C H A P T E R 13

DISORDERS OF THE GASTROINTESTINAL SYSTEM

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13.1—Examination for Disorders of the Gastrointestinal Tract

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Physical Examination

Examination of patients with disease of the gastrointestinal tract must include evaluation of the metabolic and cardiovascular status of the patient, because acute conditions of the proximal or distal intestinal tract have the potential to lead to endotoxemia and sepsis. Examination of the cardiovascular system (heart, peripheral pulse, and mucous membranes), lungs, and abdomen is essential to detect clinical signs of systemic inflammation from endotoxemia, coagulation disorders, dehydration, ileus, shock, and other abnormalities resulting from injury to the small or large intestine. Chapter 13.7 covers clinical signs of systemic inflammation from endotoxemia and sepsis.

One performs the physical examination of the abdomen primarily by auscultation, transabdominal ballottement, and transrectal palpation. Abdominal distention often indicates distention of the large intestine; however, small intestinal distention also can cause visible abdominal distention if a large proportion of the small intestine is involved. One can perform abdominal palpation in neonatal foals; after several weeks of age,

however, the abdominal wall is too rigid to allow effective palpation of intraabdominal structures.

Abdominal auscultation is particularly useful for assessing the motility of the large intestine. Progressive motility of the small intestine, conversely, is difficult to distinguish by auscultation from nonprogressive motility. The distinct character of the borborygmi produced during propulsive contractions of the cecum and ascending colon allow evaluation of the frequency and strength of retropulsion and propulsion. Propulsive contractions of the cecum and ventral colon occur every 3 to 4 minutes and give rise to prolonged rushing sounds heard over long segments of intestine. Retropulsive sounds presumably are similar to propulsive sounds, but they occur less frequently. The distinction of propulsion from retropulsion is not important clinically because both types of contractions signify normal motility. Inter- and intrahaustral mixing contractions produce nonspecific sounds of fluid and ingesta movement that are difficult to distinguish from other borborygmi, such as small intestinal contractions or spasmodic contractions.[1]

Auscultation over the right flank and proceeding along the caudal edge of the costal margin toward the xiphoid allows evaluation of the cecal borborygmi. Auscultation over a similar area on the left side allows evaluation of the pelvic flexure and ascending colon. Typical progressive borborygmi heard every 3 to 4 minutes on both sides of the abdomen indicate normal motility of the cecum and ascending colon. Less frequent progressive sounds may indicate a pathologic condition of the large intestine or may result from anorexia, nervousness (sympathetic tone), or pharmacologic inhibition of

motility (i.e., α_2-adrenergic agonists such as xylazine).[2-4] Absolute absence of any auscultable borborygmi suggests abnormal motility and indicates ileus resulting from a serious pathologic condition but is not specific to any segment of the intestine.[3,5] If borborygmi are audible but progressive sounds are not detectable, determining whether a significant abnormality exists is difficult.[5]

Borborygmi heard more frequently than normal may result from increased motility following feeding; from excessive stimulation from irritation, distention, or inflammation; or after administration of parasympathomimetic drugs such as neostigmine. Large intestinal motility increases in the early stages of intestinal distention regardless of the site.[6] Mild inflammation or irritation of the large intestinal mucosa also can stimulate motility.[3] Parasympathomimetic drugs stimulate contractions and auscultable borborygmi in the large intestine; however, an increase in parasympathetic tone may result in segmental contractions, which actually inhibit progressive motility.[2]

One can detect sand or gravel in the large intestinal ingesta by auscultation behind the xiphoid process. One can hear sand or gravel particles grinding together during progressive contractions of the ascending colon. The presence of sand in the ingesta becomes clinically detectable by auscultation or fecal sedimentation before the amount of sand is enough to produce clinical signs of pain or irritation (diarrhea).[7] If progressive contractions are audible without hearing sand sounds, clinically important quantities of sand likely are not present. If the frequency of progressive contractions is low or absent, detecting sand by auscultation is difficult.

Percussion of the abdomen during auscultation can reveal gas in the large intestine. The characteristic ping produced by simultaneous digital percussion and auscultation over a gas-filled viscus often is associated with abnormal accumulation of gas under pressure. This technique is particularly useful in foals, ponies, and Miniature horses because of the limitations of palpation per rectum.

One can use transabdominal ballottement to detect large, firm masses or an abnormal volume of peritoneal fluid. The usefulness of this technique is usually limited to animals too small to palpate per rectum. One can detect soft tissue masses or fetuses by bumping the structures with a hand or fist. If excessive peritoneal fluid is present, one can generate a fluid wave by ballottement; however, this technique is not as useful in horses older than 4 weeks because the abdominal wall is rigid.

Transrectal palpation is the most specific physical examination technique for investigation of intestinal disease and is particularly valuable when evaluating obstructive diseases.[8,9] The primary objectives of transrectal palpation are to assess the size, consistency, and position of the segments of the large intestine; to determine the presence of any small intestinal distention; and to detect intraabdominal masses. Evaluation of the wall thickness and texture and the mesenteric structures (blood and lymphatic vessels and lymph nodes) also may aid in diagnosis of large intestinal disease. The interpretation of transrectal palpation findings in light of clinical signs and laboratory results is an important diagnostic aid for developing appropriate treatment strategies for intestinal diseases manifested by abdominal pain.

Enlargement of one or more segments of large intestine detected by transrectal palpation provides evidence of obstruction at or distal to the enlarged segment. By systematically evaluating each segment, one may determine the site of obstruction. Obstruction of the pelvic flexure, for instance, results in enlargement of the pelvic flexure and ventral colon, but the dorsal and descending colons are of normal size. Enlargement of a segment of the large intestine usually is accompanied by abnormal consistency of the contents. One may distinguish accumulation of gas, fluid, or ingesta and may detect foreign bodies in palpable segments. Accumulation of gas and fluid infers complete and acute obstruction, whereas accumulation of ingesta infers chronic and incomplete obstruction. Accumulation of fluid usually indicates ileus. One must evaluate the consistency of the contents in light of the size of the segment; ingesta in the ventral colon of a dehydrated patient may be firm, but the size of the ventral colon will be normal. Conversely, if the ingesta is firm because of a distal obstruction, the ventral colon will be enlarged.

Displacement of a segment of the large intestine may create an obstruction detectable by enlargement of the segment and accumulation of gas and fluid, even if the site of obstruction is not palpable. Torsion of the ascending colon at the sternal and diaphragmatic flexures results in acute accumulation of gas and fluid proximal to the torsion, causing distention of the left dorsal and ventral colons. Depending on the degree of torsion, the position of the ventral and dorsal colons may not be significantly abnormal. Displacement of a segment of large intestine often results in incomplete obstruction, and the diagnosis relies solely on detection of the displaced segment in an abnormal position. The position of the displaced segment may not be palpable, and the diagnosis then relies on the inability to find the segment in a normal position. One must take care to ensure that the segment that appears to be displaced is not in a normal position but has become too small to palpate from a decrease in the volume of ingesta. The cecum, right dorsal and ventral colons, pelvic flexure, and descending colon are palpable in most horses. One should palpate the nephrosplenic space to detect the presence of intestine, usually pelvic flexure, entrapped within the ligament.

Small intestine is not normally palpable in the horse. Distention is an indicator of ileus with gas or fluid retention, usually following a strangulating or nonstrangulating obstruction. Strangulating obstructions result from conditions such as volvulus or torsion, lipoma, or entrapments. Such conditions often are accompanied by severe pain, dehydration, peritoneal fluid changes, and a varying degree of gastric fluid accumulation. The small intestine in these cases is turgid and firm on palpation. One should assess the mesentery and wall thickness as for large intestinal disorders. Careful palpation of the inguinal rings in stallions with small intestinal distention is crucial for determining inguinal herniation.

Evaluation of the wall thickness and mesenteric vessels can reveal venous congestion (mural edema and enlarged blood and lymphatic vessels) or inflammation (mural edema with normal vessels). Disruption of arterial blood flow does not cause venous congestion, but the arterial pulse is not detectable. Mesenteric tears may not be palpable, but the entrapped ischemic intestinal segment may be thickened with edema. One may detect acute or chronic inflammation with cellular infiltration of the intestinal wall as thickening of the wall without edema and also may note enlargement of mesenteric lymph nodes. One should interpret abnormalities in the wall or vessels in light of the size, consistency, and position of the segment of intestine and the clinical signs.

Several conditions involving small intestinal strangulating lesions do not necessarily cause abnormal rectal examination findings until the disease has been present for an extended time. These conditions include diaphragmatic herniae and epiploic foramen entrapments. Peritoneal fluid analysis may be normal in these cases as well because the fluid is trapped in the thorax or in the cranial abdomen. Surgery is usually necessary for diagnosis.

Nonstrangulating causes of small intestinal distention can be divided further into intraluminal and extraluminal obstructions. Ileal impactions are probably the most common cause of intraluminal obstructions, and on rare occasions one can palpate the impaction in the upper right quadrant, near the ileocecal opening. Intraluminal masses caused by lymphoma, eosinophilic enteritis, foreign bodies or ascarid impactions often lead to small intestinal distention and are usually indistinguishable from one another based on palpation alone. Small intestine in these cases can be moderately to severely distended, depending on the degree of obstruction. Extraluminal obstructions include abdominal masses, abscesses or tumors, and large colon displacement. One always should palpate the rest of the abdomen carefully to help rule out these causes.

Some cases of small intestinal distention result from a physiologic rather than a mechanical obstruction. Ileus may result postoperatively or following inflammatory diseases of the bowel (proximal enteritis) or peritoneal cavity (peritonitis). The bowel is usually mildly to moderately distended and almost always is accompanied by significant amounts of accumulated gastric fluid.

The small colon is easily distinguishable by the presence of normal fecal balls and an antimesenteric band. In cases of impaction of the small colon, a long, hard, tubelike structure is present in the caudal abdomen, and the band is palpable along the length. Fluid stool is often present in the rectum in these cases, as is tenesmus.

One can detect and carefully evaluate rectal tears by palpation. One can detect mural masses in palpable segments of intestine or mesentery; however, if a mass causes obstruction, one can detect the result of the obstruction in proximal segments of intestine even if the mass is unreachable. Palpation of the mesenteric vessels may reveal thickening and thrombosis, which can lead to ischemia or infarction.

One can perform visual inspection of the mucosa of the rectum and descending colon with a speculum or flexible endoscope and also can evaluate rectal tears or perforations, mural masses, strictures, or mucosal inflammation. One also can perform guided biopsy of the mucosa or masses. The obvious limitations are the amount of fecal material interfering with the examination and the distance of the lesion of interest from the anus. These techniques offer little advantage over palpation in many cases unless the patient is too small to palpate.

Examination of the oral cavity in cases of dysphagia or weight loss is a necessary part of the physical examination. One should adequately sedate the horse and should use a full-mouth speculum to allow palpation and visualization of all parts of the oral cavity. One should examine the area for abnormal dentition, foreign bodies, fractures, abscesses, and ulceration.

The presence of fluid accumulation in the stomach indicates a decrease or absence in propulsive motions of the small intestine or obstruction of gastric outflow. Decreased small intestinal motility may result from a functional or mechanical blockage. Masses, feed impactions, or strictures in the pylorus or in the proximal duodenum may obstruct gastric outflow. One routinely assesses fluid accumulation in the stomach by siphoning off the gastric contents with a nasogastric tube and examining the fluid for amount, color, and any particular odor. Normal fluid is green and may contain foamy saliva. The volume obtained by gastric lavage is usually less than 4 L.

Large volumes of fluid (>8 to 10 L) accumulate in the stomach of horses with proximal enteritis, and the fluid is foul smelling and often has an orange to yellow discoloration. If one suspects proximal enteritis, one can submit the fluid for culture and Gram staining. *Salmonella* sp. and *Clostridium* sp. have been cultured in some cases. Patients with postoperative ileus also frequently accumulate large amounts of gastric fluid. Horses with

strangulating obstructions or luminal obstructions often accumulate moderate amounts of gastric fluid, but the amount is generally less than in horses with proximal enteritis or postoperative ileus. Hemorrhage in the gastric fluid usually indicates devitalized small intestine, stomach wall, or severe gastric ulceration. Fluid with large amounts of food material often indicates a gastric impaction, and one should lavage the stomach until obtaining no more ingesta. Horses and foals with chronic gastric ulceration in the glandular mucosa of the stomach or in the duodenum may develop strictures and have fluid accumulate in the stomach. Endoscopy or contrast radiography aids in diagnosing gastric outflow obstruction.

Clinical Pathology

Evaluation of the hemogram is essential when one assesses conditions of the gastrointestinal tract. However, hematologic alterations associated with diseases of the gastrointestinal tract are often nonspecific, reflecting systemic response to inflammation, endotoxemia, or sepsis. Neutrophilic leukocytosis and normochromic, normocytic anemia with or without hyperfibrinogenemia commonly are associated with chronic inflammatory conditions of the intestine. Anemia from chronic blood loss occurs infrequently in adult horses because of the large iron stores and high concentrations of iron in their diet; usually anemia follows chronic inflammation, as do alterations in the leukon and plasma fibrinogen concentrations. Plasma protein concentrations vary depending on gastrointestinal losses of albumin and globulin and elevation of globulin concentration from antigenic stimulation. Protein-losing enteropathies may manifest predominantly as a hypoalbuminemia or may have a concurrent hypoglobulinemia. Immunoglobulin quantification can be useful in selected cases; immunosuppression with low immunoglobulin M concentration has been shown to occur in some cases of lymphosarcoma.[10] Parasitic infections, especially strongylosis, may be characterized by elevated serum immunoglobulin G(T) concentration.[11]

Significant alterations of the hemogram do not accompany acute disease of the intestine unless severe inflammation, dehydration, endotoxemia, or sepsis is present. During the early stages of endotoxemia, elevations in circulating concentrations of inflammatory mediators, epinephrine, and cortisol produce characteristic changes in the hemogram. Leukopenia, with neutropenia and a left shift, toxic changes in the neutrophil cytoplasm, and lymphopenia occur commonly.[12] Hemoconcentration and hyperfibrinogenemia are also common. Thrombocytopenia and other coagulopathies are also features of endotoxemia. Indeed, thrombocytopenia may be the earliest indicator of sepsis.[13] Endotoxemia and circulating mediators of inflammation activate the coagulation cascade, causing a hypercoagulable state that can lead to consumption of coagulation factors and coagulation defects manifested as elevated prothrombin time, partial thromboplastin time, fibrin degradation products, and bleeding time, and reduced activity of antithrombin III.[14-16] Neutrophilic leukocytosis occurs during the later stages of endotoxemia.[14]

The most common serum biochemical abnormalities with diseases of the large or small intestine are electrolyte imbalances. Serum calcium concentrations are often low with strangulating obstructions and acute inflammatory diseases.[17] Inflammation of the mucosa can disrupt electrolyte fluxes severely. Diarrhea or gastric reflux greatly exacerbates the loss of sodium, potassium, calcium, magnesium and bicarbonate. Ischemia of the intestine causing hypoxia and cellular damage may be reflected by an elevated serum phosphate concentration resulting from phosphate leakage from damaged cells.[18] Ischemia and cellular hypoxia in any segment of the intestine also causes a shift in energy metabolism to anaerobic glycolysis, resulting in increased production of lactate and elevated serum lactate concentration. Reduced perfusion of peripheral tissues from hypotensive shock and intestinal ischemia can cause elevations in serum lactate. However, obstruction of the intestine during ischemia may result in absorption of lactate from the lumen.[19,20] Anion gap is an indirect measurement of organic acid production during states of tissue hypoxia and is a reasonable estimate of serum lactate concentration.[20] Metabolic acidosis may accompany lactic acidemia, but an inconsistent association exists between the two, especially when mixed acid-base imbalances are present.[20,21] Elevations of hepatic enzymes, specifically γ-glutamyltransferase, may occur with large colon displacements, duodenal strictures, or anterior enteritis.

Relative polycythemia from hemoconcentration or splenic contraction and changes in red blood cell deformability from hypoxia or hypocalcemia may increase blood viscosity. Blood viscosity increases in patients with acute obstructive disease. Hyperviscosity reduces perfusion of capillary beds, thereby exacerbating ischemia and tissue hypoxia.[22] Hyperviscosity is one manifestation (along with lactic acidemia, coagulopathies, and clinical signs of shock) of the pathophysiologic events that take place during acute inflammatory or vascular injury to the large intestine. Laboratory tests designed to reflect the systemic effects of endotoxemia, ischemia, sepsis, and shock are important to design therapeutic strategies, and monitor response to therapy.

EXAMINATION OF PERITONEAL FLUID

Abdominocentesis and analysis of peritoneal fluid (PF) is a diagnostic technique performed on many patients with disease of the gastrointestinal tract. One can quantitate

cytologic examination of PF; white blood cell and red blood cell counts; protein, fibrinogen, lactate, phosphate, and glucose concentrations; lactate dehydrogenase, creatine kinase, and alkaline phosphatase activity; and pH. The results of PF analysis may help establish a specific diagnosis but more importantly may reflect inflammatory, vascular, or ischemic injury to the intestine requiring surgical intervention.

PF reflects a sequence of events that takes place during acute vascular injury to the intestine. The PF protein concentration first increases, followed by an increase in the red blood cell count and fibrinogen concentration. A transudative process resulting from vascular congestion and increased endothelial permeability allows small macromolecules (albumin) to escape into the PF, followed by larger macromolecules (globulin and fibrinogen), and finally diapedesis of cells (red blood cells, then white blood cells).[23,24] If ischemic inflammation of the intestine and visceral peritonitis occur, an exudative process ensues. Severe inflammation of the intestine and visceral peritoneum causes large quantities of protein and white blood cells, primarily neutrophils, to escape into the PF.[24] As damage to the bowel progresses, the protein concentration and red blood cell and white blood cell counts continue to rise. As the degree of irreversible damage to the intestine increases, the PF characteristics become more exudative.[23,24] Eventually, bacteria begin to translocate across the intestinal wall and appear in the PF as the mucosal barrier breaks down. Neutrophils predominate, and their cytoplasm becomes granulated, and Döhle bodies often are visible. If perforation occurs, bacteria and particles of ingesta appear in the PF, and the neutrophils become degenerate, that is, pyknotic, with karyorrhexis, karyolysis, and smudge cells.[23]

Elevated PF protein concentration is a sensitive indicator of early inflammation, whereas elevated red blood cell counts in the presence of normal white blood cell counts suggest vascular damage without significant tissue ischemia.[24] Elevation of the white blood cell count usually indicates severe tissue inflammation or intestinal injury.[25] The gross color of the PF can be helpful in detecting injury and necrosis of the intestine. A serosanguinous appearance indicates vascular injury, whereas orange or brown-red indicates necrosis with the release of pigments such as hemosiderin. Serial samples of PF are most useful in determining the nature and extent of damage to the intestine, but in many cases of ischemia, irreversible tissue damage has occurred by the time PF abnormalities appear.

