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# ENTERIC INFECTIOUS DISEASE IN NEONATES

## Epidemiology, Pathogenesis, and a Practical Approach to Evaluation and Therapy

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Enteric infections occurring during the neonatal period are usually brief and self-limited; however they can cause substantial morbidity in some infants and represent a potential danger to other infants in the nursery. There is a wide spectrum of clinical findings that differ depending on the gestational age of the infant and his or her environment. Exposure to an enteric pathogen can cause no infection, asymptomatic infection, illness with gastroenteritis, or septicemia with or without foci of infection.

The role of specific bacterial or viral pathogens as causes of enteric disease in neonates has been described.[48,72] This chapter reviews infectious gastrointestinal diseases in neonates and includes epidemiologic characteristics, pathogenesis, clinical manifestations, laboratory evaluation, and approaches to therapy.

### EPIDEMIOLOGIC CHARACTERISTICS

#### Host Factors

Newborns are uniquely susceptible hosts to enteric infections during the first days of life. There are many important host factors that provide

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protection against gastrointestinal infections. These include (1) local or systemic immune responses, (2) enteric flora, (3) gastric acidity, (4) gastric motility, and (5) intestinal mucus. The presence or absence of these host factors contributes to the infant's susceptibility to enteric disease.

## Modes of Transmission

Gastrointestinal infections can occur sporadically or as a result of an epidemic. Many pathogens have been associated with neonatal diarrhea (Table 1). Neonates can acquire bacteria or enteric viruses during the first days of life by vertical or horizontal transmission. Organisms are ingested at the time of birth during passage through the birth canal and across the perineum, which has been shown for infections with enteroviruses and enteropathogenic *Escherichia coli* (EPEC).[8,17,76,84] Of stool cultures obtained from women at delivery, 10% to 15% of them carry EPEC.[17,48,91,99] Many of these mothers transmit these organisms to their infants, resulting in an asymptomatic infection rate of 2% to 5% among newborns randomly cultured during nursery surveys.[17,84,91]

Bacteria and viruses can be horizontally transmitted from siblings, parents, or hospital personnel or through ingestation of contaminated formulas or water. Maternal or other asymptomatic carriers of Salmonella, Shigella, Campylobacter, EPEC, and other viral pathogens can spread these pathogens. In one outbreak investigation of echovirus 11', mouth care and gavage feeding were substantially associated with neonatal infection.[58] Sometimes the presence of a particular pathogen, such as rotavirus, can be endemic to a specific nursery and not have the characteristic seasonal variation.[14,20,44,80,105,106]

Nursery outbreaks have been associated with many enteric viruses and bacteria. In most outbreak investigations, several illnesses occur among the

**Table 1.** ENTERIC PATHOGENS RESPONSIBLE FOR NEONATAL DIARRHEA

| |
|---|
| Bacteria |
| *Escherichia coli* |
| Enterotoxigenic *E. coli* |
| Invasive *E. coli* |
| Enteropathogenic *E. coli* |
| Enterohemorrhagic *E. coli* |
| Salmonella |
| Shigella |
| Campylobacter |
| *Clostridium difficile* |
| *Yersinia enterocolitica* |
| Viruses |
| Rotavirus |
| Enterovirus |
| Enteric adenovirus |
| Small round viruses |
| Coronavirus |

infants and sometimes among the nursery staff.[39,93] Often the initiation of a nursery outbreak involves an asymptomatic infant who sheds the virus or bacteria. These infants can infect other infants in the nursery or the nursery staff. For some viral pathogens such as enteroviruses, nursery outbreaks usually coincide with seasonal peaks of disease in the community. Reported outbreaks have been due primarily to echovirus 11 or group B coxsackievirus serotypes 1 to 5, with attack rates in the nursery as high as 50%.[77]

## PATHOGENESIS

Infection of the gastrointestinal tract and subsequent clinical disease in neonates depend on several host factors and special properties of individual microbes. The mechanisms responsible for microbial colonization, virulence, and disease are complex and unique to each pathogen. However, host injuries resulting from these infections often display similar patterns. Understanding the pathogenic basis for these injuries can be helpful in making a diagnosis and planning therapy.

