Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

ELSEVIER
SAUNDERS

VETERINARY
CLINICS
Equine Practice

Vet Clin Equine 21 (2005) 295–312

Neonatal Foal Diarrhea

K. Gary Magdesian, DVM

Department of Medicine and Epidemiology, University of California School of Veterinary Medicine, 1 Garrod Drive, Davis, CA 95616, USA

Diarrhea is a significant cause of morbidity and mortality in the neonatal foal [1]. Altered fecal consistency in the foal may be a manifestation of simple diarrhea or enteritis, in which the latter is associated with a systemic inflammatory response syndrome. Foals with enteritis or enterocolitis develop varying degrees of endotoxemia and suffer a number of metabolic complications, including acidosis, hypovolemic shock, hypotension, and bacteremia. Numerous noninfectious and infectious agents are responsible for enterocolitis and enteritis in the newborn foal. This article provides an overview of the differential diagnoses for neonatal diarrhea and general and specific guidelines for therapy.

Noninfectious diarrhea

Foal heat diarrhea

Mild diarrhea is common in foals aged 5 to 15 days and is termed "foal heat" diarrhea. This form of diarrhea occurs without signs of systemic disease or inflammation and is usually not severe. Foals remain bright and alert, maintain normal hematology and laboratory results, and continue to nurse. The term foal heat is a misnomer. Because of a temporal association, this early onset diarrhea was initially believed to be caused by alterations in the composition of milk during the mare's first estrous period after parturition, hence the term foal heat. However, orphan foals raised on milk replacement formulas also develop diarrhea during this period. An analysis of mares' milk composition during the postpartum period and first estrous cycle has demonstrated that milk is not a factor in foal heat diarrhea [2]. Results of one study [3] have suggested that the developmental or maturational changes of the gastrointestinal (GI) tract that are associated with the initiation of feed ingestion and inoculation of microflora are responsible for the changes in fecal composition during this period. Fecal

E-mail address: kgmagdesian@ucdavis.edu

doi:10.1016/j.cveq.2005.04.009 *vetequine.theclinics.com*

composition during foal heat diarrhea is suggestive of a secretory-type diarrhea, with higher electrolyte concentrations than is normal [3]. In addition, the fecal pH level was found to be alkaline, and fecal osmolality and volatile fatty acid concentrations decreased with the onset of diarrhea. The authors concluded that their data suggests a hypersecretion in the small intestinal mucosa, which was not compensated for by the immature colon [3]. These findings, along with a temporal association with coprophagy, suggest that the diarrhea occurs in response to the establishment of normal GI flora. Such foals do not require therapy, although they should be monitored closely because early forms of enteritis can mimic foal heat diarrhea. Any signs of systemic disease, including depression or reduced appetite should warrant close investigation of such a neonate.

Asphyxia-associated gastroenteropathies

One of the most common causes of diarrhea is asphyxial gut injury secondary to hypoxic or ischemic insult that is believed to occur as part of a peripartum asphyxia syndrome, also referred to as hypoxic-ischemic encephalopathy. At-risk foals include those born as a result of dystocia or cesarean section, those with umbilical cord problems during delivery, and those with abnormal oxygenation in the immediate postpartum period. Gastroenteropathies may result from hypoperfusion, hypoxic-ischemic and reperfusion injury, and inflammatory mediators. The resulting clinical effects of ischemic enterocolitis include gastroduodenal reflux, ileus, intolerance to enteral feeding, colic, abdominal distention, and diarrhea. Because the organ injury is not limited to the gut, these foals require intensive care. Concurrent organ dysfunction includes neurologic dysfunction, nephropathies, and cardiac or endocrine disorders. As far as the gastrointestinal tract is concerned, foals with asphyxia-associated diarrhea should be checked for nasogastric reflux, may require prokinetic drugs, and should be fed very conservatively through the enteral route. Severely affected foals benefit from parenteral nutrition, with only small volumes of enteral milk to provide local nutrients to enterocytes. Because affected foals are at high risk of developing sepsis, they should be treated with broad-spectrum systemic antimicrobials. Ultrasonography is a useful means of monitoring the progress of GI dysfunction in these foals.

Necrotizing enterocolitis

Necrotizing enterocolitis (NEC) is the most serious gastrointestinal emergency of human infants under intensive care [4]. NEC consists of necrotic injury to the mucosal and submucosal layers of the GI tract. Although the entire GI tract, from the stomach to the rectum, is susceptible, the distal small intestine and proximal colon are most frequently involved. Symptoms of NEC in human neonates include abdominal distention, ileus,

hematochezia, and emesis, along with signs of sepsis. Suspected cases often present with nonspecific signs, including food intolerance, gastric residuals, GI bleeding, and sepsis. Foals may develop a similar syndrome. Despite decades of research and clinical investigation, a complete understanding of the pathogenesis of NEC remains unclear. The syndrome involves a complex interaction of immaturity, previous gastrointestinal mucosal injury, enteral milk feeding, and bacterial invasion [4]. The majority (70%–90%) of infants with NEC are born preterm, highlighting the importance of GI maturation to the syndrome [4]. The incidence of NEC varies inversely with gestational age and birth weight. Premature infants may experience vasoconstriction, hypotension, and thrombosis leading to decreased GI perfusion [4]. Additional contributors to reduced mucosal perfusion in preterm infants include umbilical artery catheters and patent ductus arteriosus, with the use of indomethacin possibly contributing to NEC risk [4]. There are some notable differences in NEC that affect preterm and term neonates. NEC in very low-birth weight infants occurs later than in older and larger infants. The onset of NEC is often insidious in preterm infants, with sudden signs occurring more often in older neonates. Risk factors differ as well; those for full-term infants include congenital heart disease, polycythemia, coexisting conditions such as hypothyroidism, Down syndrome or gastroschisis, aggressive enteral feedings, and conditions compromising GI oxygenation such as supraventricular tachycardia.

