism from the same O group as the original strain but differing in its H antigen. Unless complete serotyping is performed on all EPEC isolates, such an event easily could be dismissed as being a recurrence rather than a superinfection with a new organism.[258,268]

Antimicrobial agents to which the infecting organisms are susceptible often may not eradicate EPEC,[245,265,267] which may persist for weeks[264,283,344] or months[349] after the acute illness has subsided. Although reinfection cannot always be excluded, a significant number of infants are discharged from the hospital with positive rectal cultures.[231,233] Dehydration is the most common and serious complication of gastroenteritis caused by EPEC or a toxin-producing E. coli. Virtually all deaths directly attributable to the intestinal infection are caused by disturbances in fluids and electrolytes. When stools are frequent in number, large in volume, and violent in release, as they often are in severe infections with abrupt onset, a neonate can lose up to 15% of body weight in a few hours.[232,276] Rarely, fluid excretion into the lumen of the bowel proceeds so rapidly that reduction of circulating blood volume and shock may intervene before passage of even a single loose stool.[262] Before the discovery of the etiologic agent, epidemic diarrhea of the newborn was also known by the term cholera infantum.

Mild disease, particularly when aggravated by poor fluid intake, can lead to a subtle but serious deterioration of an infant's metabolic status. Sometimes, a week or more of illness elapses before it becomes apparent that an infant with borderline acidosis and dehydration who seemed to be

responding to oral fluids alone requires parenteral therapy for improvement.[272] It is incumbent on the clinician caring for small infants with gastroenteritis to follow them closely, with particular attention to serial weights, until full recovery can be confirmed.

There are few other complications, with the possible exception of aspiration pneumonia, directly related to EPEC gastroenteritis. Protracted diarrhea and nutritional failure may occur as a consequence of functional damage to the small intestinal mucosa, with secondary intolerance to dietary sugars.[265,338] Necrotizing enterocolitis, which occasionally results in perforation of the bowel and peritonitis, has not been causally related to infection with EPEC.[247,264,266] A review of most of the large clinical series describing EPEC disease in infants who ranged in age from neonates to children aged 2 years revealed only three proven instances of bacteremia,[265,278] one possible urinary tract infection,[265] and one documented case of meningitis in an infant of unspecified age.[351] Focal infections among neonates were limited to several cases of otitis media[247,262] and a subcutaneous abscess[294] from which EPEC was isolated. Additional complications include interstitial pneumonia,[319] gastrointestinal bleeding with or without disseminated intravascular coagulation,[334,352] and methemoglobinemia caused by a mutant of EPEC O127:B8 that was capable of generating large quantities of nitrite from proteins present in the gastrointestinal tract.[353]

Diagnosis

The gold standard of EPEC diagnostics is identification in the stool of E. coli carrying genes for BFP and LEE. Identification of these genes can be accomplished by molecular methods (discussed later), but lack of access to these methods has led many labs to rely on surrogate markers, such as serotyping.[19] Classic EPEC has been recovered from the vomitus, stool, or bowel contents of infected newborns. Isolation from bile[233] and the upper respiratory tract[85,238,239] has been described in those instances in which a specific search has been made. Less commonly, EPEC is isolated from ascetic fluid[252] or purulent exudates[209,215,294]; occasionally, the organism has been recovered from blood cultures,[265,278] urine,[265] and cerebrospinal fluid. Stool cultures generally are more reliable than rectal swabs in detecting the presence of enteric pathogens, although a properly obtained swab should be adequate to demonstrate EPEC in most cases.[217,296,354] Specimens should be obtained as early in the course of the illness as possible because organisms are present in virtually pure culture during the acute phase of the enteritis but diminish in numbers during convalescence. Because of the preponderance of EPEC in diarrheal stools, two cultures are adequate for isolation of these pathogens in almost all cases of active disease. Studies using fluorescent antibody methods for identification of EPEC in stool specimens have demonstrated that during the incubation period of the illness, during convalescence, and among asymptomatic carriers of EPEC, organisms can be excreted in such small numbers that they escape detection by standard bacteriologic methods in a significant proportion of infants.[245,355,356] As many as 3 to 10 specimens may be required to detect EPEC using methods that identify individual EPEC isolates in the stool.[85,346] After a stool specimen is received, it should be plated as quickly as possible onto noninhibiting media or placed in a preservative medium if it is to be held for longer

periods. Deep freezing of specimens preserves viable EPEC when a prolonged delay in isolation is necessary.[218] No selective media, biochemical reactions, or colonial variations permit differentiation of pathogenic and nonpathogenic strains. Certain features may aid in the recognition of two important serogroups. Cultures of serogroups O111:B4 and O55:B5, unlike many other coliforms, are sticky or stringy when picked with a wire loop and are rarely hemolytic on blood agar,[217,219] whereas O111:B4 colonies emit a distinctive evanescent odor commonly described as "seminal."[210,214] This unusual odor first led Bray[347] to suspect that specific strains of E. coli might be responsible for infantile gastroenteritis.

Because serotyping is simpler than molecular detection and because EPEC have long been known to belong to certain highly characteristic serotypes, serotyping can be used to identify likely EPEC strains, especially in outbreaks.[216] E. coli, like other Enterobacteriaceae members, possesses cell wall somatic antigens (O), envelope or capsular antigens (K), and if motile, flagellar antigens (H). Many of the O groups may be further divided into two or more subgroups (a, b, c), and the K antigens are divisible into at least three varieties (B, L, A) on the basis of their physical behavior. Organisms that do not possess flagellar antigens are nonmotile (designated NM). The EPEC B capsular surface antigen prevents agglutination by antibodies directed against the underlying O antigen. Heating at 100° C for 1 hour inactivates the agglutinability and antigenicity of the B antigen.

Slide agglutination tests with polyvalent O or OB antiserum may be performed on suspensions of colonies typical of E. coli that have been isolated from infants with diarrhea, especially in nursery outbreaks. However, because of numerous false-positive "cross-reactions," the O and K (or B) type must be confirmed by titration with the specific antisera.[227] The presence of EPEC does not prove that EPEC is the cause of diarrhea in an individual patient. Mixed cultures with two or three serotypes of EPEC have been demonstrated in 1% to 10% of patients.[244,245,352] This need not mean that two or three serotypes are causative agents. Secondary infection with hospital-acquired strains can occur during convalescence,[173,281,283,380] and some infants may have been asymptomatic carriers of one serotype at the time that another produced diarrheal disease. A similar explanation may pertain to mixed infections with EPEC and Salmonella or Shigella.[217,220,358] Nelson[245] reported the presence of these pathogens in combination with EPEC in 14% of infants who were cultured as part of an antibiotic therapy trial. Salmonella and Shigella that had not been identified on cultures obtained at admission were isolated only after institution of oral therapy with neomycin. The investigator postulated that the alteration in bowel flora brought about by the neomycin facilitated the growth of these organisms, which had previously been suppressed and obscured by coliform overgrowth.[245] The importance of seeking all enteric pathogens in primary and follow-up cultures of infantile diarrhea is apparent, particularly when the specimen originates from a patient in a newborn nursery or infants' ward.

Although EPEC gastroenteritis was once considered to be synonymous with "summer diarrhea," community outbreaks have occurred as frequently, if not more frequently, in the colder seasons.[133,160,172] It has been suggested that the increased incidence at that time of year might be related to the heightened chance of contact between infants and toddlers

that is bound to occur when children remain indoors in close contact.[294] Nursery epidemics, which depend on the chance introduction and dissemination of EPEC within a relatively homogeneous population and stable environment, demonstrate no seasonal prevalence. Average relative humidity, temperature, and hours of daylight have no significant effect in determining whether an outbreak will follow the introduction of enteropathogenic strains of E. coli into a ward of infants.[243]

There are no clinical studies of the variations in peripheral leukocyte count, urine, or cerebrospinal fluid in neonatal enteritis caused by EPEC. Microscopic examination of stools of infants with acute diarrheal illness caused by these organisms usually has revealed an absence of fecal polymorphonuclear leukocytes,[214,256,320,359] although data on fecal lactoferrin in human volunteers suggest that an inflammatory process may be important in EPEC diarrhea.[360,361] Stool pH can be neutral, acid, or alkaline.[61,341] Serologic methods have not proved to be useful in attempting to establish a retrospective diagnosis of EPEC infection in neonates. Rising or significantly elevated agglutinin titers rarely could be demonstrated in early investigations[210,215,231]; hemagglutinating antibodies showed a significant response in no more than 10% to 20% of cases.[245,297] Fluorescent antibody techniques have shown promise for preliminary identification of EPEC in acute infantile diarrhea. This method is specific, with few false-positive results, and it is more sensitive than conventional plating and isolation techniques.[282,361,362] The rapidity with which determinations can be performed makes them ideally suited for screening ill infants and possible carriers in determining the extent and progression of a nursery[272,282] or community[238,291] outbreak. Because immunofluorescence does not depend on the viability of organisms and is not affected by antibiotics that suppress growth on culture plates, it can be used to advantage in following bacteriologic responses and relapses in patients receiving oral therapy.[210,363] The use of fluorescent antibody techniques offers many advantages in the surveillance and epidemiologic control of EPEC gastroenteritis. Immunofluorescent methods should supplement but not replace standard bacteriologic and serologic methods for identification of enteric pathogens.

Specific gene probes and PCR primers for the BFP adhesin, the intimin-encoding gene (eae) and for a cryptic plasmid locus (EAF) are available.[98] Detection of BFP or EAF are superior to detection of eae, because many non-EPEC, including nonpathogens, carry the eae gene.[98,364] PCR and gene probe analysis can be performed directly on the stools of suspect infants. However, confirmation of infection by the identification of the organism in pure culture should be pursued.

Before widespread use of molecular methods, the HEp-2 cell adherence assay was proposed for EPEC diagnosis.[119] The presence of a focal or localized adherence (LA)[119] pattern on the surface of HEp-2 or HeLa cells after 3-hour co-incubation is a highly sensitive and specific test for detection of EPEC.[365] The requirement for cell culture and expertise in reading this assay limits its utility to the research setting. An ELISA for the BFP has been described but is not readily available.[366] The capacity of LA + EPEC to polymerize F-actin can be detected in tissue culture cells stained with rhodamine-labeled phalloidin.[367] This fluorescence-actin staining (FAS) test is cumbersome and impractical for routine clinical use.

Prognosis

The mortality rate recorded previously in epidemics of EPEC gastroenteritis is impressive for its variability. During the 1930s and 1940s, when organisms later recognized as classic enteropathogenic serotypes were infecting infants, the case-fatality ratio among neonates was about 50%.[209,210] During the 1950s and 1960s, many nursery epidemics still claimed about one of every four infected infants, but several outbreaks involving the same serotypes under similar epidemiologic circumstances had fatality rates of less than 3%.[234,241,251] In the 1970s, reports appeared in the literature of a nursery epidemic with a 40% neonatal mortality rate[285] and of an extensive outbreak in a nursery for premature infants with 4% fatalities[265]; another report stated that among "243 consecutive infants admitted to the hospital for EPEC diarrheal disease, none died of diarrheal disease per se."[368]

A significant proportion of the infants who died during or shortly after an episode of gastroenteritis already were compromised by preexisting disease[233,283,330] or by congenital malformations[214,231,240] at the time they acquired their illness. These underlying pathologic conditions appear to exert a strongly unfavorable influence, probably by reducing the infant's ability to respond to the added stresses imposed by the gastrointestinal tract infection. Although prematurity is often mentioned as a factor predisposing to a fatal outcome, the overall mortality rate among premature infants with EPEC gastroenteritis has not differed significantly over the years from that recorded for term infants.[233,262,264]

Therapy

The management of EPEC gastroenteritis should be directed primarily toward prevention or correction of problems caused by loss of fluids and electrolytes.[198] Most neonates have a relatively mild illness that can be treated with oral rehydration. Infants who appear toxic, those with voluminous diarrhea and persistent vomiting, and those with increasing weight loss should be hospitalized for observation and treatment with parenteral fluids and careful maintenance of fluid and electrolyte balance and possibly with antimicrobial therapy. Clinical studies suggest that slow nasogastric infusion of an elemental diet can be valuable in treating infants who have intractable diarrhea that is unresponsive to standard modes of therapy.[369]

There is no evidence that the use of proprietary formulas containing kaolin or pectin is effective in reducing the number of diarrheal stools in neonates with gastroenteritis. Attempts to suppress the growth of enteric pathogens by feeding lactobacillus to the infant in the form of yogurt, powder, or granules have not been shown to be of value.[370] A trial of cholestyramine in 15 newborns with EPEC gastroenteritis had no effect on the duration or severity of the diarrhea.[265] The use of atropine-like drugs, paregoric, or loperamide to reduce intestinal motility or cramping should be avoided. Inhibition of peristalsis interferes with an efficient protective mechanism designed to rid the body of intestinal pathogens and may lead to fluid retention in the lumen of the bowel that may be sufficient to mask depletion of extracellular fluid and electrolytes.

The value of antimicrobial therapy in management of neonatal EPEC gastroenteritis, if any, is uncertain. There are no adequately controlled studies defining the benefits of any antibiotic in eliminating EPEC from the gastrointestinal tract, reducing the risk of cross-infection in community or nursery outbreaks, or modifying the severity of the illness. Proponents of the use of antimicrobial agents have based their claims for efficacy on anecdotal observations or comparative studies.[245] Nonetheless, several clinical investigations have provided sufficient information to guide the physician faced with the dilemma of deciding whether to treat an individual infant or an entire nursery population suffering from EPEC diarrheal disease. It should be emphasized, however, that these guidelines must be considered tentative until rigidly controlled, double-blind studies have established the efficacy of antibiotics on a more rational and scientific basis.

Oral therapy with neomycin,[234,251] colistin,[363] or chloramphenicol[344] appears to be effective in rapidly reducing the number of susceptible EPEC organisms in the stool of infected infants. Studies comparing the responses of infants treated orally with neomycin,[233] gentamicin,[265] polymyxin,[242] or kanamycin[371] with the responses of infants receiving supportive therapy alone have shown that complete eradication of EPEC occurs more rapidly in those receiving an antimicrobial agent. In most cases, stool cultures are free of EPEC 2 to 4 days after the start of therapy.[245,363] Bacteriologic failure, defined as continued isolation of organisms during or after a course of an antimicrobial agent, can be expected to occur in 15% to 30% of patients.[245,265] Such relapses generally are not associated with a recurrence of symptoms.[231,234,245] The effectiveness of oral antimicrobial therapy in reducing the duration of EPEC excretion serves to diminish environmental contamination and the spread of pathogenic organisms from one infant to another. Breaking the chain of fecal-oral transmission by administering antimicrobial agents simultaneously to all carriers of EPEC and their immediate contacts in the nursery has appeared to be valuable in terminating outbreaks that have failed to respond to more conservative measures.[234,264,372] The apparent reduction in morbidity and mortality associated with oral administration of neomycin,[230,233,234] colistin,[246,267,285] polymyxin,[242] or gentamicin[246] during nursery epidemics has led to the impression that these drugs also exert a beneficial clinical effect in severely or moderately ill infants. Reports describing clinical,[256] bacteriologic,[265] or histopathologic[319] evidence of tissue invasion by EPEC have persuaded some investigators to suggest the use of parenteral rather than oral drug therapy in debilitated or malnourished infants. On the basis of these data, there appears to be sufficient evidence to recommend oral administration of nonabsorbable antibiotics in the treatment of severely or moderately ill newborns with EPEC gastroenteritis. The drug most frequently used for initial therapy is neomycin sulfate in a dosage of 100 mg/kg/day administered orally every 8 hours in three divided doses.[245] In communities in which neomycin-resistant EPEC has been prevalent, treatment with colistin sulfate or polymyxin B in a dosage of 15 to 20 mg/kg/day orally and divided into three equal doses may be appropriate. However, it is rarely necessary to use this approach.

Treatment should be continued only until stool cultures become negative for EPEC.[245] Because of the unavoidable delay before cultures can be reported, most infants receive therapy for 3 to 5 days. If fluorescent antibody testing of rectal swab specimens is available, therapy can be discontinued as soon as EPEC no longer is identified in smears; this takes no more than 48 hours in more than 90% of cases.[245] After diarrhea and vomiting have stopped and the infant tolerates formula feedings, shows a steady weight gain, and appears clinically well, discharge with outpatient follow-up is indicated. Bacteriologic relapses do not require therapy unless they are associated with illness or high epidemiologic risks to other young infants in the household. Because the infecting organisms in these recurrences generally continue to show in vitro susceptibility to the original drug, it should be reinstituted pending bacteriologic results.[245]

When clinical judgment suggests that a neonate may be suffering from bacterial sepsis and EPEC diarrheal disease, parenteral antimicrobial therapy is indicated after appropriate cultures have been obtained. The routine use of systemic therapy in severe cases of EPEC enteritis is not appropriate on the basis of current clinical experience.

Antimicrobial susceptibility patterns of EPEC are an important determinant of the success of therapy in infections with these organisms.[233,246,247] These patterns are unpredictable, depending on the ecologic pressures exerted by local antibiotic usage[246,247] and on the incidence of transmissible resistance factors in the enteric flora of the particular population served by an institution.[373-378] For these reasons, variations in susceptibility patterns are apparent in different nurseries[246,376] and even from time to time within the same institution.[247,248,250] Sudden changes in clinical response may even occur during the course of a single epidemic as drug-susceptible strains of EPEC are replaced by strains with multidrug resistance.[233,291,375] Because differences can exist in the susceptibilities of different EPEC serogroups to various antimicrobial agents, regional susceptibility patterns should be reported on the basis of OB group or serotype rather than for EPEC as a whole.[250] Knowledge of the resistance pattern in one's area may help in the initial choice of antimicrobial therapy.

Prevention

The prevention of hospital outbreaks of EPEC gastroenteritis is best accomplished by careful attention to infection control policies for a nursery. All infants hospitalized with diarrhea should have a bacteriologic evaluation. If the laboratory is equipped and staffed to perform fluorescent antibody testing, infants transferred from another institution to a newborn, premature, or intensive care nursery and all infants with gastroenteritis on admission during an outbreak of EPEC diarrhea or in a highly endemic area can be held in an observation area for 1 or 2 hours until the results of the fluorescent antibody test or PCR are received. Because of the difficulty in diagnosing EPEC infection, reference laboratories, such as those at the Centers for Disease Control and Prevention (CDC), should be notified when an outbreak is suspected. Infants suspected to be excreting EPEC, even if healthy in appearance, then can be separated from others and given oral therapy until the test results are negative. Some experts have suggested that when the rapid results obtainable with fluorescent antibody procedures are not available, all infants admitted with diarrhea in a setting where EPEC is common may be treated as if they were excreting EPEC or some other enteric pathogen until contrary

proof is obtained.[372] Stool cultures should be obtained at admission, and contact precautions should be enforced among all who come into contact with the infant. Additional epidemiologic studies are needed to establish the advantages of careful isolation and nursing techniques, particularly in smaller community hospitals in which the number of infants in a "gastroenteritis ward" may be small. The use of prophylactic antibiotics has been shown to be of no value and can select for increased resistance.[377-379]

Unfortunately, it can be difficult to keep a nursery continuously free of EPEC. Specific procedures have been suggested for handling a suspected outbreak of bacterial enteritis in a newborn nursery or infant care unit.[235,355,380] Evidence indicating that a significant proportion of E. coli enteritis may be caused by nontypeable strains has required some modification of these earlier recommendations. The following infection control measures may be appropriate:

1. The unit is closed, when possible, to all new admissions.

2. Cultures for enteric pathogens are obtained from nursing personnel assigned to the unit at the time of the outbreak.

3. Stool specimens obtained from all infants in the nursery can be screened by the fluorescent antibody or another technique and cultured. Identification of a classic enteropathogenic serotype provides a useful epidemiologic marker; however, failure to isolate one of these strains does not eliminate the possibility of illness caused by a nontypeable EPEC.