Tissue hypoxia and ischemia cause a rapid elevation of PF lactate dehydrogenase, creatine kinase, and alkaline phosphatase activity and lactate concentration.[19,20,26] Phosphate concentration increases when cellular disruption occurs.[18] PF enzyme activities, phosphate, and lactate concentration increase faster and higher than serum activities.[18-20,26] PF pH and glucose concentration tend to decrease during intestinal ischemia, but not as low as in septic peritonitis.[27] Although biochemical alterations may provide early indicators of intestinal ischemia and necrosis, they are nonspecific and offer no advantage over conventional methods of PF analysis in many cases. PF alkaline phosphatase has been shown to arise predominantly from degenerating white blood cells, and elevations of other enzyme activities may occur with many inflammatory diseases.[26] Thus the specificity of many tests run on PF is questionable. However, in selected cases in which conventional PF analysis and physical examination do not provide sufficient information to develop a treatment plan, biochemical analysis of the PF may be useful.

Cytologically examined cells of the PF may reflect chronic inflammatory conditions of the large intestine, especially eosinophilic or lymphocytic processes.[28] Infectious and inflammatory conditions often cause increases in the neutrophil count and may be indistinguishable unless bacteria are visible. One also may detect neoplastic diseases by PF examination. Chronic infection and inflammation may be associated with elevated PF protein and fibrinogen concentrations. Culture of PF usually is required to distinguish bacterial infections from noninfectious inflammation unless bacteria are visible on cytologic examination. However, culture of PF is often unrewarding because factors that are found in inflammatory PF inhibit bacterial growth, and leukocytes phagocytose many bacteria in the PF.[29] Decreases in PF glucose concentrations (<30 mg/dl) and pH (<7.3) are early indicators of a septic process. The glucose concentration and pH in the PF should approximately equal the blood glucose concentration and pH. A PF fibrinogen concentration greater than 200 mg/dl also indicates bacterial infection.[30]

FECAL EXAMINATION

Gross examination of the feces can provide information about digestion and transit time in the large intestine. Large fiber particles in the feces represent poor mastication or poor digestion in the large intestine. Small, mucus-covered, hard fecal balls indicate prolonged transit through the descending colon, whereas increased fluidity implies decreased transit time. Feces containing sand or gravel are not necessarily abnormal. However, a significant amount of sand implies that large quantities are present in the colon. Frank blood indicates substantial bleeding into the distal colon (right dorsal colon and/or small colon) from mucosal damage.

Laboratory analysis of the feces is performed frequently in cases of diarrhea. Fecal cytologic examination and tests for occult blood detect mucosal inflammation,

erosion, or ulceration. Severe inflammatory diseases in human beings, invasive bacterial infections in particular, have been shown to increase the shedding of leukocytes in the feces. A higher percentage of horses with salmonellosis and diarrhea have fecal leukocyte counts greater than 10 cells per high power field than horses with negative fecal cultures for *Salmonella*. These results suggest that high fecal leukocyte counts indicate salmonellosis in horses with diarrhea. However, the specificity of this test is probably low. Low fecal leukocyte counts do not rule out salmonellosis.[31]

Fecal occult blood tests detect blood in the feces, presumably from erosion or ulceration of the mucosa, but do not distinguish the source of the blood. Large volumes of blood (1 to 2 L) given by nasogastric tube were required to produce a positive test for occult blood in the feces, but the amount of blood originating from the large intestine required to produce a positive test is unknown. A positive test implies significant hemorrhage into the gastrointestinal tract. Newer, more sensitive tests detect not only occult blood but also degraded blood and may be useful to determine the site and quantity of blood loss.[32] A positive test implies significant hemorrhage into the gastrointestinal tract.

Bacteriologic examination of the fecal flora has been used to quantitate specific bacterial species in the feces of horses with diarrhea. Quantitation of clostridial species may be beneficial in diagnosing clostridial infection of the large intestine.[33] Tests to detect clostridial toxins in intestinal contents or feces are important to determine whether clostridia cultured from the feces are causing disease. The most common bacterial pathogens isolated from the feces of horses are *Salmonella* and *Clostridium*. The number of *Salmonella* organisms isolated from the feces of horses with clinical salmonellosis is usually higher than from horses with asymptomatic infections. However, the volume of feces in many cases of acute diarrhea is high, and the concentration of *Salmonella* organisms may be lower than would be expected, accounting for many false-negative fecal cultures. The sensitivity of fecal cultures for detecting *Salmonella* infection may be as low as 20%. Culture of five consecutive daily fecal samples is recommended to increase the sensitivity of the test. Because salmonellae are intracellular organisms, culture of rectal scrapings or a rectal biopsy sample, along with fecal material, may increase the sensitivity of culture for detecting *Salmonella* infection to 50%.[34] One can perform a polymerase chain reaction assay on fecal samples to detect DNA from *Salmonella* sp. The polymerase chain reaction test is more sensitive than culture and is frequently positive in clinically normal horses that continuously shed small amounts of bacteria. Polymerase chain reaction or immunologic tests also may detect *Clostridium perfringens* and *C. difficile* exotoxins in the feces.

Qualitative fecal examination is a technique to detect nematode and cestode ova, protozoan oocysts, parasitic larvae, and protozoan trophozoites. A direct smear of fecal material is a rapid method to screen feces for ova and oocysts, to detect parasite larvae and trophozoites, and to observe motility of ciliates and parasite larvae. Fecal flotation is a more sensitive technique for isolating and detecting ova and oocysts because the eggs are concentrated from the sample. Zinc sulfate and sucrose solutions are often used to concentrate less dense ova and oocysts. Zinc sulfate produces less distortion of trophozoites and larvae than sucrose solutions. Fecal sedimentation is particularly appropriate for ciliates, *Giardia,* and trichomonads. Quantitative techniques such as the Cornell-McMaster method allow one to estimate the number of eggs per gram of feces and are most appropriate in monitoring parasite control programs.[35]
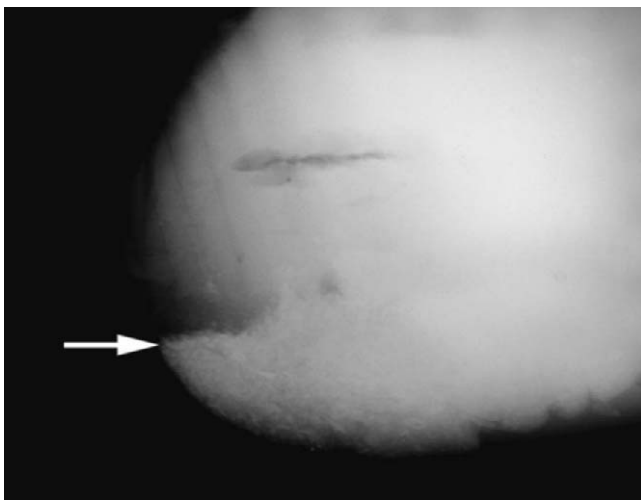
Radiography

Survey radiography of the normal esophagus is usually unrewarding but may be useful in horses with esophageal obstructions to determine the extent and location of the obstruction. One may detect foreign bodies or soft tissue masses, and in cases of esophageal rupture, one may see free air and ingesta in the tissues surrounding the esophagus and may observe pneumomediastinum.[36] Thoracic radiographs may be necessary to detect intrathoracic esophageal obstructions, megaesophagus, or cranial mediastinal masses causing extraluminal obstruction. One may use barium swallows or double-contrast esophagrams after resolution of the obstruction to determine whether a stricture or diverticulum or other underlying disorder is present.[37] Barium sulfate is the usual contrast medium and can be administered orally via a dose syringe or by nasogastric tube (50 to 100 ml of a 40% barium sulfate suspension or barium paste). Oral administration is preferred for evaluation of swallowing and lesions in the proximal esophagus. Administration of contrast using a nasogastric tube (preferably cuffed) allows for delivery of larger volumes of barium (up to 500 ml) but should be performed without sedation if possible. One can follow administration of contrast material with air insufflation to create a double-contrast effect. If one suspects a rupture of the esophagus or if the likelihood of aspiration of the contrast material is high, one should use iodinated organic compounds in an aqueous solution as contrast material.[36] Contrast radiography may be the most definitive method for the diagnosis of primary megaesophagus or other functional disorders such as autonomic dysautonomia (grass sickness) affecting the esophagus.[37] One should take care when interpreting esophageal radiographs if the horse is sedated. Acepromazine or detomidine administration causes esophageal dilation in

normal horses, especially after passage of a nasogastric tube.[38]

Radiography of the adult equine abdomen is an effective technique in detecting radiodense material in the large intestine, such as enteroliths, sand, and metallic objects.[39,40] One survey demonstrated that radiography has 76.9% sensitivity and 94.4% specificity for diagnosing enterolithiasis.[39] Radiography also can be a useful tool for detecting sand accumulation in the colon that causes diarrhea or impactions (Figure 13.1-1) and for monitoring resolution in medically treated horses.[41] The large size and density of the adult abdomen precludes evaluation of soft tissue structures because the detail and contrast of the radiographs are usually poor. One is more likely to obtain diagnostically useful abdominal radiographs from small ponies and miniature horses than from full-size adult horses. Accumulation of gas is visible on radiographs of adult horses, but distinguishing normal intestinal gas from obstruction is often difficult. Horses should be fasted for 24 to 48 hours to reduce the amount of ingesta in the large intestine before radiography.

Abdominal radiography is more useful in foals than in adult horses. Radiographs are more detailed and contrast can be good. Radiographic evidence of gas distention in the large intestine may indicate large intestinal obstruction, and radiographic signs of displacement are often diagnostic. One may diagnose impactions, intussusceptions, foreign bodies, and other disorders with the aid of radiography. Functional ileus may be difficult to distinguish from mechanical obstruction.[42,43] Administration of contrast (barium sulfate 30% at 5 ml/kg) via nasogastric tube increases the diagnostic capabilities of radiography.[44]

Figure 13.1-1 Radiograph of the cranioventral abdominal region of a weanling colt with diarrhea. The radiopaque accumulation of sand *(arrow)* in the sternal flexure of the ventral colon is notable.

Gastric ulceration also is recognizable with contrast radiography in the foal, although this is not as accurate a method as endoscopy.[45] Contrast administered retrograde via a 24-F Foley catheter inserted into the rectum at a dose of up to 20 ml/kg has excellent potential for diagnosing disorders of the small colon, transverse colon, and large colon in foals.[46]

Ultrasonography

Ultrasonographic evaluation of the abdomen can add valuable information in cases of acute or chronic gastrointestinal disease. Examination of the adult horse requires a 2.5- to 5.0-MHz transducer at minimum. One may use sector, linear, or curved linear transducers. Clipping of the hair over the area to be examined, along with the application of isopropyl alcohol and ultrasound coupling gel, enhances evaluation.

To evaluate the abdomen adequately, one must know the anatomic location and normal appearance of the individual organs. In the left cranial abdomen, one can assess the greater curvature of the stomach between the eleventh and thirteenth intercostal space, and one can use the spleen and the large splenic vein as landmarks. Cases of gastric dilation from gas or impaction appear as an enlargement of the viewing area to cover greater than five rib spaces.[47] One also can evaluate the stomach for intramural or extramural masses such as abscesses or for squamous cell carcinoma.[48] The lesser curvature is not routinely visible.

Assessment of the small intestine should include evaluation for changes in thickness, motility, location, and visibility. One may find small intestinal loops easily in the left lower quadrant of the abdomen, but these normally are visible in other locations. One can visualize the duodenum consistently on the right side of the abdomen deep to the liver in the tenth to twelfth intercostal space or deep to the right kidney at the fifteenth to sixteenth intercostal space. Mural thickening (>4 mm) may occur in cases of infiltrative or proliferative diseases, postoperative cases, enteritis, and paralytic or mechanical ileus. Thickening of the small intestinal wall in foals, with or without the presence of gas shadows within the wall, should raise suspicions of clostridial enteritis.

One can assess motility by monitoring a specific area for contractions over time. Ultrasonography is an accurate method of distinguishing strangulating versus nonstrangulating disorders of the small intestine. Strangulated small intestine has thicker small intestinal walls and larger intestinal diameter than in nonstrangulating disorders. Strangulating lesions have decreased motility in the incarcerated segments with normal motility elsewhere.[49] Cases of paralytic ileus or nonstrangulating obstruction have a diffusely decreased peristalsis, but not to the

degree observed with strangulating lesions.[47,49] One may diagnose some specific lesions of the small intestinal tract using ultrasonography. One may see ascarids in foals in cases of ascarid impaction[47] and epiploic foramen entrapments as edematous loops of small intestine found in the right cranial abdomen.[50] One may note small intestinal intussusceptions as targetlike lesions when viewed in cross sections.[51] The presence of bowel loops, stomach, or liver in the thoracic cavity indicates the presence of herniation through the diaphragm and should be confirmed using radiography or surgical exploration.

Evaluation of the large intestine may be difficult because of the large amounts of gas within the lumen. However, certain disorders are readily identifiable via ultrasonography. One can assess the nephrosplenic ligament area for bowel entrapment in the left paralumbar fossa. In cases of entrapment, the spleen will be pulled away from the body wall and fluid or gas shadows will be observable dorsal to the spleen,[52] obscuring the kidney, which is normally adjacent and abaxial to the spleen. Small colon, small intestine, or pneumoperitoneum also may produce a gas shadow and obscure the kidney from view.[47]

Sand impactions may appear as hyperechoic bands on the ventral abdominal wall.[47] One may see ileocecal and cecocolic intussusceptions in the upper right paralumbar fossa.[53] In cases of colitis, large, fluid-filled colons may be visible with or without intramural edema. One can find the right dorsal colon consistently abaxial to the liver, within the right thirteenth to fifteenth intercostal space and may be thickened (>5 mm) in cases of right dorsal colitis.

Evaluation of the abdomen always should include assessment of the peritoneal space for any evidence of an increased amount of PF or increased cellularity of the fluid as indicated by an increase in echogenicity. Ultrasonography also can be useful in determining the ideal location for abdominocentesis. One also should evaluate the liver, kidneys, and spleen. One may detect choleliths, nephroliths, masses, abscesses, or enlargement of any of these organs. Abscesses or tumors not associated with visceral organs may be difficult to visualize and interpret via ultrasonography.

Nuclear Scintigraphy

Although more commonly used to diagnose lameness and musculoskeletal problems, nuclear scintigraphy has several uses for evaluation of the gastrointestinal tract. Scintigraphy is now available at most universities and many private referral hospitals. One must use proper isolation protocols and waste disposal techniques strictly.

The procedure requires special gamma cameras and the injection of radioactive materials into the bloodstream. One can use one of two methods: injection of technetium-99m methylene diphosphonate (^{99m}Tc-MDP) directly into the blood or injection of ^{99m}Tc-labeled leukocytes. Labeling of leukocytes involves aseptically collecting heparinized blood samples, isolating the buffy coat, and mixing those leukocytes with a radioactive dye (^{99m}Tc hexamethylpropyleneamine oxime, or ^{99m}Tc-HMPAO) in vitro.[54] One then reinjects the labeled leukocytes and obtains images. The principle of nuclear scintigraphy then lies in increased uptake of the dye or the white blood cells into areas of inflammation.

One of the most common uses of nuclear scintigraphy in evaluating the gastrointestinal tract is diagnosis of dental disease. Scintigraphy using ^{99m}Tc-MDP proved to be more sensitive in cases of dental disease than was radiography. Scintigraphy was slightly less specific, however, and therefore should be used with radiography or computed tomography for ultimate accuracy.[55] Scintigraphy using radiolabeled white blood cells can support a diagnosis of right dorsal colitis in the horse.[40] Images taken of the abdomen 20 hours after injection showed an increased linear uptake of leukocytes in the region of the right dorsal colon in horses with right dorsal colitis compared with normal horses. This technique also may prove useful for diagnosing intraabdominal abscesses in the horse. Other uses of nuclear scintigraphy include evaluation of metastasis of abdominal tumors to bony areas, assessment of biliary kinetics, and determination of gastric emptying times.[56-58]

Endoscopy

Endoscopic examination of the gastrointestinal tract begins with evaluation of the pharyngeal area by examination for any signs of collapse or dysfunction. One should evaluate the ability of the horse to swallow. The floor of the pharynx should be clean and free of feed material and foreign bodies. One can examine the oral cavity with the horse under heavy sedation or anesthesia and with the help of a full-mouth speculum. One can examine the teeth for any irregularities, obvious cavities, sharp points, or hooks and the hard and soft palate for completeness and any evidence of ulceration, masses, or foreign bodies.

One should use a 3-m flexible fiberoptic endoscope to examine the esophagus, which is accomplished best by passing the endoscope into the stomach and viewing the esophagus as one withdraws the endoscope while dilating the lumen with air. The esophageal mucosa normally should be a glistening, light pink color. Ulceration can occur with cases of choke, reflux esophagitis or in horses that have had an indwelling nasogastric tube. Erosions may be punctate, linear, or circumferential. One should

evaluate carefully for any ulcers to ensure that no areas of perforation through the entire thickness of the esophageal wall exist. Distinguishing normal peristaltic contractions from areas of stricture requires observation of the area and its motility over time. One also may note diverticula as outpouchings of the mucosa, sometimes associated with a stricture distally. Megaesophagus, although rare, appears as a generalized dilation of the esophagus. One may detect food or foreign body impactions of the esophagus via endoscopy. One always should reevaluate the esophagus after removing any obstruction to detect the presence of complications (ulceration, rupture) or initiating causes (strictures, diverticula, and masses).