### Bacterial Pathogenesis

Bacterial enteric pathogens can be classified into two broad groups according to the mechanisms by which they cause disease. Some bacteria (for example, *Shigella* spp.) directly invade intestinal mucosa, resulting in host inflammatory response. Other pathogens (such as *Vibrio cholera*) colonize and cause disease by producing toxins. Although this classification is helpful in some circumstances, bacterial pathogenesis may also be due to a combination of mechanisms. In many cases the precise interactions of these mechanisms have not been well defined.

#### *Bacteria that Invade Enteric Mucosa*

*Shigella* rarely cause diarrhea in infants younger than 1 month, even in endemic areas.[52] However, the pathogenic mechanisms involved in *Shigella* infection are much studied and relevant to other bacterial agents that invade the gut mucosa (for example, enteroinvasive *E. coli* [EIEC]).[81] After inoculation, *Shigella* species attach to colonic mucosa and penetrate the enterocyte through pinocytosis. Entry into the mucosal cell is achieved when the lysosomal membrane ruptures. Neighboring mucosal and submucosal cells are subsequently invaded by bacterial-induced pseudopods, followed again by pinocytosis, vacuole lysis, and intracytoplasmic release of bacteria. Each of these intricate steps in invasion and spread depend on the complex interaction of several bacterial gene products and regulatory elements. Together these events cause enterocyte necrosis and host inflammation, manifest by shallow ulcers with exudate that appear as infectious colitis, often characterized by fever, abdominal pain, and mucus, blood, and inflammatory cells

in the stool.[52] Colonic perforation and peritonitis have been reported in neonates.[52] Despite the direct mucosal invasion, extraintestinal spread by *Shigella* is seen in only a few patients.[27,52]

A watery diarrhea phase often precedes the inflammatory phase of *Shigella* spp. infection, implying the presence of an enterotoxin. This factor has not been identified yet but is presumably similar to an enterotoxin associated with EIEC.

In addition to the invasive properties exhibited by *Shigella* spp., *S. dysenteriae* 1 elaborates the Shiga toxin.[25,27] Shiga toxin has direct effects on blood vessels and activity against absorptive cells of the villus tip, resulting in fluid accumulation in ligated rabbit ileal loops (enterotoxin assay). This toxin is also cytotoxic as measured by the activity in tissue culture assays. Although the molecular mechanisms of Shiga toxin have been investigated extensively, the pathogenic role of the toxin is not fully characterized.

Salmonella are rare but potentially serious causes of infection in newborns. Like Shigella, Salmonella invade the intestinal mucosa to produce disease.[81] However, Salmonella pass through mucosa cells to replicate in the lamina propria and invade mesenteric lymph nodes. Salmonella may then spread to distant sites through lymphatics or the bloodstream. The pathogenic potential of these organisms depends largely on their ability to survive within phagocytic lysosomes.[35] Initial colonization and invasion is likely in the distal ileum, and diffuse inflammation, crypt abscesses, and mucosal edema occur in the colon. These changes are clinically evident by loose stools with mucus, with or without blood. Watery diarrhea is frequently noted and probably relates to production of an enterotoxin closely related to cholera toxin.[97]

*Yersinia enterocolitica* and *Campylobacter jejuni* are unusual causes of neonatal diarrhea, but both of these organisms have invasive properties.[11,18,88] *Yersinia enterocolitica* pass through enterocytes, where they replicate in Peyer's patches. This invasion causes inflammation that may appear as pseudoappendicitis or mesenteric adenitis. The diarrhea associated with *Y. enterocolitica* may resemble that of Shigella or Salmonella; that is, stools containing mucus with or without blood. *Yersinia enterocolitica* also secrete a heat-stable enterotoxin, but its role in bacterial virulence is uncertain.[21] The organism also can be carried in the bloodstream by phagocytic cells to more distant sites.

In addition to its invasive properties, *C. jejuni* produces a heat-labile enterotoxin and a cytotoxin, although the role of these toxins during infection has not been characterized definitively.[61,95,108] Epithelial ulcerations and host inflammatory infiltrate occur in the lamina propria after *C. jejuni* infection. Infection is most obvious in the colon, ileum, and jejunum. The associated diarrhea is frequently bloody but may be indistinguishable from that of other invasive enteric bacteria. Sepsis is reported, with seeding to distant sites.

Enteroinvasive *E. coli* have invasive properties similar to *Shigella*, although bloody stools are noted less commonly.[65,81] In addition to mucosal invasion, an enterotoxin is apparently produced by EIEC in environments

low in iron.[34] This latter feature may explain the watery diarrhea noted with EIEC.