4. Antimicrobial therapy with oral neomycin or colistin can be considered for all infants with a positive fluorescent antibody test or culture result. The initial drug of choice depends on local patterns of susceptibility. Depending on the results of susceptibility tests, subsequent therapy may require modification.

5. If an identifiable EPEC strain is isolated, second and third stool specimens from all infants in the unit are reexamined by the fluorescent antibody technique or culture at 48-hour intervals. If this is not practical, exposed infants should be carefully followed.

6. Early discharge for healthy, mature, uninfected infants is advocated.

7. An epidemiologic investigation should be performed to seek the factor or factors responsible for the outbreak. A surveillance system may be established for all those in contact with the nursery, including physicians and other health care personnel, housekeeping personnel, and postpartum mothers with evidence of enteric disease. A telephone, mail, or home survey may be conducted on all infants who were residing in the involved unit during the 2 weeks before the outbreak.

8. When all patients and contacts are discharged and control of the outbreak is achieved, a thorough terminal disinfection of the involved nursery is mandatory.

Above all, personnel and parents should pay scrupulous attention to hand hygiene when handling infants.[381]

Enterohemorrhagic *Escherichia coli*

Since a multistate outbreak of enterohemorrhagic colitis was associated with E. coli O157:H7,[382] Shiga toxin–producing E. coli (STEC) have been recognized as emerging gastrointestinal pathogens in most of the industrialized world. A particularly virulent subset of STEC, EHEC, causes frequent and severe outbreaks of gastrointestinal disease[98,383]; the most virulent EHEC belong to serotype O157:H7. EHEC has a bovine reservoir and is transmitted by undercooked meat, unpasteurized milk, and contaminated vegetables such as lettuce, alfalfa sprouts, and radish sprouts (as occurred in more than 9000 schoolchildren in Japan).[384,387] It also spreads directly from person to person.[387,388] The clinical syndrome is that of bloody, noninflammatory (sometimes voluminous) diarrhea that is distinct from febrile dysentery with fecal leukocytes seen in shigellosis or EIEC infections.[98] Most cases of EHEC infections have been recognized in outbreaks of bloody diarrhea or HUS in daycare centers, schools, nursing homes, and communities.[388-390] Although EHEC infections often involve infants and young children, the frequency of this infection in neonates remains unclear; animal studies suggest that receptors for the Shiga toxin may be developmentally regulated and that susceptibility to disease may be age related.[391]

The capacity of EHEC to cause disease is related to the phage-encoded capacity of the organism to produce a Vero cell cytotoxin, subsequently shown to be one of the Shiga toxins.[392-394] Shiga toxin 1 is neutralized by antiserum against Shiga toxin, whereas Shiga toxin 2, although biologically similar, is not neutralized by anti-Shiga toxin.[395,396] Like Shiga toxin made by *Shigella dysenteriae*, both E. coli Shiga toxins act by inhibiting protein synthesis by cleaving an adenosine residue from position 4324 in the 28S ribosomal RNA (rRNA) to prevent elongation factor-1–dependent aminoacyl transfer RNA (tRNA) from binding to the 60S rRNA.[392,393] The virulence of EHEC also may be determined in part by a 60-MDa plasmid that encodes for a fimbrial adhesin in O157 and O26.[397,398] This phenotype is mediated by the LEE pathogenicity island, which is highly homologous to the island present in EPEC strains.[328]

EHEC and other STEC infections should be suspected in neonates who have bloody diarrhea or who may have been exposed in the course of an outbreak among older individuals. Because most cases are caused by ingestion of contaminated food, neonates have a degree of epidemiologic protection from the illness. Diagnosis of STEC diarrhea is made by isolation and identification of the pathogen in the feces. E. coli O157:H7 does not ferment sorbitol, and this biochemical trait is commonly used in the detection of this serotype.[98,399] Because some nonpathogenic E. coli share this characteristic, confirmation of the serotype by slide agglutination is required. These techniques can be performed in most clinical laboratories. However, detection of non-O157 serotypes is problematic and relies on detection of the Shiga toxin; available methods include Shiga toxin ELISA, latex agglutination, and molecular methods.[98,399] These should be performed by a reference laboratory.

HUS in infants is not necessarily caused by STEC infection. Even in older patients, however, the stool is typically negative for STEC at the time the that HUS develops.[400,401] Serum and fecal detection of cytotoxin has been performed in such patients, but no diagnostic modality is definitive once HUS has supervened.[400,401]

Antimicrobial therapy should not be administered to patients who may have STEC infection, although their role in inducing HUS remains controversial.[402,403] Management of the diarrhea and possible sequelae is supportive, with

proper emphasis on fluid and electrolyte replacement. Aggressive rehydration is helpful in minimizing the frequency of serious sequelae.

Enteroaggregative *Escherichia coli*

The Hep-2 adherence assay is useful for the detection of EPEC, which exhibit a classic LA pattern.[119] Two other adherence patterns can be discerned in this assay: aggregative (AA) and diffuse (DA). These two patterns have been suggested to define additional pathotypes of diarrheogenic *E. coli*.[98] Strains exhibiting the AA pattern (i.e., EAEC) are common pathogens of infants.[125]

EAEC cause diarrhea by colonization of the intestinal mucosa and elaboration of enterotoxins and cytotoxins.[125,404] Many strains can be shown to elicit secretion of inflammatory cytokines in vitro, which may contribute to growth retardation associated with prolonged otherwise asymptomatic colonization.[103] Several virulence factors in EAEC are under the control of the virulence gene activator AggR.[404] Presence of the AggR regulator or its effector genes has been proposed as a means of detecting truly virulent EAEC strains (called typical EAEC),[404,405] and an empirical gene probe long used for EAEC detection has been shown to correspond to one gene under AggR control.[406,407]

Epidemiology and Transmission

The mode of transmission of EAEC has not been well established. In adult volunteer studies, the infectious dose is high (>10^8 colony-forming units [CFU]), suggesting that in adults at least, person-to-person transmission is unlikely.[408,409] Several outbreaks have been linked to consumption of contaminated food.[410,411] The largest of these outbreaks involved almost 2700 schoolchildren in Japan[410]; a contaminated school lunch was the implicated source of the outbreak. Some studies have demonstrated contamination of condiments or milk, which could represent vehicles of food-borne transmission.

Several nursery outbreaks of EAEC have been observed,[412,413] although in no case has the mechanism of transmission been established. The fist reported nursery outbreak involved 19 infants in Nis, Serbia, in 1995. Because these infants did not ingest milk from a common source, it is presumed that horizontal transmission by environmental contamination or hands of health care personnel was possible. Most of the infants were full term and previously well, and they were housed in two separate nursery rooms.

The earliest epidemiologic studies of EAEC implicated this organism as a cause of endemic diarrhea in developing countries.[414-416] In this setting, EAEC as defined by the AA pattern of adherence to Hep-2 cells can be found in upward of 30% of the population at any one time.[417] Newer molecular diagnostic modalities have revised this figure downward, although the organism remains highly prevalent in many areas. Several studies from the Indian subcontinent implicated EAEC among the most frequent enteric pathogens.[414,415,418] Other sites reproducibly reporting high incidence rates include Mexico[416] and Brazil.[417,419] There is evidence that EAEC may be emerging in incidence. A study from São Paulo, Brazil, implicated EAEC as the prevalent *E. coli* pathotypes in infants[419]; EPEC had previously been shown to be the most common pathogen in this community. Many other sites

in developing countries of Africa,[421] Asia,[405,422] and South America[420] have described high endemic rates.

Several studies have suggested that EAEC is also a common cause of infant diarrhea in industrialized countries.[423-425] Using molecular diagnostic methods, a large prospective study in the United Kingdom implicated EAEC as the second most common enteric bacterial pathogen after *Campylobacter*.[426] A similar study from Switzerland found EAEC to be the most common bacterial enteropathogen.[423] Studies from the United States also have demonstrated a high rate of EAEC diarrhea in infants; using molecular diagnostic methods, EAEC was implicated in 11% and 8% of outpatient and in-patient diarrhea cohorts, respectively, compared with less than 2% of asymptomatic control infants ($P < .05$).[427] Although epidemiologic studies have shown that EAEC can cause diarrhea in all age groups, several studies suggest that the infection is particularly common in infants younger than 12 months old.[405,420]

Clinical Manifestations

Descriptions from outbreaks and volunteer studies suggest that EAEC diarrhea is watery in character with mucus but without blood or frank pus.[408,409,412] Patients typically are afebrile. Several epidemiologic studies have suggested that many infants may have bloody diarrhea,[416] but fecal leukocytes are uncommon.

The earliest reports of EAEC infection suggested that this pathogen may be particularly associated with persistent diarrhea (>14 days).[414-416] However, later studies suggest that persistent diarrhea may occur in only a subset of infected infants.[410] In the Serbian outbreak of 19 infected infants, the mean duration of diarrhea was 5.2 days[412]; diarrhea persisted more than 14 days in only three patients. Infants in this outbreak had frequent, green, odorless stools. In three cases, the stools had mucus, but none had visible blood. Eleven babies developed temperatures in excess of 38°C; only one had vomiting.

Despite a lack of clinical evidence suggesting inflammatory enteritis, several clinical studies have suggested that EAEC is associated with subclinical inflammation, including the shedding of fecal cytokines and lactoferrin.[103,428] Studies in Fortaleza, Brazil, suggest that children asymptomatically excreting EAEC may exhibit growth shortfalls compared with uninfected peers.[103] A study from Germany reported an association between EAEC isolation and infant colic in infants without diarrhea.[425] This observation has not been repeated. EAEC should be considered in the differential diagnosis of persistent diarrhea and failure to thrive in infants.

Diagnosis and Therapy

Diagnosis of EAEC requires identification of the organism in the patient's feces. The HEp-2 adherence assay can be used for this purpose[119]; some reports suggest that the adherence phenotype can be observed using formalin-fixed cells,[429,430] thereby obviating the need to cultivate eukaryotic cells for each assay. PCR and gene probe for typical EAEC are available.

Successful antibiotic therapy has been reported using fluoroquinolones in adult patients,[431] although preliminary studies suggest that azithromycin[432] or rifaximin[433] also may be effective. Therapy in infected infants should be guided by the results of susceptibility testing, as EAEC frequently is antibiotic resistant.[421]

Other *Escherichia coli* Pathotypes

Additional *E. coli* pathotypes have been described, including diffusely adherent *E. coli* (DAEC),[434] and cytodetaching *E. coli*.[435] DAEC has been specifically associated with diarrhea outside of infancy, as infants may have some degree of inherent resistance to infection.[436] Cytodetaching *E. coli* represent organisms that secrete the *E. coli* hemolysin.[437] It is not clear whether these latter organisms are true enteric pathogens.

SALMONELLA

Nature of the Organism

Salmonella classification tends to be confusing. Although taxonomists classify *Salmonella* narrowly as a single species, with *Salmonella typhi*, *Salmonella choleraesuis*, and *Salmonella enteritidis* technically being serovars or subspecies, for clinical purposes, these subspecies conventionally are referred to as *species*. For example, clinical laboratories tend to use the shorthand *S. typhimurium* rather than the more formal designation *Salmonella enterica* serovar *typhimurium*. Biochemical traits are used routinely by hospital laboratories to differentiate *S. typhi*, *S. choleraesuis*, and *S. enteritidis* from each other. *S. typhi* is unlike other salmonellae in that it does not produce gas from glucose.[438] Because there are several thousand serotypes included in the species *S. enteritidis*, serotyping of *S. enteritidis* is usually performed by state health departments rather than by hospital laboratories. The most common serogroups and representative serotypes are listed in Table 20-3. Infection of humans with the other serogroups (e.g., C_3, D_2, E_2, E_3, F, G, H, I) is uncommon.

There are differences in invasiveness of *Salmonella* strains related to serotype. *S. typhi*, *S. choleraesuis*, *Salmonella heidelberg*,[439,440] and *Salmonella dublin*[441] are particularly invasive, with bacteremia and extraintestinal focal infections occurring frequently. *Salmonella* species possess genes closely related to those for the *Shigella* invasion plasmid antigens; these genes are probably essential to intestinal infection.[442,4436] Virulence plasmids, which increase invasiveness in some serotypes, have been recognized, although the precise mechanisms of virulence remain to be elucidated; resistance to complement-mediated bacteriolysis by inhibition of insertion of the terminal C5b-9 membrane attack complex into the outer membrane may be important.[444,445] Laboratory studies have demonstrated dramatic strain-related difference in the ability of *S. typhimurium* to evoke fluid secretion, to invade intestinal mucosa, and to disseminate beyond the gut.[446] Production of an enterotoxin immunologically related to cholera toxin by about two thirds of *Salmonella* strains may be related to the watery diarrhea often seen.[447] The significance of protein synthesis-inhibiting cytotoxins[448] remains to be proved, although such toxins can damage gut epithelium, which could facilitate invasion. The cytotoxins produced by *Salmonella* are not immunologically related to Shiga toxin made by *Shigella dysenteriae* type 1[449] or *E. coli* O157:H7.

Salmonellae have the ability to penetrate epithelial cells and reach the submucosa, where they are ingested by phagocytes.[450] In phagocytes, salmonellae are resistant to killing, in

Table 20-3   Common Serotypes and Serogroups of *Salmonella*

Serogroups	Serotypes
A	Paratyphi A
B	Agona
	Derby
	Heidelberg
	Paratyphi B *(schottmuelleri)*
	Saint-paul
	Typhimurium
C_1	Choleraesuis
	Eimsbuettel
	Infantis
	Montevideo
	Oranienburg
	Paratyphi C *(hirschfeldii)*
	Thompson
C_2	Blockley
	Hadar
	Muenchen
	Newport
C_3	Kentucky
D_1	Dublin
	Enteritidis
	Javiana
	Panama
	Typhi
D_2	Maarssen
E_1	Anatum
E_2	London Newington
E_3	Illinois
E_4	Krefeld
	Senftenberg

part because of the properties of their lipopolysaccharides.[451,452] Persistence of the organism within phagolysosomes of phagocytic cells may occur with any species of *Salmonella*. It is not completely clear how the organisms have adapted to survive in the harsh intracellular environment, but their survival has major clinical significance. It accounts for relapses after therapy. It explains the inadequacy of some antimicrobial agents that do not penetrate phagolysosomes. It perhaps is the reason for prolonged febrile courses that occur even in the face of appropriate therapy. Although humoral immunity and cell-mediated immunity are stimulated during *Salmonella* infections, it is believed that cell-mediated immunity plays a greater role in eradication of the bacteria.[453] T cell activation of macrophages appears to be important in killing intracellular *Salmonella*.[454] Defective interferon-γ production by monocytes of newborns in response to *S. typhimurium* lipopolysaccharide may explain in part the unusual susceptibility of infants to *Salmonella* infection.[455] Studies in mice suggest that helper T cell (T_H1) responses in Peyer's patches and mesenteric lymph nodes may be central to protection of the intestinal mucosa.[456] Humans who lack the IL-12 receptor and therefore have impaired T_H1 responses and interferon-γ production are at increased risk for *Salmonella* infection.[457]

In typhoid fever, presence of an envelope antigen, Vi, is known to enhance virulence. Patients who develop classic enteric fever have positive stool cultures in the first few days after ingestion of the organism and again late in the course after a period of bacteremia. This course reflects early

colonization of the gut, penetration of gut epithelium with infection of mesenteric lymph nodes, and reseeding of the gut during a subsequent bacteremic phase.[458] Studies of *S. typhimurium* in monkeys suggest similar initial steps in pathogenesis (e.g., colonization of gut, penetration of gut epithelium, infection of mesenteric lymph nodes) but failure of the organism to cause a detectable level of bacteremia.[459]

Although both *Salmonella* and *Shigella* invade intestinal mucosa, the resultant pathologic changes are different. *Shigella* multiplies within and kills enterocytes with production of ulcerations and a brisk inflammatory response, whereas *Salmonella* passes through the mucosa and multiplies within the lamina propria, where the organisms are ingested by phagocytes; consequently, ulcer formation is less striking,[446] although villus tip cells are sometimes sloughed. Acute crypt abscesses can be seen in the stomach and small intestine, but the most dramatic changes occur in the colon, where acute diffuse inflammation with mucosal edema and crypt abscesses are the most consistent findings.[460,461] With *S. typhi* there also is hyperplasia of Peyer's patches in the ileum, with ulceration of overlying tissues.

Epidemiology and Transmission

Salmonella strains, with the exception of *S. typhi*, are well adapted to a variety of animal hosts; human infection often can be traced to infected meat, contaminated milk, or contact with a specific animal. Half of commercial poultry samples are contaminated with *Salmonella*.[462] Definition of the serotype causing infection can sometimes suggest the likely source. For example, *S. dublin* is closely associated with cattle; human cases occur with a higher-than-predicted frequency in people who drink raw milk.[441] For *S. typhimurium*, which is the most common serotype and accounts for more than one third of all reported human cases, a single source has not been established, although there is an association with cattle. Despite the 1975 ban by the U.S. Food and Drug Administration (FDA) on interstate commercial distribution of small turtles, these animals continue to be associated with infection, as illustrated by a series of cases in Puerto Rico.[463] Various pet reptiles are an important source of a variety of unusual *Salmonella* serotypes such as *Salmonella marina*, *Salmonella chameleon*, *Salmonella arizonae*, *Salmonella java*, *Salmonella stanley*, *Salmonella poona*, *Salmonella jangwain*, *Salmonella tilene*, *Salmonella pomona*, *Salmonella miami*, *Salmonella manhattan*, *Salmonella litchfield*, *Salmonella rubislaw*, and *Salmonella wassenaar*.[464-466] *Salmonella* organisms are hardy and capable of prolonged survival; organisms have been documented to survive in flour for nearly a year.[467] *Salmonella tennessee* has been shown to remain viable for many hours on non-nutritive surfaces (i.e., glass, 48 hours; stainless steel, 68 hours; enameled surface, 114 hours; rubber mattress, 119 hours; linen, 192 hours; and rubber tabletop, 192 hours).[468]

Infection with *Salmonella* is, like most enteric infections, more common in young children than in adults. The frequency of infection is far greater in the first 4 years of life; roughly equal numbers of cases are reported during each decade beyond 4 years of age. Although the peak incidence occurs in the second through sixth months of life, infection in the neonate is relatively common. Researchers at the CDC have

estimated the incidence of *Salmonella* infection in the first month of life at nearly 75 cases per 100,000 infants.[469]

Adult volunteer studies suggest that large numbers of *Salmonella* (10^5 to 10^9) need to be ingested to cause disease.[470] However, it is likely that lower doses cause illness in infants. The occurrence of nursery outbreaks[468,471-496] and intrafamilial spread[497] suggests that organisms are easily spread from person to person; this pattern is typical of low-inoculum diseases transmitted by the fecal-oral route. The neonate with *Salmonella* infection infrequently acquires the organism from his or her mother during delivery. Although the index case in an outbreak can often be traced to a mother,[474-477,495] subsequent cases result from contaminated objects in the nursery environment[498,499] serving as a reservoir coming in contact with hands of attending personnel.[468,483] The mother of an index case may be symptomatic[479,480,500,501] or asymptomatic with preclinical infection,[484] convalescent infection,[477,481,502] or chronic carriage.[503] The risk of the newborn becoming infected once *Salmonella* is introduced into a nursery has been reported to be as high as 20% to 27%,[487,493] but the frequency of infection may be lower because isolated cases without a subsequent epidemic are unlikely to be reported.