A 3-m flexible endoscope also allows examination of the stomach. The horse should be fasted for at least 12 hours before endoscopy. One can examine the cardia and fundus easily, as well as the margo plicatus. The squamous mucosa should resemble the esophageal mucosa. The glandular mucosa should be glistening red and may have a reticulated pattern. One should carefully examine for evidence of ulceration or masses. One can obtain transendoscopic biopsy material easily from esophageal, pharyngeal, or gastric masses, and because the biopsy size will be small, one should take several samples for histopathologic examination. Pharmacologic agents (bethanechol) to empty the stomach and provide complete visualization of the entire fundic region, the pylorus, and the duodenum may be useful. For a complete description of gastroscopy and evaluation of gastric and gastroduodenal ulceration, please refer to Chapter 13.10.

Tests of Absorption and Digestion

D-Glucose or D-xylose absorption tests are useful in determining malabsorption of carbohydrates from the small intestine in horses. The protocol for absorption tests using either carbohydrate is similar. The horse should be fasted for 18 to 24 hours before testing. Increased periods of fasting actually have been shown to decrease absorption of D-xylose and interfere with results.[59] One administers a dosage of 0.5 to 1 g/kg of D-glucose or D-xylose via a nasogastric tube. Administration of sedatives may increase the blood glucose levels falsely and interfere with gastrointestinal transit times. One then collects blood samples to measure glucose or xylose concentrations at 0, 30, 60, 90, 120, 150, 180, 210, and 240 minutes after administration. One may take additional samples up to 6 hours after dosing if the results are questionable. One should measure glucose in blood samples collected with sodium fluoride as an anticoagulant and measure xylose in samples collected in heparinized plasma.

A normal D-glucose absorption test, also known as an oral glucose tolerance test, should have a peak between 90 and 120 minutes, and this peak should be greater than 85% above the resting glucose value.[60] *Complete malabsorption* is defined as a peak less than 15% above the resting levels, and *partial malabsorption* is defined as a peak between 15% and 85% above the resting level. One must keep in mind that gastric emptying, gastrointestinal transit time, length of fasting, cellular uptake and metabolism, and endocrine function influence glucose absorption curves. Malabsorption demonstrated by the oral glucose tolerance test is sensitive but not specific. Diseases that may cause a lowered or delayed peak include infiltrative lymphosarcoma, inflammatory bowel disease (lymphocytic-plasmacytic or eosinophilic), cyathostomiasis, chronic colitis (*Salmonella* sp.), multisystemic eosinophilic epitheliotropic disease, food allergies, and small intestinal bacterial overgrowth.[61]

D-Xylose absorption tests have some advantages over the oral glucose tolerance test because xylose is not metabolized in the small intestinal mucosa and insulin does not influence its absorption. Gastric and intestinal motility, intraluminal bacterial overgrowth, and renal function still influence xylose absorption, because the kidneys clear xylose.[61] The other main drawback to D-xylose is that it is generally available only in research settings. However, xylose measurements are available at most major universities. A normal D-xylose absorption curve should peak between 20 and 25 mg/dl at 60 to 120 minutes after dosing.[62] Decreased xylose absorption can occur in horses with inflammatory bowel disease, lymphosarcoma, multisystemic eosinophilic epitheliotropic disease, cyathostomiasis, extensive small intestinal resections, and any cause of villous atrophy.[61]

Maldigestion is a common occurrence in foals with diarrhea. Bacteria (especially *Clostridium* sp.) and viruses (especially rotavirus or coronavirus) may invade and destroy the villous epithelial cells that manufacture lactase and other disaccharidases, resulting in an inability to digest lactose. In this case, continued ingestion of the mare's milk may cause an osmotic diarrhea, which may exacerbate the underlying enterocolitis. One can perform lactose tolerance testing to assess the degree of maldigestion. One administers D-lactose at 1 g/kg as a 20% solution via nasogastric tube and measures glucose concentrations in the blood at 0, 30, 60, 90, 120, 150, 180, 210, and 240 minutes. A normal curve shows doubling of glucose levels compared with baseline by 60 minutes after administration.[63]

Evaluation of Gastric Emptying

Assessment of gastric emptying may be useful in evaluating delayed emptying of feed or fluids from the stomach in cases of gastric and esophageal ulceration, pyloric stenosis, proximal enteritis, and postoperative ileus. However,

accurate measurement of gastric emptying can be difficult to assess. Several methods are currently available.

Multiple diagnostic imaging techniques have been used to study gastric emptying times. One can use contrast radiography to assess gastric emptying in foals. In the normal foal, barium remains in the stomach for varying amounts of time, but a significant amount should be gone within 2 hours.[44] Gastric emptying of solid, non-digestible, radiopaque markers also has been used in adult horses and ponies, but the results were variable and unpredictable even in the normal horse.[64] Nuclear scintigraphy is used commonly in human beings to measure gastric emptying and can be used in horses where available. This technique requires oral administration of ^{99m}Tc pentenate (10 mCi), and serial images taken of the cranial abdomen. The tracer is usually not visible 60 minutes after administration in normal horses.[58]

Alternatively, if nuclear scintigraphy is not available, one can use acetaminophen absorption testing as an indirect determination of gastric emptying.[58,65] One performs this test by administering 20 mg/kg of acetaminophen orally and measuring subsequent blood values and calculating the time to reach maximum serum concentrations and the absorption constant. In human beings, the proximal small intestine absorbs almost all of the acetaminophen.[66] The median time to reach peak plasma levels using acetaminophen absorption in horses was 47.7 minutes.[58]

Histopathologic Examination

One often requires histopathologic examination of tissues from the intestine to diagnose chronic inflammatory, infiltrative, or neoplastic conditions, and such examination can be useful in evaluating the extent of injury after obstruction or ischemia. Rectal mucosal biopsies are easy to collect with few complications. However, to collect a full-thickness biopsy of the intestine requires a surgical approach (flank or ventral midline approach). Laparoscopy offers a safer technique to observe the large intestine and other abdominal structures.[67] One can obtain biopsies of masses, lymph nodes, mesentery, or intestinal serosa via laparoscopy and mucosal biopsies of the upper gastrointestinal tract via endoscopy.

Advanced Diagnostics

Other diagnostics, specifically laparoscopy and computed tomography, are available but require specialized equipment and personnel with specific training. Flexible or rigid endoscopes used for laparoscopic evaluation of the abdomen allow for visualization of visceral organs and potentially for collection of biopsy material from masses or organs. Full-thickness biopsies of the intestines are not routinely possible through the laparoscope and usually require flank or ventral midline laparotomy. The laparoscopic procedure can be done in the standing or recumbent horse. Advantages of this technique over a flank or ventral midline celiotomy include smaller incisions, less healing time, and less procedure time. Disadvantages include the large amount of equipment needed, skill involved, and the limitation as a diagnostic modality, rather than a treatment.[68] Clinical applications of diagnostic laparoscopy include rectal tears, percutaneous abscess drainage, assessment of adhesions, displacements, and integrity of the serosa of various bowel segments, and biopsy of abdominal masses.[67]

Computed tomography scans are available at several universities across the country. They have been used frequently to evaluate dental disease and may be useful in evaluating tumors and masses of the head, larynx, pharynx, and proximal esophagus.[69] Computed tomography also has promise for evaluating abdominal disorders in foals. Most equipment can accommodate up to 400 lb. Restrictions to computed tomography as a diagnostic aid include expense, availability, expertise, and weight and size limitation.

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13.2—Pathophysiology of Gastrointestinal Inflammation

Samuel L. Jones

The inflammatory response of the gastrointestinal tract is a mechanism ultimately aimed at eliminating pathogens, initiating tissue repair, and restoring the gastrointestinal barrier. Inflammation alters blood flow, endothelial permeability increases, cells are recruited rapidly into the tissue, plasma protein cascades are activated, and a myriad of soluble products are released that coordinate the response, trigger innate and adaptive immunity, and mobilize reparative elements. Although the cellular and vascular response and the secreted mediators of inflammation are important for killing pathogens and limiting invasion of injured tissues by commensal organisms, they can be damaging to host cells and proteins if not tightly regulated. Thus if the inciting stimulus is not eliminated quickly, the inflammatory response itself causes significant tissue injury. The mechanism regulating inflammation has been the focus of much research to identify therapeutic targets to modulate the damage to host tissues during many gastrointestinal diseases. Recent work has provided some of the molecular and cellular details of this complex physiology and has led to novel therapeutic strategies for treating inflammation.

Initiation of the Inflammatory Response

EPITHELIUM

The gastrointestinal epithelium interfaces with a luminal environment inhabited by potentially hostile microbial organisms. The epithelium presents a physical barrier to invasion by the flora of the gastrointestinal tract, consisting of the apical cellular membrane, intercellular tight junctions the permeability of which is highly regulated, and a secreted layer of mucus. Breaching of the mucosal barrier by invading pathogens generates potent soluble and neural signals that initiate an inflammatory response.[1] Conceptually, the epithelium can be thought of as a sensory organ detecting pathogen invasion to trigger an appropriate host defense and reparative response.

Noninfectious mucosal injury or invasion of epithelial cells by pathogenic organisms such as *Salmonella* activates synthesis of proinflammatory chemokines (chemoattractants) by epithelial cells and triggers a robust influx of neutrophils into the tissue within hours of the damage.[1] Of the chemoattractants produced by epithelium, interleukin-8 (IL-8) has a particularly important role in initiating inflammation by recruiting neutrophils from blood[2-4] and regulating neutrophil migration through tissue matrix adjacent to epithelium.[5,6] Bacteria-derived formylated chemotactic peptides also act as potent chemoattractants that are fully capable of stimulating a robust inflammatory response in the intestine if the epithelial barrier permits the diffusion of the peptides across the mucosa.

Epithelial cells activated during infection produce cytokines such as tumor necrosis factor α (TNF-α),

arachidonic acid metabolites, and other proinflammatory mediators that activate recruited leukocytes.[7] Bacterial products, particularly lipopolysaccharide and other cell wall components, are potent activators of leukocytes recruited into the tissue. Once the inflammatory response has been initiated, TNF-α, IL-1β, and other pro-inflammatory products of neutrophils, monocytes, mast cells, and epithelial cells amplify the inflammatory response.

The enteric nervous system has a key role in sensing and regulating inflammatory responses in the intestine. For example, *Clostridium difficile* toxin A activates a neural pathway that triggers mast cell degranulation and neutrophil influx into the tissue.[8,9] Blockade of this neural pathway is sufficient to abolish the profound inflammatory response induced by toxin A and many of the effects of toxin A on enterocyte secretion. Other pathogens and immune-mediated hypersensitivity reactions similarly stimulate inflammation by mechanisms that involve the enteric nervous system. Thus the epithelium interacts in a highly complex manner with the intestinal milieu, the enteric nervous system, and inflammatory cells to regulate the tissue response to injury and infection.

MACROPHAGES

Resident macrophages located in the lamina propria, submucosa, and intestinal lymphoid organs are among the first cells beyond the epithelium to respond to infection or injury. Macrophages are activated by bacterial products via pattern recognition receptors and begin to produce proinflammatory molecules important for recruiting and activating neutrophils and monocytes. Pattern recognition receptors recognize microbial products ranging from lipopolysaccharide to peptidoglycan and even CpG-containing bacterial DNA and signal the invasion by pathogens. Of the pattern recognition receptors, the lipopolysaccharide receptor complex is perhaps the best defined. Lipopolysaccharide activates macrophages via the CD14–Toll-like receptor complex to initiate transcription of the inflammatory cytokines TNF-α and IL-1β, which synergize with lipopolysaccharide to amplify the macrophage response.[10] Lipopolysaccharide, particularly in concert with inflammatory cytokines, stimulates macrophages to produce copious amounts of nitric oxide, which is microbicidal and vasoactive. Nitric oxide and other nitrogen radicals react with reactive oxygen intermediates (ROIs) to produce some of the most toxic molecules of the host defense system: the peroxynitrites.[11] IL-8 is produced as well to recruit neutrophils. As the response progresses, other inflammatory mediators, particularly the arachidonic acid–derived lipids, are produced. These lipids have potent vasoactive effects and are important stimuli of endothelial cells, neutrophils, and platelets.

Vascular Response During Inflammation

Four important changes occur in the intestinal vasculature during inflammation:
1. Alteration of blood flow
2. Increased vascular permeability
3. Increased adhesiveness of endothelial cells, leukocytes, and platelets
4. Exposure of the basement membrane and activation of the complement, contact, and coagulation cascades

A wide range of mediators alters blood flow during intestinal tract inflammation, from gasses such as nitric oxide (a major vasodilator of the intestinal vasculature) to lipids (prostaglandins, leukotrienes, thromboxanes, and platelet-activating factor), cytokines, bradykinin, histamine, and others. The major sources for these mediators include activated leukocytes, endothelial cells, epithelial cells, and fibroblasts. The primary determinant of blood flow early in inflammation is vascular caliber, which initially decreases in arterioles, but then quickly changes to vasodilation coincident with opening of new capillary beds, increasing net blood flow. The increase in blood flow is short lived, for the viscosity of the blood increases because of fluid loss and tissue edema through leaky capillaries. Leukocyte margination, platelet adhesion to endothelial cells and exposed matrix, and areas of coagulation protein accumulation further decrease local circulation.

Inflammatory mediator actions on the endothelial cells initially increase vascular permeability. Histamine, leukotrienes, platelet-activating factor, prostaglandins, bradykinin, and other mediators stimulate endothelial cell contraction, and interendothelial gaps form.[12,13] This stage of increased vascular permeability is readily reversible. Concurrently, mediators such as the cytokines TNF-α and IL-1β induce a structural reorganization of the interendothelial junctions, resulting in frank discontinuities in the endothelial monolayer.[14] Cytokines also stimulate endothelial cells to express adhesion molecules that support adhesion of leukocytes and platelets,[15] leading to the next and perhaps most devastating event. Leukocytes (primarily neutrophils) and platelets adhere to exposed basement membranes and activated endothelial cells. Adherent neutrophils and platelets then are exposed to the mediators of inflammation present in the surrounding milieu, which activates the cells to release oxidants and proteases (particularly elastase) that injure the endothelium and have the potential to cause irreparable harm to the microvasculature.[16-18] Marginated neutrophils begin to transmigrate between endothelial cells (as described in later sections), and if their numbers

are large enough, they disrupt the integrity of the interendothelial junctions, worsening the vascular leakage.[17]

Conceptually, these stages of enhanced vascular permeability can be thought of as a mechanism to allow plasma proteins to enter the tissues and to potentiate the critical influx of leukocytes into tissues. However, if not regulated precisely, alterations in hydrostatic and oncotic forces and irreversible damage to the vascular bed may have devastating consequences. Moreover, inappropriate activation of plasma protein cascades and leukocytes by activated endothelium and exposed matrix proteins can contribute to systemic inflammation (systemic inflammatory response syndrome; see Chapter 13.7 for more information) characterized by hypotension, generalized vascular leak syndrome, and multiorgan dysfunction, which may be fatal. Phosphodiesterase inhibitors reduce endothelial permeability in ischemia-reperfusion injury and other models of inflammation-induced vascular leakage[19,20] by increasing endothelial tight junction integrity and thus may be a viable therapeutic strategy to prevent or reduce the permeability alterations associated with inflammation.

Cellular Effectors of Inflammation

ENDOTHELIAL CELLS
Endothelial cells respond to products of activated epithelial cells and macrophages in the intestinal tissue to recruit cells and humoral mediators of inflammation into the tissue. Activated endothelial cells display a range of molecules critical for neutrophil and platelet adhesion. Intercellular permeability increases to expose basement membrane proteins that trigger humoral defense systems (complement, coagulation, and contact system cascades) and to provide access for these macromolecules to the tissue. Endothelial cells are an important source of inflammatory mediators that amplify the response and vasoactive substances (particularly nitric oxide) that alter blood flow.
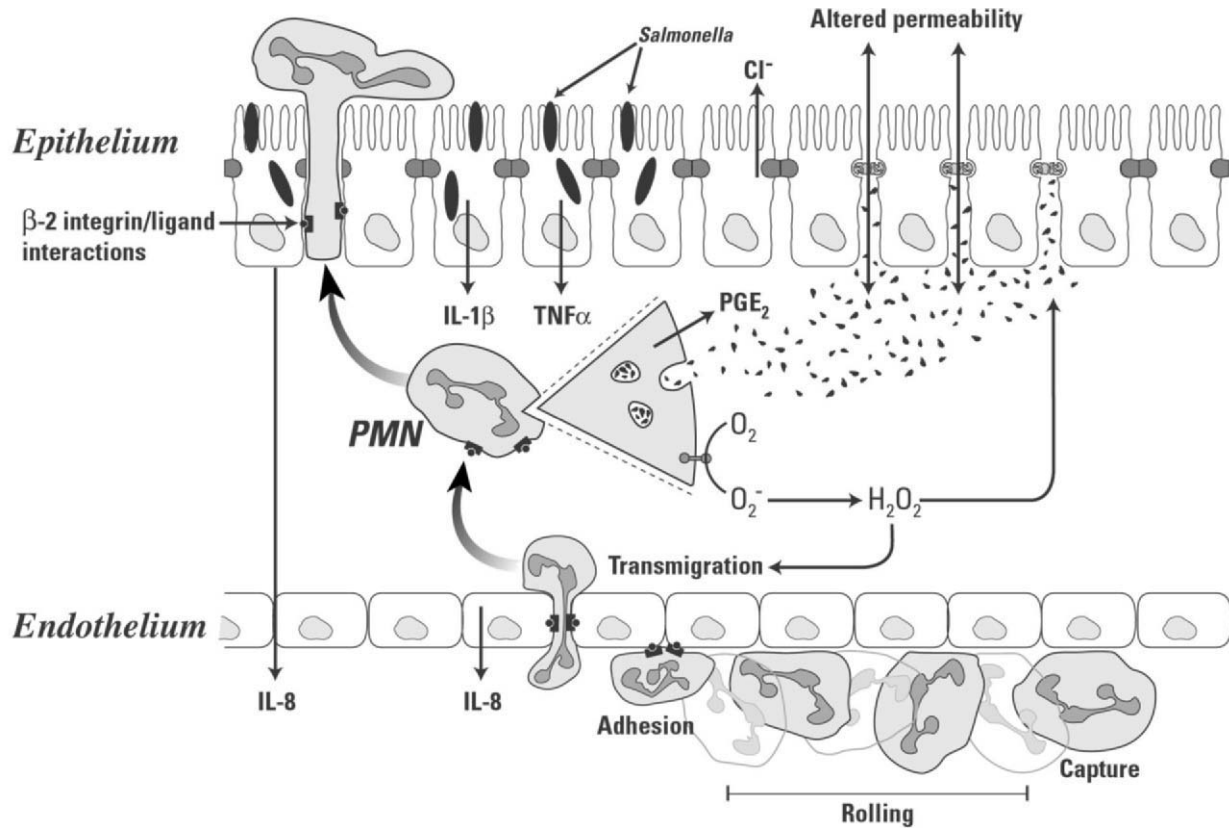
NEUTROPHILS
Recruitment
Infection or injury to the gastrointestinal mucosa causes an influx of leukocytes from the blood that lay the foundation of the inflammatory response. Neutrophils, being the first to arrive during inflammation, have a dominant role in the acute response. Within minutes, neutrophils are recruited into the tissue where they are activated to release products that not only are proinflammatory and lethal to pathogens but also may damage host cells and tissues. Not surprisingly, much attention has been paid to the role of neutrophils in the pathophysiology of many inflammatory conditions.[21] Neutrophil depletion is protective in many models of gastrointestinal inflammatory

disease. Of interest to clinicians, blockade of neutrophil migration into inflamed tissues prevents many of the pathophysiologic events associated with infectious enteritis, ischemia-reperfusion injury, and other gastrointestinal diseases.[16,22-26]

Neutrophil transendothelial migration is a multistep process that is temporally and spatially regulated and has a degree of cell type specificity (Figure 13.2-1). The predominant sites of neutrophil transendothelial migration are in the postcapillary venules and, in some tissues, the capillaries. Endothelial cells in these vessels respond to cytokines and other soluble signals by expressing molecules that promote neutrophil adhesion and transmigration, including selectins and counter-receptors for integrins. As neutrophils flow through these vessels, they are first tethered to activated endothelium. Tethering is mediated by selectin molecules expressed on neutrophils (L-selectin) and on activated endothelial cells (P- and E-selectins) that bind to P-selectin glycoprotein ligand-1 (PSGL-1), E-selectin ligand-1 (ESL-1), and other mucin counterreceptors.[27,28] Tethering functions to increase the exposure of the neutrophil to activating chemokines presented on the surface of the endothelial cells.