### *Bacterial Pathogenesis by Enterotoxins*

Neonates rarely have symptomatic cholera. *Vibrio cholerae* 01 induce profuse watery diarrhea in the absence of mucosal invasion. These organisms serve as a classic model for enterotoxin-induced gastrointestinal disease.[81] The molecular structure of cholera toxin and the diarrhea mechanisms have been studied intensively.[81] Regulatory control of *V. cholerae* 01 virulence is also the subject of concentrated investigations. After inoculation, attachment to mucosal cells, and bacterial multiplication, *V. cholerae* 01 elaborate an enterotoxin composed of an A subunit ($A_1 + A_2$) and five B subunits. The B subunit binds to $GM_1$ gangliosides on the enterocyte apical membrane and allows penetration by the $A_1$ subunit. This $A_1$ subunit is responsible for prolonged stimulation of cellular adenylate cyclase, which enhances chloride secretion from villus crypt cells and decreases absorption at the villus tips. The resulting imbalance in fluid and electrolyte metabolism results in profound, debilitating watery diarrhea without the blood, mucus, or inflammatory cells noted with invasive enteric bacteria.

Strains of enterotoxigenic *E. coli* (ETEC) may elaborate either a heat-labile toxin, heat-stable toxin, or both.[65,81] Heat-labile toxin closely resembles cholera toxin in structure and function, and strains of ETEC that produce LT may cause a watery diarrhea. The heat-stable toxin STa activates guanylate cyclase with an accumulation of cyclic guanosine monophosphate and secretory diarrhea.

*Clostridium difficile* produces at least two potent toxins: toxin A (enterotoxin), which is responsible for pathologic reactivity in the intestines, and toxin B, which is responsible for cytotoxic changes in tissue culture cells.[62] Although no evidence of bacterial invasion of intestinal mucosa exists, *C. difficile* toxin can cause inflammatory changes in the lamina propria, and pseudomembranous colitis in severe cases. Toxin-producing *C. difficile* often colonizes in neonates without evidence of disease.[26,64,107] This phenomenon is poorly understood and complicates interpretation of laboratory assays for *C. difficile.*

### *Enteric Bacteria with Mixed or Uncertain Pathologic Mechanisms*

Enteropathogenic *E. coli* produce watery diarrhea with vomiting and fever with a pathologic lesion in the small intestine marked by tight adherence of bacteria to epithelial cells and brush border destruction.[24,65,81] Mucosal invasion generally is not found. Recent work has increased our understanding some of the virulence features of EPEC, but the mechanisms involved in pathogenesis are not fully characterized.

The pathogenesis of enterohemorrhagic *E. coli* (EHEC) associated with hemolytic uremic syndrome is not well understood.[65,81] Mucosal invasion is

not a prominent feature, but EHEC produce Shiga-like cytotoxins. Infection with these bacteria can cause hemorrhagic necrosis of villus tips without substantial inflammation. The focus of this infection is mainly in the colon.

## Viral Infections

Rotaviruses are the most commonly recognized viral agents infecting the intestinal tract during the neonatal period.[5,96] Although asymptomatic shedding of rotaviruses are frequently noted, infection with these viruses can also result in substantial disease in the first month after birth.[50] The structure of rotavirus particles is well understood, but controversy remains concerning the mechanisms involved in virus attachment and entry into host cells.[10,16] Replication of rotaviruses and host mucosal diseases usually involve only mature enterocytes located at villous tips in the small intestine. Infection is lytic and causes destruction of villous tip epithelium with sparing of crypt cells. Mononuclear cell infiltration of the lamina propria is also documented in children by biopsy obtained during acute infection. In humans it is associated with abnormally low levels of disaccharidases, consistent with the carbohydrate malabsorption and profuse water diarrhea often observed.[9] The formation of syncytia in infected intestinal epithelium appears to be characteristic only for group B rotaviruses.[54] These agents are antigenically and genetically distinct from the rotaviruses usually associated with infantile gastroenteritis, but neonatal group B rotavirus infections have been noted in China.[19] Resolution of the clinical symptoms of rotavirus infection correlates with reconstitution of mature enterocytes from villous crypt cells. Although the pathogenic lesions associated with enteric adenovirus infection have not been studied extensively in humans, investigations in animals have contributed to descriptions of intestinal injury with these viruses.[51]

Adenoviruses appear to infect gut enterocytes, as shown by intranuclear inclusions, immunoperoxidase staining, and direct visualization of virus particles by electron microscopic examination. This infection causes infected enterocytes to rupture and development of villus stunting and crypt cell hypertrophy. A host mononuclear cell response is observed with infiltration of villous lamina propria. Experimental astrovirus infection of animals has indicated species-specific differences in pathologic mechanisms, and it is not clear how these differences relate to human infection.[51] In lambs, astroviruses infect mature enterocytes, and exfoliation of these cells causes stunted villi and crypt hypertrophy. Infection in calves involves M cells and enterocytes on dome villi. Host neutrophil response may be detected in dome villi lamina propria.