Gastric acidity is an important barrier to *Salmonella* infection. Patients with anatomic or functional achlorhydria are at increased risk of developing salmonellosis.[504,505] The hypochlorhydria[25] and rapid gastric emptying typical of early life[28] may in part explain the susceptibility of infants to *Salmonella*. Premature and low-birth-weight infants appear to be at higher risk of acquiring *Salmonella* infection than term neonates.[483,485] Whether this reflects increased exposure because of prolonged hospital stays or increased susceptibility on the basis of intestinal or immune function is unclear. Contaminated food or water is often the source of *Salmonella* infection in older patients; the limited diet of the infant makes contaminated food a less likely source of infection. Although human milk,[506-508] raw milk,[509] powdered milk,[510-512] formula,[493] and cereal[513] have been implicated in transmission to infants, more often fomites, such as delivery room resuscitators,[471] rectal thermometers,[486,514] oropharyngeal suction devices,[515-517] water baths for heating formula,[517] soap dispensers,[518] scales,[468,472,519] "clean" medicine tables,[468] air-conditioning filters,[468] mattresses, radiant warmers,[498] and dust,[472] serve as reservoirs. One unusual outbreak involving 394 premature and 122 term infants was traced to faulty plumbing, which caused massive contamination of environment and personnel.[493] After *Salmonella* enters a nursery, it is difficult to eradicate. Epidemics lasting 6 to 7 weeks,[486,491] 17 weeks,[468] 6 months,[485,490] 1 year,[480] and 27 to 30 months[487,493] have been reported. Spread to nearby pediatric wards has occurred.[488,494]

The incubation period in nursery outbreaks has varied widely in several studies where careful attention has been paid to this variable. In one outbreak of *Salmonella oranienburg* involving 35 newborns, 97% of cases occurred within 4 days of birth.[487] In an outbreak of *S. typhimurium*, each of the ill infants presented within 6 days of birth.[477] These incubation periods are similar to those reported for *Salmonella newport* in older children and adults, 95% of whom have been reported to be ill within 8 days of exposure.[520,521] Conversely, one outbreak of *Salmonella nienstedten* involving newborns was characterized by incubation periods of 7 to 18 days.[488]

The usual incubation period associated with fecal-oral nursery transmission is not found with congenital typhoid. During pregnancy, typhoid fever is associated with bacteremic infection of the fetus. The congenitally infected infants are symptomatic at birth. They are usually born during the second to fourth week of untreated maternal illness.[522] Usually, the mother is a carrier; fecal-oral transmission of S. typhi can occur with delayed illness in the newborn.[523]

Clinical Manifestations

Several major clinical syndromes occur with nontyphoidal Salmonella infection in young infants. Colonization without illness may be the most common outcome of ingestion of Salmonella by the neonate. Such colonization usually is detected when an outbreak is under investigation. Most infected infants who become ill have abrupt onset of loose, green, mucus-containing stools, or they have bloody diarrhea; an elevated temperature is also a common finding in Salmonella gastroenteritis in the first months of life.[440] Grossly bloody stools are found in the minority of patients, although grossly bloody stools can occur in the first 24 hours of life. Hematochezia is more typically associated with non-infectious causes (e.g., swallowed maternal blood, intestinal ischemia, hemorrhagic diseases, anorectal fissures) at this early age.[524] There appear to be major differences in presentation related to the serotype of S. enteritidis causing infection. For example, in one epidemic of S. oranienburg[487] involving 46 newborns, 76% had grossly bloody stools, 11% were febrile, 26% had mucus in their stools, and only 11% were healthy. In a series of S. newport infections involving 11 premature infants,[474] 90% of infants with gastroenteritis had blood in their stools, 10% had fever, 10% had mucus in their stools, and 9% were asymptomatic. In an outbreak of S. typhimurium[477] involving 11 ill and 5 healthy infants, none had bloody stools; all of the symptomatic infants were febrile and usually had loose, green stools. Of 26 infants infected by Salmonella virchow, 42% were asymptomatic; the rest had mild diarrhea.[482] Seals and colleagues[488] described 12 infants with S. nienstedten, all of whom had watery diarrhea and low-grade fever; none had bloody stools. In a large outbreak in Zimbabwe of S. heidelberg infection reported by Bannerman,[485] 38% of 100 infants were asymptomatic, 42% had diarrhea, 16% had fever, 15% had pneumonia, and 2% developed meningitis. An outbreak of Salmonella worthington was characterized primarily by diarrhea, fever, and jaundice, although 3 of 18 infants developed meningitis and 17% died.[515] In dramatic contrast to these series, none of 27 infants with positive stool cultures for S. tennessee had an illness in a nursery found to be contaminated with that organism.[469] A few infants with Salmonella gastroenteritis have developed necrotizing enterocolitis,[492,525] but it is not clear whether Salmonella was the cause.

Although gastroenteritis is usually self-limited, chronic diarrhea has sometimes been attributed to Salmonella.[503,526] Whether chronic diarrhea is caused by Salmonella is uncertain. Although some infants develop carbohydrate intolerance after a bout of Salmonella enteritis[527,528] and Salmonella is typically listed as one of the causes of postinfectious protracted diarrhea,[529] it is difficult to be sure that the relationship is causal. The prolonged excretion of Salmonella after a bout of gastroenteritis may sometimes cause non-specific chronic diarrhea to be erroneously attributed to Salmonella.

Major extraintestinal complications of Salmonella infection may develop in the neonate who becomes bacteremic. Extraintestinal spread may develop in infants who initially present with diarrhea and in some who have no gastrointestinal tract signs. Bacteremia appears to be more common in the neonate than in the older child.[530] A study of more than 800 children with Salmonella infection showed that extraintestinal infection occurred significantly more often (8.7% versus 3.6%) in the first 3 months of life.[531] Several retrospective studies suggest that infants in the first month of life may have a risk of bacteremia as high as 30% to 50%.[440] One retrospective study[439] suggests that the risk is not increased in infancy and estimates that the risk of bacteremia in childhood Salmonella gastroenteritis is between 8.5% and 15.6%. Prospective studies of infants in the first year of life suggest that the risk of bacteremia is 1.8% to 6.0%.[532,533] Although selection biases in these studies limit the reliability of these estimates, the risk is substantial. The Salmonella species isolated from infants include some serotypes that appear to be more invasive in the first 2 months of life than in older children or healthy adults (S. newport, S. agona, S. blockley, S. derby, S. enteritidis, S. heidelberg, S. infantis, S. javiana, S. saint-paul, and S. typhimurium) and serotypes that are aggressive in every age group (S. choleraesuis and S. dublin). Other serotypes appear more likely to cause bacteremia in adults (S. typhi, S. paratyphi A, and S. paratyphi B).[530]

Virtually any Salmonella serotype can cause bacteremic disease in neonates. A few infants with Salmonella gastroenteritis have died with E. coli or Pseudomonas aeruginosa sepsis,[494] but the role of Salmonella in these cases is unclear. Unlike the situation in older children in whom bacteremic salmonellosis often is associated with underlying medical conditions, bacteremia may occur in infants who have no immunocompromising conditions.[534] Salmonella bacteremia is often not suspected clinically because the syndrome is not usually distinctive.[439,440] Even afebrile, well-appearing children with Salmonella gastroenteritis have been documented to have bacteremia that persists for several days.[535] Although infants with bacteremia may have spontaneous resolution without therapy,[536] a sufficient number develop complications to warrant empirical antimicrobial therapy when bacteremia is suspected. The frequency of complications is highest in the first month of life. Meningitis is the most feared complication of bacteremic Salmonella disease. Between 50% and 75% of all cases of nontyphoidal Salmonella meningitis occur in the first 4 months of life.[537] The serotypes associated with neonatal meningitis (S. typhimurium, S. heidelberg, S. enteritidis, S. saint-paul, S. newport, and S. panama)[497] are serotypes frequently associated with bacteremia. Meningitis has a high mortality rate, in part because of the high relapse rates. Relapse has been reported in up to 64% of cases.[538] In some studies, more than 90% of patients with meningitis have died,[539] although more typically, 30% to 60% of infants die.[540,541] The survivors suffer the expected complications of gram-negative neonatal meningitis, including hydrocephalus, seizures, ventriculitis, abscess formation, subdural empyema, and permanent neurologic impairment. Neurologic sequelae have included retardation, hemiparesis, epilepsy, visual impairment, and athetosis.[537]

In large nursery outbreaks, it is common to find infants whose course is complicated by pneumonia,[485] osteomyelitis,[542,543] or septic arthritis.[483,485] Other rare complications of salmonellosis include pericarditis,[544] pyelitis,[545] peritonitis,[477] otitis media,[477] mastitis,[546] cholecystitis,[547] endophthalmitis,[548] cutaneous abscesses,[492] and infected cephalohematoma.[542] Other focal infections seen in older children and adults, such as endocarditis and infected aortic aneurysms, rarely or never have been reported in neonates.[537,549] Although the mortality rate in two reviews of nursery outbreaks was 3.7% to 7.0%,[495,496] in some series, it reached 18%.[485]

Enteric fever, most often related to S. typhi but also occurring with S. paratyphi A, S. paratyphi B, S. paratyphi C, and other Salmonella species, is reported much less commonly in infants than in older patients. Infected infants develop typical findings of neonatal sepsis and meningitis. Current data suggest that mortality is about 30%.[550] In utero infection with S. typhi has been described. Typhoid fever[518,551] and nontyphoidal Salmonella infections[552] during pregnancy put women at risk of aborting the fetus. Premature labor usually occurs during the second to the fourth week of maternal typhoid if the woman is untreated.[522] In a survey of typhoid fever in pregnancy during the preantibiotic era, 24 of 60 women with well-documented cases delivered prematurely, with resultant fetal death; the rest delivered at term, although only 17 infants survived.[553] The outlook for carrying the pregnancy to term and delivering a healthy infant appears to have improved dramatically during the antibiotic era. However, one of seven women with typhoid in a series still delivered a dead fetus with extensive liver necrosis.[554] In the preantibiotic era, about 14% of pregnant women with typhoid fever died.[555] With appropriate antimicrobial therapy, pregnancy does not appear to put the woman at increased risk of death. Despite these well-described cases, typhoid fever is rare early in life.

Of 1500 cases of typhoid fever that Osler and McCrae[556] reported, only 2 were in the first year of life. In areas where typhoid fever is still endemic, systematic search for infants with enteric fever has failed to find many cases. The few infections with S. typhi documented in children in the first year of life often present as a brief nondescript "viral syndrome" or as pneumonitis.[557,558] Fever, diarrhea, cough, vomiting, rash, and splenomegaly may occur; the fever may be high, and the duration of illness may be many weeks.[522]

Diagnosis

The current practice of early discharge of newborn infants, although potentially decreasing the risk of exposure, can make recognition of a nursery outbreak difficult. Diagnosis of neonatal salmonellosis should trigger an investigation for other cases. Other than diarrhea, signs of neonatal Salmonella infection are similar to the nonspecific findings seen in most neonatal infections. Lethargy, poor feeding, pallor, jaundice, apnea, respiratory distress, weight loss, and fever are common. Enlarged liver and spleen are common in those neonates with positive blood cultures. Laboratory studies are required to establish the diagnosis because the clinical picture is not distinct. The fecal leukocyte examination reveals polymorphonuclear leukocytes in 36% to 82%[359,559] of persons with Salmonella infection, but it has not been evaluated in neonates. Obviously, the presence of fecal leukocytes is consistent with colitis of any cause and therefore is a nonspecific finding. Routine stool cultures usually detect Salmonella if two or three different enteric media (i.e., MacConkey's, eosin-methylene blue, Salmonella-Shigella, Tergitol 7, xylose-lysine-deoxycholate, brilliant green, or bismuth sulfite agar) are used. Stool, rather than rectal swab material, is preferable for culture, particularly if the aim of culture is to detect carriers.[560] On the infrequent occasions when proctoscopy is performed, mucosal edema, hyperemia, friability, and hemorrhages may be seen.[461] Infants who are bacteremic often do not appear sufficiently toxic to raise the suspicion of bacteremia.[561] Blood cultures should be obtained as a routine part of evaluation of neonates with suspected or documented Salmonella infection. Ill neonates with Salmonella infection should have a cerebrospinal fluid examination performed. Bone marrow cultures also may be indicated when enteric fever is suspected. There are no consistent abnormalities in the white blood cell count. Serologic studies are not helpful in establishing the diagnosis, although antibodies to somatic[562,563] and flagellar antigens[487] develop in many infected newborns.

If an outbreak of salmonellosis is suspected, further characterization of the organism is imperative.[464] Determination of somatic and flagellar antigens to characterize the specific serotype may be critical to investigation of an outbreak. When the serotype found during investigation of an outbreak is a common one (e.g., S. typhimurium), antimicrobial resistance testing[475,565] and use of molecular techniques such as plasmid characterization[565] can be helpful in determining whether a single-strain, common-source outbreak is in progress.

Therapy

As in all enteric infections, attention to fluid and electrolyte abnormalities is the first issue that must be addressed by the physician. Specific measures to eradicate Salmonella intestinal infection have met with little success. Multiple studies show that antibiotic treatment of Salmonella gastroenteritis prolongs the excretion of Salmonella.[566-573] Almost one half of the infected children in the first 5 years of life continue to excrete Salmonella 12 weeks after the onset of infection; more than 5% have positive cultures at 1 year.[574] No benefit of therapy has been shown in comparisons of ampicillin or neomycin versus placebo,[570] chloramphenicol versus no antibiotic treatment,[569] neomycin versus placebo,[571] ampicillin or trimethoprim-sulfamethoxazole versus no antibiotic,[568] and ampicillin or amoxicillin versus placebo.[572] In contrast to these studies, data suggest that there may be a role for quinolone antibiotics in adults and children,[573,575] but these drugs are not approved for use in neonates, and resistance has been encountered.[576] Because these studies have few data as to the risk-benefit ratio of therapy in the neonate, it is uncertain whether they should influence treatment decisions in neonates. Studies that have included a small number of neonates suggest little benefit from antimicrobial therapy.[477,487,568,577,578] However, because bacteremia is common in neonates, antimicrobial therapy for infants younger than 3 months who have Salmonella gastroenteritis often is recommended,[532,533,561] especially if the infant appears toxic. Premature infants and those who have other

significant debilitating conditions also should probably be treated. The duration of therapy is debatable but should probably be no more than 3 to 5 days if the infant is not seriously ill and if blood cultures are sterile. If toxicity, clinical deterioration, or documented bacteremia complicates gastroenteritis, prolonged treatment is indicated. Even with antimicrobial therapy, some infants develop complications. The relatively low risk of extraintestinal dissemination must be balanced against the well-documented risk of prolonging the carrier state. For infants who develop chronic diarrhea and malnutrition, hyperalimentation may be required; the role of antimicrobial agents in this setting is unclear. The infant with typhoid fever should be treated with an antimicrobial agent; relapses sometimes occur after therapy.

Colonized healthy infants discovered by stool cultures during evaluation of an outbreak ought to be isolated but probably should not receive antimicrobial therapy. Such infants should be discharged from the nursery as early as possible and followed carefully as outpatients.

Antimicrobial treatment of neonates who have documented extraintestinal dissemination must be prolonged. Bacteremia without localization is generally treated with at least a 10-day course of therapy. Therapy for *Salmonella* meningitis must be given for at least 4 weeks to lessen the risk of relapse. About three fourths of patients who have relapses have been treated for three weeks or less.[537] Similar to meningitis, treatment for osteomyelitis must be prolonged to be adequate. Although cures have been reported with 3 weeks of therapy, 4 to 6 weeks of therapy is recommended.

In vitro susceptibility data for *Salmonella* isolates must be interpreted with caution. The aminoglycosides show good in vitro activity but poor clinical efficacy, perhaps because of the low pH of the phagolysosome. Aminoglycosides have poor activity in an acid environment. The stability of some drugs in this acid environment also may explain in vitro and in vivo disparities. The intracellular localization and survival of *Salmonella* within phagocytic cells also presumably explains the relapses encountered with virtually every regimen. Resistance to antibiotics has long been a problem with *Salmonella* infection.[566,579,580] There has been a steady increase in resistance to *Salmonella* in the United States over the last 20 years.[581] With the emergence of *typhimurium* type DT 104, resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline has increased from 0.6% in 1979 and 1980 to 34% in 1996.[582] Resistance plasmids have been selected and transmitted, partly because therapy has been given for mild illness that should not have been treated[566] and partly because of use of antibiotics in animal feeds. Resistance to chloramphenicol and ampicillin has made trimethoprim-sulfamethoxazole increasingly important for the treatment of *Salmonella* infection in those patients who require therapy. However, with increasing resistance to all three of these agents in Asia,[583] the Middle East,[584] Africa,[585] Europe,[586,587] Argentina,[580] and North America,[579,588,589] the third-generation cephalosporins and quinolones represent drugs of choice for invasive salmonellosis. The quinolones currently are not approved for persons younger than 18 years. Cefotaxime, ceftriaxone, and cefoperazone represent acceptable alternative drugs for typhoidal and nontyphoidal salmonellosis when resistance is encountered.[590,591] Because the second-generation cephalosporins, such as cefuroxime, are less active in vitro than the third-generation cephalosporins

and are not consistently clinically effective, they should not be used.[590,592] Data suggest that cefoperazone may sterilize blood and cause patients with typhoid fever to become afebrile more rapidly than with chloramphenicol,[593] perhaps because cefoperazone is excreted into bile in high concentrations.[594] The third-generation cephalosporins may have higher cure and lower relapse rates than ampicillin or chloramphenicol in children with *Salmonella* meningitis.[595] The doses of ampicillin, chloramphenicol, or cefotaxime used in infants with gastroenteritis pending results of blood cultures are the same as those used in treatment of sepsis. Because of the risk of gray baby syndrome, chloramphenicol should not be used in neonates unless other effective agents are not available. Trimethoprim-sulfamethoxazole, although useful in older children and adults, is not used in neonates because of the risk of kernicterus. Nosocomial infection with strains of *Salmonella* resistant to multiple antibiotics, including third-generation cephalosporins, has emerged as a problem in South America.[580]

Nonantibiotic interventions are important in the control of *Salmonella* infections. Limited data suggest that intravenous immune globulin (IGIV) (500 mg/kg on days 1, 2, 3, and 8 of therapy) along with antibiotic therapy may decrease the risk of bacteremia and death in preterm infants with *Salmonella* gastroenteritis.[596]

Prevention

Early recognition and intervention in nursery outbreaks of *Salmonella* are crucial to control. When a neonate develops salmonellosis, a search for other infants who have been in the same nursery should be undertaken. When two or more cases are recognized, environmental cultures, cultures of all infants, cohorting and contact isolation of infected infants, rigorous enforcement of hand hygiene, early discharge of infected infants, and thorough cleaning of all possible fomites in the nursery and delivery rooms are important elements of control. If cases continue to occur, the nursery should be closed to further admissions. Cultures of nursery personnel are likely to be helpful in the unusual situation of an *S. typhi* outbreak in which a chronic carrier may be among the caretakers. Culture of health care personnel during outbreaks of salmonellosis caused by other *Salmonella* species is debatable, although often recommended. Data suggest that nurses infected with *Salmonella* rarely infect patients in the hospital setting.[597] The fact that nursing personnel are sometimes found to be colonized during nursery outbreaks[468,474,487,489,490] may be a result rather than a cause of those epidemics.