Mucosal injury is the second factor in the development of NEC. Mucosal compromise is associated with impaired circulation dynamics, for example, hypoxic-ischemic insults. Other forms of injury are inflammatory, with release of interleukins (IL) such as IL-6. Histologic findings include ulceration, edema, hemorrhage, congestion, and in severe cases, transmural coagulation necrosis with perforation. The initial mucosal injury produced by ischemia in an immature infant was believed to predispose the infant to bacterial invasion. Milk was thought to serve as a substrate for bacterial proliferation and subsequent infection, the final factors known to contribute to development of NEC. Abnormal intestinal gas produced by the bacteria then appears as pneumatosis intestinalis or portal venous gas on abdominal radiography or ultrasonography. These risk factors have been questioned recently because of cases of NEC in full term infants and those that were never fed enterally. However, prematurity remains the primary risk factor, because most cases are seen among immature infants.

Necrotizing enterocolitis has been reported in equine neonates [5]. This report describes two foals with a gastrointestinal syndrome characterized by ileus, gastric reflux, intolerance to enteral feeding, and pneumatosis intestinalis on radiography. Both foals developed perforations of the ventral colon. One of the foals was preterm, and the other was full term but had experienced a prolonged delivery and suspected hypoxia. Foals with suspected NEC should be withheld from enteral feeding and instead be placed on parenteral nutritional support. Antimicrobials that target

anaerobic overgrowth are likely indicated, as are broad-spectrum antimicrobials to guard against sepsis.

Prevention in at-risk foals should include monitoring for gastric residuals. A nasogastric (NG) tube placed too high (in the esophagus or upper stomach segments) may fail to accurately measure residuals. Both the syringe diameter and the size of the NG tube may affect the volume of aspirate. Residuals should be measured before each feeding, and the meal should be withheld if significant amounts of milk or fluid are aspirated. The ideal feeding volume and maximal allowable residuals have not been calculated in foals. Certainly, a gradual or slow advancement of feedings and small frequent meals or continuous feeding should be applied to premature foals or those with suspected mucosal injury [6]. Foals with ileus, as reflected by hypomotility on ultrasonographic examination, persistent reflux or residuals, abdominal distention, gaseous distention of the GI tract on abdominal radiography, and the absence of stool passage should not be fed enterally. In addition to the amount of feed, the type of enteral nutrition also is important in the prevention of NEC. In humans, a number of studies [4] have demonstrated that breast milk is more protective than formula. Extrapolating this to foals, mare's milk should be used whenever possible, particularly for preterm foals and those with GI injury. The dams of compromised neonates can be milked by hand or with syringes every 1 to 2 hours to provide enteral nutrition for their foals.

Gastroduodenal ulceration and diarrhea

Common signs of gastric ulcers include bruxism, ptyalism, dorsal recumbency, colic, poor thrift, and lethargy. One of the less consistent clinical signs of gastric ulcer syndrome includes diarrhea. In addition, foals with enteritis are at an increased risk for developing ulcers, particularly in the glandular region of the stomach. This occurs secondary to physiologic stress, including hemodynamic derangements, anorexia, inflammatory mediators, and endocrine perturbations [7]. Severe diarrhea therefore warrants consideration of the prophylactic use of antiulcer medications.

Mechanical enterocolitis

Pica, an inappropriate appetite, can result in diarrhea. The ingestion of abnormal material can result in the accumulation of these foreign substances within the GI tract. Most commonly, sand and dirt are implicated in causing diarrhea, because they can result in mechanical irritation to the GI tract and subsequent diarrhea [8]. Diagnosis is easily made with gentle manual (digital) palpation of the rectum, with an evaluation of the feces. Abdominal radiography is definitive for radio-dense material such as sand [8]. Recently, serial monitoring of the evacuation of sand through ultrasonography has been described [9]. Bedding and other

materials, such as rice or almond hulls, also can cause diarrhea and enteritis when inappropriately ingested. Colic and abdominal distention are commonly present with these forms of diarrhea.

The treatment of foals with sand accumulation includes good supportive care consisting of intravenous fluid therapy and enteral laxatives, including mineral oil. Although controversy exists regarding the efficacy of psyllium hydrophilic mucilloid in eliminating sand impactions, the present author does recommend its use. It was temporally effective in alleviating sand accumulation as the primary therapy in one filly with sand-induced diarrhea [9]. Caution should be used in the amount of psyllium administered. Occasionally, foals with pica and sand impactions require surgical evacuation. The response to analgesics, medical therapy, and degrees of abdominal distention and pain are important considerations when contemplating surgery.

Nutritional or dietary causes of diarrhea

Dietary intolerances can cause diarrhea in orphan or hospitalized foals receiving enteral nutrition other than mare's milk. Foals fed with milk replacers develop loose feces more often than those on mare's or goat's milk do, particularly if the replacer is prepared using a solution that is too concentrated or too diluted [10]. The energy content of milk replacers should be evaluated in comparison with mare's milk because some may be more energy dense, which necessitates lower volumes of feeding. Bovine milk also may result in diarrhea, most likely from the higher fat content compared with mare's milk.

Diarrhea caused by infectious agents may be compounded by secondary lactase deficiency [11]. Any condition leading to the loss of the small intestinal mucosal brush border may cause lactose intolerance, but rotavirus and *Clostridium difficile* are particularly noted to cause lactase deficiency in foals [10,11]. Supplementation with a lactase enzyme (6000 Food Chemical Codex units/50-kg foal, orally [PO], every 3–8 h) is indicated in foals with suspected lactase deficiency. Lactose intolerance can be confirmed with a lactose tolerance test, but this is usually not necessary because supplementation is very inexpensive and practical [10,11].

Infectious diarrhea

Clostridial enteritis caused by Clostridium difficile *and* Clostridium perfringens

Clostridial organisms are common causes of enterocolitis in the neonate, and *Clostridium perfringens* and *C difficile* are the most common clostridial agents involved. Although both species cause diarrhea in the adult horse secondary to antimicrobial or other stressor-induced colonic flora

disruption and colitis, they can act as primary pathogens in foals without any preceding risk factors. Host, agent, and environmental factors play a role in determining whether these two agents cause diarrhea because both can be found in clinically healthy foals [12].