Enteroviruses may gain entry through the upper respiratory or intestinal tracts, with subsequent viremia and spread to distant organ systems. Despite the initial replication in the gastrointestinal tract, enteroviruses usually do not produce enteric disease. In outbreaks, clinical findings among infants vary. In echovirus outbreaks, infants tend to have a self-limiting illness that includes fever, rash, diarrhea, and aseptic meningitis.

With coxsackie virus outbreaks, fever, irritability, lethargy, poor feeding, and apnea are the most common findings. However, in some coxsackie outbreaks, aseptic meningitis is the primary manifestation,[12,30,33,89] but in others myocarditis predominates.[30,33,56,60,78,89] The mortality rate among the infants with myocarditis ranges from 50% to 60%.[56,60] Vomiting, diarrhea, or both are less commonly reported in neonates infected with these viral agents. Diarrhea may be part of the devastating systemic illness that can occur after maternal–perinatal enterovirus infection. In such instances, hemorrhagic necrosis of gastrointestinal and other organs is noted at autopsy.

## CLINICAL DIAGNOSIS OF ENTERIC INFECTION

It is difficult to identify a specific enteric agent based only on signs and symptoms. Diagnosis can be aided by close attention to the character of the diarrheal feces, potential environmental exposures, and history of the illness.[37,47,83,87] The presence of diarrhea among close contacts or family members can be an important guide to identification of illness in the neonate. Gross inspection of the fecal specimen can offer clues about the underlying disease.[103] For example, profuse, watery diarrhea without blood, mucus, or pus indicates a malabsorption state or secretory diarrhea. This is characteristic of bacteria that produce enteroxins but do not directly invade and destroy bowel mucosa (such as *Cholera vibrio,* ETEC). Enteropathogenic *E. coli* also produce predominantly watery diarrhea that may have a characteristic "seminal" odor.[66] Gross blood after the onset of watery diarrhea is found frequently with EHEC infection.[81] In addition to bacterial causes, watery stools are also observed with most enteric viruses, including rotaviruses, adenovirus types 40 and 41, and astroviruses. Although *Salmonella* infections often occurs with watery diarrhea, the invasive properties of this organism can cause blood or mucus in the feces.[81]

Classic dysenteric stools are the hallmark of infection with Shigella because of its highly invasive nature.[81] These stools may be scant in volume but contain blood, mucus, and pus. This type of diarrhea is also described with *Y. enterocolitica* and *C. jejuni* infections.

In addition to diarrhea, many enteric pathogens also induce fever and vomiting. Unfortunately, the presence or absence of these findings in the neonate usually is not helpful in differentiating the enteric agents. For example, vomiting occurs frequently with rotavirus infections but can be present in patients infected with many other bacteria and viruses.

In making a differential diagnosis, the clinician must also consider the full spectrum of disease associated with specific enteric microbes. Systemic disease is always a concern with neonates infected with Salmonella and can also complicate gastrointestinal infection with Shigella, *Y. enterocolitica,* and *C. jejuni.*[48] Bacteremia may occur in 30% to 50% of neonates infected with Salmonella, including those with no evidence of gastroenteritis.[55,82,104] Focal infections of almost every organ system (for example bone, joint, or lung) are reported with Salmonella gastroenteritis, but meningitis is the most

feared of these complications and emphasizes the vigilance required to evaluate infants who are infected with Salmonella. Shigella also may be cultured from the blood in as many as 10% of infected neonates, and sepsis with other gut flora may follow Shigella-induced bowel injury or perforation.[1,52,100] Seizures may precede any other signs or symptoms of *Shigella* infection, but apparently they are toxin mediated and rarely the result of central nervous system infection.