Stimulation of neutrophils by IL-8 and other chemokines activates the second step of transendothelial migration. Chemokine binding to their receptors on the neutrophil generates signals that activate the binding of integrin adhesion receptors to their ligands, called intracellular adhesion molecules or vascular cell adhesion molecules expressed on endothelial cells in inflamed mucosa. Integrin ligation to cellular adhesion molecules arrests the tethered neutrophils, resulting in firm adhesion to the endothelium. Of the integrins expressed on neutrophils, the β_2 integrins have a particularly important role in transendothelial migration. Calves and human beings with a disorder known as leukocyte adhesion deficiency illustrate the requirement for β_2 integrin–mediated adhesion in neutrophil function. Leukocyte adhesion deficiency results from an autosomal recessive trait causing the lack of the β_2 integrin expression. The neutrophils from these individuals cannot migrate into most tissues and do not function normally, resulting in poor tissue healing and profound susceptibility to infection, especially at epithelial barriers.[29,30] Other integrins also have a role in transendothelial migration. β_1 Integrins mediate transendothelial migration in some cells and seem to be particularly important for mediating emigration of monocytes into many tissues.[31]

Following this firm adhesion step, neutrophils migrate through the endothelium along a chemotactic gradient of IL-8 and other chemoattractants such as leukotriene B_4.[3,17,32] Neutrophils migrate across the endothelial monolayer at intercellular junctions via a mechanism involving

Figure 13.2-1 Depiction of neutrophil responses during intestinal inflammation in response to salmonella infection. Salmonellae infect epithelial cells, stimulating the production of chemokines (interleukin-8 [IL-8]), cytokines (IL-1β and tumor necrosis factor-α [TNF-α]), and other proinflammatory mediators. Endothelial cells stimulated by inflammatory mediators produce chemoattractants (such as IL-8) and display adhesion molecules that promote neutrophil emigration. The three steps of neutrophil (polymorphonuclear [PMN]) emigration—capture/rolling (mediated by selectins), adhesion (mediated by β₂ integrins), and transendothelial migration (mediated by integrins and platelet/endothelial cellular adhesion molecule [PECAM])—occur on activated endothelium. Chemoattractant molecules, such as IL-8 trigger neutrophil emigration. In inflamed tissues, cytokines (IL-1β and TNF-α) and a variety of other proinflammatory mediators stimulate the neutrophil oxidase complex to produce reactive oxygen intermediates (ROIs; O_2^- and H_2O_2 and their derivatives). Activated neutrophils degranulate to release proteases and other hydrolases, cationic peptides (defensins), myeloperoxidase, and other products into the tissue. Activated neutrophils synthesize a variety of inflammatory mediators, including prostaglandins (PGE_2) that modulate the inflammatory response. The products of activated neutrophils (ROIs, proteases, and mediators) stimulate epithelial secretion and alter tight junction permeability, promoting diarrhea. Neutrophils eventually migrate across the infected epithelium by a mechanism that involves integrins, disrupting tight junction integrity and increasing permeability to bacterial products, thus exacerbating the inflammatory response.

a series of integrin-ligand interactions mediated by β₂ and β₁ integrins and other adhesion molecules[28] that is generally capable of maintaining the integrity of the endothelial barrier.[33] However, massive flux of neutrophils through the endothelium alters endothelial tight junctions and injures the basement membrane, resulting in increased endothelial permeability to molecules as large as plasma proteins and even endothelial cell detachment from the basement membrane.[17,18] Nonintegrin molecules such as platelet/endothelial cell adhesion molecules (PECAMs) also are involved in transendothelial migration of neutrophils.[28] Homotypic binding of PECAMs on adjacent endothelial cells form part of the intercellular junction. Neutrophils express an integrin of the β₃ family that can bind PECAM, and via sequential binding of β₃ integrins to PECAM, the neutrophil can

"unzip" the intercellular junction and migrate through, closing it behind itself.

Activation

A key feature of neutrophils and other leukocytes is the requirement for integrin-mediated adhesion to extracellular matrix proteins (ECMs) or other cells to achieve an optimal effector phenotype.[34] Critical components of the ECMs in inflamed tissues include fibronectin, fibrinogen, and vitronectin, deposited in tissues as a result of plasma leakage and by synthesis of new proteins by stromal cells and resident macrophages in response to inflammatory mediator activation. The changing composition of the matrix proteins deposited in tissues during inflammation serves as a clue as to the nature of the tissue environment for recruited inflammatory cells as they become activated. Individual gene expression studies have demonstrated that adhesion to matrix proteins induces the expression of cytokines and chemokines and their receptors, arachidonic acid–derived lipid mediator synthases, metalloproteinases, growth factors, transcription factors, and other genes that influence the differentiation and activation of inflammatory cells.[35] ROI production, phagocytosis, degranulation, and other effector functions stimulated by inflammatory mediators and bacterial products are optimal only when neutrophils adhere to the ECMs.[34] Adhesion to distinct ECM proteins selectively activates signaling pathways and gene expression of neutrophils, monocytes, and other leukocytes with differing abilities to promote certain functions such that the composition of ECMs in many ways controls the development of the ultimate effector phenotype. Thus integrin-mediated adhesion provides a mechanism by which neutrophils and other leukocytes can sense the complex tissue environment and respond appropriately.

Of the activators of neutrophils at sites of inflammation, complement (C3-opsonized particles), cytokines (TNF-α and IL-1β), platelet-activating factor, immune complexes, and bacterial products are among the most potent stimuli. Other mediators produced during inflammation may modify neutrophil activity, particularly formylated bacterial peptides, chemokines, complement fragments (C5a), leukotriene B_4, and prostaglandins. Activated neutrophils are highly phagocytic; produce large amounts of ROIs; degranulate to release myeloperoxidase, cationic antimicrobial peptides (defensins), serine proteases (mainly elastase), and metalloproteinases; and secrete inflammatory mediators (TNF-α, IL-1β, prostaglandins, leukotrienes, and others) (see Figure 13.2-1).

MAST CELLS

Mast cells strategically reside in mucosal tissues, including the submucosa and lamina propria of the gastrointestinal tract, and constitute a crucial first line of defense at epithelial barriers. However, they are also important effector cells of the pathophysiology of inflammatory gastrointestinal diseases.[36] Experimental depletion of mast cells, genetic deficiency in the development of mast cells, or pharmacologic stabilization of mast cells to prevent degranulation have a protective effect in a variety of models of gastrointestinal inflammatory disease, including dextran- or trinitrobenzenesulfonic acid–induced colitis,[37,38] ischemia-reperfusion injury,[39,40] and immediate hypersensitivity responses.[41]

Mast cells are activated by a wide variety of microbial products and host-derived mediators.[42] Among the activators of mast cells the so-called anaphylatoxins (complement fragments C3a, C5a, and C4a), are potent stimuli causing release of mediators of inflammation. In addition, mast cells are the primary effector cells of immunoglobulin E–mediated anaphylaxis (type I hypersensitivity reactions) by virtue of their high affinity receptors for immunoglobulin E. Cross-linking of receptor-bound immunoglobulin E on mast cell surface by antigens (i.e., food antigens) causes rapid degranulation, resulting in the explosive release of granule contents.[43] Neural pathways in the intestine also regulate mast cells. Mast cells respond to enteric pathogen invasion via neural reflexes that stimulate the release of inflammatory mediators.

Activated mast cells release preformed histamine, 5-hydroxytryptamine, proteases, heparin, and cytokines from granules. Activation also stimulates de novo synthesis of a range of inflammatory mediators, including prostaglandins, platelet-activating factor, and leukotrienes. Transcription of a number of peptide mediators, such as the cytokines TNF-α and IL-1β among many others, also increases on stimulation of mast cells. Mast cell products have profound effects on the vasculature, increasing endothelial permeability and causing vasodilation.[44] Moreover, mast cell–derived mediators greatly enhance epithelial secretion by a mechanism that activates neural pathways of epithelial secretion and directly stimulates epithelial cells.[43] Mast cell products significantly alter intestinal motility, generally increasing transit and expulsion of intestinal contents. Mast cell–derived leukotrienes and TNF-α also have a crucial role in host defense against bacterial pathogens, acting to recruit and activate neutrophils.[45,46]

Mast cells have a newly identified role in host defense and inflammatory responses to bacterial pathogens, which in part is caused by the release of proinflammatory mediators during bacterial infection, which is critical for recruiting and activating other innate host defense cells such as neutrophils. However, mast cells are also phagocytic, have microbicidal properties, and can act as antigen-presenting cells to the adaptive immune system.[47] Although accumulating evidence was establishing the

role of mast cells in innate immunity, a seminal study that unconditionally identified the importance of mast cells in host defense demonstrated that mast cell–deficient W/W^v mice have impaired responses to gram-negative bacterial peritonitis, resulting in a significant increase in mortality. The role for mast cells in host protective responses appears to be as a sensor of bacterial invasion. Unlike immunoglobulin E–mediated responses, bacterial products seem to elicit a highly regulated and selective response from mast cells.

Humoral Mediators of Inflammation

COMPLEMENT

The complement cascade is a fundamental part of the inflammatory response. Activation of the complement cascade by immune complexes (classical pathway) or by bacteria or bacterial products, polysaccharides, viruses, fungi, or host cells (alternative pathway) results in the deposition of complement proteins on the activating surface and the release of soluble proteolytic fragments of several complement components. In particular, activation of either pathway results in the deposition of various fragments of the complement protein C3, which are potent activators of neutrophils and monocytes.[48] Opsonization of particles with C3 fragments constitutes a major mechanism of target recognition and phagocyte activation.[49] During the activation of the complement cascade culminating in deposition of C3, soluble fragments of C3 (C3a), C5 (C5a), and C4 (C4a) are liberated. These fragments, termed *anaphylatoxins,* have potent effects on tissues and cells during inflammation. Perhaps most notably, anaphylatoxins are chemotactic for neutrophils (particularly C5a), activate neutrophil and mast cell degranulation, and stimulate ROI release from neutrophils.[48] The termination of the complement cascade results in the formation of a membrane attack complex in membranes at the site of complement activation, and if this occurs on host cells such as endothelium, it may cause irreversible cell injury. Although the primary source of complement is plasma, epithelial cells of the gastrointestinal tract also produce C3, suggesting that local production and activation of the complement cascade during inflammation occurs in intestinal tissues.

Clearly, if the regulatory mechanisms of the complement cascade fail, then the inflammatory response may be inappropriate and tissue injury can occur. The role of complement in gastrointestinal inflammation has been most studied extensively in models of ischemia-reperfusion injury. Activation of the complement cascades has a major role in altered endothelial and epithelial permeability in these models. Several lines of evidence support the importance of complement in intestinal injury. Mice deficient in C3 or C4 are protected against

ischemia-reperfusion injury.[50] Moreover, administration of monoclonal antibodies against C5 reduced local and remote injury and inflammation during intestinal reperfusion injury in a rat model.[51] Administration of a soluble form of complement receptor 1, a regulatory protein that halts the complement cascade by dissociating C3 and C5 on host cell membranes, reduced mucosal permeability, neutrophil influx, and leukotriene B$_4$ production during ischemia-reperfusion injury in rats and mice.[50,52] Although neutrophils and mast cells mediate many of the pathophysiologic effects of the complement cascade, the membrane attack complex may have a primary role in altered vascular permeability during ischemia-reperfusion injury.[53]

CONTACT SYSTEM

Four components initiate the contact system of coagulation: Hageman factor (HF), prekallikrein, factor XI, and high-molecular-weight kininogen. HF is a large plasma glycoprotein that binds avidly to negatively charged surfaces.[54] Bacterial cell walls, vascular basement membranes, heparin, glycosaminoglycans, and other negatively charged surfaces in the intestine capture HF and the other three important initiators of the contact system in a large multimolecular complex. Of the surfaces that bind HF, the extracellular matrix is a potent activator of the contact system. Once bound, HF is converted to HF-α, which cleaves prekallikrein to kallikrein and factor XI to factor XIa. The ultimate result is further cleavage of HF by kallikrein and triggering of the contact system cascade, activation of intrinsic coagulation by factor XIa, activation of the alternative pathway by HF, and proteolytic cleavage of high-molecular-weight kininogen by kallikrein, releasing biologically active kinins.

The products of the contact system, particularly bradykinin, have several important biologic properties that drive many of the vascular and leukocytic responses during inflammation.[54] Bradykinin induces endothelial cell contracture and intracellular tight junction alterations that increase vascular permeability to fluid and macromolecules. Bradykinin also affects vascular smooth muscle contracture, resulting in vasoconstriction or vasodilation depending on the location. Bradykinin also increases intestinal motility, enhances chloride secretion by the intestinal mucosa, and intensifies gastrointestinal pain. In neutrophils, kinins stimulate the release of many inflammatory mediators, including cytokines, prostaglandins, leukotrienes, and ROIs.[55] Kallikrein cleaves C5 to release C5a, a potent chemotactic factor for neutrophils, and thus has a role in recruiting and activating inflammatory leukocytes.

The plasma kallikrein-bradykinin system is activated in a variety of acute and chronic inflammatory diseases of the gastrointestinal tract.[56,57] Recent evidence has

demonstrated that blockade of the pathophysiologic effects of bradykinin has clinical applications. Oral or intravenous administration of the bradykinin receptor antagonist icatibant reduces the clinical signs, onset of diarrhea, and many of the histopathologic changes in experimental models of colitis in mice.[58] Inhibition of kallikrein by oral administration of P8720 attenuated the intestinal inflammation, clinical score, and systemic manifestations in a model of chronic granulomatous enterocolitis.[57] Thus the contact system is a viable therapeutic target for inflammatory diseases of the intestine.

Tissue Injury During Inflammation

Changes in blood flow to the mucosa and other regions of the intestine that reduce perfusion of the tissues can potentiate the initial damage caused by infection or injury. For example, reperfusion of ischemic tissues is associated with platelet and neutrophil clumping in the small vessels of the mucosa, which can impede blood flow.[59] Platelets are activated and adhere to exposed basement membrane and activated endothelial cells and provide a surface for leukocyte adhesion. The accumulation of platelets and leukocytes can reduce vessel diameter and blood flow significantly while potentiating local coagulation and thrombus formation.

Soluble mediators released by activated leukocytes and endothelial cells also affect blood flow. Histamine and the vasoactive lipids derived from arachidonic acid (leukotrienes, prostaglandins, thromboxane, prostacycline, and platelet-activating factor) have a prominent role in regulating local perfusion during inflammation and also may have systemic effects on blood flow. Procoagulant mediators released by inflammatory cells in response to the inflammatory process (i.e., tissue factor produced by macrophages or endothelial cells), exposed basement membrane proteins, and bacterial components can trigger the contact system and the coagulation and complement cascades, the products of which affect blood flow. Nitric oxide, whether produced by endothelial cells or leukocytes (macrophages), is a potent regulator of blood flow and has a significant role in the control of perfusion during inflammation.[60] Many of the mediators that affect perfusion also affect endothelial permeability, altering osmotic and hydrostatic balance and tissue edema. In extreme cases, local and systemic coagulopathies initiated by vascular injury and absorption of microbial products and inflammatory mediators induce a hypercoagulable state, leading to microthrombus formation, which can reduce blood flow, or macrothrombus formation, which causes tissue infarction.

The cellular mediators of inflammation have the potential to inflict severe injury to intestinal tissues.

Neutrophils have an important role in the pathophysiology of many intestinal diseases, including ischemia-reperfusion injury,[16,22] infectious enterocolitis,[23-25] nonsteroidal antiinflammatory drug–induced mucosal ulceration,[26] and others. Depletion of neutrophils, blockade of their emigration into tissues, or inhibition of neutrophil activation reduce the severity of these and other inflammatory diseases.[61] Thus many antiinflammatory therapies are emerging that specifically target neutrophil adhesion, migration, and activation.