The potential role of vaccines in control of neonatal disease is minimal. For the vast number of non–*S. typhi* serotypes, there is no prospect for an immunization strategy. Multiple doses of the commercially available oral live attenuated vaccine (Ty21a; *Vivotif*, Berna), has been shown in Chilean schoolchildren to reduce typhoid fever cases by more than 70%.[598,599] However, the vaccine is not recommended for persons younger than 6 years, in part because immunogenicity of Ty21a is age dependent; children younger than 24 months fail to respond with development of immunity.[600] Vi capsular polysaccharide vaccine is available for children older than 2 years and is effective in a single dose. Whether some degree of protection of infants could

Table 20–4   *Shigella* Serogroups

Serogroups	Species	No. of Serotypes
A	S. dysenteriae	13
B	S. flexneri	15 (including subtypes)
C	S. boydii	18
D	S. sonnei	1

occur if stool carriage were reduced or could be transferred to infants by the milk of vaccinated mothers' remains to be studied. Data suggest that breast-feeding may decrease the risk of other *Salmonella* infections.[601]

SHIGELLA

Nature of the Organism

On the basis of DNA relatedness, shigellae and *E. coli* organisms belong to the same species.[602] However, for historical reasons and because of their medical significance, shigellae have been maintained as separate species. Shigellae are gram-negative bacilli that are unlike typical *E. coli* in that they do not metabolize lactose or do so slowly, are non-motile, and generally produce no gas during carbohydrate use. They are classically divided into four species (serogroups) on the basis of metabolic and antigenic characteristics (Table 20-4). The mannitol nonfermenters usually are classified as *S. dysenteriae*. Although the lipopolysaccharide antigens of the 13 recognized members of this group are not related to each other antigenically, these serotypes are grouped together as serogroup A. Serogroup D (*Shigella sonnei*) are ornithine decarboxylase positive and slow lactose fermenters. All *S. sonnei* share the same lipopolysaccharide (O antigen). Those shigellae that ferment mannitol (unlike *S. dysenteriae*) but do not decarboxylate ornithine or ferment lactose (*S. sonnei*) belong to serogroups B and C. Of these, the strains that have lipopolysaccharide antigens immunologically related to each other are grouped together as serogroup B (*Shigella flexneri*), whereas those whose O antigens are not related to each other or to other shigellae are included in serogroup C (*Shigella boydii*). There are six major serotypes of *S. flexneri* and 13 subserotypes (1a, 1b, 2a, 2b, 3a, 3b, 4a, 4b, 5a, 5b, 6, X and Y variant). There are 19 antigenically distinct serotypes of *S. boydii*. For *S. dysenteriae* and *S. boydii* serogroup confirmation, pools of polyvalent antisera are used.

The virulence of shigellae has been studied extensively since their recognition as major pathogens at the beginning of the 20th century. The major determinants of virulence are encoded by a 120- to 140-MDa plasmid.[603,604] This plasmid, which is found in all virulent shigellae, encodes the synthesis of proteins that are required for invasion of mammalian cells and for the vigorous inflammatory response that is characteristic of the disease.[605,606] Shigellae that have lost this plasmid, have deletions of genetic material from the region involved in synthesis of these proteins, or have the plasmid inserted into the chromosome lose the ability to invade eukaryotic cells and become avirulent[607]; maintenance of the plasmid can be detected in the clinical microbiology lab by

ability to bind Congo red. The ability to invade cells is the basic pathogenic property shared by all shigellae[608,609] and by the *Shigella*-like invasive *E. coli*, which also possesses the *Shigella* virulence plasmid.[205,605,606,610-611] In the laboratory, *Shigella* invasiveness is studied in tissue culture (HeLa cell invasion), in animal intestine, or in rabbit or guinea pig eye, where instillation of the organism causes keratoconjunctivitis (Sereny test).[128] Animal model studies have shown that bacteria penetrate and kill colonic mucosal cells and then elicit a brisk inflammatory response.

In addition to the virulence plasmid, several chromosomal loci enhance virulence.[612,613] This has been best studied in *S. flexneri* in which multiple virulence-enhancing regions of the chromosome have been defined.[604,612-614] The specific gene products of some of the chromosomal loci are not known; one chromosomal virulence segment encodes for synthesis of the O repeat units of lipopolysaccharide. Intact lipopolysaccharide is necessary but not sufficient to cause virulence.[612,615] At least two cell-damaging cytotoxins that also are chromosomally encoded are produced by shigellae. One of these toxins (Shiga toxin) is made in large quantities by *S. dysenteriae* serotype 1 (the Shiga bacillus) and is made infrequently by other shigellae.[616] Shiga toxin is a major virulence factor in *S. dysenteriae*, enhancing virulence at the colonic mucosa and also giving rise to sequelae similar to those caused by STEC (discussed earlier). This toxin kills cells by interfering with peptide elongation during protein synthesis.[617-619] Additional toxins may also be secreted by shigellae, although their roles in virulence are not established.[620]

Epidemiology

Although much of the epidemiology of shigellosis is predictable based on its infectious dose, certain elements are unexplained. Shigellae, like other organisms transmitted by the fecal-oral route, are commonly spread by food and water, but the low infecting inoculum allows person-to-person spread. Because of this low inoculum, *Shigella* is one of the few enteric pathogens that can infect swimmers.[621] The dose required to cause illness in adult volunteers is as low as 10 organisms for *S. dysenteriae* serotype 1,[622] about 200 organisms for *S. flexneri*,[623] and 500 organisms for *S. sonnei*.[624] Person-to-person transmission of infection probably explains the continuing occurrence of *Shigella* in the developed world. Enteropathogens that require large inocula and hence are best spread by food or drinking water are less common in industrialized societies because of sewage disposal facilities, water treatment, and food-handling practices. In the United States, daycare centers currently serve as a major focus for acquisition of shigellosis.[625] Numerous outbreaks of shigellosis related to crowding, poor sanitation, and the low dose required for diseases have occurred in this setting.

Given the ease of transmission, it is not surprising that the peak incidence of disease is in the first 4 years of life. It is, however, paradoxical that symptomatic infection is uncommon in the first year of life.[626-629] The best data on the age-related incidence of shigellosis come from Mata's[625] prospective studies of Guatemalan infants. In these studies, stool cultures were performed weekly on a group of children followed from birth to 3 years old. The rate of infection was more than 60-fold lower in the first 6 months of life than
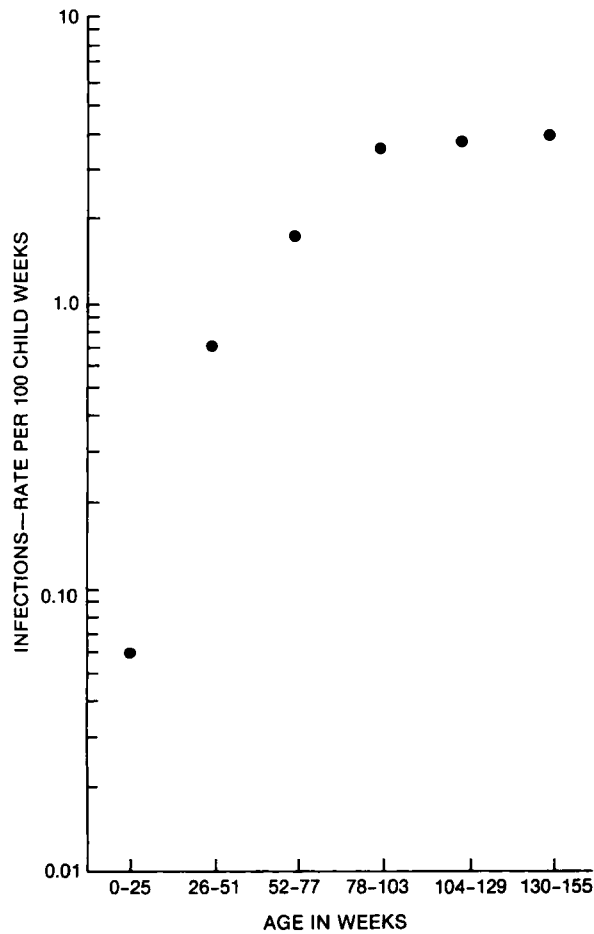
Figure 20–1   Age-related incidence of *Shigella* infection. (Data from Mata LG: The Children of Santa Maria Cauque: A Prospective Field Study of Health and Growth. Cambridge, Mass, MIT Press, 1978.)

between 2 and 3 years (Fig. 20-1).[626] The same age-related incidence has been described in the United States[629] and in a rural Egyptian village.[628] This anomaly has been explained by the salutary effects of breast-feeding.[630-632] However, it is likely that breast-feeding alone does not explain the resistance of infants to shigellosis.

A review of three large case series[633-635] suggests that about 1.6% (35 of 2225) of shigellosis cases occur in infants in the neonatal period. The largest series of neonatal shigellosis[632] suggests that the course, complications, and etiologic serogroups are different in neonates than in older children. Although newborns are routinely contaminated by maternal feces, neonatal shigellosis is rare.

Other aspects of the epidemiology of shigellosis elude simple explanation. The seasonality (summer-fall peak in the United States, rainy season peak in the tropics) is not well explained. The geographic variation in species causing infection likewise is not well understood. In the United States, most *Shigella* infections are caused by *S. sonnei* or, less commonly, *S. flexneri*. In most of the developing world, the relative importance of these two species is reversed, and other *Shigella* serotypes, especially *S. dysenteriae* serotype 1, are identified more frequently. As hygiene improves, the proportion of *S. sonnei* increases and that of *S. flexneri*

decreases.[636] Data from Bangladesh suggest that *S. dysenteriae* is less common in neonates, but *S. sonnei* and *S. boydii* are more common.[632]

Clinical Manifestations

There appear to be some important differences in the relative frequencies of various complications of *Shigella* infection related to age. Some of these differences and estimates are based on data that are undoubtedly compromised by reporting biases. *S. dysenteriae* serotype 1 characteristically causes a more severe illness than other shigellae with more complications, including pseudomembranous colitis, hemolysis, and HUS. However, illnesses caused by various *Shigella* serotypes usually are indistinguishable from each other and conventionally are discussed together.

The incubation period of shigellosis is related to the number of organisms ingested, but in general, it is between 12 and 48 hours. Volunteer studies have shown that after ingestion, illness may be delayed for a week or more. Neonatal shigellosis seems to have a similar incubation period. More than one half of the neonatal cases occur within 3 days of birth, consistent with fecal-oral transmission during parturition. Mothers of infected neonates are sometimes carriers, although more typically they are symptomatic during the perinatal period. Intrauterine infection is rare. In the older child, the initial signs are usually high fever, abdominal pain, vomiting, toxicity, and large-volume watery stools; diarrhea may be bloody or may become bloody. Painful defecation and severe, crampy abdominal pain associated with frequent passage of small-volume stools with gross blood and mucus are characteristic findings in older children or adults who develop severe colitis. Many children, however, never develop bloody diarrhea. Adult volunteer studies have demonstrated that variations in presentation and course are not related to the dose ingested because some patients develop colitis with dysentery but others develop only watery diarrhea after ingestion of the same inoculum.[623] The neonate with shigellosis may have a mild diarrheal syndrome or a severe colitis.[633,637-645] Fever in neonates is usually low grade (<102° F) if the course is uncomplicated. The neonate has less bloody diarrhea, more dehydration, more bacteremia, and a greater likelihood of death than the older child.[632] Physical examination of the neonate may show signs of toxicity and dehydration, although fever, abdominal tenderness, and rectal findings are less striking than in the older child.[634]

Complications of shigellosis are common.[646] Although the illness is self-limited in the normal host, resolution may be delayed for a week or more. In neonates and malnourished children, chronic diarrhea may follow a bout of shigellosis.[637,645] Between 10% and 35% of hospitalized children with *Shigella* have convulsions before or during the course of diarrhea.[646-648] Usually, the seizures are brief, generalized, and associated with high fever. Seizures are uncommon in the first 6 months of life, although neonates have been described with seizures.[639,649] The cerebrospinal fluid generally reveals normal values in these children, but a few have mild cerebrospinal fluid pleocytosis. The neurologic outcome generally is good even with focal or prolonged seizures, but fatalities do occasionally occur, often associated with toxic encephalopathy.[650] Although the seizures had been postulated to

result from the neurotoxicity of Shiga toxin, this explanation was proved to be incorrect because most shigellae make little or no Shiga toxin and the strains isolated from children with neurologic symptoms do not produce Shiga toxin.[616,651] Hemolysis with or without development of uremia is a complication primarily of S. dysenteriae serotype 1 infection.[652]

Sepsis during the course of shigellosis may be caused by the Shigella itself or by other gut flora that gain access to the bloodstream through damaged mucosa.[632,653,654] The risk of sepsis is higher in the first year of life, particularly in neonates,[632,637-639,649,656] in malnourished children, and in those with S. dysenteriae serotype 1 infection.[654] Sepsis occurs in up to 12% of neonates with shigellosis.[631,646,653,655] Given the infrequency of neonatal shigellosis, it is striking that 9% of reported cases of Shigella sepsis have involved infants in the first month of life.[657] One of the infants with bacteremia[658] reportedly had no discernible illness. Disseminated intravascular coagulation may develop in those patients whose course is complicated by sepsis. Meningitis has been described in a septic neonate. Colonic perforation has occurred in neonates,[630,659] older children,[660] and adults.[661] Although this complication of toxic megacolon is rare, it appears to be more common in neonates than in older individuals. Bronchopneumonia may complicate the course of shigellosis, but shigellae are rarely isolated from lungs or tracheal secretions.[662] The syndrome of sudden death in the setting of extreme toxicity with hyperpyrexia and convulsions but without dehydration or sepsis (i.e., Ekiri syndrome)[663-665] is rare in neonates. In the nonbacteremic child, other extraintestinal foci of infection, including vagina[666,667] and eye,[668] rarely occur. Reiter's syndrome, which rarely complicates the illness in children, has not been reported in neonates.

Although infection is less common in infants than in toddlers, case fatality rates are highest in infants.[669,670] The mortality rate in newborns appears to be about twice that of older children.[632] In industrialized societies, less than 1% of children with shigellosis die, whereas in developing countries, up to 30% die. These differences in mortality rates are related to nutrition,[633] availability of medical care, antibiotic resistance of many shigellae, the frequency of sepsis, and the higher frequency of S. dysenteriae serotype 1 infection in the less-developed world.[654]

Diagnosis

Although the diagnosis of shigellosis can be suspected on clinical grounds, other enteropathogens can cause illnesses that are impossible to distinguish clinically. Shigellosis in the neonate is rare. The neonate with watery diarrhea is more likely to be infected with E. coli, Salmonella or rotavirus than Shigella. Infants presenting with bloody diarrhea may have necrotizing enterocolitis or infection with Salmonella, EIEC, Yersinia enterocolitica, C. jejuni, or Entamoeba histolytica. Before cultures establish a diagnosis, clinical and laboratory data may aid in making a presumptive diagnosis. Abdominal radiographs demonstrating pneumatosis intestinalis suggest the diagnosis of necrotizing enterocolitis. A history of several weeks of illness not associated with fever and with few fecal leukocytes suggests E. histolytica rather than Shigella infection.[671]

The definitive diagnosis of shigellosis depends on isolation of the organism from stool. Unfortunately, culture may be insensitive.[672] In volunteer studies, daily stool cultures failed to detect shigellae in about 20% of symptomatic subjects.[623] Optimal recovery is achieved by immediate inoculation of stool (as opposed to rectal swabs) onto culture media. Use of transport media in general decreases the yield of cultures positive for Shigella[673] when compared with immediate inoculation.

Examination of stool for leukocytes as an indication of colitis is useful in support of the clinical suspicion of shigellosis. The white blood cell count and differential count also are used as supporting evidence for the diagnosis. Leukemoid reactions (white blood cells $> 50,000/mm^3$) occur in almost 15% of children with S. dysenteriae serotype 1 but in less than 2% of children with other shigellae.[651] Leukemoid reactions are more frequent in infants than in older children.[652] Even when the total white blood cell count is not dramatically elevated, there may be a striking left shift. Almost 30% of children with shigellosis have greater than 25% bands on the differential cell count.[674-676] Few reports address the white blood cell count in newborns, but those that do suggest that normal or low rather than elevated counts are more common. Although serum and fecal antibodies develop to lipopolysaccharides and the virulence plasmid-associated polypeptides,[677] serologic studies are not useful in the diagnosis of shigellosis. PCR can identify Shigella and EIEC in feces.[678] Colonoscopy typically shows inflammatory changes that are most severe in the distal segments of colon.[679]

Therapy

Because dehydration is particularly common in neonatal shigellosis, attention to correction of fluid and electrolyte disturbances is always the first concern when the illness is suspected. Although debate continues over the indications for antimicrobial therapy in the patient with shigellosis, the benefits of therapy generally appear to outweigh the risks. The chief disadvantages of antimicrobial therapy include cost, drug toxicity, and emergence of antibiotic-resistant shigellae. Because of the self-limited nature of shigellosis, it has been argued that less severe illness should not be treated. However, children can feel quite ill during the typical bout of shigellosis, and appropriate antimicrobial therapy shortens the duration of illness and eliminates shigellae from stool, decreasing secondary spread. Complications are probably decreased by antibiotics. Given the high mortality rates of neonatal shigellosis, therapy should not be withheld.

The empirical choice of an antimicrobial agent is dictated by susceptibility data for strains circulating in the community at the time the patient's infection occurs. Multiresistant shigellae complicate the choice of empirical therapy before availability of susceptibility data for the patient's isolate. Plasmid-encoded resistance (R factors) for multiple antibiotics has been observed frequently in S. dysenteriae serotype 1 outbreaks[682] and with other shigellae.[683-685] Antimicrobial resistance patterns fluctuate from year to year in a given locale.[686] However, despite the guesswork involved, early preemptive therapy is indicated when an illness is strongly suggestive of shigellosis. In vitro susceptibility does not always adequately predict therapeutic responses. Cefaclor,[687] furazolidone,[688] cephalexin,[689] amoxicillin,[690] kanamycin,[691] and cefamandole[692] all are relatively ineffective agents.