In contrast to the severe systemic illness that may be associated with enteric disease, asymptomatic infections also occur during epidemics in the nursery. Enteropathogenic *E. coli* and Salmonella are examples of pathogenic bacteria that can be carried in the intestinal tract without apparent clinical manifestations. *Clostridium difficile* and associated toxins are also found in the intestinal tracts of many neonates who never show signs of gastrointestinal disease.[26,64,107] By comparison, in adults *C. difficile* toxin is associated with antibiotic-related diarrhea and pseudomembranous colitis and usually is not found in the absence of disease.[4,62] This asymptomatic carrier state is not well understood but may be related to differences in neonatal intestinal maturity, local environmental differences in the neonatal gut, absence of toxin-related receptors, or as yet undescribed protective factors. These findings indicate that laboratory tests for *C. difficile* should be interpreted with caution in neonates. Detection of *C. difficile* and toxin in a newborn with diarrhea does not necessarily mean that the causative organisms has been identified. In many instances, *C. difficile* may be unrelated to gastrointestinal illness in the neonate, and disease may be due to other agents.

Although severe diarrhea can result from rotavirus infection in neonates, many show few or no clinical manifestations after infection.[50] Such asymptomatic infections in newborns may even be protective against severe infection at later ages. The mechanisms that prevent rotavirus disease in many neonates are not clearly defined. This attenuation of disease may be immune medicated or related to differences in immature neonatal enterocytes. Specific neonatal rotavirus strains with low pathogenic potential also have been proposed to explain the high percentage of asymptomatic carriers in some nurseries, but the proof of such strains has been questioned.[98]

## LABORATORY DIAGNOSIS OF NEONATAL ENTERIC INFECTIONS

### Gross Examination of Fecal Specimens

Direct microscopic examination of fecal specimens by an experienced observer can help distinguish agents of infectious diarrhea.[23,37,47,87] Methylene blue staining can reveal fecal leukocytes, an indicator of infection with Shigella, *C. jejuni*, EIEC, Salmonella, *Y. enterocolitica*, and *C. difficile*. Phase-

contrast or darkfield examination of wet mounts can reveal the characteristic darting motility of Vibrio and Campylobacter.

## Submission of Specimens to the Clinical Bacteriology Laboratory

The increasing cost of health care has prompted re-examination of routine use of the clinical laboratory services to diagnose enteric infections.[49,63,102] Inappropriate testing of stool specimens results in a low diagnostic yield in many institutions (2.4% in one report).[63] When gauged according to the cost per positive result, stool examinations can be the most expensive cultures performed in the bacteriology laboratory.[49,63,102] These findings emphasize the need to evaluate closely the need for submission of fecal samples and the delineation of criteria for more cost-effective use of the diagnostic microbiology laboratory services. Such criteria have included the incorporation of historical variables in the outpatient setting (such as abrupt onset of disease, more than four loose stools, or no vomiting). Other investigators have emphasized the low yield of bacterial stool cultures and examinations for ova and parasites in patients in whom diarrhea develops more than 3 days after hospital admission.[79] Criteria have not been defined for submission of cultures from neonates. However, knowledge of the epidemiologic characteristics of neonatal diarrhea should be useful in selecting the most appropriate laboratory examinations. For example, submission of fecal specimens from neonates for ova and parasites would be of little diagnostic help in the United States unless indicated specifically by family or travel history.

Diagnosis of enteric bacterial infections is determined primarily by culture.[40,103] Although the exact procedures used in the laboratory are usually not of direct interest to the clinician, physicians should be familiar with the proper methods for collection and transport of fecal specimens.[40,103] Specimens should be obtained when diarrhea is active for best results. Fresh stool specimens should be sent immediately to the bacteriology laboratory in a clean container made of nonabsorbable material. If a delay longer than 2 hours is anticipated, the specimens for bacterial culture should be stored at 4°C in Cary-Blair transport media. In older persons, little additional yield has been reported by submission of more than two cultures.

In most bacteriology laboratories, culture is performed routinely for Salmonella, Shigella, and *C. jejuni.* If culture for other bacteria (such as EPEC, ETEC, EHEC, *Y. enterocolitica,* or Vibrio) is indicated by history, physical findings, or direct stool examination, the laboratory should be notified specifically.

Fecal specimens to diagnose *C. difficile* infection can be submitted to the clinical laboratory in a manner similar to that recommended for bacteria culture of fecal specimens.[86] Culture and toxin detection should both be assayed on the specimen, with additional assay for toxin production from the cultured organisms if the result of fecal toxin assay is negative. As noted

previously, the clinician should exercise appropriate caution in interpreting positive results.