Migration of neutrophils through endothelium during emigration into inflamed tissues is remarkable in that the permeability of the endothelial monolayer is preserved under most circumstances. However, a limit exists above which neutrophil migration alters the permeability characteristics of the endothelium. The effect is in part physical in that mere movement of large numbers of neutrophils through the endothelium is sufficient to disrupt the tight junctions mechanically and is caused in part by toxic products of neutrophils that damage endothelial cells and basement membranes.[59,62] Serine proteases (particularly elastase) and metalloproteinases released by degranulating neutrophils destroy tissue matrix proteins and cell-surface proteins that make up endothelial intercellular junctions. These degradative enzymes are particularly damaging to basement membranes and the cellular barriers of the endothelium, thus contributing to vascular permeability (and local tissue edema) and thrombosis. The permeability may be affected to the extent that not only water but macromolecules (albumin, matrix proteins, complement, etc.) leak into the interstitium. Blockade of neutrophil adhesion to endothelium with anti–β_2 integrin antibodies has a sparing effect on the microvasculature in experimental intestinal ischemia-reperfusion injury, reducing the alterations in vascular permeability and histopathologic evidence of microvascular damage.[59]

Similar to the endothelium of inflamed tissues, massive neutrophil transmigration occurs across the epithelium in response to infection or injury. Neutrophil transepithelial migration increases epithelial permeability by disrupting tight junctions.[62] Like the endothelium, neutrophils disrupt the epithelial barrier mechanically as they migrate through (see Figure 13.2-1). Proteases, particularly elastase, degrade basement membrane components and tight junction proteins. Products of activated neutrophils (TNF-α and interferon-γ) increase tight junction permeability by direct effects on the enterocytes. Prostaglandins released by activated neutrophils stimulate epithelial secretion, thus contributing to diarrhea. Subepithelial accumulation of neutrophils can lead to deadhesion of the epithelial cells from the basement membrane and mild to severe ulceration. The physiologic results of the effects of neutrophils and their products on

the epithelial barrier include protein-losing enteropathy and absorption of bacterial cell wall constituents, which potentiates the local and systemic inflammatory responses.

Neutrophils in inflamed tissues stimulated by potent host-derived activators (such as IL-1β and TNF-α) and bacterial products (lipopolysaccharide) release copious amounts of ROIs (see Figure 13.2-1). Although these oxygen and oxyhalide radicals are important for killing pathogens, they are also potentially toxic to epithelial and endothelial cells and matrix proteins. Reactive nitrogen intermediates produced primarily by macrophages during inflammation combine with ROIs to form peroxynitrites, which are particularly toxic.[11] In addition to injury to mucosal tissues, ROIs also have an as yet ill-defined role in recruiting and activating neutrophils, thereby potentiating the inflammatory response.[63] In support of the role of ROIs in inflammatory diseases of the gastrointestinal tract, administration of inhibitors of ROI production or pharmacologic ROI scavengers can be protective in many models of reperfusion injury or enterocolitis. Many therapies are aimed at inhibiting neutrophil activation and effector functions in tissues have been evaluated for use in intestinal diseases. Phosphodiesterase inhibitors, by causing cyclic adenosine monophosphate accumulation in neutrophils, are antiinflammatory by virtue of their ability to suppress neutrophil activation and ROI production. New phosphodiesterase inhibitors selective for the predominant neutrophil isoform of phosphodiesterase hold promise for use in many inflammatory diseases.

Subepithelial mast cells also have an important role in altering epithelial permeability in inflamed intestine. During the intestinal hypersensitivity response, subepithelial mast cell release of mast cell protease II by degranulation increases epithelial permeability via an effect on tight junctions.[41,64,65] This alteration in tight junction permeability results in enhanced transepithelial flux of macromolecules, including proteins and bacterial products. Cytokines released by mast cells and phagocytes also regulate tight junction permeability. Interleukin-4, a product of mast cells and macrophages, increases epithelial permeability.[66] Moreover, TNF-α and interferon-γ, products of many inflammatory cells, synergistically increase tight junction permeability.[67]

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13.3—Pathophysiology of Diarrhea

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Acute equine colitis causes rapid, severe debilitation and death in horses (more than 90% of untreated horses die or require euthanasia).[1] Since 1919, several reports have described a number of different acute diarrheal conditions in the horse that appear to share a common characteristic clinical presentation.[2-10] Diarrhea associated with acute equine colitis occurs sporadically, is highly fatal, and is characterized by intraluminal sequestration of fluid, moderate to severe colic (abdominal pain), and profuse watery diarrhea with resultant endotoxemia, leukopenia, and hypovolemia.[7,10,11] The condition can affect adult horses of all ages but usually occurs in horses between 2 and 10 years of age. Disease onset is sudden with a rapid progression and often is preceded by a stressful event. A definitive diagnosis is made in only about 20% to 30% of cases.[7,11] Most ante- and postmortem diagnostic tests remain speculative.

Treatment of the condition in horses is costly because of the massive fluid therapy required. Currently, no curative treatment is available for acute colitis in horses, human beings, or other mammals. Treatment regimens provide rehydration, electrolyte and plasma protein replacement, mitigation of the effects of circulating endotoxin, and antimicrobial therapy when indicated. Attempts during the past 40 years to develop appropriate treatments (i.e., vaccines or pharmacologic agents) have been hampered by the unavailability of acceptable equine models and have been unsuccessful because of the complex pathophysiology of the intestinal epithelium.

Although the mechanisms responsible for the fluid losses are not known, inflammatory cells may play an integral role because this condition is characterized by large numbers of granulocytes infiltrating the large intestinal mucosa.[12-16] Equine cecal and colonic tissues collected during the acute stages of experimentally induced acute equine colitis (equine ehrlichial colitis, lincomycin with and without *Clostridium* spp. inoculation, nonsteroidal antiinflammatory drug administration) reveal the presence of numerous neutrophils and eosinophils in the lamina propria and submucosa.[12,15,17,18] Granulocyte-derived reactive oxygen intermediates are crucial to antimicrobial defenses in the gut and stimulate chloride and water secretion by interactions with enterocytes.[19,20] Normal equine intestinal tissue is unique compared with that in most other mammalian species for a preponderance of eosinophils located in the intestinal mucosa and submucosa.[6,21] Production of reactive oxygen intermediates by stimulated phagocytic granulocytes following mucosal barrier disruption may be responsible for the massive fluid secretory response that occurs during the early stages of acute equine colitis.

Colitis refers to inflammation and mucosal injury of the colon and cecum (typhlocolitis) that may occur in response to a number of causes.[22,23] The cause of the colonic injury may be well-defined such as in naturally occurring infectious or experimentally induced colitis. However, many cases of human and animal diarrhea have a speculative or unknown diagnosis or no diagnosis.[11,24,25] Irrespective of the underlying or initiating cause of colonic injury, the colon apparently has a limited repertoire of responses to damage because most forms of colitis demonstrate similarities in histopathologic appearance and clinical presentation. Various degrees of mucosal erosion and ulceration, submucosal/mucosal edema, goblet cell depletion, and presence of an inflammatory cellular infiltrate within the mucosa and submucosa are common to many types of human and animal colitis.[21,23-25] Characteristic clinical manifestations include intraluminal fluid sequestration, abdominal discomfort, hypovolemia, and most often profuse, watery diarrhea.

Pathophysiology of Colitis

Large bowel diarrhea results from abnormal fluid and ion transport by cecal and colonic mucosa. Loss of fluid by the large intestine can result from malabsorptive or hypersecretory processes and is often a combination of the two.[26] Colonic secretory processes are a function of the crypt epithelium, whereas absorptive processes are limited to surface epithelial cells.[27] Under normal baseline conditions, an underlying secretion by crypt epithelium is masked by a greater rate of surface epithelial cell absorption. Abnormal forces influencing the rates of

secretion and absorption can result in massive, uncontrolled secretion and malabsorption by large intestinal mucosal epithelial cells, leading to rapid dehydration and death.[26,27]

Two intracellular processes control colonic secretion: the cyclic nucleotide (cyclic adenosine monophosphate [cAMP] and cyclic guanosine monophosphate [cGMP]) and the calcium system.[28,29] Agents may activate adenyl cyclase (vasoactive intestinal peptide, prostaglandin E_2 [PGE_2]) or guanyl cyclase (bacterial enterotoxins) and induce increases in cAMP or cGMP, respectively. This reaction causes phosphorylation of specific protein kinases that induce the actual apical and basolateral membrane transport events. Increases in intracellular free calcium may arise from cyclic nucleotide–dependent release of stored calcium within the cell or from increased calcium entry across the cell membrane.[26,27] Calcium may act through calmodulin, which then can activate membrane-phosphorylating protein kinases.

At least four central systems control intestinal secretion: (1) the hormonal system, (2) the enteric nervous system, (3) bacterial enterotoxins, and (4) the immune system.[29,30] Hormonal control of colonic electrolyte transport is exerted primarily through the renin-angiotensin-aldosterone axis.[31,32] The enteric nervous system controls transport through three separate components: (1) extrinsic nerves of the parasympathetic and sympathetic pathways; (2) intrinsic ganglia and nerves, secreting a variety of neurotransmitters including peptides; and (3) neuroendocrine cells (intraepithelial lymphocytes) that reside in the epithelium and release messengers onto the epithelial cells in a paracrine manner.[26,29-32] Many bacterial enterotoxins can induce intestinal secretion by cAMP or cGMP signal transduction.[33] Bacterial enterotoxins can stimulate enteric neurons, providing evidence for interaction between two controlling systems.[34]

Preformed inflammatory mediators such as histamine, serotonin, or adenosine and newly synthesized mediators such as prostaglandins, leukotrienes, platelet-activating factor, various cytokines, the inducible form of nitric oxide, and reactive oxygen metabolites can initiate intestinal secretion by directly stimulating the enterocyte and by acting on enteric nerves indirectly to induce neurotransmitter-mediator intestinal secretion.[30] For instance, when added to the T84 colonic cell line, the known mast cell mediators histamine, adenosine, and PGD_2 induce chloride secretion.[35-37] Prostaglandins of the E and F series can cause an increase in chloride secretion in intact tissue and isolated colonic cells.[38-40] Leukotrienes, platelet-activating factor, and a number of cytokines have been shown to have no effect on T84 cell secretion but have a significant effect on electrolyte transport in intact tissue, suggesting that intermediate cell types may be involved in these secretory responses.[41-43]

The epithelial cell chloride secretory response occurs via prostaglandin- and adenosine-mediated increases in cellular cAMP, whereas histamine acts by H_1 receptor induction of phosphatidylinositol turnover, production of inositol triphosphate, and mobilization of intracellular calcium stores.[30,33] Lipoxygenase products (leukotrienes) are capable of activating a colonic secretory response and do not appear to involve the cyclic nucleotides or calcium ions.[41] Phagocyte-derived reactive oxygen mediators (ROMs) can induce colonic electrolyte secretion in vitro, suggesting that oxidants may contribute directly to the diarrhea associated with colitis.[44-48] Reactive oxygen species initiate the secretory response by increasing cellular cAMP or stimulating mesenchymal release of PGE_2 or prostacyclin, which in turn stimulates the epithelial cell or enteric neuron, respectively.[44-49] Sodium nitroprusside, an exogenous source of nitric oxide, stimulated an increase in chloride secretion in rat colon that was mediated by cyclooxygenase products and enteric neurons.[50] Table 13.3-1 summarizes inflammatory mediator–induced epithelial cell chloride secretion.

Role of Inflammatory Cells

Acute colitis rarely develops by a simple cause or effect phenomenon but is influenced by many extrinsic and intrinsic host and microorganism factors. Inflammatory mediators released from mast cells and monocytic or granulocytic phagocytes cause intestinal chloride and water secretion and inhibit neutral sodium and chloride absorption.[29,30,67] Inflammatory cells, particularly the phagocytic granulocytes, play an important role in mucosal pathophysiology in cases of colitis.[20,68] Large numbers of these cells are observed on histopathologic examination of tissues from human and animal cases of colitis. Products of cell activation stimulate direct and indirect secretory responses in intestinal cells and tissues.[28-30,45-49] Products of phagocyte secretion may amplify the inflammatory signal or have effects on other target cells in intestine such as enterocytes and smooth muscle cells (Table 13.3-2).

Role of Phagocyte-Derived Reactive Oxygen Metabolites

The NADPH-oxidase system of phagocytes (neutrophils, eosinophils, monocytes/macrophages) is a potent inducer of superoxide radicals used as a host defense mechanism to kill invading microorganisms.[20,69] During inappropriate stimulation such as inflammation, trauma, or ischemia followed by reperfusion, increased levels of toxic oxygen species are produced, causing damage to host tissues. Engagement of any of several receptor and nonreceptor

TABLE 13.3-1

Inflammatory Mediators That Stimulate Epithelial Cell Chloride Secretion

MEDIATOR	ACTION	REFERENCE
Prostaglandin E_2	Increases Cl secretion.	51
	Decreases neutral NaCl absorption.	
Vasoactive intestinal peptide	Increases cAMP-mediated NaCl secretion.	52
	Activates cholinergic nerves.	53
Endotoxin	Increases Na absorption.	54
	Increases cell membrane permeability.	
Serotonin	Increases fluid and electrolyte secretion.	55
Interferon-γ	Decreases tight junctions and causes increase in cell membrane permeability.	56
Interleukin-1α and interleukin-1β	Increase prostaglandins E_2 and $F_{1\alpha}$ and thromboxane B_2.	57
Histamine (H_1)	Increases Cl secretion via Ca-mediated pathways.	58 and 59
Bradykinin	Increases Cl secretion through prostaglandin-mediated pathways.	60 and 61
Reactive oxygen mediators	Increase Cl secretion.	44 and 62
Thromboxanes	Increase Cl secretion.	63
	Decrease neutral NaCl absorption.	
Lipoxygenase products	Increase Cl secretion via prostaglandin-mediated pathways.	64
Platelet-activating factor	Increases Isc (Cl secretion).	65
Adenosine	Increases Cl secretion.	66

cAMP, Cyclic adenosine monophosphate.

types including phagocytosis mediators, chemotactic agents, various cytokines, and microbial products can stimulate phagocytes.[20] Resident phagocytes or those recruited to colonic mucosa early in the disease process are considered to augment mechanisms causing fluid and electrolyte secretory processes, a so-called amplification process.[70,71]

Activation of the respiratory burst results in the production and release of large amounts of superoxide anion (O_2^-) and H_2O_2.[69,72] In addition to these ROMs, activated phagocytes secrete peroxidase enzyme (myeloperoxidase from neutrophils and eosinophil peroxidase from eosinophils) into the extracellular space. The peroxidases catalyze the oxidation of Cl^- by H_2O_2 to yield HOCl, the active ingredient in household bleach products. The peroxidase-H_2O_2-halide system is the most cytotoxic system of the phagocytes; HOCl is 100 to 1000 times more toxic than O_2^- or H_2O_2.[69] HOCl is a nonspecific oxidizing and chlorinating agent that reacts rapidly with a variety of biologic compounds including DNA, sulfhydryls, nucleotides, amino acids, and other nitrogen-containing compounds. HOCl reacts rapidly with primary amines (RNH_2) to produce the cytotoxic N-chloramines (RNHCl). The mechanisms by which HOCl and RNHCl damage cells and tissue remain speculative, but possibilities include direct sulfhydryl oxidation, hemoprotein inactivation, protein and amino acid degradation, and inactivation of metabolic cofactors of DNA.[73] Peroxidase-derived oxidants have been shown to degrade hyaluronic acid and collagen.[74] In addition, luminal perfusion of specific ROMs increased mucosal permeability and serosal application caused increases in Cl^- secretion in vitro.[75]

Tissue myeloperoxidase activity, an index of tissue granulocyte infiltration, is used clinically and

TABLE 13.3-2

Phagocyte-Derived Inflammatory Mediators

ENZYME	MEDIATOR	MONOKINE	REACTIVE OXYGEN MEDIATOR
Protease	Platelet-activating factor	Interleukin-1	O_2^-
Kallikrein	Prostaglandin	Tumor necrosis factor	H_2O_2
Phospholipase	HPETE	Interferon-γ	OH^-
	Leukotriene		HOCl

HPETE, Hydroperoxyeicosatetraenoic acid.

experimentally to assess degree of intestinal inflammation.[76,77] Myeloperoxidase activity is elevated in acute flare-ups of human inflammatory bowel disease and various animal models of acute colitis.[76-80]

The acute inflammatory response in these conditions is characterized predominantly by neutrophils, the predominant source of myeloperoxidase activity. However, this assay measures total hemoprotein peroxidase, which includes monocyte and eosinophil peroxidase in addition to neutrophils.[77] Moreover, levels of peroxidase activity in equine circulating eosinophils are greater than in circulating neutrophils,[81] and this may apply to resident tissue eosinophils as well.

Arachidonic acid metabolites are thought to play a role in intestinal inflammation in diarrheal disease.[30,45,82] Elevated levels of these intermediate metabolites have been demonstrated in natural disease and experimental models of colitis and appear to parallel increases in ROMs in inflamed intestine.[82] Addition of H_2O_2 or HOCl to rat colonic tissue in Ussing chambers has been shown to induce PGE_2 release and active Cl^- secretion.[47,48] Prostaglandins can stimulate increases in Cl^- secretion in intact intestinal tissue[45,46,48] and in isolated colonic T84 cells.[47,49] Interactions between ROMs and mesenchymal release of PGE_2/PGI_2 may be relevant to the mechanisms producing the diarrheic condition. Fibroblasts co-cultured or juxtaposed to colonic T84 cells greatly increased the Cl^- secretory response to H_2O_2 in vitro through the release of PGE_2.[49] In addition, equine colonic mucosa has an increased sensitivity to endogenously released prostaglandin by exhibiting a significant secretory response under in vitro conditions.[83]

Role of Endotoxin, Malnutrition, Immunodeficiency, and Intestinal Microflora

ENDOTOXIN
Endotoxin, the lipopolysaccharide component of the outer cell wall of gram-negative bacteria, is present in large quantities in the large intestine of healthy horses.[81,83] Endotoxins are released into the immediate surroundings when gram-negative bacteria undergo rapid proliferation or die.[84,85] The intact bowel forms an effective barrier to the transport of significant amounts of these highly antigenic toxins, but the diseased gut absorbs these macromolecules in large amounts, causing the subsequent adverse systemic effects that are often life threatening.[86]

Disruption of the intestinal barrier (i.e., ischemia, trauma, inflammatory conditions) overwhelms the capacity of the liver to clear endotoxins, and systemic endotoxemia ensues. Endotoxins have been shown to be potent activators of the inflammatory process, stimulating the production and release of numerous cytokines by activated macrophages and other immunocytes.[87] In vitro studies suggest that endotoxin activates phagocytic granulocytes to secrete ROMs, increase release of lysozymes, and enhance the migratory response to chemotactic stimuli.[88] Prostacyclin and thromboxane A_2 mediate hemodynamic dysfunction, and lipoxygenase products may induce tissue ischemia.[89] The cytokine interleukin-1 causes a febrile response and initiates the acute phase response.[90] Tumor necrosis factor contributes to many of the abnormal physiologic responses, particularly hemostatic functions that potentiate coagulopathy.[91] Additional mediators include interleukin-6, platelet-activating factor, procoagulant mediators, and various other speculated substances.[84]

Endotoxins trigger mucosal immune cells and subsequent release of inflammatory mediators in cases of colitis. The first report of experimentally induced endotoxemia described clinical signs and hematologic findings that closely paralleled those reported for severe colitis in horses.[92] Studies in which endotoxin was administered intravenously in human beings and laboratory animals caused significant dose-related gastrointestinal changes, ranging from mild diarrhea to bloody, watery diarrhea.[93,94] In vitro studies on the effects of endotoxin on intestinal water and electrolyte transport in adult male rats showed a significant decrease in net colonic sodium absorption and increased colonic permeability.[55]

In animal models of protein energy deficiency, endotoxin-induced mortality increased compared with that of well-nourished control animals. Endotoxin depresses lymphocyte responses to specific mitogens.[95] Thus the adverse effects of malnutrition and endotoxin are mutually aggravating.