The optimal duration of therapy is debatable. Studies in children older than 2 years and in adults suggest that single-dose regimens may be as effective in relieving symptoms as courses given for 5 days. The single-dose regimens generally are not as effective in eliminating shigellae from the feces as are the longer courses. A third-generation cephalosporin, such as ceftriaxone, may be the best empirical choice. Optimal doses for newborns with shigellosis have not been established. Trimethoprim at a dose of 10 mg/kg/day (maximum, 160 mg/day) and sulfamethoxazole at a dose of 50 mg/kg/day (maximum, 800 mg/day) in two divided doses for a total of 5 days are recommended for the older child if the organism is susceptible.[693-695] If the condition of the infant does not permit orally administration, the drug usually is divided into three doses given intravenously over 1 hour.[696] Ampicillin at a dose of 100 mg/kg/day in four divided doses taken orally for 5 days may be used if the strain is susceptible.[676]

For the rare newborn who acquires shigellosis, appropriate therapy often is delayed until susceptibility data are available. This occurs because shigellosis is so rare in newborns that it is almost never the presumptive diagnosis of the child with watery or bloody diarrhea. Although a sulfonamide is as efficacious as ampicillin when the infecting strain is susceptible,[675] sulfonamides are avoided in neonates because of concern about the potential risk of kernicterus. The risk of empirical ampicillin therapy is that shigellae are frequently resistant to the drug; 50% of shigellae currently circulating in the United States are ampicillin resistant.[696,697] For the neonate infected with ampicillin-resistant *Shigella*, there are few data on which to base a recommendation. Ceftriaxone is generally active against shigellae, but in the neonate, this drug can displace bilirubin-binding sites and elicit clinically significant cholestasis. Data on children and adults suggest that clinical improvement occurs with ceftriaxone.[698,699] Quinolones, such as ciprofloxacin and ofloxacin, have been shown to be effective agents for treating shigellosis[700,701] in adults, but they are not approved for use in children younger than 18 years. Other drugs sometimes used to treat diarrhea pose special risks to the infant with shigellosis. The antimotility agents, in addition to their intoxication risk, may pose a special danger in dysentery. In adults, diphenoxylate hydrochloride with atropine has been shown to prolong fever and excretion of the organism.[702]

The response to appropriate antibiotic therapy is generally gratifying. Improvement is often obvious in less than 24 hours. Complete resolution of diarrhea may not occur until a week or more after the start of treatment. In those who have severe colitis or those infected by *S. dysenteriae* serotype 1, the response to treatment is somewhat delayed.

Prevention

For most of the developing world, the best strategy for prevention of shigellosis during infancy is prolonged breast-feeding. Specific antibodies in milk appear to prevent symptomatic shigellosis[66,68]; nonspecific modification of gut flora and the lack of bacterial contamination of human milk also may be important. Breast-feeding, even when other foods are consumed, decreases the risk of shigellosis; children who continue to consume human milk into the third year of life are still partially protected from illness.[703] In the United States, the best means of preventing infection in the infant is good hand hygiene when an older sibling or parent develops diarrhea. Even in unsanitary environments, secondary spread of shigellae can be dramatically decreased by hand hygiene after defecation and before meals.[704] Spread of shigellae in the hospital nursery can presumably be prevented by the use of contact isolation for infants with diarrhea and attention to thorough hand hygiene. Although nursery personnel have acquired shigellosis from infected newborns,[685] further transmission to other infants in the nursery, although described,[705] is rare. In contrast to *Salmonella*, large outbreaks of nosocomial shigellosis in neonates are rare.

Unfortunately, good hygiene is a particularly difficult problem in daycare centers. The gathering of susceptible children, breakdown in hand hygiene, failure to use different personnel for food preparation and diaper changing, and difficulty controlling the behavior of toddlers all contribute to daycare-focused outbreaks of shigellosis.

Immunization strategies have been studied since the turn of the 20th century, but no satisfactory immunization has been developed. Even if immunizations are improved, a role in managing neonates seems unlikely.

CAMPYLOBACTER

Nature of the Organism

Campylobacter was first recognized in an aborted sheep fetus in the early 1900s[706] and was named *Vibrio fetus* by Smith and Taylor in 1919.[707] This organism subsequently was identified as a major venereally transmitted cause of abortion and sterility and as a cause of scours in cattle, sheep, and goats.[708,709] It was not until 1947, when it was isolated from the blood culture of a pregnant woman who subsequently aborted at 6 months' gestation, that the significance of *Campylobacter* as a relatively rare cause of bacteremia and perinatal infections in humans was appreciated.[710-712] During the 1970s, *Campylobacter* was recognized to be an opportunistic pathogen in debilitated patients.[713,714] In 1963, *V. fetus* and related organisms were separated from the vibrios (such as *V. cholerae* and *V. parahaemolyticus*) and placed in a new genus, *Campylobacter* (Greek word for "curved rod").[715] Since 1973, several *Campylobacter* species have been recognized as a common cause of enteritis[716-732] and, in some cases, extraintestinal infections.

The genus *Campylobacter* contains 15 species, most of which are recognized as animal and human pathogens. The most commonly considered causes of human disease are *Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Campylobacter lari,* and *Campylobacter upsaliensis* (Table 20-5),[730-732] although *Campylobacter mucosalis* has been isolated from stool of children with diarrhea.[733] DNA hybridization studies have shown that these species are distinct, sharing less than 35% DNA homology under stringent hybridization conditions.[734,735] *Helicobacter pylori* was originally named *Campylobacter pylori*, but because of differences in DNA, it was reclassified and is no longer considered in the *Campylobacter* genus.

Strains of *C. fetus* are divided into two subspecies: *C. fetus* subsp. *fetus* and *C. fetus* subsp. *venerealis*. The first subspecies causes sporadic abortion in cattle and sheep[736,737]; in

Table 20-5   *Campylobacter* Species That Infect Humans

Current Nomenclature	Previous Nomenclature	Usual Disease Produced
C. fetus	Vibrio fetus V. fetus var. intestinalis C. fetus subsp. intestinalis	Bacteremia, meningitis, perinatal infection, intravascular infection
C. jejuni	Vibrio jejuni	Diarrhea
C. coli	C. fetus subsp. jejuni	Diarrhea

C. lari	Grouped with C. jejuni, nalidixic acid–resistant,
	  thermophilic Campylobacter,
	  C. laridis I
		Diarrhea, bacteremia

C. upsaliensis	None	Diarrhea, bacteremia
C. hyointestinalis	None	Diarrhea, bacteremia
C. concisus	None	Diarrhea

the human fetus and newborn, it causes perinatal and neonatal infections that result in abortion, premature delivery, bacteremia, and meningitis.[710-712,736-748] Outside the newborn period, *Campylobacter* is a relatively infrequent cause of bacteremia, usually infecting those with impaired host defenses, including the elderly or the debilitated; less frequently, it causes intravascular infection.[713-715,749,750]

By far the most common syndrome caused by a *Campylobacter* species is enteritis. *C. jejuni* and *C. coli* cause gastroenteritis and generally are referred to collectively as *C. jejuni*, although DNA hybridization studies show them to be different. In the laboratory, *C. jejuni* can be differentiated from *C. coli* because it is capable of hydrolyzing hippurate, whereas *C. coli* is not. Most isolates that are associated with diarrhea (61% to 100%) are identified as *C. jejuni*,[751-754] and in some cases, individuals have been shown to be simultaneously infected with *C. jejuni* and *C. coli*.[752]

Because of the fastidious nature of *C. jejuni*, which is difficult to isolate from fecal flora, its widespread occurrence was not recognized until 1973.[716-732] Previously called *related vibrios* by King,[749] this organism had been associated with bloody diarrhea and colitis in infants and adults only when it had been associated with a recognized bacteremia.[755-757] In the late 1970s, development of selective fecal culture methods for *C. jejuni* enabled its recognition worldwide as one of the most common causes of enteritis in persons of all ages. It is an uncommon infection in neonates who generally develop gastroenteritis when infected.[718,758-881] Bacteremia with *C. jejuni* enteritis also is uncommon.[718,759,764,769,772-778] Maternal symptoms considered to be related to *C. jejuni* infection generally are mild and include fever (75%) and diarrhea (30%). In contrast to the serious disease in newborns that is caused by *C. fetus*, neonatal infections with *C. jejuni* usually result in a mild illness,[758,760,762,763,765-768,771,778] although meningitis occurs in rare instances.[761,769] Third trimester infection related to *C. fetus* or *C. jejuni* may results in abortion or stillbirth.

Pathogenesis

C. fetus does not produce recognized enterotoxins or cytotoxins and does not appear to be locally invasive by the Sereny test.[714,731] Instead, these infections may be associated with penetration of the organism through a relatively intact intestinal mucosa to the reticuloendothelial system and bloodstream.[714] Whether this reflects a capacity to resist

serum factors or to multiply intracellularly remains to be determined.

C. jejuni is capable of producing illness by several mechanisms. These organisms have been shown to produce an LT enterotoxin and a cytotoxin.[779-782] This enterotoxin is known to be a heat-labile protein with a molecular mass of 60 to 70 MDa.[779,782] It shares functional and immunologic properties with cholera toxin and *E. coli* LT. *C. jejuni* and *C. coli* also elaborate a cytotoxin that is toxic for a number of mammalian cells.[783-785] The toxin is heat labile, trypsin sensitive, and not neutralized by immune sera to Shiga toxin or the cytotoxin of *Clostridium difficile*. The role of these toxins as virulence factors in diarrheal disease remains unproved.[779,784]

Several animal models have been tested for use in the study of this pathogen.[786] Potential models for the study of *C. jejuni* enteritis include dogs, which may acquire symptomatic infection[787]; 3- to 8-day old chicks[788-790]; chicken embryo cells, which are readily invaded by *C. jejuni*[725]; rhesus monkeys[791]; and rabbits by means of the removable intestinal tie adult rabbit technique. An established small mammal model that mimics human disease in the absence of previous treatment or surgical procedure has not been successful in adult mice.[792] An infant mouse model[793,794] and a hamster model[795] of diarrhea appear promising. *C. jejuni* is negative in the Sereny test for invasiveness,[796] and most investigators report no fluid accumulation in ligated rabbit ileal loops.

Pathology

The pathologic findings of *C. fetus* infection in the perinatal period include placental necrosis[711] and, in the neonate, widespread endothelial proliferation, intravascular fibrin deposition, perivascular inflammation, and hemorrhagic necrosis in the brain.[797] The tendency for intravascular location and hepatosplenomegaly in adults infected with *C. fetus* has been shown.[714]

The pathologic findings in infants and children infected with *C. fetus* can include an acute inflammatory process in the colon or rectum, as evidenced by the tendency for patients to have bloody diarrhea with numerous fecal leukocytes.[798] There also can be crypt abscess formation and an ulcerative colitis or pseudomembranous colitis–like appearance[799,800] or a hemorrhagic jejunitis or ileitis.[717,725,801,802] Mesenteric lymphadenitis, ileocolitis and acute appendicitis also have been described.

Epidemiology

Infection with *Campylobacter* species occurs after ingestion of contaminated food, including unpasteurized milk, poultry, and contaminated water.[726,803-812] Many farm animals and pets, such as chickens,[813] dogs,[814,815] and cats (especially young animals), are potential sources. The intrafamilial spread of infection in households,[717,816] the occurrence of outbreaks in nurseries,[769,770,817] and the apparent laboratory acquisition of *C. jejuni*[818] all suggest that *C. jejuni* infection may occur after person-to-person transmission of the organism. Outbreaks of *C. jejuni* in the child daycare setting are not common. Volunteer studies[819] have shown a variable range in the infecting dose, with many volunteers developing no illness. The report of illness after ingestion of 10^6 organisms in a glass of milk[728] and production of illness in a single volunteer by 500 organisms[819] substantiate the variation in individual susceptibility. The potential for low-inoculum disease has significant implications for the importance of strict enteric precautions when infected persons are hospitalized, particularly in maternity and nursery areas. When diarrhea in neonates caused by *C. jejuni* has been reported,[758-771] maternal-infant transmission during labor has generally been documented.[758-763,765-768,770,771] The Lior serotyping system, restriction length polymorphism, and pulse-field gel electrophoresis [820] have been used to confirm the identity of the infant and maternal isolates. Most mothers gave no history of diarrhea during pregnancy.[762,763,765,766] Outbreaks have occurred in neonatal intensive care units because of person-to-person spread.[820]

The frequency of asymptomatic carriage of *C. jejuni* ranges from 0% to 1.3%[716,717] to as high as 13% to 85%.[716,717,732,821-823] In a cohort study in Mexico, 66% of all infections related to *C. jejuni* were asymptomatic.[732] Infected children, if untreated, can be expected to excrete the organisms for 3 or 4 weeks; however, more than 80% are culture negative after 5 weeks.[721,722] Asymptomatic excreters pose a significant risk in the neonatal period, in which acquisition from an infected mother can be clinically important.[718,760,762,766] *C. jejuni* has increasingly been recognized as a cause of watery and inflammatory diarrhea in temperate and tropical climates throughout the world. It has been isolated from 2% to 11% of all fecal cultures from patients with diarrheal illnesses in various parts of the world.[716-724,728,824-829] There is a tendency for *C. jejuni* enteritis to occur in the summer in countries with temperate climates.[825]

The reservoir of *Campylobacter* is the gastrointestinal tract of domestic and wild birds and animals. It infects sheep, cattle, goats, antelope, swine, chickens, domestic turkeys, and pet dogs. *C. fetus* often is carried asymptomatically in the intestinal or biliary tracts of sheep and cattle. During the course of a bacteremic illness in pregnant animals, *C. fetus* organisms, which have a high affinity for placental tissue, invade the uterus and multiply in the immunologically immature fetus. The infected fetuses generally are aborted. Whether this organism is acquired by humans from animals or is carried asymptomatically for long periods in humans, who may then transmit the organism through sexual contact as appears to occur in animals, is unclear. It is believed that this subspecies rarely is found in the human intestine and that it is not a cause of human enteritis.[725] *C. fetus* infections predominantly occur in older men with a history of farm or animal exposure and in pregnant women in their third trimester.[710,711,716,717] Symptomatically or asymptomatically infected women may have recurrent abortions or premature deliveries and are the source of organisms associated with life-threatening perinatal infections of the fetus or newborn infant.[710,739-748,830] In several instances of neonatal sepsis and meningitis, *C. fetus* was isolated from culture of maternal cervix or vagina.[712,747,795] A nosocomial nursery outbreak has been associated with carriage in some healthy infants.[831] Other outbreaks have been associated with meningitis [832,833] Cervical cultures have remained positive in women who have had recurrent abortions and whose husbands have antibody titer elevations.[738]

The most commonly incriminated reservoir of *C. jejuni* is poultry.[808,812,834,835] Most chickens in several different geographic locations had a large number (mean, 4×10^6/g) of *C. jejuni* in the lower intestinal tract or feces. This occurred in some instances despite the use of tetracycline, to which the *Campylobacter* was susceptible in vitro, in the chicken feed.[828] The internal cavities of chickens remain positive for *Campylobacter* even after they have been cleaned, packaged, and frozen.[834] However, unlike *Salmonella*, *C. jejuni* organisms that survive usually do not multiply to high concentrations.[725] Domestic puppies or kittens with *C. jejuni* diarrhea also can provide a source for spread, especially to infants or small children.[717,755,812,836-838]

C. jejuni enteritis also has been associated in a number of outbreaks with consumption of unpasteurized milk.[725,809-811,839-841] In retrospect, the first reported human cases of *C. jejuni* enteritis were probably in a milk-borne outbreak reported in 1946.[842] Because *Campylobacter* infections of the udder are not seen, milk is probably contaminated from fecal shedding of the organism. These organisms are killed by adequate heating.

Fecally contaminated water is a potential vehicle for *C. jejuni* infections.[843] Several phenotypic and genotypic methods have been used for distinguishing *C. jejuni* strains from animals and humans involved in epidemics.[844] *C. jejuni* is associated with traveler's diarrhea among those traveling from England or the United States.[720]

Clinical Manifestations

Clinical manifestations of infection caused by *Campylobacter* depend on the species involved (see Table 20-5). Human infections with *C. fetus* are rare and generally are limited to bacteremia in patients with predisposing conditions[749,750] or to bacteremia or uterine infections with prolonged fever and pneumonitis that lasts for several weeks in women during the third trimester of pregnancy. Unless appropriately treated, symptoms usually resolve only after abortion or delivery of an infected infant.[710,712,739-748,750] These infected neonates, who are often premature, develop signs suggesting sepsis, including fever, cough, respiratory distress, vomiting, diarrhea, cyanosis, convulsions, and jaundice. The condition typically progresses to meningitis, which may be rapidly fatal or may result in serious neurologic sequelae.[712] Additional systemic manifestations include pericarditis, pneumonia, peritonitis, salpingitis, septic arthritis, and abscesses.[823]

C. jejuni infection typically involves the gastrointestinal tract, producing watery diarrhea or a dysentery-like illness with fever and abdominal pain and stools that contain blood

and mucus.[715,732,800] Older infants and children generally are affected, but neonates with diarrhea have been reported. Infection in neonates generally is not clinically apparent or is mild. Stools can contain blood, mucus, and pus[712,721,762,763]; fever often is absent.[721,762] The illness usually responds to appropriate antimicrobial therapy,[760,762,816] which shortens the period of fecal shedding.[845] Extraintestinal infections related to C. jejuni other than bacteremia are rare but include cholecystitis,[846] urinary tract infection,[847] and meningitis.[761] Bacteremia is a complication of gastrointestinal infection,[848] especially in malnourished children.[849] Meningitis that appears to occur secondary to intestinal infection also has been reported in premature infants who have had intraventricular needle aspirations for neonatal hydrocephalus.[712] Complications in older children and adults that have been associated with C. jejuni enteritis include Reiter's syndrome,[850] Guillain-Barré syndrome,[851,852] and reactive arthritis.[853,854] Persistent C. jejuni infections have been described in patients infected with human immunodeficiency virus.[855] Extraintestinal manifestations generally occur in patients who are immunosuppressed or at the extremes of age.[714] Campylobacter lari has caused chronic diarrhea and bacteremia in a neonate.[856]

Diagnosis

Most important in the diagnosis of Campylobacter infection is a high index of suspicion based on clinical grounds. C. fetus and C. jejuni are fastidious and may be overlooked on routine fecal cultures. Isolation of Campylobacter from blood or other sterile body sites does not represent the same problem as isolation from stool. Growth occurs with standard blood culture media, but it may be slow. In the case of C. fetus infecting the bloodstream or central nervous system, blood culture flasks should be blindly subcultured and held for at least 7 days or the organism may not be detected because of slow or inapparent growth.[742] The diagnosis of C. fetus infection should be considered when there is an unexplained febrile illness in the third trimester of pregnancy or in the event of recurrent abortion, prematurity, or neonatal sepsis with or without meningitis. A high index of suspicion and prompt, appropriate antimicrobial therapy may prevent the potentially serious neonatal complications that may follow maternal C. fetus infection.