### *Laboratory Detection of Enteric Viruses*

Neonatal gastroenteritis has been associated with adenoviruses, astroviruses, "small round viruses," and coronaviruses, but rotavirus infection appears to be more common than any of these other agents during the neonatal period.[5,90,96] Specimens for viral examination may be submitted as whole fecal specimens or rectal swabs.[101] Culture of enteric viruses is not routine in diagnostic clinical laboratories, and alternative means generally are used for detection.[101] Direct negative-staining electron microscopic examination can detect many viruses with a single assay, but immune electron microscopic analysis can contribute additional specificity and sensitivity for virus detection in stool samples. However, most laboratories use solid-phase immunoassays or latex agglutination assays to detect rotaviruses and enteric adenoviruses (types 40 and 41).[101] These assays offer convenience and rapid performance, but false-positive tests for rotavirus are reported with some commercial immunoassays, especially when stools are submitted from asymptomatic infants.[22,68,94] Thus the clinician should be aware of the type of assay used to detect rotaviruses and consult with laboratory personnel concerning interpretation of the results in neonates. When confirmation of immunoassays is vital (for example, with necrotizing enterocolitis [NEC]), rotavirus immunoassay results can be confirmed by electron microscopic analysis or examination for the typical rotavirus genomic pattern on sodium dodecyl sulfate-polyacrylamide gel electrophoresis.

## Future Trends in Laboratory Diagnosis of Enteric Infection

Tremendous advances were made in the last 20 years in the detection of enteric pathogens in the microbiology laboratory, specifically in the identification and detection of pathogens such as *C. difficile* and rotaviruses. However, improvements are still needed to increase sensitivity of detection and to decrease time required to identify infectious organisms in fecal specimens. For example, the growth of pathogenic bacteria can be severely inhibited by unintended delays in transport of fecal specimens. To identify organisms such as EPEC, reference laboratory examination is usually required, causing delays of days or weeks. Researchers hope to improve the detection of these and other enteric pathogens using direct assays of fecal specimens and obviating the need for time-consuming cultures and biochemical identification. Application of nucleic acid hybridization techniques and the polymerase chain reaction have provided encouraging results for classification of several enteric pathogens.[110] Adaption of these methods to the clinical laboratory might improve the routine diagnosis of enteric pathogens. However, development of strict quality controls for these techniques are needed to ensure specificity and sensitivity.

Research efforts are also aimed at definition of new or previously

unrecognized enteric pathogens. Prospective survey of diarrhea episodes in very young infants indicates that routine screening may not reveal pathogens in most patients.[36,96] Such episodes may be due to noninfectious causes or infectious agents that are not detected by routine assays. Electron microscopic examination of fecal specimens from older infants revealed the presence of "small round viruses" and "mini-rotaviruses" in addition to rotaviruses, adenoviruses, and astroviruses during episodes of gastroenteritis.[75,90] Evaluation for these viruses and other bacterial agents in neonates with diarrhea should be important in future investigations.

## THERAPY FOR DIARRHEAL DISEASE

### General Considerations

The most important aspect of therapy for diarrheal disease in the newborn infant, regardless of gestational age, is maintenance of fluid and electrolyte balance. Often milk feedings are temporarily stopped to allow for "gut rest" while oral rehydration or parenteral solutions with appropriate electrolytes are administered. The infant should be examined and weighed frequently so proper rehydration and prevention of complications are ensured. If associated vomiting occurs, a nasogastric tube may be used to decompress the gut. Any infant with diarrhea should be isolated from other infants in the nursery and strict infection control measures must be instituted.

Selection of appropriate antimicrobial therapy depends on the cause of the diarrhea and the status of the infant. Use of antibiotics is not appropriate for disease caused by rotavirus, adenovirus, or enterovirus but would be appropriate and beneficial for disease caused by some bacterial pathogens. The selection of antibiotics depends on the mechanism of bacterial diarrhea, on the antibiotic susceptibility of the isolated pathogen, and on the safety of a particular drug used in neonates.