C perfringens causes diarrhea both sporadically and in outbreak situations. Some strains of the microorganism, particularly type A isolates, are part of the normal gastrointestinal microflora of horses and foals and can be cultured readily from feces. However, other strains are pathogenic; the number of colony-forming units (CFU) per gram of feces is another determinant of whether colonization is associated with clinical disease. Concentrations less than 10^2 CFU/mL are consistent with benign colonization, whereas most foals with clinical disease show concentrations greater than 10^3 CFU/mL [13]. *C perfringens* isolates are typed as A, B, C, D, and E, based on the production of one or more large protein exotoxins (α, β, β-2, ε, and enterotoxin). Types A and C are most commonly associated with diarrhea in foals less than 10 days of age. Type A produces α toxin, whereas type C produces both α and β toxins. Enterotoxin is variably produced by all types of *C perfringens* but most commonly by type A isolates. Typing of isolates is performed using polymerase chain reaction analysis for toxin gene sequences after isolates are cultured [13]. Commercial immunoassays for toxin detection in feces are available only for enterotoxin, which is present only in a minority of cases. Type C causes hemorrhagic and often severe diarrhea, with a higher mortality than type A [13]. Other clinical signs associated with *C perfringens* infection include colic, dehydration, tachypnea, and obtunded mentation. In the study by East and colleagues [14], foals born on dirt, sand, or gravel and those kept stalled or in dry-lot conditions during the first 3 days of life were found more likely to develop *C perfringens*-associated disease. Most foals in one study were less than 6 days of age on presentation, and 88% manifested acute onset disease ($\leq$24 h) [13]. Common hematologic findings include an increased number of band neutrophils, leukopenia with neutropenia, toxic cytologic changes, and hyperfibrinogenemia [13]. Hypoproteinemia also is common, although this can be masked on presentation caused by hemoconcentration. Interestingly, most foals (96% in one study [13]) demonstrate adequate passive transfer of colostral antibodies [13]. This has led some authors to speculate that trypsin inhibitors in colostrum may protect against gastric degradation of toxins, thereby potentiating toxigenicity [13]. The serum biochemistry profile of affected foals is variable, but severely affected foals may have hyperbilirubinemia, azotemia, and increased hepatic enzymes if they exhibit severe sepsis or systemic inflammatory response syndrome (SIRS) [13]. Abdominocentesis can reflect an exudate in foals with severe enteritis. Abdominal ultrasonography and radiography may show gas- and fluid-distended small and large intestines. In the study by East and colleagues [13], the overall mortality rate of foals with *C perfringens* infections was 54%; those with type A had a 28% mortality (including both death and

euthanasia), whereas those with type C had a mortality rate of 83%. In that study, treatment did not appear to alter the mortality rate for most foals that had a positive culture for type C [13], highlighting the importance of early and aggressive intervention. A predominance of large, gram-positive rods or spores found on a fecal smear or Gram stain may suggest the presence of clostridial overgrowth and allows for an early clinical suspicion of infection [13].

C difficile also can produce enteritis, with severe, watery to hemorrhagic diarrhea. Like *C perfringens,* it also can affect foals sporadically or in outbreak situations. Toxins A (enterotoxin) and B (cytotoxin) and binary (ADP ribosyltransferase) toxins play an important role in the pathogenesis of enterocolitis caused by *C difficile*. They alter epithelial cytoskeletal integrity, increase mucosal permeability, and incite inflammation. Interestingly, foals may be asymptomatic carriers of *C difficile* as well, and it has been hypothesized that they may serve as potential reservoirs of infection for their dams [12,15]. Up to 29% of healthy foals less than 14 days of age, in one study, were found to be culture-positive for *C difficile* [12]. This same phenomenon occurs in group-housed human infants. It is unknown why human infants and some foals can become asymptomatically colonized with toxigenic *C difficile,* whereas others develop severe disease. Diarrheal disease also can be experimentally reproduced in foals [16]. *C difficile* can act as a primary pathogen in neonates, without requiring antimicrobial administration as a risk factor, as in most adult horses [16–18]. Specific tests include fecal culture and toxin assays. These tests should be coupled because nontoxigenic isolates cannot be differentiated from toxigenic isolates based on culture alone. Commercial immunoassays for toxins A or B and fecal cell culture cytotoxin assays (for toxin B) allow for the differentiation between toxigenic and nontoxigenic infections. Either toxin A or B alone can provide enough virulence to cause disease, and both are not required as believed previously. As for *C perfringens,* a fecal smear showing large numbers of gram-positive rods or spores suggests clostridial overgrowth, although this is not specific for either organism.

The therapy of foals with clostridial enterocolitis includes intensive and supportive care in addition to specific therapies. Supportive measures include correction of fluid, acid–base, and electrolyte derangements. Hemodynamic support in the form of inotrope and vasopressor therapy may be needed if the volume replacement is not enough to normalize blood pressure. The correction of low oncotic pressure from hypoproteinemia or hypoalbuminemia is performed by administering plasma or synthetic colloids. Affected foals should be monitored for the development of coagulopathy, for which plasma or low-molecular weight heparin may be necessary. Specific therapy includes the early use of metronidazole (10–15 mg/kg intravenous [IV] or PO, every 8–12 h). Bacitracin is not recommended in horses (unlike human patients with *C difficile* infections) because of a high prevalence of resistance among equine *C difficile* isolates

[12,19]. Some *C difficile* isolates from foals have been reported to be resistant to metronidazole, and vancomycin has been used in those circumstances [19,20]. This finding is of concern and is somewhat unusual relative to human isolates. Fortunately, resistance appears to be geographic, because other authors have not found equine isolates in their hospitals to be metronidazole-resistant [12]. Nasogastric administration of di-tri-octahedral smectite (Biosponge, Platinum Performance, Buellton, CA) may be indicated as evidenced by the in vitro neutralization of *C difficile* toxins A and B and *C perfringens* enterotoxins [21]. Plasma products are controversial, but anecdotal or empirical use of *C perfringens* type C and D antitoxin has been reported in foals [13]. Slow administration and pretreatment with diphenydramine are warranted. Foals with *C difficile* enteritis can develop lactase deficiency secondary to the loss of small intestinal mucosal brush border. The supplementation of foals with lactase enzyme (Lactaid tablets, 6000 U/50-kg foal PO, every 3–8 h) may be helpful.