IMMUNODEFICIENCY
The importance of a normal immune system to the defense of the mucosal surface of the gastrointestinal tract is evident in the immunosuppressed state. Primary immunodeficiencies affecting the gastrointestinal tract are well documented.[96-98] Common agammaglobulinemia is the most frequently reported gastrointestinal disease and causes B cell deficiency–associated giardiasis.[99] Interestingly, selective immunoglobulin A (IgA) deficiency rarely results in intestinal disease because of a speculated increase in mucosal IgM response. However, combined IgA and IgM deficiencies with a higher incidence of intestinal disease occur. A selective deficiency of secretory IgA has been associated with intestinal candidiasis. Certain mucosal pathogens may enhance their pathogenicity by producing IgA proteases.[99] Defects in cell-mediated immunity are associated most commonly with intractable diarrhea, and organisms frequently involved include

TABLE 13.3-3

Vitamin and Mineral Deficiency–Related Immunodeficiencies

DEFICIENCY	FUNCTION
Pyridoxine, folic acid, vitamin C, vitamin E	Impairs cell-mediated immunity and reduces antibody response.
Vitamin B_6	Decreases lymphocyte stimulation response to specific mitogens.
Zinc	Deficiency affects humoral and cell-mediated immunity.
Iron	Inhibits bacterial multiplication.
Copper	Depresses antibody response.

Salmonella spp., *Escherichia coli,* and *Shigella* spp.[100] Acquired immunodeficiency or immunosuppression in adults can result from infectious diseases (particularly viral), nutritional deficiencies, aging phenomenon, and drugs (corticosteroids, azathioprine, cyclophosphamide).

NUTRITIONAL DEFICIENCIES

Nutrition is a critical determinant of immunocompetence and risk of illness.[101,102] Impaired systemic and mucosal immunity contribute to an increased frequency and severity of intestinal infections observed in cases of undernourishment. Abnormalities occur in cell-mediated immunity, complement system, phagocytic function, mucosal secretory antibody response, and antibody affinity. Morbidity caused by diarrheal disease is increased particularly among individuals with stunted growth rate because of malnourishment.[102]

The critical role of several vitamins and minerals in immunocompetence has been substantiated in animals deprived of one dietary element and findings in human patients with single-nutrient deficiency. Tables 13.3-3 and 13.3-4 summarize nutritional-related immune system abnormalities.

TABLE 13.3-4

Vitamin and Mineral Excess–Related Immunodeficiencies

EXCESSES	FUNCTION
Vitamin A	Increases the immune response.
β-Carotene	Increases the number of $CD4^+$ cells.
Vitamin E and selenium	Enhance immunocompetence and increase resistance to microorganisms.
Zinc	Depresses neutrophil function and lymphocyte responses.
Iron	Needed by neutrophils and lymphocytes for optimal function, which may be related to myeloperoxidase and ribonucleotidyl reductase deficiencies.

In summary, nutritional deficiency can cause increased colonization of the intestine with microorganisms, alter the symbiotic characteristics of resident intestinal bacterial populations, and impair defenses of the gastrointestinal tract, allowing increased risk of systemic spread of infection and absorption of macromolecules (in particular, endotoxin).

INTESTINAL MICROFLORA

Indigenous microflora greatly impede colonization of the gastrointestinal mucosa by pathogenic organisms. The ability of a potential pathogen to initiate an infection depends on its ability to breach the mucosal epithelial barrier. One mechanism by which the normal flora inhibit establishment of pathogens is by preventing adherence of the pathogen to mucosal cells by occupying the site or by stearic hindrance.[102-105] Resident microbes also produce byproducts such as antibacterial factors that allow symbiosis rather than competition between them. Another hindrance mechanism is production of volatile fatty acids by normal microbial digestive processes to create an environment that is toxic to many bacterial populations, particularly the Enterobacteriaceae.[106]

Factors Affecting Motility

Disturbances in motility patterns occur during inflammatory diseases of the colon, but the role of motility alterations in the pathogenesis of diarrhea remains unclear. Invasive bacteria cause characteristic motor patterns in the colon consisting of rapid bursts of motor activity that appear to decrease transit time through the large intestine. The result is reduced clearance of bacteria from the large intestine, which may contribute to the virulence of the organism.[107] Absorption of endotoxin and the release of inflammatory mediators such as prostaglandins disrupts the motility patterns of the large intestine, resulting in less coordinated contractions, and may contribute to the alterations in motility seen with invasive bacteria. Although the effect of endotoxin and prostaglandins on transit time is not profound, the disruption of coordinated activity may play a role in causing diarrhea.[108] Thorough mixing and prolonged retention time of ingesta are important not only in microbial digestion of nutrients but also in absorption of microbial byproducts and fluid.[32,109] The ingesta is viscous and therefore must be mixed to bring luminal ingesta in contact with the mucosa for absorption.[109] In addition, poor mixing increases the thickness of the unstirred layer, decreasing contact of ingesta with the mucosa and decreasing absorption.[32,109]

Progressive motility must be present, however, if a diarrheal state is to occur.[32,109] Ileus may be accompanied by increased fluid in the lumen of the large intestine,

but without progressive motility the fluid is not passed. Frequently, acute colitis causes a period of ileus characterized by scant stool. Diarrhea is apparent only when motility returns and the ingesta is passed. Increased progressive motility has been suggested to cause diarrhea by decreasing transit time and is thought to play a role in irritant catharsis and in the mechanism of action of some laxatives.[110] Irritation and distention increase motility and may well decrease transit time, but increased secretion also is thought to contribute to diarrhea caused by these substances.[111]

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13.4—Malabsorption Syndromes and Maldigestion: Pathophysiology, Assessment, Management, and Outcome

Malcolm C. Roberts

Pathophysiology

Malabsorption and maldigestion are recognized clinical problems in human medicine. In the horse the clinician often reaches the diagnosis of malabsorption for a condition by exclusion in the workup of a horse with chronic weight loss and wasting. The term *malabsorption* implies impairment of digestive and absorptive processes arising from functional or structural disorders of the small intestine and related organs, the pancreas, liver, and biliary tract. The condition can affect absorption of carbohydrates, proteins, fats, vitamins, minerals, and to a lesser extent, water and electrolytes. In the horse the resulting pathophysiologic changes may influence large intestinal function adversely through alterations in the substrate presented for fermentation. Malabsorption syndromes are encountered more frequently in human beings and small animals than they are in horses.

One should direct the clinical investigation of malabsorption at ascertaining and trying to localize the source of the abnormality. In medical practice, impairment of one or more phases of the digestion and absorption of dietary constituents may precipitate clinical signs that are associated primarily with carbohydrate, protein, or fat malabsorption. This level of differentiation is not possible in the horse because of the herbivorous diet and the contribution of large intestinal functions.

In human and small animal medicine, disturbances in digestive processes especially from exocrine pancreatic insufficiency or reduced intestinal bile salt concentration are principal determinants of many clinical malabsorption syndromes. The rarity of pancreatic problems in horses and the herbivorous diet makes maldigestion less of a concern and difficult to pursue diagnostically. Nevertheless, maldigestion undoubtedly contributes to chronic weight loss conditions in horses, which may be significant with severe infiltrative disease of the small intestine with partial to total villous atrophy and flattened mucosa. Impairment of digestive processes may exacerbate diarrhea in the suckling foal through reduced intestinal bile salt concentrations from hepatic or ileal dysfunction.

Malabsorption is not synonymous with diarrhea, although diarrhea may be a feature. Adult horses rarely exhibit diarrhea with small intestinal problems unless large intestinal involvement is concomitant. Chronic diarrhea is predominantly a large intestinal disorder that reflects an overload of water and electrolytes and thus may be considered a state of impaired absorption. Primary small intestinal disease is more likely to occur in neonates and young foals. For example, acquired small intestinal brush border lactase deficiency may result in increased lactose fermentation in the large intestine and induction of osmotic diarrhea.[1] Box 13.4-1 lists conditions that have been or potentially could be associated with malabsorption syndromes and maldigestion in the horse.

BOX 13.4-1

CONDITIONS THAT HAVE BEEN OR COULD BE ASSOCIATED WITH MALABSORPTION SYNDROMES AND MALDIGESTION IN THE HORSE

Malabsorption

Inadequate absorptive surface area
- Small intestinal resection (short bowel syndrome), villous atrophy (idiopathic), and mucosal atrophy

Small intestinal bacterial overgrowth (ileocecal valve bypass; physiologic)

Inflammatory or infiltrative disorders: chronic inflammatory bowel disease
- Granulomatous enteritis
- Multisystemic eosinophilic epitheliotropic disease (includes all eosinophilic conditions, such as eosinophilic granulomatosis, chronic eosinophilic gastroenteritis, and chronic eosinophilic dermatitis, except eosinophilic enterocolitis)
- Basophilic enterocolitis
- Lymphocytic-plasmacytic enterocolitis
- Lymphosarcoma, alimentary form; other forms with alimentary involvement
- Amyloidosis

Parasitic causes (larval cyathostomes)

Infectious causes (response to infectious agents)
- *Mycobacterium* spp., *Rhodococcus equi*, *Salmonella* spp., *Lawsonia intracellulare* (proliferative enterocolitis), *Histoplasma* spp., and others

Immunologic causes
- Immediate hypersensitivity to antigens presented to or absorbed from intestinal tract; food allergy

Biochemical defects (with or without microscopic cellular damage)
- Disaccharidase deficiency: acquired lactase deficiency in foals and monosaccharide transport defects

Lymphatic obstruction
- Lymphadenopathy; lymphangiectasia abscesses

Miscellaneous
- Partial intestinal obstruction, adhesions, mural thickening, and toxin-induced

Maldigestion

Gastric disorders
- Deficiency or inactivation of pancreatic lipase
- Exocrine pancreatic insufficiency: chronic pancreatitis and pancreatic carcinoma

Reduced intestinal bile salt concentration (with impaired lipid micelle formation)
- Hepatic dysfunction: parenchymal liver disease and cholestasis
- Interrupted enterohepatic bile circulation; ileal inflammatory disease or resection
- Abnormal bacterial proliferation in the small intestine: stagnant (blind) loops, incompetent ileocecocolic valve, bypass and resection, and hypomotility
- Drug-induced sequestration of bile salts: neomycin and calcium carbonate
- Small intestinal brush border enzyme deficiency

Malabsorption in horses has no pathognomonic clinical syndrome. Case recognition derives from the robust investigation of horses with chronic wasting. Prevalence is unknown. No strict case definition exists, even for chronic wasting. Interest generated by unusual clinical test results and their related pathologic findings has stimulated publication of reports of cases considered as malabsorption in horses. Pathologic description of the predominant cellular infiltrate and the pattern of intestinal distribution have resulted in the classification of many conditions as representing examples of chronic inflammatory bowel disease (CIBD) (see Box 13.4-1), drawing analogies from human medicine. In the affected animal, coexistent enteric protein loss reflecting changes in mucosal integrity from extensive infiltration and inflammation in the intestinal tract is likely to be more debilitating than the malabsorption.

Clinical Assessment

The principal concern of the owner is the weight loss and poor condition of the horse. Many clinical examination findings, except for body condition, may appear within normal limits. Investigation of the weight loss, together with the clinical pathologic findings, helps to eliminate other more commonly encountered causes of wasting. Box 13.4-2 lists clinical signs that may be associated with malabsorption syndromes.

BOX 13.4-2

CLINICAL SIGNS THAT MAY BE ASSOCIATED WITH MALABSORPTION SYNDROMES

Vital signs usually within normal limits: occasional slight fever, diurnal or cyclic (inflammation)

Mucosa: pallor; chronic anemia

Appetite: anorexia; poor, normal, or ravenous

Body condition: weight loss, chronic wasting, or more rapid and dramatic decline

Demeanor: normal, dull, or depressed

Energy and activity level: normal, decreased, or lethargic

Fecal consistency: formed, scant, increased, or diarrhea

Large intestinal involvement: diarrhea, unstructured feces, or blood

Pain: persistent low grade or intermittent abdominal discomfort

Edema: reduced albumin absorption, enteric protein loss, lymphatic obstruction, or liver disease

Palpable rectal abnormalities: thickened bowel wall or enlarged mesenteric lymph nodes

Extraintestinal signs: generalized skin lesions, exudative dermatitis, ulcerative coronitis, or arthritis

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No characteristic clinical pathologic profile of malabsorption exists. Findings relate to the stage of the underlying disease process and intercurrent problems. The syndrome tends to cause anemia (normocytic, normochromic) and neutrophilia. Hemolytic or macrocytic anemia and thrombocytopenia have been observed in alimentary lymphosarcoma. Lymphocytosis (leukemia) rarely is encountered. Eosinophilia is uncommon even with suspected immune-mediated conditions and widespread tissue eosinophilia. Many animals are hypoalbuminemic and hypoproteinemic; horses with alimentary lymphosarcoma may exhibit hyperproteinemia and hypergammaglobulinemia. Serum or plasma may be lipemic. The clinician may find elevated hepatic and biliary tract enzymes (γ-glutamyltransferase and alkaline phosphatase) in multisystemic conditions; for example, eosinophilic granulomatosis (multisystemic eosinophilic epitheliotropic disease; EG [MEED]). Abdominocentesis has been of diagnostic value in several alimentary lymphosarcoma cases, but rarely in the granulomatous conditions.

Ultrasonographic examination of the abdomen can yield infomation on intestinal distention, wall thickness, and unexplained masses detected on rectal palpation. Rectal biopsy is easy to perform and may provide an indication of cellular infiltration that could be present at more proximal locations. However, pathologists examine few equine rectal samples, and the interpretation is frequently equivocal. Adoption of standardized grading or classification would improve the diagnostic value. A proposed classification system was based on a retrospective study of 130 rectal biopsies from 116 horses ages 1 to 18 years with clinical signs of intestinal disease. Necropsy results were studied from 40 horses. Biopsy specimens (21 horses) and necropsy rectal tissue (9 horses) from 30 horses ages 4 to 22 years served as controls. Simple proctitis, the presence of neutrophils in the crypt or surface epithelium, was an abnormal finding compared with mild scattered neutrophil infiltration in controls. Simple proctitis was found in association with malignant lymphoma and other inflammatory disorders. Inflammatory bowel disease was diagnosed from rectal biopsy specimens in 6 of 12 EG (MEED) cases and 4 of 9 granulomatous enteritis cases confirmed at necropsy.[2] Rectal biopsy aided diagnosis for 3 of 7 horses in a series of lymphocytic-plasmacytic enterocolitis cases.[3] Eosinophils were demonstrated on impression smears of rectal mucosal biopsies from 1 of 2 horses with eosinophilic enterocolitis.[4]

Skin biopsies or ultrasound-guided biopsies of liver, lymph node, or lung may reveal evidence of multisystemic disease. One can obtain intestinal and lymph node biopsies via a standing laparotomy. Exploratory laparotomy facilitates rigorous inspection of the gastrointestinal

tract and associated organs to obtain multiple biopsies from intestinal sites and lymph nodes. The procedure may provide a diagnosis, enabling one to make decisions on potential treatment and management options. Cost and potential postoperative complications may limit surgical procedures for diagnosis. Laparoscopy may provide an alternative means to facilitate biopsy of certain tissues. However, one should consider surgical exploration as an option early in the process rather than as a last resort.

The noninvasive breath hydrogen test used to assess carbohydrate malabsorption in human beings has not proved reliable in equine studies.[5]

CARBOHYDRATE ABSORPTION TESTS AND INTESTINAL FUNCTION TESTS

Intestinal function tests can provide a practical and inexpensive means to assess the absorptive capability of the small intestine. For clinical practice purposes this is limited to carbohydrate absorption. Abnormality of carbohydrate absorption has become an important precept on which to base a diagnosis of malabsorption in the horse. However, results of the oral glucose tolerance test (OGTT) or D-xylose absorption test require cautious interpretation. Pathologic changes in the mucosa and submucosa must be extensive and widely distributed to greatly affect the peak plasma concentration and shape of the curve. The tests are easy to perform in practice and require a baseline blood sample predosing and further samples for up to 6 hours after administration of the solution. Many commercial laboratories conduct glucose and xylose assays.

Oral Glucose Tolerance Test

The immediate dietary history, gastric emptying rate, intestinal transit, age, and hormonal effects of the horse influence glucose peak and curve shape. Higher glucose peaks are recorded from healthy animals eating grass or hay than from those eating concentrates. Recent appetite or the level of cachexia may affect test results. Maximum plasma glucose level (>85% baseline) is reached by 120 minutes in healthy animals given 1 g glucose per kilogram body mass as a 20% solution.[6,7] Break points below which the probability increases of carbohydrate malabsorption associated with intestinal morphology changes have been proposed.[7]

A referral population of 42 mature horses with chronic weight loss was divided into three groups based on OGTT results to determine if any concurrence with the morphologic diagnoses existed. Group 1 ($n = 5$) had a normal OGTT (peak glucose concentration at 120 minutes >85% baseline) and contained animals that had normal small intestinal morphology, and a few with large intestinal lesions. Group 2 ($n = 25$) had partial malabsorption and included 18 horses with small intestinal

infiltrative disease that allowed some glucose uptake. Diagnoses included lymphosarcoma, villous atrophy, granulomatous enteritis and EG (MEED). Seven horses had normal small intestinal histologic findings. Peak glucose concentrations were less than 85% and greater than 15% of baseline at 120 minutes. Seventeen horses in the group had large intestinal pathologic conditions. Group 3 horses ($n = 12$) had total malabsorption; the peak concentration at 120 minutes was less than 15% above baseline. These horses had severe infiltration throughout most of the small intestine that was attributed predominantly to lymphosarcoma or granulomatous enteritis.