Loose watery stools in association with temperature instability, lethargy or irritability, apnea, vomiting, gastric residuals, and abdominal distention in a preterm infant are consistent with NEC.[13] Discontinuation of oral feedings and initiation of parenteral nutrition and antibiotics are the mainstays of medical management. Because of the frequency of associated sepsis, broad-spectrum antibiotics such as ampicillin and gentamicin are started. Vancomycin may be an alternative to ampicillin to treat gram-positive in infants who have been hospitalized for some time, when there may be concern for resistent gram-positive organisms. If perforation is suspected, clindamycin may be added to the antibiotic regimen to treat anaerobic bacteria.[6,7,92] However, the one randomized, controlled trial of ampicillin and gentamicin plus clindamycin compared with ampicillin and gentamicin alone in infants with NEC[31] showed that clindamycin did not reduce the incidence of bowel necrosis and was associated with an increase in late-onset strictures. Finally, if sepsis is documented, that is a positive blood culture is obtained, antibiotics should be changed according to sus-

ceptibility of the organism. Traditionally clinicians administer parenteral antibiotics and withhold enteral feeding for 10 to 14 days. When and how to initiate feeding in the full-term and preterm infant is controversial.[13,45,74] Many low birthweight infants have multiple episodes of "NEC scares," have oral feedings withheld with each one, and are often started on antibiotics and parenteral nutrition. Long-term use of parenteral nutrition has been associated with complications, such as metabolic bone disease, sepsis, and cholestatic jaundice, and does little to support the function of the gastrointestinal tract.[73] In animals and human studies, enteral feedings are necessary to maintain normal gastrointestinal structure, integrity, and hormonal function.[28,45,67,69] Further studies are needed to determine when and how to initiate enteral feedings in these young infants.

## The Role of Immunoglobulin

The role of immunoglobulin therapy for enteric diseases and NEC is unclear. Several studies have addressed the role of intravenous gammaglobulin to prevent nosocomial infection and NEC in low birthweight and full-term infants, with little emphasis on gastrointestinal disease.[2,32,59] The results from these studies are contradictory, and only one of them addressed gastrointestinal illness in full-term and preterm infants.[59] It showed that administration of intravenous immunoglobulin had no substantial effect. In another study, an intramuscular immunoglobulin preparation or placebo given with each feeding during the first week of life to 75 low-birth-weight infants in a nursery with endemic rotavirus was associated with delayed excretion of rotavirus and milder symptoms of infection.[3]

The results of these immunoglobulin clinical trials have been disappointing because the risk of systemic bacterial infection, NEC, and gastroenteritis are important problems for hospitalized, high-risk neonates. Other more specific therapies have been suggested, such as use of an oral immunoglobulin preparation to prevent NEC.[29] Eibl and coworkers[29] performed a randomized clinical trial of use of an oral immunoglobulin preparation (73% IgA and 26% IgG) to prevent NEC in infants who weighed between 800 and 2000 g at birth. No cases of NEC occurred among the 88 infants receiving the oral IgA-IgG compared with six cases of NEC that occurred among 91 control infants.

The most effective way to administer IgA to the newborn is through breast milk, which contains many components that provide specific and nonspecific defenses against infectious agents.[42,43,53,84,109,111] The predominant human breast milk immunoglobulin is secretory IgA.[42,43,53] Secretory IgA, which is synthesized and stored in the breast, reaches levels as high as 5 mg/mL in colostrum and decreases to 1 mg/mL in mature milk.[42] Secretory IgA acts on the intestinal mucosal surface, resisting breakdown by gastrointestinal fluid, and blocks adhesion of potential pathogens. The protective effects of breast milk are most striking in communities with poor sanitation, poverty, and malnutrition, where infant morbidity and mortality rates are high.[15,41,46,71] Breast-feeding decreases gastroenteritis by providing

protective factors and reducing exposure to other foods and water that may contain enteropathogens. It has also been shown to be protective against NEC in premature infants.[70] The importance of breast-feeding to prevent diarrheal disease in preterm and full-term infants has been well established, and promotion of breastfeeding for these infants should be the responsibility of health professionals.[38]

## CONCLUSIONS

Many bacterial and viral pathogens have been associated with enteric disease during the newborn period. These pathogens have widely different mechanisms on the intestinal epithelium and are associated with many clinical findings. Infected infants can be asymptomatic, have gastroenteritis, or have fulminant sepsis. Physicians must recognize the clinical syndrome and interpret the laboratory results properly to determine therapy and institute appropriate infection-control measures. All of these principles can be applied to premature infants in the neonatal intensive care nursery and to full-term infants at home in the community.

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