Preventing clostridial enteritis depends on good hygiene, particularly in the foaling area. Strict isolation protocols should be maintained. Vaccination of mares with *C perfringens* type C and D toxoid has been tried on farms with a history of affected foals, but the documentation of the safety and efficacy of such measures are not available. Spores are virtually impossible to eliminate totally, but their numbers can be reduced with good manure control and the use of scrubbing with subsequent disinfection with bleach.

Other bacterial causes

Salmonellosis can cause enterocolitis in horses of any age [22]. Affected foals usually demonstrate signs ranging from sepsis to sepsis syndrome, including fever, diarrhea, depression, and hypotensive shock. Colic and hemorrhagic diarrhea are variable findings. Foals with salmonellosis should be monitored closely for signs of localized infection, including uveitis, synovitis, osteomyelitis, and physitis. The greatest risk for bacteremia and sepsis are posed by enteroinvasive serotypes of salmonellae, including those belonging to group B, such as *Salmonella typhimurium*. All neonatal foals with enteric salmonellosis should therefore be treated with systemic antimicrobials that are effective against salmonellae, including aminoglycosides or third-generation cephalosporins.

Even though *Escherichia coli* is one of the most common causes of sepsis in foals, it has only rarely been associated with diarrhea. *E coli* isolates, particularly enterotoxigenic strains with attaching, effacing, and Shiga-like toxin genes, have been suspected to be associated with sporadic cases of diarrhea in foals [23]. *E coli* is commonly cultured from the feces of horses and foal; therefore, if *E coli* is suspected as a cause of diarrhea, the culture isolate should be further investigated using polymerase chain reaction analysis for toxin genes. The exact role of *E coli* in neonatal diarrhea thus remains to be elucidated.

Other bacteria have been suspected to be associated with diarrhea in foals, but their roles remain undefined. Browning and colleagues [24] found a prevalence of 9% of *Aeromonas hydrophila* among diarrheic foals, but its exact role in diarrhea is currently unknown [24]. *Streptococcus durans* has been isolated from one foal with profuse, watery diarrhea [25] and was subsequently associated with severe diarrhea when inoculated into seven healthy experimental foals.

Anaerobes other than *C difficile* and *C perfringens* have been speculated to play a role in neonatal foal diarrhea. Both *C sordelli* and *Bacteroides fragilis* have been reported as rare or sporadic potential pathogens [26,27]. The diagnosis of diarrhea caused by *Bacteroides* spp is difficult because the microorganism can be isolated from normal, healthy foals, and not all isolates are enterotoxigenic. Enterotoxigenic *B fragilis* often is present with other potential pathogens, including salmonellae and rotavirus [26]. Treatment should include administration of metronidazole, as for clostridiosis.

Septic foals may develop diarrhea from hemodynamic perturbations leading to GI mucosal hypoperfusion, inflammatory mediators associated with SIRS, and dysmotility. Foals with bacteremia caused by *Actinobacillus* sp were found to be six times more likely to have diarrhea compared with foals with bacteremia caused by other bacterial agents, in one study [28].

Viral enteritis

Rotavirus is the most common viral cause of neonatal diarrhea. Equine rotaviruses belong to group A rotaviruses, with a number of different serotypes identified, including G3, G5, G10, G13, G14, P7, P12, and P18 [29,30]. Rotavirus infections often occur as outbreaks on farms. Experimentally, the incubation period appears to be as short as 2 days [31]. Most affected foals are between 5 and 35 days old but the majority are at the younger end of this range [31]. It appears that older foals (up to 60 days old) can be infected, although diarrhea tends to be milder in this age group, but they can serve as reservoirs for neonates and should be isolated when identified. Transmission occurs directly by animal-to-animal and indirectly through personnel or fomites. Clinical signs of rotaviral diarrhea are similar to those of other infectious diarrheas, with a wide range from mild diarrhea to severe, watery diarrhea with dehydration. Some clinicians have suggested an association between gastroduodenal ulcer syndrome and rotaviral infections, although this requires study [10]. The virus affects the small intestine, causing blunting of the microvillus. Maldigestion and malabsorption result. With villous atrophy and compensatory crypt cell proliferation, a net decrease in fluid absorption and an increase in secretion occur. With maldigestion, lactose may enter the colon, with subsequent fermentation and osmotic contribution to diarrhea.

Rotaviral infections are diagnosed through the demonstration of virus particles in feces using commercial immunoassays or electron microscopy.

The virus is highly contagious and warrants strict isolation protocols of affected foals. Morbidity can approach 100% of neonates in outbreak situations. Disinfection should include the use of substituted phenolic compounds or quaternary ammonium disinfectants. The virus can persist for several months in the environment. The mortality rate of rotavirus is lower than with clostridiosis and, in general, is considered low, particularly with good supportive care. The treatment of rotaviral diarrhea is largely supportive.

Prevention of rotavirus outbreaks includes the use of rotavirus vaccines in mares during gestation. Studies [29,30] have demonstrated a variable reduction in morbidity, length of diarrhea, and degree of shedding of viral particles in foals resulting from vaccinated dams. One study [30] has revealed no apparent adverse reactions with the vaccine. Antibody titers were significantly increased at the time of foaling in vaccinated mares and for 90 days after birth in their foals compared with the nonvaccinated group. The incidence of rotaviral diarrhea was lower in foals born to vaccinated mares compared with foals born to controls; however, the difference was not statistically significant [30]. The administration of bovine colostral immunoglobulins has been used in an effort to reduce the prevalence of diarrhea on endemic farms. In one study [32], the morbidity of diarrhea was lower during the year after initiating a protocol of administering bovine colostral immunoglobulin powder orally to all foals compared with a preceding year when it was not administered. However, this was not a randomized or controlled study, and therefore, conclusions are difficult to make. Further study is required.