Campylobacter is distinguished from the Vibrio organisms by its characteristics of carbohydrate nonfermentation and by its different nucleotide base composition.[715,733-735,738] Campylobacter is 0.2 to 0.5 fm wide and 0.5 to 8.0 long. It is a fastidious, microaerophilic, curved, motile gram-negative bacillus that has a single polar flagellum and is oxidase and catalase positive, except for C. upsaliensis, which is generally catalase negative or weakly positive. C. jejuni and C. fetus are separated by growth temperature (C. fetus grows best at 25° C but can be cultured at 37° C; C. jejuni grows best at 42° C) and by nalidixic acid and cephalosporin susceptibilities, because C. jejuni is susceptible to nalidixic acid and resistant to cephalosporins. C. jejuni grows best in a microaerobic environment of 5% oxygen and 10% carbon dioxide at 42° C. It grows on a variety of media, including Brucella and Mueller-Hinton agars, but optimal isolation requires the addition of selective and nutritional supplements. Growth at 42° C in the presence of cephalosporins is used to culture selectively for C. jejuni from fecal specimens. In a study of six

media, charcoal-based selective media and a modified charcoal cefoperazone deoxycholate agar were the most selective for identification of Campylobacter species. Extending the incubation time from 48 to 72 hours led to an increase in the isolation rate regardless of the medium used.[857] Its typical darting motility may provide a clue to identification, even in fresh fecal specimens, when viewed by phase-contrast microscopy.[721,858]

When the organism has been cultured, it is presumptively identified by motility and by its curved, sometimes sea gull–like appearance on carbolfuchsin stain. Polymorphonuclear leukocytes are usually found in stools when bloody diarrhea occurs and indicate the occurrence of colitis.[762,798] To avoid potentially serious C. jejuni infection in the newborn infant, careful histories of any diarrheal illnesses in the family should be obtained, and pregnant women with any enteric illness should have cultures for this and other enteric pathogens. Detection of C. jejuni and C. coli by PCR has been reported[859] and in the future may be useful for the rapid and reliable identification of this organism.

The differential diagnosis of C. fetus infections include the numerous agents that cause neonatal sepsis or meningitis, especially gram-negative bacilli. Diagnostic considerations for inflammatory or bloody enteritis include necrotizing enterocolitis, allergic proctitis, and Salmonella; rarely Shigella, and other infectious agents occur. Agglutination, complement fixation, bactericidal, immunofluorescence, and ELISA tests have been used for serologic diagnosis of C. jejuni infection and to study the immune response, but these assays are of limited value in establishing the diagnosis during an acute infection.[731]

Therapy

The prognosis is grave in newborn infants with sepsis or meningitis caused by C. fetus. In infants with C. jejuni gastroenteritis, limited data suggest that appropriate, early antimicrobial therapy results in improvement and rapid clearance of the organism from stool.[845] Campylobacter species are often resistant to β-lactams, including ampicillin and cephalosporins.[860,861] Most strains are susceptible to erythromycin, gentamicin, tetracycline, chloramphenicol, and the newer quinolones, although resistance to these agents has been reported.[862,863] It appears that a parenteral aminoglycoside is the drug of choice for C. fetus infections, pending in vitro susceptibility studies. In the case of central nervous system involvement, cefotaxime and chloramphenicol are potential alternative drugs. Depending on in vitro susceptibilities, which vary somewhat with locale, erythromycin is the drug of choice for treating C. jejuni enteritis.[717,721,722] If erythromycin therapy is initiated within the first 4 days of illness, a reduction in excretion of the organism and resolution of symptoms occur.[845] Although data regarding treatment of asymptomatic or convalescent carriers are not available, it seems appropriate to treat colonized pregnant women in the third trimester of pregnancy when there is a risk of perinatal or neonatal infection. The failure of prophylactic parenteral gentamicin in a premature infant has been documented, followed by successful resolution of symptoms and fecal shedding with erythromycin. Because there appears to be an increased risk of toxicity with erythromycin estolate during pregnancy and infancy,[864] other

forms of erythromycin should probably be used in these settings. Azithromycin appears to be effective if the organism is susceptible.[865] Strains that are erythromycin resistant often are resistant to azithromycin.[866] Campylobacter tends to have higher minimal inhibitory concentrations for clarithromycin than for azithromycin.[867] Furazolidone has been used in children and ciprofloxacin in nonpregnant patients older than 17 years.

Prevention

Contact precautions should be employed during any acute diarrheal illness and until the diarrhea has subsided. Hand hygiene after handling raw poultry and washing cutting boards and utensils with soap and water after contact with raw poultry may decrease risk of infection. Pasteurization of milk and chlorination of water are critically important. Infected food handlers and hospital employees who are asymptomatic pose no known hazard for disease transmission if proper personal hygiene measures are maintained. Ingestion of human milk that contains anti–C. jejuni antibodies has been shown to protect infants from diarrhea due to C. jejuni.[63,868]

CLOSTRIDIUM DIFFICILE

Nature of the Organism and Pathophysiology

C. difficile is a spore-forming, gram-positive, anaerobic bacillus that produces two toxins. In the presence of antibiotic pressure, C. difficile colonic overgrowth and toxin production occur. The virulence properties of C. difficile are related to production of an enterotoxin that causes fluid secretion (toxin A) and a cytotoxin detectable by its cytopathic effects in tissue culture (toxin B).[869,870] Both toxin genes have been cloned and sequenced, revealing that they encode proteins with estimated molecular masses of 308 kDa for toxin A and 270 kDa for toxin B.[871]

A wide variety of antibacterial, antifungal, antituberculosis, and antineoplastic agents have been associated with C. difficile colitis, although penicillin, clindamycin, and cephalosporins are associated most frequently. Rarely, no precipitating drug has been given.[872-876] C. difficile and its toxins can be demonstrated in up to one third of patients with antibiotic-associated diarrhea and in about 98% of patients with pseudomembranous colitis.[877]

Epidemiology

C. difficile can be isolated from soil and frequently exists in the hospital environment. Spores of C. difficile are acquired from the environment or by fecal-oral transmission from colonized individuals or from items in the environment such as thermometers and feeding tubes.[878-883] C. difficile has been demonstrated to persist on a contaminated floor for 5 months.[879] Nosocomial spread is related to organisms on the hands of personnel[879,880,884] and to contaminated surfaces, which may serve as reservoirs.[885,886] Although all groups are susceptible to infection, newborn infants represent a special problem. Less than 5% of healthy children older than 2 years[887] and healthy adults carry C. difficile,[877] but more than

50% of neonates can be demonstrated to have C. difficile and its cytotoxin in their stools, usually in the absence of clinical findings.[880,886,888-890] Infants in neonatal intensive care units have high rates of colonization, in part because of frequent use of antimicrobial agents in these units.[889-890] Clustering of infected infants suggests that much of the colonization of newborn infants represents nosocomial spread[886] rather than acquisition of maternal flora. The number of C. difficile organisms present in stools of well infants is similar to that found in older patients with pseudomembranous colitis.[890] The high frequency of colonization has led to justified skepticism about the pathogenic potential of this organism in the very young.[891] Although some episodes of diarrhea in early infancy may be caused by C. difficile,[892] the diagnostic criteria used in older children and adults are inadequate to establish a definite diagnosis in this age group.

Clinical Manifestations

The usual manifestations of C. difficile disease in older children and adults include watery diarrhea, abdominal pain and tenderness, nausea, vomiting, and low-grade fever. Grossly bloody diarrhea is unusual, although occult fecal blood is common. Leukocytosis is present during severe illness. Diarrhea usually begins 4 to 9 days into a course of antimicrobial therapy but may be delayed until several weeks after completion of the therapeutic course. Usually, the illness is mild and self-limited if the offending drug is discontinued. Severe colitis with pseudomembranes is less common now than in previous years because the risk of diarrhea developing during antimicrobial therapy is recognized and the antimicrobial agent typically is stopped.

It is unclear whether this organism causes disease in newborns. One study from a newborn intensive care unit suggests that toxin A in stools is associated with an increased frequency of abnormal stools.[893]

Diagnosis

Endoscopic findings of pseudomembranes and hyperemic, friable rectal mucosa suggest the diagnosis of pseudomembranous colitis. Pseudomembranes are not always present in C. difficile colitis; mild cases are often described as nonspecific colitis. Several noninvasive techniques are used to establish the diagnosis, including enzyme immunoassay (EIA) for toxin detection and PCR.[893-896] Isolation of C. difficile from stool does not distinguish between toxigenic and nontoxigenic isolates. If C. difficile is isolated, testing for toxin by cell culture or EIA should be performed to confirm the presence of a toxigenic strain. There are multiple commercially available EIAs that detect either toxin A or both toxins A and B.[893-895] These assays are sensitive and easy to perform. Other assays are available for epidemiologic investigation of outbreaks of disease due to C. difficile.[896]

In older children and adults, the diagnosis is confirmed by culture of C. difficile and demonstration of toxin in feces. In neonates, these data are inadequate to prove that an illness is related to C. difficile. When the clinical picture is consistent, the stool studies are positive for C. difficile and no other cause for illness is found, a diagnosis of "possible" C. difficile is made. A favorable response to eradication of C. difficile is supportive evidence that the diagnosis is correct.[872]

Because of the uncertainty implicit in the ambiguity of neonatal diagnostic criteria, other diagnoses must be considered.

Therapy

When the decision is made that a neonate's illness might be related to C. difficile, the initial approach should include fluid and electrolyte therapy and discontinuation of the offending antimicrobial agent. If the illness persists or worsens or if the patient has severe diarrhea, specific therapy with metronidazole[886,897] should be instituted. Metronidazole is considered to be the treatment of choice for most patients with C. difficile colitis.[898] Rarely is there a need to consider orally administered vancomycin or bacitracin in neonates.[899,900]

After initiation of therapy, signs of illness generally resolve within several days, titers decrease, and fecal toxins disappear eventually. Recurrence of colitis after discontinuation of metronidazole or vancomycin has been documented in 10% to 20% of adults.[901] Relapses are treated with a second course of metronidazole or vancomycin. Drugs that decrease intestinal motility should not be administered.

Neutralizing antibody against C. difficile cytotoxin has been demonstrated in human colostrum.[902] Secretory component of sIgA binds to toxin A to inhibit its binding to receptors [903] Data show that there are nonantibody factors present in milk that interfere with the action of toxin B in addition to secretory IgA directed at toxin A.[904] Breast-feeding appears to decrease the frequency of colonization by C. difficile.[905]

Prevention

In addition to standard precautions, contact precautions are recommended for the duration of illness. Meticulous hand hygiene techniques, proper handling of contaminated waste and fomites, and limiting the use of antimicrobial agents are the best available methods for control of C. difficile infection.

VIBRIO CHOLERAE

Nature of the Organism

V. cholerae is a gram-negative, curved bacillus with a polar flagellum. Of the many serotypes, only enterotoxin-producing organisms of serotype O1 and O139 cause epidemics. V. cholerae O1 is divided into two serotypes, Inaba and Ogawa, and two biotypes, classic and El Tor; the latter is the predominant biotype. Nontoxigenic O1 strains and non-O1 strains of V. cholerae can cause diarrhea and sepsis but do not cause outbreaks.[906-908]

Pathogenesis

V. cholerae O group 1 is the classic example of an entero-pathogen whose virulence is caused by enterotoxin production. Cholera toxin is an 84-MDa protein whose five B subunits cause toxin binding to the enterocyte membrane ganglioside GM_1 and whose A subunit causes adenosine diphosphate ribosylation of a guanosine triphosphate–binding regulatory subunit of adenylate cyclase.[105,908] The elevated cAMP levels

that result from stimulation of enterocytes by cholera toxin cause secretion of salt and water with concomitant inhibition of absorption. Two other toxins are also encoded within the virulence cassette that encodes cholera toxin. These toxins, zona occludens toxin (zot) and accessory cholera toxin (ace), are consistently found in illness-causing strains of O1 and O139 but not usually in V. cholerae organisms that are less virulent.

Epidemiology

Since 1960, V. cholerae O1, biotype El Tor, has spread from India and Southeast Asia to Africa, the Middle East, southern Europe, and the southern, western, and central Pacific islands (Oceania). In late January of 1991, toxigenic V. cholerae O1, serotype Inaba, biotype El Tor, appeared in several coastal cities of Peru.[907,908] It rapidly spread to most countries in South and North America. In reported cases, travel from the United States to Latin America or Asia and ingestion of contaminated food transported from Latin America or Asia have been incriminated. V. cholerae O139 (Bengal) arose on the Indian subcontinent as a new cause of epidemic cholera in 1993.[910-915] It rapidly spread through Asia and continues to periodically reemerge as a cause of epidemic cholera. In the United States, an endemic focus of a unique strain of toxigenic V. cholerae O1 exists on the Gulf Coast of Louisiana and Texas.[906,916] This strain is different from the one associated with the epidemic in South America. Most cases of disease associated with the strain endemic to the U.S. Gulf Coast have resulted from the consumption of raw or undercooked shellfish. Humans are the only documented natural host, but free-living V. cholerae organisms can exist in the aquatic environment. The usual reported vehicles of transmission have included contaminated water or ice; contaminated food, particularly raw or undercooked shellfish; moist grains held at ambient temperature; and raw or partially dried fish. The usual mode of infection is ingestion of contaminated food or water. Boiling water or treating it with chlorine or iodine and adequate cooking of food kill the organism.[907] Asymptomatic infection of family contacts is common but direct person-to-person transmission of disease has not been documented. Persons with low gastric acidity are at increased risk for cholera infection.

Clinical Manifestations

Cholera acquired during pregnancy, particularly in the third trimester, is associated with a high incidence of fetal death.[917] Miscarriage can be attributed to a fetal acidosis and hypoxemia resulting from the marked metabolic and circulatory changes that this disease induces in the mother. It is not surprising that the likelihood of delivering a stillborn child is closely correlated with the severity of the maternal illness. The inability to culture V. cholerae from stillborn infants of infected mothers, together with the usual absence of bacteremia in cholera, suggests that transplacental fetal infection is not a cause of intrauterine death.

Neonatal cholera is a rare disease. This generalization also applies to the new O139 strains, although mild[918] and severe forms of illness have rarely been described in newborns.[919] Among 242 neonates admitted to a cholera research hospital in Dacca, Bangladesh, there were 25 infants ill with cholera.[920]

Even infants born to mothers with active diarrheal disease may escape infection, despite evidence that rice-water stools, almost certain to be ingested during the birth process, may contain as many as 10^9 organisms/mL.[920] The reason for this apparently low attack rate among newborns is not certain; however, it probably can be attributed in large part to the protection conferred by breast-feeding.[921] Human milk contains antibodies[62] and receptor-like glycoprotein that inhibit adherence of *V. cholerae*[64] and gangliosides that bind cholera toxin.[65] The role of transplacentally acquired vibriocidal maternal antibodies has not been determined.[922] Because *V. cholerae* causes neither bacteremia nor intestinal invasion, protection against illness is more likely to be a function of mucosal rather than serum antibodies.[923,924] Additional factors that may reduce the incidence of neonatal cholera include the large inoculum required for infection[925] and the limited exposure of the newborn to the contaminated food and water.[229]

Diagnosis

Clinicians should request that appropriate cultures be performed for stool specimens from persons suspected of having cholera. The specimen is plated on thiosulfate citrate bile salts sucrose agar directly or after enrichment in alkaline peptone water. Isolates of *V. cholerae* should be confirmed at a state health department and then sent to the CDC for testing for production of cholera toxin. A fourfold rise in vibriocidal antibody titers between acute and convalescent serum samples or a fourfold decline in titers between early and late (>2 months) convalescent serum specimens can confirm the diagnosis. Probes have been developed to test for cholera toxin.[926,927]

Therapy and Prevention

The most important modality of therapy is administration of oral or parenteral rehydration therapy to correct dehydration and electrolyte imbalance and maintain hydration.[907] Antimicrobial therapy can eradicate vibrios, reduce the duration of diarrhea, and reduce requirements for fluid replacement. One cholera vaccine, which is administered parenterally, is licensed in the United States but is of very limited value. Several experimental oral vaccines are being tested.[928-930]

YERSINIA ENTEROCOLITICA

Nature of the Organism, Epidemiology, and Pathogenesis

Y. enterocolitica is a major cause of enteritis in much of the industrialized world.[931,932] Enteritis due to this organism primarily occurs in infants and young children, and infections in the United States are reported to be more common in the North than in the South.[933-938] Animals, especially swine, have been shown to serve as the reservoir for *Y. enterocolitica*. A history of recent exposure to chitterlings (i.e., pig intestine) is common. Transmission has also occurred after ingestion of contaminated milk and infusion of contaminated blood products.[939,940]

Virulence of *Y. enterocolitica* is related primarily to a virulence plasmid, which is closely related to the virulence plasmids of *Yersinia pseudotuberculosis* and *Yersinia pestis*.[941,942] An ST enterotoxin, which is closely related to the ST of ETEC,[943] may also be important.

Clinical Manifestations

Infection with *Y. enterocolitica* is recognized as one of the causes of bacterial gastroenteritis in young children, but knowledge of neonatal infection with this organism is fragmentary. Even in large series, isolation of *Yersinia* from newborns is rare.[931,932,944] The youngest infants whose clinical course has been described in detail were 11 days to several months old at the onset of their illness.[932,944-952] There were no features of the gastroenteritis to distinguish it from that caused by other invasive enteric pathogens such as *Shigella* or *Salmonella*. Infants presented with watery diarrhea or with stools containing mucus with streaks of blood. Sepsis was common in these infants particularly in the first 3 months of life when 28% of enteritis was complicated by sepsis.[948,949,953,954] Fever is not a consistent finding in children with bacteremia, and meningitis is rare. In older children, fever and right lower quadrant pain mimicking appendicitis are often found.[940]

Diagnosis

Y. enterocolitica can be recovered from throat swabs, mesenteric lymph nodes, peritoneal fluid, blood, and stool. Because laboratory identification of organisms from stool requires special techniques, laboratory personnel should be notified when *Yersinia* is suspected. Because avirulent environmental isolates occur, biotyping and serotyping are useful in assessing the clinical relevance of isolates. PCR has been used to detect pathogenic strains.[955,956]

Therapy

The effect of antimicrobial therapy on the outcome of gastrointestinal infection is uncertain. It has been recommended that antibiotics be reserved for sepsis or prolonged and severe gastroenteritis[931]; however, there are no prospective studies comparing the efficacy of various antimicrobial agents with each other or with supportive therapy alone. Most strains of *Y. enterocolitica* are susceptible to trimethoprim-sulfamethoxazole, the aminoglycosides, piperacillin, imipenem, third-generation cephalosporins, amoxicillin-clavulanate potassium, and chloramphenicol, and resistant to amoxicillin, ampicillin, carbenicillin, ticarcillin, and macrolides.[957-959] Therapy in individual cases should be guided by in vitro susceptibility testing, although cefotaxime has been successfully used in bacteremic infants.[954]

AEROMONAS HYDROPHILA

Nature of the Organism, Epidemiology, and Pathogenesis

Aeromonas hydrophila is widely distributed in animals and the environment. Although wound infection, pneumonia,

and sepsis (especially in immunocompromised hosts) represent typical Aeromonas infections, gastroenteritis increasingly is being recognized. The organism is a gram-negative, oxidase-positive, facultatively anaerobic bacillus belonging to the family Vibrionaceae. Like other members of this family, it produces an enterotoxin[960] that causes fluid secretion in rabbit ileal loops.[961] Some strains cause fluid accumulation in the suckling mouse model,[962] whereas other strains are invasive[963] or cytotoxic.[964] The enterotoxin is not immunologically related to cholera toxin or the heat LT of E. coli.[965]

Although volunteer studies and studies with monkeys have failed to provide supportive evidence for enteropathogenicity,[966,967] there is good reason to believe that A. hydrophila does cause diarrhea in children. The earliest description of Aeromonas causing diarrhea was an outbreak that occurred in a neonatal unit.[968] Although several studies have failed to show an association with diarrhea,[969-974] most studies have found more Aeromonas isolates among children with gastroenteritis than among controls.[974-976] Part of the controversy may be caused by strain differences; some strains possess virulence traits related to production of gastroenteritis, whereas others do not.[970,977]

The diarrhea described in children is a disease of summer, primarily affecting children in the first 2 years of life. In one study, 7 (13%) of 55 cases of Aeromonas detected during a 20-month period occurred in infants younger than 1 month.