However, the test is far from definitive; one cannot assume a flat curve indicates malabsorption and a poor prognosis. Two horses with chronic weight loss initially diagnosed with malabsorption based on flat OGTT curves subsequently showed more normal OGTT responses.[8] Full-thickness intestinal biopsies were unremarkable. One horse had an elevated serum immunoglobulin E to oat allergen. Oats and oat straw were removed from access. Dexamethasone was given on a tapered protocol, and a repeat OGTT was normal at 18 months. The other horse received oral probiotics to counter suspected small intestinal bacterial overgrowth, was clinically normal in 2 months, and had an improved OGTT with a 60 minute peak. Therefore malabsorption, as defined by an absorption test and weight loss, may occur in the horse without significant morphologic changes in the intestine, and the condition may be transient. Demonstration of carbohydrate malabsorption in 16 of 24 horses with chronic diarrhea showed poor diagnostic sensitivity for small intestinal involvement. Impaired glucose absorption was recorded in horses with predominantly large intestinal problems, cyathostomiasis, chronic colitis, alimentary lymphosarcoma, and MEED.[9]

D-Xylose Absorption Test

Although prior dietary history influences peak plasma xylose concentration, xylose is not confounded by hormonal effects or mucosal metabolism. Gastric emptying rate, intestinal motility, intraluminal bacterial overgrowth, and renal clearance do affect curve shape. Healthy mares not fed for up to 96 hours had flatter curves and a slower decrease in plasma xylose than when deprived for 12 to 36 hours.[10] Hence recent appetite or the level of cachexia may influence test results.

Abnormal D-xylose absorption represented by a flat curve or delayed absorption is considered indicative of significant jejunal disease and has been observed with most examples of CIBD, parasitism, and idiopathic villous atrophy.[11,12] Ponies may have lower peak D-xylose concentrations at 60 and 90 minutes than horses, although the range of peak values at the test dosage (0.5 g D-xylose per kilogram body mass in a 10% solution) is wide.

Potentially diagnostic discriminatory cut off points for peak plasma xylose concentrations have not been determined.

Abnormal absorption curves have been detected in the absence of small intestinal histologic changes,[13] and interpretation is clouded further by findings from small intestinal resection studies in healthy ponies. Nine ponies with 70% distal small intestinal resection and four sham-operated controls were placed on interval feeding for 5 weeks and then turned out to pasture until 6 months after surgery. Grazing was supplemented by twice daily (meal feeding) concentrate rations. All ponies gained weight and were clinically normal, and none developed diarrhea. However, the mean peak xylose concentration at 60 minutes declined progressively (at monthly intervals) over the study period in the resection group to 15% of that of controls. Lack of clinical malabsorption was attributed to adaptation of the residual 30% of healthy small intestine and of large intestinal function.[14] Bacterial overgrowth in the small bowel remnant from refluxed cecal contents (resected ponies had ileocecal valve bypass) may have contributed to the abnormal xylose assimilation. By contrast, xylose absorption decreased over 6 months, associated with substantial weight loss, lethargy, and diarrhea, in an earlier study of extensive (≥60%) small intestinal resection in ponies.[15] An important difference was the feeding pattern; those ponies received pelleted feed twice daily for the entire 6 month follow-up period.

Consequently, horses with suspected malabsorption may adapt to an interval feeding regimen. The critical factor could be the availability of sufficient unaffected or minimally affected small intestine and large intestinal functional capacity. The outcome for animals with small intestinal disease and some unknown degree of large intestinal pathologic dysfunction may be less successful than shown in the experimental study.

Abnormal xylose absorption reverted to normal following 35 days of corticosteroid therapy in an adult Thoroughbred gelding with a 6-week history of weight loss and diarrhea for 3 weeks; peak xylose concentration at 60 minutes was within normal limits and the horse had gained weight.[4] D-xylose absorption was abnormal in an adult Standardbred gelding with a 2-month history of poor performance, weight loss, intermittent fever, mesenteric lymphadenopathy, elevated fibrinogen, and decreased albumin and globulin levels. Multiple full-thickness small intestinal biopsies revealed evidence of granulomatous enteritis. The horse received antibiotics postoperatively and then corticosteroids parenterally for 4 to 5 months. After 3 weeks, peak plasma xylose had increased, although absorption was delayed. Five months after cessation of corticosteroid therapy, the horse had regained weight and was bright and alert, and D-xylose absorption was normal.[16]

Diagnostic predictions were made retrospectively by examining D-xylose absorption in horses with granulomatous enteritis compared with those with EG.[17] Peak xylose concentrations were much lower in horses with granulomatous enteritis than those with EG, whereas in EG the absorption curve shifted to the right with the peak occurring at 240 minutes. The small intestine is affected predominantly in granulomatous enteritis with extensive villous atrophy and more diffuse lesions in the large intestine, whereas in EG (MEED) the large intestine is more involved. Hence, the extent and distribution of pathologic changes in the small and large intestines may influence xylose absorption test results.

Management, Therapy, and Outcome

The chronic wasting horse with suspected malabsorption and probable enteric protein loss has at best a guarded to poor prognosis. Prognosis may be improved through early and aggressive investigation to achieve a diagnosis, and perhaps assess the stage in the natural progression of the disorder. The owner may elect euthanasia of the animal or may be willing to determine whether the condition can be improved. In the short term, intravenous infusion of plasma or colloids, with or without fluids and electrolytes, may be necessary to stabilize the condition. Prognosis is much worse for the horse that is inappetent. Prolonged intensive total parenteral nutrition and/or oral alimentation may not be a realistic course of action. The overall therapeutic and management plan can prove to be expensive. The owner must be cognizant from the start that the outcome may not be altered, even after protracted therapy. One cannot make predictions for outcome of therapy without meaningful data because only a few case reports of successful responses with long-term follow up exist.

NUTRITION

Some level of digestive and absorptive capability remains in the diseased small intestine. Interval feeding of small quantities of food may be beneficial if the horse continues to eat, and particularly for animals with ravenous appetites that seem able to maintain their reduced state of body condition without further losses. Diet should include feeds with a high fiber content to favor large intestinal fermentation, including grass hay and access to pasture complemented by commercial high-fiber rations based on beet pulp and soybean hulls. Energy intake can be increased through feeding high-energy dense fats that provide 2.25 times more calories than carbohydrates. Most affected horses should tolerate high fat (5% to 10%) processed feeds containing vegetable oils or rice bran (up to 20% of the concentrate mix, equivalent to 8% vegetable oil) to achieve the higher-fat composition.

Changeover to a higher-fat concentrate should be gradual. Even in healthy animals that can eat up to 20% added fat, appetite may decrease as the percentage increases, and fecal consistency may change. Clearly, the objective for the horse with suspected malabsorption is to sustain, and preferably increase, dietary intake, value, and efficiency.

The owner of an affected horse must be prepared to experiment with feeds, must be patient, and must keep records. No standard procedure exists. Exposure to a feed component may contribute to the problem as an allergen eliciting a hypersensitivity reaction. Identifying the potential allergen through immunologic testing or by stepwise removal and outcome assessment over a longer period may be difficult. The clinician should give immunosuppressive drugs early in the process.

DRUG THERAPY

Immunosuppressive agents have produced the most promising responses to ameliorate the effects of conditions associated with malabsorption, particularly CIBD. Short-duration, and in some cases more prolonged and sustained, improvements in body condition, weight gain, demeanor, energy and activity levels have occurred following corticosteroid administration. One should start treatment as early as possible. One should follow initial parenteral (intramuscular or intravenous) loading doses of dexamethasone (sodium phosphate) with a series of depot injections, or orally administered prednisolone or prednisone, on a tapered dose protocol over a period of months. Interval low-dose therapy may be necessary if clinical signs return after treatment ends. One uses the lowest dose to control the clinical signs for alternate-day therapy. Clinical benefits far outweigh concerns over potential adverse effects. Chemotherapeutic agents such as vincristine, cytosine, cyclophosphamide, and hydroxyurea have been tried in a few cases of CIBD or lymphosarcoma with no apparent success, probably related to the advanced stage of the disease when treatment was initiated and the dose selected.

SURGERY

Resection of a segment of intestine that is edematous, hemorrhagic, or constricted is an option in localized forms of CIBD,[18,19] particularly if gross changes are not discernible in adjacent or distant parts of the intestinal tract, that is, malabsorption is not a feature. Long-term outcome has been favorable. Removal of a substantial proportion of the diseased small intestine may be indicated in a horse with malabsorption, considering that resection of 70% distal small intestine was performed in healthy animals without inducing adverse effects. However, because pathologic changes may exist in normal-appearing small or large intestine that is not resected or biopsied, the prognosis remains guarded. Two young horses with granulomatous enteritis had the thickened terminal small intestine resected with positive outcomes; one survived 4 months, the other has a follow up extending more than 10 years.[20]

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13.5—Pathophysiology of Mucosal Injury and Repair

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Mucosal Barrier Function

To gain an appreciation of the mechanisms whereby the mucosa is injured and subsequently repaired, one must understand how the integrity of the mucosa is regulated physiologically. Regulation of mucosal integrity is referred to as mucosal barrier function, which is vital because it prevents bacteria and associated toxins from gaining access to subepithelial tissues and the circulation. However, the mucosa has two conflicting functions: it must serve as a protective barrier and continue to absorb solutes necessary to maintain well-being of the host. This conflict is most notable at the intercellular (paracellular) space, which allows passage of select solutes and water,[1-4] but which does not admit large molecules, including bacterial toxins.[5] The paracellular space is regulated almost exclusively by the tight junction,[6] which is the interepithelial junction at the apical-most aspect of the paracellular space. Although these tight junctions originally were viewed as inert cellular adhesion sites, what has become clear in recent years is that tight junction permeability depends on tissue-specific molecular structure and is regulated by a complex array of intracellular proteins and the cytoskeleton. Tight junctions consist of a group of transmembrane proteins that interdigitate from adjacent cells. Although occludin originally was thought to be the predominant tight junction transmembrane protein, a group of proteins termed *claudins* appear to be more critical.[7] These transmembrane proteins interact with the cytoskeleton via a series of intracellular proteins, including zonula occludens 1, 2, and 3; cingulin; and others.[8] In addition, local regulatory proteins such as the small guanosine triphosphatase-Rho are also critical to tight junction function. In general the relative contractile state of the actin cytoskeleton determines the degree to which tight junctions are open or closed, but the complexities of regulation of this process are understood poorly.[9,10]

The most sensitive measure of mucosal barrier function is transepithelial electric resistance, which is measured by mounting mucosa in an ex vivo system called an Ussing chamber, because this measurement is largely a reflection of the permeability of mucosa to ions.[11,12] Ions may follow one of two routes when traversing epithelium: transcellular and paracellular.[5]

Because cell membranes have a resistance to passive flow of ions 1.5 to 3 log units greater than that of the epithelium as a whole, measurements of transepithelial resistance largely reflect the resistance of the paracellular space, and in particular the tight junctions that regulate paracellular flow of ions.[12] Because tight junctions differ in structure from different portions of the mucosa,[13] measurements of transepithelial resistance reflect the net resistance of epithelium of variable permeability within a given tissue. For example, tight junctions in the intestinal glandular structures called crypts are leakier than those in the surface epithelium because of fewer and less organized tight junction strands.[11,14] Conversely, surface epithelium has a greater number of well-organized tight junction strands that result in epithelium with a high resistance.[11] This correlates well with the absorptive function of epithelium located on the mucosal surface and the secretory function of crypt epithelium. Structure of tight junctions also varies with the segment of intestine. For example, tight junctions have more strands in the ileum than in the jejunum, which is reflected by a higher transepithelial resistance in the ileum.[15]

GASTRIC MUCOSAL BARRIER FUNCTION

The stomach has four regions based on the type of mucosal lining (in an orad to aborad order): nonglandular stratified squamous epithelium, cardiac epithelium, proper gastric mucosa, and pyloric mucosa.[16] Stratified squamous epithelium has distinct differences in terms of barrier function compared with the remainder of the gastrointestinal tract. This epithelium has baseline transepithelial resistance measurements of approximately 2000 to 3000 Ω/cm^2, which is an order of magnitude higher than the adjacent cardiac mucosa.[17,18] Thus the stratified squamous mucosa is exceptionally impermeable. This in effect is the only mechanism this mucosa has to defend itself against injury. The stratified squamous epithelium consists of four layers: the outer stratum corneum, stratum transitionale, stratum spinosum, and the basal stratum germinativum. However, not all layers contribute equally to barrier function, the barrier being composed mostly of interepithelial tight junctions in the stratum corneum and mucosubstances secreted by the stratum spinosum.[17,19] The relative impermeability of stratified squamous mucosa can be demonstrated by the effects of HCl on this type of epithelium in vitro, which has little effect until it reaches a pH of 2.5 or lower.[18] Thus although most of the literature on equine ulceration pertains to the effects of HCl and inhibitors of HCl secretion,[20-23] other factors may be critical to the development of gastric ulcer disease.

The site of HCl secretion (proper gastric mucosa) also is protected from so-called back-diffusion of H^+ by a high transepithelial electric resistance (compared with

cardiac mucosa), but a number of other critical mechanisms also exist to prevent acid injury. The gastric mucosa secretes mucus and bicarbonate, which together form a HCO_3^--containing gel that titrates acid before it reaches the lumen.[24,25] The mucus layer is formed principally by glycoproteins (mucins) secreted by goblet cells but also includes other gastric secretions and sloughed epithelial cells. Mucins consist of core peptides with a series of densely packed O-linked polysaccharide side chains that, once secreted, become hydrated and form a viscoelastic gel. However, the mucus layer does not form an absolute barrier to back-diffusion of acid. Thus for acid that does back-diffuse into the gastric mucosa, epithelial Na^+/H^+ exchangers are capable of expelling H^+ once the cell reaches a critical pH.[25]

Recent studies have renewed interest in the protective mechanisms of mucus because of the discovery of a group of compounds secreted by goblet cells called trefoil peptides. The name of these peptides is derived from a highly conserved cloverleaf structural motif, which confers substantial resistance to degradation by proteases including pepsin. Three members of this group are known, pS2, SP, and intestinal trefoil factor, the latter of which is secreted solely by goblet cells in the small and large intestine. pS2 and SP are secreted by goblet cells within the stomach and are believed to intercalate with mucus glycoproteins, possibly contributing to the barrier properties of mucus.[26] These peptides also play a critical role in repair of injured mucosa.

An additional mucosal function that serves to reduce the level of injury is adaptive cytoprotection, wherein application of topical irritants to gastric mucosa results in subsequent protection of mucosa in response to repeated exposure to damaging agents. For example, pretreatment with 10% ethanol protected against mucosal damage in response to subsequent application of absolute ethanol, and this effect was abolished by treatment with the cyclooxygenase inhibitor indomethacin.[27] The cytoprotective effect of prostaglandins has been demonstrated directly in studies in which preadministration of prostaglandins protected gastric mucosa from damage by agents such as concentrated HCl and hypertonic saline.[28] Prostaglandins appear to be cytoprotective in the stomach at doses less than those used to inhibit gastric acid secretion, ruling out a simple antacid mechanism.[29] Although not fully characterized, cytoprotection has been attributed in part to prostaglandin-stimulated mucus production.[30] An associated beneficial effect of prostaglandins is the increased production of bicarbonate, which is trapped within mucus on the surface of the mucosa.[31,32] Interestingly, prostaglandin E_2 (PGE_2) appears to lose its cytoprotective activity in the presence of the mucolytic agent N-acetylcysteine. Attention also has been directed at enhanced mucosal blood flow as a potential mechanism

for prostaglandin-mediated cytoprotection. For example, pretreatment with PGI_2 protected against ethanol-induced mucosal damage as a result of increased mucosal blood flow.[33] Although PGE_2, which is also cytoprotective, does not increase blood flow,[34] it may prevent vascular stasis associated with irritant-induced vascular damage resulting from inhibition of neutrophil adherence to damaged endothelium.[35]

Sensory nerves also have been implicated in cytoprotective mechanisms. These nerves are distributed throughout gastrointestinal mucosa. As an example of their importance in mucosal cytoprotection, pretreatment of newborn rats with capsaicin (to which sensory nerves are sensitive) renders the mature rats more susceptible to gastric injury.[36] Alternatively, use of a low dose of capsaicin, which stimulates rather than destroys sensory nerves, protects gastric mucosa against injurious agents.[37,38] Sensory nerves contain neuropeptides such as calcitonin–gene-related peptide (CGRP) and substance P, which may play a protective role via vascular mechanisms. For instance, CGRP stimulates increased gastric blood flow, which is theorized to reduce injury in much the same way as prostaglandins do. In fact, recent studies suggest that the roles of prostaglandins and CGRP in gastric cytoprotection are intertwined intimately. In particular, PGI_2 is believed to sensitize sensory nerves following treatment with a mild irritant, with resultant increases in CGRP release and mucosal flow. Similar studies have shown that antagonists of CGRP inhibit the cytoprotective action of PGE_2.[39] Another neural mediator, nitric oxide, also has been implicated in adaptive cytoprotection. Interestingly, nitric oxide has a number of actions that are similar to those of prostaglandins, including maintenance of mucosal blood flow.[40]

Intestinal Barrier Function

Regulation of barrier function in the intestine is not as well characterized as that of the stomach, although mechanisms of barrier function, including secretion of mucus and regulation of mucosal blood flow, are presumed to be similar. The proximal duodenum also has to protect itself from acid damage as it receives gastric contents, and this involves secretion of mucus and bicarbonate in much the same way as the stomach. One other mechanism that helps the stomach and the intestine to maintain mucosal barrier function is the speed with which the mucosa repairs. Thus for a defect to develop in the mucosal barrier, injurious factors have to outpace mucosal recovery. Such recovery initially involves epithelial migration across denuded regions of basement membrane (restitution),[26] a process so rapid that epithelial defects may be resurfaced within minutes.