Coronavirus is another cause of viral enteritis in foals, but it has been reported in only a few studies [33,34]. Foals appear to be most susceptible to coronavirus during the neonatal period. Equine coronavirus is molecularly similar to bovine and human coronaviruses and is a member of mammalian group 2 coronaviruses. One case report [33] describes a 5-day-old foal with severe diarrhea, dehydration, hypoalbuminemia, anemia, and thrombocytopenia. The foal was euthanized when the hoof wall detached from the sensitive laminar structures. Ischemic necrosis of the distal extremities, with reddening of the coronary band and loss of hoof integrity, was found [33]. An antemortem diagnosis of coronaviral enteritis can be made using fecal-capture ELISA, electron microscopy, and serology using bovine assays [33,34]. Immunohistochemistry can be used at postmortem examination. The highest viral load appears to be shed in the feces during the acute stages, highlighting the importance of an early diagnosis and isolation.

The exact role of adenovirus in neonatal equine diarrhea is unknown. It has been identified in the intestinal epithelium of a 9-month-old foal with chronic diarrhea [35]. In addition to that report, intestinal lesions in Arabian foals with severe, combined immunodeficiency syndrome (SCID) with diarrhea have been reported as exfoliated duodenal epithelial cells containing inclusion bodies consistent with adenovirus [36].

Parasitic and protozoal agents of diarrhea

The role of *Strongyloides westeri* in diarrhea of the neonatal foal is unclear. It is unlikely to cause diarrhea except when present in very large numbers because even foals passing high egg counts can be asymptomatic. In one study [37], *Str westeri* was associated with diarrhea only when more than 2000 eggs/g of feces were detected. Although patent infestations are rare in horses older than 6 months of age, foals can establish patent infestations, with embryonated eggs passed in the feces at approximately 10 to 14 days postpartum. The major source of infection to the foal is the mare's milk, caused by arrested larvae in the mammary tissues that become activated during lactation [38]. Ivermectin, administered to the mare shortly after delivery, is effective as a dewormer to reduce the passage of larvae through the milk.

Cryptosporidium parvum was initially regarded as a pathogen of immunocompromised foals, such as those with SCID. However, more recently it has been associated with both sporadic and outbreak cases of diarrhea in even immunocompetent foals [39,40]. Most foals are 4 to 21 days of age when they show clinical signs. Supportive care and the use of bovine colostrum have been the primary focus of therapy in foals. The diagnosis is made by fecal sample evaluation for oocysts by means of acid-fast staining, immunofluorescence assay, electron microscopy, or flow cytometry [39]. Exposure to cattle is a controversial risk factor [40]. Treatment is largely supportive, but specific drug therapy with the aminoglycoside paromomycin could be attempted, although data in foals are lacking [10]. Because *Cryptosporidium parvum* is both contagious and zoonotic, affected foals should be isolated and handled with caution. Other protozoa, including *Giardia* sp and *Eimeria leukarti* oocysts can be found in both healthy and diarrheic foals, but their causal role in diarrhea has not been established.

Principles of management of the foal with diarrhea

Specific therapy

Specific therapies are available for some of the causes of diarrhea, as discussed above. For example, metronidazole is indicated in treating clostridiosis.

Fluid balance

The neonate with enteritis can have significant fluid derangements. Severe sepsis, septic shock, and hypovolemic shock are often present. A combination of crystalloids and colloids are preferred by the present author for volume resuscitation of such foals. The use of crystalloids alone may compound hypoproteinemia and hypo-oncotic states because most foals with enteritis have at least some degree of protein-losing enteropathy. The

types, volumes, and rates of fluid administration are highly variable, and the ideal selections are best tailored to the individual foal. However, as general guidelines, good replacement crystalloid choices for the foal with enteritis include lactate Ringer's solution, Normosol R, and Plasma-Lyte 148. Physiologic saline (0.9%) is another choice but is considered less ideal by this author because of its high chloride (154 mEq/L) relative to normal foal plasma. This makes saline mildly acidifying by decreasing the strong ion difference. Saline may be indicated, however, in the hyperkalemic foal because the other commercial replacement fluids contain potassium. Hyperkalemia may be present in the foal with concurrent acute renal disease or hyperkalemic periodic paralysis. Saline also is indicated in the concurrently hyponatremic and hypochloremic foal, in which both are decreased to the same relative extent. Isotonic bicarbonate is another replacement fluid that can be used in the foal with severe metabolic acidemia that is inorganic in origin. Hypertonic saline (7%) also is available as a rapid and temporary expander of intravascular volume. However, serum sodium concentrations should be monitored closely to avoid marked swings. Doses for hypertonic saline include 2 to 4 mL/kg.

Recommendations for volume are based on estimates of hypovolemia and dehydration. As general guidelines, rates of 10 to 20 mL/kg given as slow boluses (over 20–30 min) can be used until signs of hypovolemia improve or plateau, urine is produced, and central venous pressures (CVP) approach maximum (10 cm H_2O). Central venous pressures are measured easily in the neonatal foal through the use of 20-cm jugular catheters.

Colloid options include plasma and synthetic colloids, particularly hetastarch. If these fluids are used then volumes should be used that are lower than those for crystalloids are. In contrast to replacement crystalloids, which distribute to the entire extracellular fluid space (ECF), colloids are largely limited to the intravascular space, assuming relatively normal capillary integrity. Therefore, boluses of 3 to 5 mL/kg colloids should be used. Plasma should be administered slowly to avoid or minimize the risks for anaphylactoid reactions. It can be administered at a rate of 10 mL/kg/h for a total volume of 1 to 2 L, or alternatively it can be used as a constant rate infusion (CRI) of 1 to 2 mL/kg/h as needed for colloid and albumin replacement. Plasma is a cost-effective colloid in foals and has the additional benefit of providing antibodies, clotting factors, antithrombin, and other proteins. Hetastarch can be used in small boluses; however, a total volume of 10 mL/kg/day should not be exceeded, to avoid coagulopathy. Hetastarch causes a decrease in von Willebrand's factor and clotting factor VIII concentrations when administered at volumes at or above 15 mL/kg. Hetastarch should not be used in the hypocoagulable or thrombocytopenic foal.