Clinical Manifestations

Typically, watery diarrhea with no fever has been described; although there are descriptions of watery diarrhea with fever.[978] However, in 22%, a dysentery-like illness occurred. Dysentery-like illness has been described in the neonate.[979] In one third of children, diarrhea has been reported to last for more than 2 weeks.[970] There may be species-related differences in clinical features of Aeromonas-associated gastroenteritis in children.[980] Organisms that were formerly classified as A. hydrophila are now sometimes labeled as Aeromonas sobria or Aeromonas caviae.[981,982] Fever and abdominal pain appear to be particularly common with A. sobria. One series of A. hydrophila isolates from newborns in Dallas showed more blood cultures than stool cultures positive for Aeromonas.[983]

Diagnosis and Therapy

Diagnosis of enteric infection associated with Aeromonas often is not made because this organism is not routinely sought in stool cultures. When the organism is suspected, the laboratory should be notified so that oxidase testing can be performed. The organism is usually susceptible to aztreonam, imipenem, meropenem, third-generation cephalosporins, trimethoprim-sulfamethoxazole, and chloramphenicol.[984-986]

PLESIOMONAS SHIGELLOIDES

Plesiomonas shigelloides is a gram-negative, facultative anaerobic bacillus that, like Aeromonas, is a member of the Vibrionaceae family. It is widely disseminated in the environment; outbreaks of disease are usually related to ingestion of contaminated water or seafood.[987] Although it has been associated with outbreaks of diarrheal disease[988] and has been found more commonly in ill than well controls, the role of P. shigelloides in diarrheal disease has remained controversial.[989] If it is a true enteropathogen, the mechanism by which it causes disease is unclear.[990,991] The role of this organism in neonatal diarrhea has not been extensively investigated. Infections of neonates have been reported,[992-995] but most cases of enteric disease currently reported in the United States are in adults.[987] Typical illness consists of watery diarrhea and cramps; sometimes, fever, bloody stools, and emesis occur and last for 3 to 42 days.

Diagnosis is not usually made by clinical microbiology laboratory testing because, as with Aeromonas, coliforms can be confused with P. shigelloides unless an oxidase test is performed.[996] The true frequency of infection is unknown. The organism has antibiotic susceptibilities similar to those of Aeromonas.[997,998]

OTHER BACTERIAL AGENTS AND FUNGI

Proving that an organism causes diarrhea is difficult, particularly when it may be present in large numbers in stools of healthy persons. Bacteria that have been associated with acute gastroenteritis may be considered causative when the following criteria are met:

1. A single specific strain of the organism should be found as the predominant organism in most affected infants by different investigators in outbreaks of enteric disease in different communities.
2. This strain should be isolated in a significantly lower percentage and in smaller numbers from stool specimens of healthy infants.
3. Available methods must be used to exclude other recognized enteropathogens, including viruses and parasites, enterotoxigenic agents, and fastidious organisms such as Campylobacter.
4. Demonstration of effective specific antimicrobial therapy and specific antibody responses and, ultimately, production of experimental disease in volunteers are helpful in establishing the identity of a microorganism as a pathogen.

Optimally, the putative pathogen should have virulence traits that can be demonstrated in model systems. Most bacteria that have been suggested as occasional causes of gastroenteritis in neonates fail to fulfill one or more of these criteria. Their role in the cause of diarrheal disease is questionable. This is particularly true of microorganisms described in early reports in which the possibility of infection with more recently recognized agents could not be excluded. Much of the clinical, bacteriologic, and epidemiologic data collected earlier linking unusual enteropathogens to infantile diarrhea must be reevaluated in light of current knowledge and methodology.

Several reports of acute gastroenteritis believed to have been caused by Klebsiella suggest that, rather than playing an etiologic role, these organisms had probably proliferated within an already inflamed bowel.[999-1001] The recovery of Klebsiella-Enterobacter in pure culture from diarrheal stools has led several investigators to suggest that these bacteria

may occasionally play a causative role in infantile gastro-enteritis and enterocolitis.[1002-1007] Ingestion of infant formula contaminated with *Enterobacter sakazakii* has been associated with development of bloody diarrhea and sepsis.[1008] However, *Klebsiella* species also may be isolated in pure culture from stools of newborns with no enteric symptoms.[1009-1011] In one study, certain capsular types of *Klebsiella* were more often isolated from infants with diarrheal disease than from normal infants.[1002] Later work has shown that *Klebsiella pneumoniae, Enterobacter cloacae,* and *Citrobacter* species are capable of producing enterotoxins.[139,166,167,175,193,1008,1012,1013] Reports of isolation of *Citrobacter* species, such as those of *Klebsiella* species, describe associations with enteric illnesses in up to 7% of cases.[1014-1016] There is inadequate evidence to define the roles of *Klebsiella, Enterobacter,* and *Citrobacter* species as etiologic agents of enteric illnesses.

Listeria monocytogenes, one of the classic causes of neonatal sepsis and meningitis (see Chapter 14), has been linked to outbreaks of febrile diarrheal disease in immunocompetent adults and children.[1017-1021] Seventy-two percent of ill individuals have had fever.[1022] Outbreaks have been related to ingestion of contaminated foods. *Listeria* has rarely been described as a cause of neonatal gastroenteritis.[1023-1026]

Infection with enterotoxin-producing *Bacteroides fragilis* has been associated with mild watery diarrhea.[1027] These infections have a peak incidence in 2- to 3-year-old infants.[1028] These toxin-producing organisms cannot be detected in routine hospital laboratories.

A variety of organisms has been isolated from infant stools during episodes of diarrhea. Most of these reports have failed to associate illness with specific organisms in a way that has stood the test of time. For example, *P. aeruginosa* [1029-1034] and *Proteus* [1017,1035-1041] have been associated with diarrhea, but there are few convincing data suggesting that either is a true enteropathogen. These organisms generally are recovered as frequently from healthy infants as from infants with diarrheal disease, suggesting that their presence in stool cultures is significant.[273,1042-1046] An association between *Providencia* and neonatal enteritis has been substantiated largely by anecdotal reports of nursery outbreaks.[215,271,1016,1047] These bacteria are rarely isolated from infants with sporadic or community-acquired diarrheal disease.[1042-1044,1048-1050]

Candida albicans usually is acquired during passage through the birth canal and is considered a normal, although minor, component of the fecal flora of the neonate (see Chapter 33).[1051] Intestinal overgrowth of these organisms frequently accompanies infantile gastroenteritis,[211,233,1051,1054] particularly after antimicrobial therapy.[233,247,1052-1055] The upper small gut may become colonized with *Candida* in malnourished children with diarrhea[1056]; whether the presence of the organism is cause or effect is unclear. Stool cultures obtained from infants with diarrheal disease are therefore inconclusive, and although *Candida* enteritis has been reported in adults,[1057] the importance of this organism as a primary cause of neonatal gastroenteritis has been difficult to prove. Clinical descriptions of nursery epidemics of candidal enteritis are poorly documented, generally preceding the recognition of EPEC and rotaviruses as a cause of neonatal diarrhea. Even well studied cases of intestinal involvement add little in the way of substantive proof because secondary invasion of *Candida* has been shown to be a complication of coliform enteritis.[211,233,247]

Although diarrhea has sometimes been described as a finding in neonatal disseminated candidiasis, more typically, gastrointestinal tract involvement with disseminated *Candida* is associated with abdominal distention and bloody stools mimicking necrotizing enterocolitis.[247,1056-1061] Typically, affected infants are premature and have courses complicated by antibiotic administration, intravascular catheter use, and surgical procedures during the first several weeks of life. A trial of oral anticandidal therapy may be helpful in neonates suffering from diarrhea in the presence of oral or cutaneous candidiasis. If the therapy is appropriate, a response should be forthcoming within 2 to 5 days.

Diarrhea sometimes occurs as a manifestation of systemic infection. Patients with staphylococcal toxic shock syndrome, for example, often have diarrhea. Loose stools sometimes occur in sepsis, but it is unclear whether the diarrhea is a cause or an effect. The organisms isolated from blood cultures in a group of Bangladeshi infants and children with diarrhea included *Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae, P. aeruginosa,* and various gram-negative enteric bacilli.[1062] It is unknown whether the bacteriology of sepsis associated with diarrhea is similar in the well-nourished infants seen in industrialized countries.

PARASITES

Acute diarrhea associated with intestinal parasites is infrequent during the neonatal period. In areas with high endemicity, infection of the newborn is likely to be associated with inadequate maternal and delivery care, insufficient environmental sanitation, and poor personal hygiene standards. The occurrence of symptomatic intestinal parasitic infection during the first month of life requires acquisition of the parasite during the first days or weeks; the incubation period for *E. histolytica* and *G. lamblia* is 1 to 4 weeks, and for *Cryptosporidium parvum,* it is 7 to 14 days. The newborn can be infected during delivery by contact with maternal feces,[1063] in the hospital through contact with the mother or personnel, or in the household through contact with infected individuals in close contact with the child. Contaminated water can be an important source of infection for *G. lamblia* and *C. parvum.*

Entamoeba histolytica

Organisms formerly identified as *E. histolytica* have been reclassified into two species that are morphologically identical but genetically distinct: *E. histolytica* and *E. dispar.* The former can cause acute nonbloody and bloody diarrhea, necrotizing enterocolitis, ameboma, and liver abscess, and the latter is a noninvasive parasite that does not cause disease. Early acquisition of disease tends to be more severe in young infants; rarely, amebic liver abscess and rapidly fatal colitis have been reported in infants.[1064-1070] For example, a 19-day-old child from India who presented with 10 to 12 episodes of watery and mucous diarrhea, lethargy, jaundice, and mildly elevated liver enzymes has been described; the child recovered completely after 10 days of intravenous omidazole.[1064] However, asymptomatic colonization of neonates with various species of ameba is common in areas of high endemicity.[1071]

Diagnosis can be established by stool examination for cysts and trophozoites and by serologic studies.[1072] Through the use of PCR, isoenzyme analysis, and antigen detection assays, E. histolytica and E. dispar can be differentiated.[1073,1074] Serum antibody assays may be helpful in establishing the diagnosis of amebic dysentery and extraintestinal amebiasis with liver involvement. The efficacy of treatment with metronidazole for colitis or liver abscess has not been established for the newborn period, although this therapy has been used with success.[1065] Patients with colitis or liver abscess caused by E. histolytica are treated also with iodoquinol, as are asymptomatic carriers.

Giardia lamblia

G. lamblia is a binucleate, flagellated protozoan parasite with trophozoite and cyst stages. It is spread by the fecal-oral route through ingestion of cysts. Child-care center outbreaks reflecting person-to-person spread have demonstrated high infectivity.[1075-1078] Foodborne transmission and waterborne transmission also occur. Infection is often asymptomatic or mildly symptomatic; cases of severe symptomatic infection during the immediate newborn period have not been reported. Symptoms in giardiasis are related to the age of the patient, with diarrhea, vomiting, anorexia, and failure to thrive typical in the youngest children. Seroprevalence studies have demonstrated evidence of past or current infection in 40% of Peruvian children by the age of 6 months.[1081] In a study of lactating Bangladeshi mothers and their infants, 82% of women and 42% of infants excreted Giardia once during the study; in some infants, this occurred before they were 3 months old.[1082] Of these infected infants, 86% had diarrhea, suggesting that the early exposure to the parasite resulted in disease. In a prospective study of diarrhea conducted in Mexico, infants frequently were infected with Giardia from birth to 2 months, with a crude incidence rate of first Giardia infection of 1.4 infections per child-year in this age group.[6] The symptom status of these children was not reported but this study strongly suggests that G. lamblia may be more common than currently recognized among newborns living in developing areas.

The diagnosis of giardiasis can be made on the basis of demonstration of antigen by EIA or by microscopy of feces, duodenal fluid or, less frequently, duodenal biopsy.[1079,1080] Breast-feeding is believed to protect against symptomatic giardiasis.[6,69,1083] This protection may be mediated by cellular and humoral immunity[67,1084,1085] and nonspecifically by the antigiardial effects of unsaturated fatty acids.[1086] Giardia infections causing severe diarrhea may respond to metronidazole or furazolidone.[1080]

Cryptosporidium

C. parvum is a coccidian protozoon related to Toxoplasma gondii, Isospora belli, and Plasmodium species.[1087,1088] The life cycle involves ingestion of thick-walled oocysts; release of sporozoites, which penetrate intestinal epithelium; and development of merozoites. There is asexual and sexual reproduction, with the latter resulting in formation of new oocysts that can be passed in stools.

Cryptosporidium species are ubiquitous. Infection often occurs in persons traveling to endemic areas.[1089] Because Cryptosporidium infects a wide variety of animal species,

there is often a history of animal contact among infected individuals.[1090] Person-to-person spread, particularly in household contacts[1091-1094] and daycare centers,[1095,1096] is well documented and suggests that the organism is highly infectious. Waterborne outbreaks of cryptosporidiosis occur and can be of massive proportions.[1097]

The clinical manifestations of illness in immunocompetent persons resemble those of Giardia infection but are somewhat shorter in duration[1098]; asymptomatic carriage is rare. Symptoms and signs include watery diarrhea, abdominal pain, myalgia, fever, and weight loss.[1089,1090,1095,1096,1098,1099] Infection in the first month of life has been described.[1100,1101] Because symptoms resolve before excretion of oocysts ceases, a newborn whose mother has been ill with cryptosporidiosis in the month before delivery might be at risk even if the mother is asymptomatic at the time of the child's birth.[1102] With the increasing frequency of human immunodeficiency virus infection, it is likely that women with symptomatic cryptosporidiosis occasionally will deliver an infant who will become infected. Infants infected early in life may develop chronic diarrhea and malnutrition.[1103]

The diagnosis of cryptosporidiosis is most typically made by examination of fecal smears using the Giemsa stain, Ziehl-Neelsen stain, auramine-rhodamine stain, Sheather's sugar flotation, an immunofluorescence procedure, a modified concentration-sugar flotation method, or an EIA.[1104,1105] Nitazoxanide is effective therapy of immunocompetent adults and children ill with cryptosporidiosis.[1106] Because illness is usually self-limited in the normal host, attention to fluid, electrolyte, and nutritional status usually suffices. Enteric isolation of hospitalized infants with this illness is appropriate because of the high infectivity. Several studies suggest that the risk of infection early in life may be decreased by breast-feeding.[1101,1107]

VIRUSES

Enteric Viruses

Viruses that infect the intestinal mucosa and cause primarily gastroenteritis are referred to as enteric viruses; they should not be confused with enteroviruses, members of Picornaviridae family that are associated primarily with systemic illnesses. Enteric viruses include rotaviruses, enteric adenoviruses, human caliciviruses, and astroviruses. Other viruses such as coronaviruses, Breda viruses, pestiviruses, parvoviruses, toroviruses, and picobirnaviruses have been sporadically associated with acute diarrhea but are currently considered of uncertain relevance. Extensive reviews on the role of enteric viruses in childhood diarrhea can be found elsewhere.[1108-1111]

All four enteric viruses could conceivably infect the newborn, but the extent of exposure and clinical manifestations are largely unknown for astrovirus, enteric adenovirus, and human caliciviruses. Rotavirus is the most extensively studied enteric virus. Neonatal rotavirus infections have similar virologic and clinical characteristics to infection in older children, although some differences exist.

Rotavirus

Rotavirus is a 75-nm, nonenveloped virus composed of three concentric protein shells: a segmented genome (11

segments), an RNA-dependent polymerase, and enzymes required for messenger RNA synthesis are located within the inner core. Each segment codes for at least one viral protein (VP). The VP can be part of the structure of the virus, or it may be a nonstructural protein (NSP) required for replication, viral assembly, budding, determination of host range, or viral pathogenesis.[1110]

Six distinct rotavirus groups (A through F) have been identified serologically based on common group antigens,[1112,1113] of which three (A, B, and C) have been identified in humans.[1108] Because group A rotaviruses represent more than 95% of isolated strains in humans worldwide, further discussion focuses on this group. Group A rotaviruses are subclassified into serotypes based on neutralization epitopes located on the outer capsid. Both rotavirus surface proteins, VP4 and VP7, can induce production of neutralizing antibodies.[1114,1115] At least 10 VP7 types (G serotypes: G1 to G6, G8 to G10, and G12) and nine VP4 types (P serotypes: P1A, P1B, P2A, P3, P3B, P4, P5, P8, and P12) have been detected among human rotaviruses.[1116-1123] By sequencing the VP4-coding gene, eight genomic P types (genotypes) have been identified that correspond to one or more of the described P antigenic types (genotype 8 to antigenic type P1A, 4 to P1B, 6 to P2A, 9 to P3, 13 to P3B, 10 to P4, 3 to P5, and 11 to P8).[1110] Combining G antigenic with P antigenic and genetic typing, a specific rotavirus strain can be identified: P antigenic type (P genetic type), G type. As an example, the human neonatal M37 strain is described as P2A[6], G1.

Four combined GP types: P1A[8], G1; P1B[4], G2; P1A[8], G3; and P1A[8], G4 account for more than 95% of the organisms isolated from children, and of these, P1A[8], G1 represents the single most common type.[1118-1123] Isolation of less common types appears to be more frequent among neonates with nosocomial rotavirus infections.[1123-1130] Some of these strains seem to be associated with occurrence of asymptomatic infections, although the existence of naturally acquired asymptomatic strains is controversial. Strains P2A[6], G9; P2A[6], G4; P2A[6], G2; and P2A[6], G8 have been reported[1128-1131] from newborn nurseries, some of which seem to be endemic to the newborn units with high rates of asymptomatic infection,[1129-1131] and less commonly, outbreaks of symptomatic infection.[1128] These findings suggest that specific conditions of the newborn environment (e.g., child, nursery, personnel) may increase the possibility of reassortments between human strains; such strains may persist in these settings possibly through constant transmission involving asymptomatic newborns, adults, and contaminated surfaces.