Once hypovolemia has been corrected, fluid therapy should consist of a maintenance rate combined with estimates of ongoing losses. Relatively hypotonic maintenance fluids should be used for the maintenance portion of

fluid therapy if the foal is fed by routes other than orally. These include Plasma-Lyte 56, Normosol M, or 0.45% saline/2.5% dextrose. The ongoing GI losses, however, should be replaced with a replacement fluid because they represent losses from the ECF.

Acid–base balance

The foal with severe diarrhea often has metabolic acidemia. If the acidosis is caused by hypoperfusion (hyperlactatemia), the primary treatment consists of reversing the circulatory perturbations. Treatment consists of volume replacement until no further correction in blood pressure occurs, blood lactate concentrations improve ($\leq$2 mmol/L), or alternatively, until CVP approaches 10 cm H_2O. Once these occur, inotropes and vasopressors should be used if perfusion is still inadequate. Dobutamine (2–10 μg/kg/min, CRI) is an excellent inotrope. If pressures and perfusion are still inadequate, vasopressors such as norepinephrine or vasopressin can be tried. Norepinephrine should be diluted in 5% dextrose and is administered at a rate of 0.01 to 0.1 μk/kg/min. Vasopressin has been used more recently in foals, and a suggested dose range is 0.25 to 0.5 mU/kg/min. During vasopressor therapy, the foal should be monitored for excessive vasoconstriction and worsening of hypoperfusion, despite showing increases in blood pressure by monitoring serial blood lactate concentrations, urine output, and clinical parameters of perfusion. A word of caution should be added about lactate: Many foals with SIRS or sepsis remain hyperlactatemic despite volume replacement because of inflammatory mediator-induced decreases in pyruvate dehydrogenase (through activation of pyruvate dehydrogenase kinase) or increases in the production of lactate caused by catecholamine stimulation of the sodium–potassium ATP pump activity. Therefore, urine production and clinical signs of perfusion parameters are very important monitoring tools in addition to blood pressure.

If the acidemia is a result of hyponatremia or relative hyperchloremia, the treatment consists of sodium bicarbonate. The amount of bicarbonate needed is calculated as 0.3 $\times$ body weight (kg) $\times$ base deficit. Sodium bicarbonate should be administered slowly and carefully because of the potential drawbacks to rapid administration, including hypernatremia, hyperosmolarity, hypokalemia, ionized hypocalcemia, a left shift in the oxygen dissociation curve, and paradoxical intracellular acidosis.

Electrolytes

Foals with enteritis develop a number of electrolyte derangements. Sodium derangements are common, particularly hyponatremia. Neurologic signs may be present in foals with diarrhea and sodium concentrations below a range of 110 to 115 mEq/L [41]. Sodium concentrations can be corrected fairly rapidly up to 115 to 120 mEq/L in order to correct neurologic deficits, but beyond this amount, concentrations should be

corrected slowly, at approximately 0.5 mEq/h to avoid central pontine myelinolysis. Serum sodium concentrations should be monitored frequently to avoid overcorrection. Occasionally, hypernatremia may be encountered, particularly if foals have been oversupplemented with oral sodium-containing fluids before presentation. Hypernatremia should also be corrected slowly to avoid increases in intracranial pressure (0.5 mEq/h).

Potassium disorders also may be present in foals with diarrhea. Hyperkalemia is common with concurrent renal disease or with significant inorganic acidemia. Hypokalemia may be present if the foal has been anorexic for prolonged periods, with potassium loss in the diarrheic fluids.

Gastrointestinal protectants

Enteral protective modalities include kaolin/pectin compounds and bismuth subsalicylate. Bismuth is believed to coat the mucosa, whereas the salicylate portion has antiprostaglandin activity. Kaolin/pectin combinations act primarily as mucosal coating agents. Care should be taken to stagger these medications with other oral drugs to avoid nonspecific binding and a reduction in bioavailability of the concurrently administered drugs. These agents are administered at 0.5 to 4 mL/kg, once to four times daily [42].

Activated charcoal and di-tri-octahedral smectite are adsorbents that can bind endotoxin and reduce its absorption. Smectite also has been shown to neutralize toxins of *C difficile* and *C perfringens* in vitro [21].

The modulation of enteric flora with the use of probiotics is a controversial area in equine medicine. Documentation of efficacy is lacking. There is currently on going investigation in this area, including the use of the yeast *Saccharomyces boulardii* for use in enteric clostridiosis. Probiotics must be used with caution in the neonatal foal, particularly the foal less than 24 h of age, because of a potential for bacterial or fungal translocation. Information on gastrointestinal protectants and probiotics is described elsewhere [42].

Gastric ulcer medications

The prophylactic use of antiulcer medications is controversial. However, because foals with enteritis are at risk for developing ulcers, particularly glandular ulcers, this author currently recommends the use of ulcer medications in these foals [7]. Medications may consist of histamine type-2 receptor antagonists, sucralfate, or proton pump inhibitors. Histamine type-2 antagonists include ranitidine (1.5 mg IV, every 8–12 h or 6.6 mg/kg PO, every 8 h) and famotidine (2.8 mg/kg PO, every 12 h or 0.3 mg/kg IV, every 12h). Omeprazole, the most commonly used proton pump inhibitor, has been studied recently in the healthy neonatal foal. A dose of 4 mg/kg PO, every 24 h, increases the gastric pH level within 2 h of administration and for 22 hours [43]. Sucralfate has a number of advantages, including

binding glandular ulcers and increasing local prostaglandin E production, thereby increasing mucosal blood flow and mucus and bicarbonate secretion. The recommended dosage of sucralfate is 10 to 20 mg/kg PO, every 6 to 8 h.