Pathogenesis

Rotavirus primarily infects mature enterocytes located in the mid and upper villous epithelium.[1132-1136] Lactase, which is present only on the brush border of the differentiated epithelial cells at these sites, may act as a combined receptor and uncoating enzyme for the virus, permitting transfer of the particles into the cell.[1137] Perhaps for this reason, infection is limited to the mature columnar enterocytes; crypt cells and crypt-derived cuboidal cells, which lack a brush border, appear to be resistant to rotaviral infection.[1137,1138] This concept also may explain why rotavirus infection is less common in infants younger than 32 weeks' gestational age than in more mature infants[1139]; between 26 and 34 weeks'

gestational age, lactase activity is approximately 30% of that found in term infants.[1140]

The upper small intestine is most commonly involved, although lesions may extend to the distal ileum and rarely to the colon.[1141,1142] Interaction between intestinal cell and rotavirus structural and nonstructural proteins occurs, resulting in death of infected villous enterocytes.[1143] Once infected, the villous enterocyte is sloughed, resulting in an altered mucosal architecture that becomes stunted and flattened. The gross appearance of the bowel is usually normal; however, under the dissecting microscope, scattered focal lesions of the mucosal surface are apparent in most cases. Light microscopy also shows patchy changes in villous morphology, compatible with a process of infection, inflammation, and accelerated mucosal renewal. The villi take on a shortened and blunt appearance as tall columnar cells are shed and replaced by less mature cuboidal enterocytes.[1133,1135,1144] Ischemia may also play a role in the loss and stunting of villi[1145] and activation of the enteric nervous system; active secretion of fluid and electrolytes may be another pathogenic mechanism.[1146] During the recovery phase, the enteroblastic cells mature and reconstruct the villous structure. Because of the loss of mature enterocytes on the tips of the villi, the surface area of the intestine is reduced. Diarrhea that occurs may be a result of this decrease in surface area, disruption in epithelial integrity, transient disaccharidase deficiency, or altered countercurrent mechanisms and net secretion of water and electrolytes.[1133,1140,1142,1146,1147,1148] NSP4 has been found to induce age-dependent diarrhea in CD1 mice by triggering calcium-dependent chloride and water secretion.[1149] The potential role of this "viral enterotoxin" in human disease is not yet clear.[1150,1151]

Infection and Immunity

Infants with asymptomatic rotavirus infections in the nursery are less likely than uninfected nursery mates to experience severe rotavirus infection later in life[1152-1153]; this finding suggested protective immunity and supported vaccine development. Most studies have indicated that serum and intestinal antirotavirus antibody levels are correlated with protection against infection[1153-1161] although this correlation has not been universal.[1162-1163] Breast-feeding protects against rotavirus disease during the first year of life,[57] probably including newborns.[1146] The high prevalence of antirotaviral antibodies in colostrum and human milk has been demonstrated by numerous investigators in widely diverse geographic areas.[8] Maternal rotavirus infection or immunization is accompanied by the appearance of specific antibodies in milk, probably through stimulation of the enteromammary immune system.[1164-1169] Between 90% and 100% of women examined in London, Bangladesh, Guatemala, Costa Rica, and the United States had antirotaviral IgA antibodies in their milk for up to 2 years of lactation.[8,1164-1170] Rotavirus-specific IgG antibodies have been found during the first few postpartum days in about one third of human milk samples assayed,[1164,1167] whereas IgM antibodies were detectable in about one half.[1167]

Glycoproteins in human milk have been shown to prevent rotavirus infection in vitro and in an animal model.[1170] The concentration of one milk glycoprotein, lactadherin, was found to be significantly higher in human milk ingested by

infants who developed asymptomatic rotavirus infection than in milk ingested by infants who developed symptomatic infection.[45]

Epidemiology

Rotaviruses probably infect neonates more commonly than previously recognized, although most infections seem to be asymptomatic or mildly symptomatic.[1128-1130,1131,1172-1187] In a prospective study, the prevalence of rotavirus infection among neonatal intensive care unit patients was 18.4%. Rotavirus has a mean incubation period of 2 days, with a range of 1 to 3 days in children and in experimentally infected adults. Fecal excretion of virus often begins a day or so before illness and maximal excretion usually occurs during the third and fourth days, and generally diminishes by the end of the first week, although low concentrations of virus have been detected in neonates for up to 8 weeks.[1140,1186-1189]

Rotavirus infections are markedly seasonal (autumn and winter) in many areas of the world, although in some countries seasonality is less striking; the reason for this is unclear.[1190-1195] In nurseries in which persisting endemic infection has permitted long-term surveillance of large numbers of neonates, rotavirus excretion can follow the seasonal pattern of the community but can also show no seasonal fluctuation.[1196-1198] It is not clear how units in which infection remains endemic for months or years differ from those with a low incidence of rotavirus. Some nurseries are free of rotavirus infection[1198-1200] or minimally affected[45,1201] whereas others have rotavirus diarrheal disease throughout the year or in outbreaks that involve 10% to 40% of neonates.[1128,1139,1179,1202-1203]

Low birth weight does not seem to be an important factor in determining the attack rate among infants at risk but may be important in mortality.[1204] Infants in premature or special-care nurseries, despite their prolonged stays and the increased handling necessary for their care, do not demonstrate a higher susceptibility to infection; data regarding shedding of the virus are inconsistent.[45,1200]

After infection is introduced into a nursery, rotavirus probably will spread steadily and remain endemic until the nursery is closed to new admissions or nursing practices permit interruption of the cycle.[1205] Exactly how the virus is introduced and transmitted is uncertain, although limited observations and experience with other types of enteric disease in maternity units suggest several possibilities. The early appearance of virus in stools of some neonates indicates that infection probably was acquired at delivery. Virus particles can be detected on the first[45,1186] or second[1198] day of life in a significant number of infected infants. By day 3 or 4, most infected infants who will shed virus, with or without signs of illness, are doing so.[1174,1186,1198] The large numbers of virus particles excreted[1174,1198] suggest a fairly large and early oral inoculum. It is unlikely that contamination from any source other than maternal feces could provide an inoculum large enough to cause infection by the second day.

Transfer of particles from infant to infant on the hands of nursing and medical staff is probably the most important means of viral spread. With 10^8 to 10^{11} viral particles usually present in 1 g of stool, the hands of personnel easily could become contaminated after infection is introduced into a nursery. There are numerous reports of nosocomial and daycare center rotavirus gastroenteritis outbreaks that attest to the ease with which this agent spreads through a hospital or institutional setting.[1108] Admission of a symptomatic child usually is the initiating event, although transfer of a neonate with inapparent infection from one ward to another also has been incriminated. The most important factors influencing the incidence of rotavirus diarrhea in a nursery are the proximity to other newborns and the frequency of handling.[1187] During a 4-month study, infants cared for by nursing staff and kept in communal nurseries experienced three epidemics of diarrhea with attack rates between 20% and 50%. During the same period, only 2% of infants rooming in with their mothers became ill, even though they had frequent contact with adult relatives and siblings.

There is no clear evidence of airborne or droplet infection originating in the upper respiratory tract or spread by aerosolization of diarrheal fluid while diapers are changed. Indirect evidence of airborne transmission includes the high infection rate in closed settings, the isolation of the virus from respiratory secretions,[1206] and the experimental observation of transmission by aerosol droplets in mice.[1207] However, the respiratory isolation achieved by placing an infant in a closed incubator is not fully protective.[1187] No evidence indicates that transplacental or ascending intrauterine infection occurs. Transmission of virus through contaminated fomites, formula, or food is possible but has not been documented in newborns. Rotavirus particles have not been found in human milk or colostrum.[1166,1170]

Clinical Manifestations

Exposure of a newborn to rotavirus can result in asymptomatic infection or cause mild or severe gastroenteritis.[1129,1130,1173,1179,1196,1197,1201,1208] Outbreaks with high attack rates as measured by rotavirus excretion have been described but the extent of symptomatic infection varies.[1175,1177,1186,1198,1203] Severe rotavirus infection is seldom reported during the newborn period[1203] but the extent of underreporting of severe disease, especially in the less developed areas of the world, has not been evaluated.

It has been hypothesized that asymptomatic infections during the newborn period are the result of naturally attenuated strains circulating in this environment. RNA electrophoretic patterns of rotaviruses found in certain nurseries have shown uniform patterns[1180,1182,1184,1208], and it has been suggested that these strains may be attenuated. The presence of unusual antigenic types such as the P2A[6] type within nurseries also suggests "less virulent strains." At least 10 rotavirus strains were documented to co-circulate in a tertiary care center during a 2-month period[1209] and in a different setting the same rotavirus strains by electropherotype produced asymptomatic infection in neonates and symptomatic infection in older infants.[1183] Newborns within a nursery exposed to a given rotavirus strain can develop symptomatic or asymptomatic infection.[1130,1210,1211] Because newborns routinely have frequent relatively loose stools, it is possible that mild diarrhea episodes caused by rotavirus are being wrongly labeled as asymptomatic episodes.

No clinical feature is pathognomonic of rotaviral gastroenteritis. Early signs of illness, such as lethargy, irritability, vomiting, and poor feeding, usually are followed in a few hours by the passage of watery yellow or green stools free of blood but sometimes containing mucus.[1187,1212-1214] Diarrhea usually decreases by the second day of illness and is much

improved by the third or fourth day. Occasionally, intestinal fluid loss and poor weight gain may continue for 1 or 2 weeks, particularly in low-birth-weight infants.[1175] Although reducing substances frequently are present in early fecal samples[1139,175,1176,1187] this finding is not necessarily abnormal in neonates, particularly those who are breast-fed.[1215] Nevertheless, infants with prolonged diarrhea should be investigated for monosaccharide or disaccharide malabsorption or intolerance to cow's milk protein or both.[1216] In a prospective study,[1185] 49% of newborns with gastrointestinal symptoms in a neonatal intensive care unit had rotavirus detected in their stools. Frequent stooling (present in 60%), bloody mucoid stool (42%), and watery stools (24%) were risk factors for a rotavirus infection. Bloody mucoid stools, intestinal dilatation, and abdominal distention were significantly more common in preterm infants, but severe outcomes such as necrotizing enterocolitis and death did not differ among infected term and preterm infants.

Longitudinal studies in newborn nurseries and investigations of outbreaks among neonates rarely describe a severe adverse outcome or death.[1139,1168,1187] Because these infants are under constant observation, early detection of excessive fluid losses and the availability of immediate medical care are probably major factors in determining outcome. Rotavirus gastroenteritis causes almost 400,000 deaths of infants every year,[1217] concentrated largely in the poorest regions of the world. It is likely that in places where hospital-based care is uncommon, rotavirus causes neonatal deaths secondary to dehydration.

Group A rotavirus has been associated with a wide array of diseases in infants and children; Reye syndromes, encephalitis-aseptic meningitis, sudden infant death syndrome, inflammatory bowel disease, and Kawasaki syndrome have been described but not systematically studied.[1108] Case reports and small case series have associated neonatal rotavirus infection with necrotizing enterocolitis.[1218,1219] Rotavirus infection may play a role in a small proportion of cases of necrotizing enterocolitis, although it probably represents one of many potential triggering factors. A significant association between neonatal rotavirus infection and bradycardia-apnea episodes was detected in one prospective study.[1220] The possible association between natural rotavirus infection and intussusception[1221-1223] gained support after the association was made between the human-simian reassortant vaccine and intussusception in infants older than 2 months (attributable risk ≈ 1:10,000).[1224] Intussusception is extremely uncommon in the newborn; it is highly unlikely that rotavirus triggers this disease in neonates.

Diagnosis

There are many methods used for detection of rotavirus in stool specimens, including electron microscopy, immune electron microscopy, ELISA, latex agglutination, gel electrophoresis, culture of the virus, and reverse transcriptase–polymerase chain reaction. ELISA and latex agglutination currently are the most widely used diagnostic techniques for detection of rotavirus in clinical samples. Many commercial kits are available that differ in specificity and sensitivity.[1225-1229] In general, latex agglutination assays are more rapid than ELISAs but are less sensitive. The sensitivity and specificity of the commercially available ELISAs surpass 90%. Checking of the ELISA by another method such as gel electrophoresis

or PCR amplification may be desirable if there is concern about false-positive results.

Fecal material for detection of rotavirus infection should be obtained during the acute phase of illness. Whole-stool samples are preferred, although suspensions of rectal swab specimens have been adequate for detection of rotavirus by ELISA.[1230,1231] Rotavirus are relatively resistant to environmental temperatures, even tropical temperatures,[1232] although 4°C is desirable for short-term storage and -70°C for prolonged storage.[1108] Excretion of viral particles may precede signs of illness by several days[1190]; maximal excretion by older infants and children usually occurs 3 to 4 days after onset of symptoms.[1233] Neonates can shed virus for 1 to 2 weeks after onset of symptoms.

Therapy and Prevention

The primary goal of therapy is restoration and maintenance of fluid and electrolyte balance. Despite the documented defect in carbohydrate digestion with rotavirus diarrhea, rehydration often can be accomplished with glucose-electrolyte or sucrose-electrolyte solutions given orally.[199,1234-1236] Intravenous fluids may be needed in neonates who are severely dehydrated, who have ileus, or who refuse to feed. Persistent or recurrent diarrhea after introduction of milk-based formulas or human milk warrants investigation for secondary carbohydrate or milk protein intolerance.[1139,1217] Disaccharidase levels and xylose absorption return to normal within a few days[1144] to weeks after infection.[1133]

Intractable diarrhea related to severe morphologic and enzymatic changes of the bowel mucosa is possible although rare in the newborn; it may require an elemental diet or parenteral nutrition. Efficacy of anti-rotavirus antibodies (e.g., hyperimmune colostrum, antibody-supplemented formula, human serum immunoglobulin) and of probiotics has been postulated,[1238-1241] although not convincingly shown[1242]; the widespread clinical use of these measures seems remote. One study suggests that use of lactobacillus during the diarrheal episode may decrease the duration of rotavirus-associated hospital stays, especially when used early in the course of the disease, although more studies are needed before recommending widespread use.[1241]

Hand hygiene before and after contact with each infant remains the single most important means of preventing the spread of infection. Because rotavirus is often excreted several days before illness is recognized, isolation of an infant with diarrhea may be too late to prevent cross-infection unless all nursing personnel and medical staff have adhered to this fundamental precaution. Infants who develop gastroenteritis should be moved out of the nursery area if adequate facilities are available and the infant's condition permits transfer. The use of an incubator is of value in reducing transmission of disease only by serving as a reminder that proper hand-hygiene and glove techniques are required, but is of little value as a physical barrier to the spread of virus.[1187] Encouraging rooming-in of infants with their mothers has been shown to be helpful in preventing or containing nursery epidemics.[1243] Temporary closure of the nursery may be required for clinically significant outbreaks that cannot be controlled with other measures.[1128]

Vaccines

Development of rotavirus vaccines began in the early 1980s. Candidate vaccines included bovine and rhesus monkey

Table 20–6   Differential Diagnosis of Neonatal Diarrhea

Diagnosis	Reference(s)
Anatomic Disorders	
Microvillous inclusion disease	1245
Hirschsprung's disease	1246
Massive intestinal resection (short-bowel syndrome)	1247
Intestinal lymphangiectasis	1248
Metabolic and Enzymatic Disorders	
Congenital disaccharidase deficiency (lactase, sucrase-isomaltase deficiency)	1249,1250
Congenital glucose-galactose malabsorption	1251,1252
Secondary disaccharide, monosaccharide malabsorption	337,528,1252-1258
After gastrointestinal surgery	
After infection	
With milk-soy protein sensitivity	
Cystic fibrosis	1259
Syndrome of pancreatic insufficiency and bone marrow dysfunction (Shwachman's syndrome)	1260
Physiologic deficiency of pancreatic amylase	1261
Intestinal enterokinase deficiency	1262
Congenital bile acid deficiency syndrome	1263
Alpha/beta-lipoproteinemia	1264
Acrodermatitis enteropathica	1265,1266
Congenital chloride diarrhea	1267,1268
Primary hypomagnesemia	1269
Congenital adrenal hyperplasia	1270
Intestinal hormone hypersecretion	1271,1272
Non–beta islet cell hyperplasia (Wolman's disease)	1273
Transcobalamin II deficiency	1274
Congenital iron storage	1275
Hartnup's disease	1276
Congenital Na⁺ diarrhea	1277
Inflammatory Disorders	
Cow's milk protein intolerance	1278
Soy protein intolerance	1279,1280
Regional enteritis	1281
Ulcerative colitis	1282,1283
Primary Immunodeficiency Disorders	
Wiskott-Aldrich syndrome	1284
Thymic dysplasia	1284
Acquired immunodeficiency syndrome	1285
Miscellaneous	
Irritable colon of childhood (chronic nonspecific diarrhea)	1286
Phototherapy for hyperbilirubinemia	1287
Familial dysautonomia (Riley-Day syndrome)	1288
Familial enteropathy	1289,1290
High sulfates in water	1291
Phenolphthalein poisoning/child abuse	1292

attenuated strains, human attenuated strains, and bovine-human and rhesus-human reassortant strains.[1109] In August 1998, the first licensed rotavirus vaccine, Rotashield, an oral formulation of a simian-human quadrivalent reassortant vaccine, was recommended for use in children when they were 2, 4, and 6 months old. After approximately 500,000 children were vaccinated with more than 1 million doses, a significantly increased risk of intussusception was observed among vaccinated children, with an overall odds ratio of 1.8.[1244] Use of this vaccine was terminated. Two new vaccine candidates are undergoing phase III clinical trials: a "pentavalent" bovine-human reassortant vaccine including G types G1-G4 and P type P1A[8] and a monovalent human attenuated P1A[8]G1 vaccine. The epidemiology of rotavirus infection will change significantly if one or both candidates become widely available in the future. The impact on neonatal infection will depend on the effect of herd immunity in decreasing circulation of rotavirus strains.

DIFFERENTIAL DIAGNOSIS

Stools from breast-fed neonates are typically watery and yellow, green, or brown. The frequency of stooling can vary from one every other day to eight evacuations per day. In an active, healthy infant who is feeding well, has no vomiting, and has a soft abdomen, these varied patterns of stooling are not a cause for concern. Physicians need to consider the child's previous frequency and consistency of stools and establish a diagnosis of acute diarrhea on an individual basis. Close follow-up of weight increase in infants with non-formed stools can help confirm the clinical impression. A normal weight gain should direct medical action away from stool exams or treatment.

Diarrhea during the neonatal period is a clinical manifestation of a wide variety of disorders (Table 20-6). The most common initiating factor is a primary infection of the gastrointestinal tract that is mild to moderate in severity,

self-limited, and responsive to supportive measures. Acute diarrhea can also be an initial manifestation of a systemic infection, including bacterial and viral neonatal sepsis. Infants with moderate to severe diarrhea require close monitoring until the etiologic diagnosis and the clinical evolution are clarified. There are noninfectious diseases leading to chronic intractable diarrhea that may result in severe nutritional disturbances or even death unless the specific underlying condition is identified and treated appropriately. The differential diagnosis of a diarrheal illness requires a careful clinical examination to determine whether the child has a localized or a systemic process. Lethargy, abnormalities in body temperature, hypothermia or hyperthermia, decreased feeding, abdominal distention, vomiting, pallor, respiratory distress, apnea, cyanosis, hemodynamic instability, hypotension, hepatomegaly or splenomegaly, coagulation or bleeding disorders, petechiae, and exanthemas should lead to an intense laboratory investigation directed at systemic viral or bacterial infection. If the process is deemed a localized intestinal infection, initial evaluation can be focused on differentiating an inflammatory-invasive pathogen from those that cause a noninflammatory process. For this, stool examination for fecal leukocytes, red blood cells, and lactoferrin can be a helpful indicator of the former.

Inflammatory diarrhea can be caused by *Shigella, Salmonella, Campylobacter, V. parahaemolyticus, Y. enterocolitica,* EIEC, EAEC, *C. difficile,* necrotizing enterocolitis, antibiotic-associated colitis, and allergic colitis (i.e., milk or soy intolerance). Noninflammatory causes of diarrhea include ETEC, EPEC, rotaviruses, enteric adenoviruses, calicivirus, astrovirus, *G. lamblia* and *Cryptosporidium.* Although supportive fluid therapy is mandatory for all types of diarrhea, the brief examination for fecal leukocytes and red blood cells can direct the diagnostic and therapeutic approach. Pathogens such as *Shigella, Salmonella,* and EHEC can cause watery or bloody diarrhea, depending on the specific host-pathogen interaction and the pathogenic mechanisms involved. Some of the noninfectious diseases responsible for neonatal diarrhea are listed in Table 20-6.[337,528,1245-1292] The evaluation and management of persistent infantile diarrhea has been reviewed.[1293]

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