Antiendotoxin measures

Most of the antiendotoxin modalities used in adult horses have not been studied in foals. The present author prefers not to use flunixin meglumine in the neonatal foal because of the potential for reducing gastrointestinal perfusion. Polymyxin B has been studied experimentally in older foals [44].

Nutrition

Nutritional support is a very important aspect of managing the neonatal foal with diarrhea. Foals with abdominal distention, gastric residuals, ileus, or colic should be withheld from milk temporarily. Foals with profuse diarrhea, particularly those types of diarrhea suspected to be associated with lactose intolerance or an osmotic diarrhea, should be restricted at least partially in terms of milk intake. In these cases, parenteral nutrition should be provided. Dextrose supplementation (4–8 mg/kg/min with frequent monitoring of blood glucose concentrations) of crystalloids can be used in the short term (first 12–24 h). If enteral nutrition is not tolerated by this time, parenteral nutrition should be instituted. This author uses the following formula as a starting point for making a total parenteral nutrition solution: 1000 mL 50% dextrose + 1500 mL 8.5% amino acid solution + 500 mL 20% intralipid to make a total volume of 3000 mL.

This solution has a caloric content of 1.07 kcal/mL digestible energy, 0.0425 g/mL amino acids, and 0.033 g/mL lipid. The energy requirements of the neonatal foal with diarrhea are unknown. General guidelines for the energy requirements of the neonatal foal include a range of 45 to 50 kcal/kg/day for basal energy requirement and 100 to 170 kcal/kg/day for normal, healthy foals. This author usually targets a value between these amounts, approximately 70 to 75 kcal/kg/day, with gradual advancement as parenteral nutrition is tolerated. Vitamins and minerals must be added to this solution or alternatively to the crystalloids being administered. Serum glucose, serum triglycerides, electrolytes, and acid–base status should be monitored closely in foals receiving parenteral nutrition. Foals intolerant of glucose may benefit from insulin (regular insulin, 0.005–0.01 IU/kg/h, titrated to glucose concentrations). The lipid fraction is decreased if triglyceride concentrations exceed 200 mg/dL. Information on foal nutrition and parenteral nutrition has been described elsewhere [45,46].

Parenteral nutrition should only be viewed as a bridge to enteral nutrition. For foals tolerant of minimal enteral nutrition, even small volumes frequently are beneficial for providing local nutrition to enterocytes.

The neonate should be fed conservatively at first, and volumes should be advanced gradually as enteral feedings are tolerated. A reasonable starting point is 10% of body weight per day divided into hourly or 2-hour feeding intervals through a nasogastric tube. Foals that are bright and strong enough to nurse should be allowed to do so.

Systemic antimicrobials

Broad-spectrum antimicrobials should be administered to the neonatal foal with enteritis because of the risks of bacterial translocation across the compromised GI barrier. Choices include a combination of aminoglycoside (such as amikacin or gentamicin) and β-lactam, or alternatively a third-generation cephalosporin. Foals receiving aminoglycoside therapy should undergo therapeutic drug monitoring to ensure adequate peak and trough plasma concentrations of drug, as well as monitoring of renal function.

References

[1] Cohen ND. Causes of and farm management factors associated with disease and death in foals. J Am Vet Med Assoc 1994;204:1644–51.
[2] Johnston RH, Kamstra LD, Kohler PH. Mares' milk composition as related to "foal heat" scours. J Anim Sci 1970;31:549–53.
[3] Masri MD, Merritt AM, Gronwall R, et al. Faecal composition in foal heat diarrhea. Equine Vet J 1986;18:301–6.
[4] Noerr B. Part 1. current controversies in the understanding of necrotizing enterocolitis. Adv Neonatal Care 2003;3:107–20.
[5] Cudd T, Pauly TH. Necrotizing enterocolitis in two equine neonates. Compendium on Continuing Education for the Practicing Veterinarian 1987;9:88–96.
[6] Paradis MR. Nutritional support: enteral and parenteral. Clin Tech Eq Pract 2003;2:87–96.
[7] Furr MO, Murray MJ, Ferguson DC. The effects of stress on gastric ulceration, T3, T4, reverse T3 and cortisol in neonatal foals. Equine Vet J 1992;37–40.
[8] Ramey DW, Reinertson EL. Sand-induced diarrhea in a foal. J Am Vet Med Assoc 1984;185: 537–8.
[9] Korolainen R, Kaikkonen R, Ruohoniemi M. Ultrasonography in monitoring the resolution of intestinal sand accumulations in the horse. Equine Veterinary Education 2003;5:423–32.
[10] Lester GD. Foal diarrhea. In: Robinson NE, editor. Current therapy in equine medicine. 5th edition. Philadelphia: WB Saunders; 2003. p. 677–80.
[11] Weese JS, Parsons DA, Staempfli HR. Association of *Clostridium difficile* with enterocolitis and lactose intolerance in a foal. J Am Vet Med Assoc 1999;214:229–32.
[12] Baverud V, Gustafsson A, Franklin A, et al. Clostridium difficile: prevalence in horses and environment, and antimicrobial susceptibility. Equine Vet J 2003;35:465–71.
[13] East LM, Savage CJ, Traub-Dargatz JL, et al. Enterocolitis associated with *Clostridium perfringens* infection in neonatal foals: 54 cases (1988–1997). J Am Vet Med Assoc 1998;212: 1751–6.
[14] East LM, Dargatz DA, Traub-Dargatz JL, et al. Foaling-management practices associated with the occurrence of enterocolitis attributed to *Clostridium perfringens* infection in the equine neonate. Prev Vet Med 2000;46:61–74.

[15] Baverud V, Franklin A, Gunnarsson A, et al. Clostridium difficile associated with acute colitis in mares when their foals are treated with erythromycin and rifampicin for *Rhodococcus equi* pneumonia. Equine Vet J 1998;30:482–8.
[16] Arroyo LG, Weese JS, Staempfli HR. Experimental *Clostridium difficile* enterocolitis in foals. J Vet Int Med 2004;18:734–8.
[17] Jones RL, Shideler RK, Cockerell GL. Association of *Clostridium difficile* with foal diarrhea. In: Proceedings of the 5th International Conference of Equine Infectious Diseases 1988; 236–40.
[18] Jones RL, Adney WS, Shideler RK. Isolation of *Clostridium difficile* and detection of cytotoxin in the feces of diarrheic foals in the absence of antimicrobial treatment. J Clin Microbiol 1987;25:1225–7.
[19] Jang SS, Hansen LM, Breher JE, et al. Antimicrobial susceptibilities of equine isolates of *Clostridium difficile* and molecular characterization of metronidazole-resistant strains. Clin Infect Dis 1997;25(Suppl 2):S266–7.
[20] Magdesian KG, Hirsh DC, Jang SS, et al. Characterization of *Clostridium difficile* isolates from foals with diarrhea: 28 cases (1993–1997). J Am Vet Med Assoc 2002;220:67–73.
[21] Weese JS, Cote NM, deGannes RVG. Evaluation of in vitro properties of di-tri-octahedral smectite on clostridial toxins and growth. Equine Vet J 2003;35:638–41.
[22] Walker RL, Madigan JE, Hird DW, et al. An outbreak of equine neonatal salmonellosis. J Vet Diagn Invest 1991;3:223–7.
[23] Holland RE, Sriranganathan N, DuPont L. Isolation of enterotoxigenic *Escherichia coli* from a foal with diarrhea. J Am Vet Med Assoc 1989;194:389–91.
[24] Browning GF, Chalmers RM, Snodgrass DR, et al. The prevalence of enteric pathogens in diarrhoeic Thoroughbred foals in Britain and Ireland. Equine Vet J 1991;23:405–9.
[25] Tzipori S, Hayes J, Sims L, et al. *Streptococcus durans:* an unexpected enteropathogen of foals. J Infect Dis 1984;150:589–93.
[26] Myers LL, Shoop DS, Byars TD. Diarrhea associated with enterotoxigenic *Bacteroides fragilis* in foals. Am J Vet Res 1987;48:1565–7.
[27] Hibbs CM, Johnson DR, Reynolds K, et al. *Clostridium sordelli* isolated from foals. Equine Practice 1977;72:256–8.
[28] Stewart AJ, Hinchcliff KW, Saville WJA, et al. *Actinobacillus* sp. Bacteremia in foals: clinical signs and prognosis. J Vet Int Med 2002;16:464–71.
[29] Barrandeguy M, Parreno V, Lagos Marmol M, et al. Prevention of rotavirus diarrhoea in foals by parenteral vaccination of the mares: field trail. Dev Biol Stand 1998;92:253–7.
[30] Powell DG, Dwyer RM, Traub-Dargatz JL, et al. Field study of the safety, immunogenicity, and efficacy of an inactivated equine rotavirus vaccine. J Am Vet Med Assoc 1997;211:193–8.
[31] Conner ME, Darlington RW. Rotavirus infection in foals. Am J Vet Res 1980;41: 1699–703.
[32] Watanabe T, Ohta C, Shirahata T, et al. Preventive administration of bovine colostral immunoglobulins for foal diarrhea with rotavirus. J Vet Med Sci 1993;55:1039–40.
[33] Davis E, Rush BR, Cox J, et al. Neonatal enterocolitis associated with coronavirus infection in a foal: a case report. J Vet Diagn Invest 2000;12:153–6.
[34] Guy JS, Breslin JJ, Breuhaus B, et al. Characterization of a coronavirus isolated from a diarrheic foal. J Clin Microbiol 2000;38:4523–6.
[35] Corrier DE, Montgomery D, Scutchfield WL. Adenovirus in the intestinal epithelium of a foal with prolonged diarrhea. Vet Pathol 1982;19:564–7.
[36] McChesney AE, England JJ, Rich LJ. Adenoviral infection in foals. J Am Vet Med Assoc 1973;162:545–9.
[37] Netherwood T, Wood JLN, Townsend HGG, et al. Foal diarrhoea between 1991 and 1994 in the United Kingdom associated with *Clostridium perfringens*, rotavirus, *Strongyloides westeri*, and *Cryptosporidium sp*. Epidemiol Infect 1996;117:375–83.
[38] Ludwig KG, Craig TM, Bowen JM, et al. Efficacy of ivermectin in controlling *Strongyloides westeri* infections in foals. Am J Vet Res 1983;44:314–6.

[39] Cole DJ, Cohen ND, Snowden K, et al. Prevalence of and risk factors for fecal shedding of *Cryptosporidium parvum* oocysts in horses. J Am Vet Med Assoc 1998;213:1296–302.
[40] Grinberg A, Oliver L, Learmonth JJ, et al. Identification of *Cryptosporidium parvum* 'cattle' genotype from a severe outbreak of neonatal foal diarrhoea. Vet Rec 2003;153:628–31.
[41] Lakritz J, Madigan J, Carlson GP. Hypovolemic hyponatremia and signs of neurologic disease associated with diarrhea in a foal. J Am Vet Med Assoc 1992;200:1114–6.
[42] Tillotson K, Traub-Dargatz JL. Gastrointestinal protectants and cathartics. Vet Clin North Am Equine Pract 2003;599–615.
[43] Sanchez LC, Murray MJ, Merritt AM. Effect of omeprazole paste on intragastric pH in clinically normal neonatal foals. Am J Vet Res 2004;65:1039–41.
[44] Durando MM, MacKay RJ, Linda S, et al. Effects of polymyxin B and *Salmonella typhimurium* antiserum on horses given endotoxin intravenously. Am J Vet Res 1994;55: 921–7.
[45] Magdesian KG. Nutrition for critical gastrointestinal illness: feeding horse with diarrhea or colic. Vet Clin North Am Equine Pract 2003;19:617–45.
[46] Dunkel BM, Wilkins PA. Nutrition and the critically ill horse. Vet Clin North Am Equine Pract 2004;20:107–27.