For example, in bile salt–injured colon, denuded surface mucosa was covered completely by restitution.[41] In the small intestine, villi greatly amplify the surface area of the mucosal luminal surface, which in turn takes far longer to resurface with restituting epithelium once it has become denuded.[42] However, intestinal villi are able to reduce the denuded surface area considerably by extensively contracting.[43] These mechanisms are described in detail under Mechanisms of Gastrointestinal Mucosal Repair.

Mechanisms of Gastric Injury

ULCERATION OF STRATIFIED SQUAMOUS MUCOSA

Although the stratified squamous epithelium is relatively impermeable to HCl, a number of factors can enhance the damaging effects of HCl in this epithelium. In particular, bile salts and short-chain fatty acids are capable of breaking down the squamous epithelial barrier at an acid pH, thereby exposing deep layers to HCl, with subsequent development of ulceration.[18,44] High concentrations of short-chain fatty acids normally exist within the equine stomach because of microbial fermentation.[17] These weak acids penetrate squamous mucosa and appear to damage Na^+ transport activity principally located in the stratum germinativum. Bile salts also may be present in the proximal stomach because of reflux from the duodenum. Although such reflux has a high pH, bile salts appear to adhere to stratified squamous epithelium, becoming lipid soluble and triggering damage once the pH falls below 4.[45] Diet and management (e.g., periods of fasting) also play crucial roles in the development of conditions conducive to gastric ulceration. Typically, a pH gradation in horses exists from proximal to distal compartments of the stomach, with the lowest pH values in the distal stomach.[46] However, fasting disrupts this stratification such that low pH values may be recorded in the proximal stomach.[47] Fasting conditions also increase the concentration of duodenal contents within the proximal stomach, particularly bile.[45]

ULCERATION OF PROPER GASTRIC MUCOSA

Proper gastric mucosa is exposed to injurious agents, including pepsin, bile, and acid. Parietal cells in the horse secrete acid constantly as an adaptation to near-continuous intake of roughage,[16] but the enterochromaffin-like cells within the proper gastric mucosa and G and D cells within the pyloric mucosa tightly regulate acid secretion. Histamine released by enterochromaffin-like cells amplifies acid secretion and interacts with H_2 receptors on parietal cells and G cells, which release the prosecretory hormone gastrin. A combination of histamine and gastrin can have a synergistic effect on parietal cell gastric secretion, because these mediators have distinct receptors and second messengers. However, D cells are sensitive to an acidic environment and release somatostatin, which inhibits acid secretion.[48] Nonetheless, gastric mucosa may be exposed to acid for prolonged periods of time, particularly in horses that are extensively meal fed and that do not have the benefit of roughage, which tends to buffer stomach contents.[45,48]

Aside from peptic ulceration induced by combinations of acid and pepsin, research in human medicine has revealed the tremendous importance of *Helicobacter pylori* in inducing ulceration. Infection with this organism has the effect of raising gastric pH because of disruption of gastric glands and also induces an inflammatory reaction that causes damage.[49] However, little evidence to date indicates that this organism is involved in gastric ulcers in horses. In the absence of a known role for infectious agents in gastric ulceration in animals, ulceration likely develops from injurious factors similar to those found in the proximal stomach, including gastric acid and bile. However, some factors that are important to induction of squamous epithelial ulceration may not be important in development of proper gastric mucosal ulceration. For example, feed deprivation and intensive training reproducibly induce squamous epithelial ulceration in horses but have little effect on proper gastric mucosa in horses.[50] Gastric acid likely plays a key role, whereas other factors such as nonsteroidal antiinflammatory drugs (NSAIDs) serve to reduce gastric defense mechanisms. In particular, inhibition of prostaglandin production reduces mucus and bicarbonate secretion while also reducing gastric mucosal blood flow.[51] Some of the NSAIDs also have a topical irritant effect, although this appears to be of minor significance because the route of administration (oral or parenteral) seems to have little influence on development of ulceration.[52]

The source of prostaglandins responsible for gastric protection originally was assumed to be cyclooxygenase 1 (COX-1), because this isoform is expressed constitutively in gastric mucosa, whereas COX-2 is not expressed in the stomach unless induced by inflammatory mediators. However, mice in which the COX-1 gene has been knocked out fail to develop spontaneous gastric lesions,[53] possibly because of compensatory increases in prostaglandin production by COX-2.[54] This concept agrees with recent data indicating that inhibition of both COX isoforms is required to induce gastric ulceration.[55] From a clinical perspective this data indicate that drugs selective for COX-1 or COX-2 may be less ulcerogenic in the horse. Because COX-2 elaborates prostaglandins induced by inflammatory stimuli, selective inhibitors of COX-2 may be particularly useful because of their ability to serve as antiinflammatory agents that are less ulcerogenic.[56]

Intestinal Ischemia-Reperfusion Injury

The most notable cause of intestinal mucosal injury in horses, particularly those suffering from colic, is ischemia. Initially, that a reduction in gastrointestinal blood supply leads to mucosal injury seems intuitive. However, the anatomy of the gastrointestinal tract and the differing structure of the intestinal mucosa at various anatomic locations have a significant influence on the extent of mucosal injury. Furthermore, ischemic injury may be induced by several different mechanisms, including occlusion of arterial supply by a thrombus, strangulation of intestinal vasculature, and generalized reduction in blood flow associated with various shock states. In addition, a number of seemingly distinct mechanisms of intestinal injury, such as intestinal distention, also trigger mucosal injury via an ischemic mechanism. Finally, reperfusion injury also may influence the extent of mucosal injury following an ischemic episode and has been proposed as a potential site of therapeutic intervention.[57,58] Thus understanding the mechanisms of ischemia-reperfusion injury is critical to developing an understanding of the severity of various clinical conditions and beginning to formulate a therapeutic approach to diseases characterized by this devastating form of injury.

REGULATION OF INTESTINAL BLOOD FLOW

The intestinal circulation is capable of closely regulating blood flow during periods of low systemic perfusion pressure.[59,60] In particular, local regulation of resistance vessels within the microvasculature is particularly prominent, whereby metabolic end products of adenosine triphosphate (ATP) result in continued dilation of resistance vessels despite reductions in systemic arterial pressure. Dilation results in continued perfusion of gastrointestinal tissues during the early stages of shock, while other organs such as skeletal muscle undergo massive shunting of blood resulting from increased constriction of resistance vessels. The reasons for these differences in regulation are not entirely clear but may relate to the high level of energy required to fuel the intestinal mucosa and the serious systemic effects of breaches in the mucosal barrier. However, as blood flow falls below a critical level, regulatory systems are no longer effective and oxygen uptake by the gastrointestinal tissue decreases, culminating in tissue damage.[59]

The tip of the villus is the most susceptible region affected by hypoxia in the equine small intestine, largely because of the countercurrent exchange mechanism of blood flow in the small intestinal villus.[59] This countercurrent exchange mechanism is attributable to the vascular architecture, which consists of a central arteriole that courses up the core of the villus, arborizes at the tip, and is drained by venules coursing down the periphery of

the villus.[61] As oxygenated blood flows into the central arteriole, oxygen tends to diffuse across to the adjacent venules, which flow in the opposite direction. This series of events takes place along the length of the villus, resulting in a tip of the villus that is hypoxic even under normal conditions. Furthermore, reduced blood flow as occurs in shock exacerbates the countercurrent exchange of oxygen, and the tip becomes absolutely hypoxic.[59] This mechanism might explain why the small intestinal mucosa is more susceptible to ischemic injury, compared with the colon, which has no villi. For example, the duration required to produce severe morphologic damage to the equine colon is approximately 25% longer than in the small intestine.[62]

ISCHEMIC EPITHELIAL INJURY

Intestinal mucosal epithelium is susceptible to hypoxia because of the high level of energy required to fuel the Na^+/K^+-ATPase that directly or indirectly regulates ion and nutrient flux. The first biochemical event to occur during hypoxia is a loss of oxidative phosphorylation. The resulting diminished ATP concentration causes failure of the energy-dependent Na^+/K^+-ATPase resulting in accumulation of sodium, and subsequently intracellular water. The pH of the cytosol drops as lactic acid and inorganic phosphates accumulate from anaerobic glycolysis. The falling pH damages cell membranes, including lysosomal membranes, resulting in the release and activation of lysosomal enzymes into the cytosol, further damaging cellular membranes. Damage to the cell membrane allows the accumulation of high concentrations of calcium in the cytosol, which activates calcium-dependent degradative enzymes.[63] These events result in cytoplasmic blebbing of the basal membrane with subsequent detachment of cells from the underlying basement membrane.

Recent studies on epithelial injury during ischemia suggest that most epithelial cells undergo programmed cell death (apoptosis) during ischemia and reperfusion rather than necrosis, allowing retention of reusable components of irreversibly injured cells.[64] In one study, 80% of detached epithelium during small intestinal ischemia and reperfusion underwent apoptosis.[65] Although the most obvious result of apoptosis is loss of surface epithelium, a number of cells on the lower portion of the villus (in the small intestine) and cells within the crypts also may undergo apoptosis that only may become evident up to 24 hours following reperfusion of ischemic tissue.[66]

Morphologic changes observed in ischemic-injured small intestinal mucosa follow a similar sequence regardless of whether ischemia alone or ischemia and reperfusion induce injury (Table 13.5-1).[67] Initially, epithelium separates from the underlying basement

TABLE 13.5-1

Grading System for Ischemia-Reperfusion Injury in Small Intestinal Mucosa

GRADE	DESCRIPTION
1	Separation of epithelium at the tip of the villus, creating a small space between epithelium and basement membrane called Grüenhagen's space
2	Loss of epithelium from the tip of the villus
3	Loss of epithelium from the upper third of the villus
4	Complete loss of villus epithelium
5	Injury or loss of epithelium within the crypt in addition to complete loss of villus epithelium

Modified from Chiu CJ, McArdle AH, Brown R et al: Intestinal mucosal lesion in low-flow states. 1. A morphological, hemodynamic, and metabolic reappraisal, *Arch Surg* 101:478-483, 1970.

membrane, forming a fluid-filled space termed *Grüenhagen's space* (Figure 13.5-1). The mechanism of fluid accumulation in this space is not understood entirely but may result from continued epithelial absorption of NaCl and water before it has detached fully from neighboring epithelial cells. This fluid accumulation likely exacerbates epithelial separation from the basement membrane. Subsequently, epithelium progressively sloughs from the tip of the villus toward the crypts, which are the last
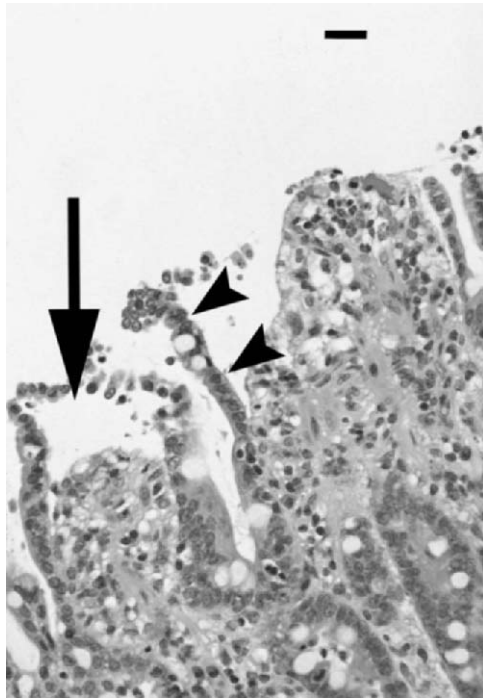
Figure 13.5-1   Histologic appearance of Grüenhagen's space in ischemic injured ileal mucosa. Separation of epithelium at the tip of the villous from its basement membrane creates a space *(arrows)*. Epithelium subsequently sloughs into the lumen *(arrowheads)*. 1-cm bar = 100 μm.

component of the intestinal mucosa to become injured.[68-70] Injury of crypts likely relates to the vascular architecture, because crypts receive a blood supply separate from the vasculature involved in the villous countercurrent exchange mechanism. The early morphologic changes observed in the equine large colon during ischemia are different from those described in the equine small intestine because of the lack of intestinal villi. However, as might be expected, the more superficially located surface cells are sloughed before those in crypts.[62,71] The orderly progression of tissue injury has been used by one group of investigators to predict accurately the survival of horses with large colon volvulus. The researchers took biopsies from the pelvic flexure, which has been shown previously to reflect mucosal changes along the length of the colon accurately,[72] and examined them histologically for the width of the crypts and intercrypt interstitial space. They expressed the latter measurements as a ratio of interstitium to crypt width (I:C) and defined nonviable colon as that which has greater than 60% loss of crypt and an I:C ratio greater than 3. Using this methodology, researchers correctly predicted survival in 94% of horses.[73]

STRANGULATING OBSTRUCTION

Because of the dramatic decline in *Strongylus vulgaris*–induced colic, which was associated frequently with infarction of intestinal arterial blood supply,[74] most ischemic lesions are associated with strangulating obstruction. Therefore considering mechanisms of ischemic injury in horses with naturally occurring strangulating lesions is important. The majority of experimental work has assessed complete ischemia (complete occlusion of the arterial blood supply)[62] or low-flow ischemia (during which arterial blood flow is reduced).[75,76] However, during intestinal strangulation, a disparity between the degree of occlusion of the veins and arteries occurs whereby veins are occluded before arteries because of differences in compliance of vascular walls. Thus strangulating lesions are typically hemorrhagic (hemorrhagic strangulating obstruction) as the arteries continue to supply blood to tissues that have little or no venous drainage. The result is ischemic injury, as previously outlined, but also a tremendous congestion of the tissues. Such hemorrhagic congestion has two opposing effects: it disrupts tissue architecture, including the mucosa and its epithelium, and continues to provide oxygenated blood to the tissues during much of the ischemic episode. In contrast, when strangulation results in sudden cessation of arterial blood flow (ischemic strangulating obstruction), tissues appear pale, and the mucosa rapidly degenerates because of a complete lack of oxygenated blood.[70] From a clinical standpoint, this makes assessing the degree of mucosal injury in horses with strangulating injuries difficult

because intestine that may look nonviable (dark red) may in fact have less mucosal injury than that of ischemic strangulated intestine.[77]

An additional consideration in clinical strangulating obstruction is the degree of ischemia that intestinal distention may induce. For example, experimental distention (18 cm of H_2O for 2 hours) and decompression (2 hours) of jejunum resulted in a significant increase in microvascular permeability and a significant decrease in tissue oxygenation similar to that which would be expected with low-flow ischemia.[78,79] In particular, microscopic evaluation of vasculature revealed capillary endothelial cell damage and local edema formation.[80] This data suggest that distended intestine proximal to an obstruction may undergo mucosal injury despite its normal appearance. Indeed, in one study, intraluminal pressures greater than 15 cm H_2O in naturally occurring cases of colic correlated with a poor prognosis for survival.[81]

REPERFUSION INJURY

Although that reperfusion of ischemic tissues results in exacerbation of mucosal injury recently has been taken for granted, one should remember that mechanisms underlying intestinal reperfusion injury have been defined largely in laboratory animals under specific conditions.[82-86] However, studies on reperfusion injury in horses have had some conflicting results.[68,76,87] The conflict may be attributable to the way in which the studies have been performed. In particular, the type of ischemia used in most laboratory animal studies has been low-flow ischemia (in which the blood flow typically is reduced to 20% of baseline flow), whereas studies in horses have used a number of different ischemic models, including various types of strangulating obstruction.

Although strangulating obstruction is of great clinical relevance, this type of ischemic insult is less likely to develop reperfusion injury.[68,88,89] Conversely, low-flow ischemia appears to prime tissues for subsequent injury once the tissue is reperfused, and considerable evidence supports the presence of reperfusion injury in horses following low-flow ischemia.[75,76,80,90] Nonetheless, low-flow ischemia may not be a common clinical entity.

In addition to the type of ischemia, other factors are involved in priming tissues for reperfusion injury, including species and anatomic-specific variation in oxidant enzyme and neutrophil levels (Table 13.5-2). For example, the foal appears to have low levels of small intestinal xanthine oxidase, an enzyme that has been shown to play a critical role in triggering reperfusion injury in laboratory animals,[84,85,91] whereas adult levels are much greater, particularly in the proximal small intestine.[92] In addition, horses appear to have low numbers of resident neutrophils in the intestinal mucosa,[93] and this population of neutrophils (rather than those recruited from the circulation) appears to be most critical for induction of reperfusion injury.[86] However, studies demonstrating reperfusion injury in the equine colon following low-flow ischemia have shown significant accumulation of neutrophils within the mucosa.[75] Therefore a complete understanding of mechanisms of neutrophilic infiltration and the mechanisms whereby they damage tissue requires further study.

Reperfusion injury is initiated during ischemia when the enzyme xanthine dehydrogenase is converted to xanthine oxidase and when its substrate, hypoxanthine, accumulates simultaneously because of ATP use (Figure 13.5-2).[57,94] However, little xanthine oxidase activity occurs during ischemia, because oxygen is required as an electron acceptor. During reperfusion,

|	TABLE 13.5-2			
	Comparison of Mean Levels of Xanthine Oxidase/Xanthine Dehydrogenase and Myeloperoxidase (as an Indication of Granulocyte Numbers) in the Small Intestine of Various Species			
SPECIES	**INTESTINAL SEGMENT**	**TOTAL XO/XDH (mU/g TISSUE)**	**MYELOPEROXIDASE (U/g TISSUE)**	**REFERENCE**
Cat (adult)	Jejunum	80	12	86,143
	Ileum	NR	NR	
Rat (adult)	Jejunum	405-523	1.9	96,144
	Ileum	150	NR	96,145
Pig (6-8 weeks)	Jejunum	3.4 (0)*	NR	96
	Ileum	0.4 (0.9)	2.2	
Horse (adult)	Jejunum	100-131 (60)†	0.02	92,96
	Ileum	30-48 (0)	0.1	96

XO/XHD, Xanthine oxidase/xanthine dehydrogenase; *NR,* not reported.
*Value in parentheses for the neonatal piglet.
†Value in parentheses for the foal.
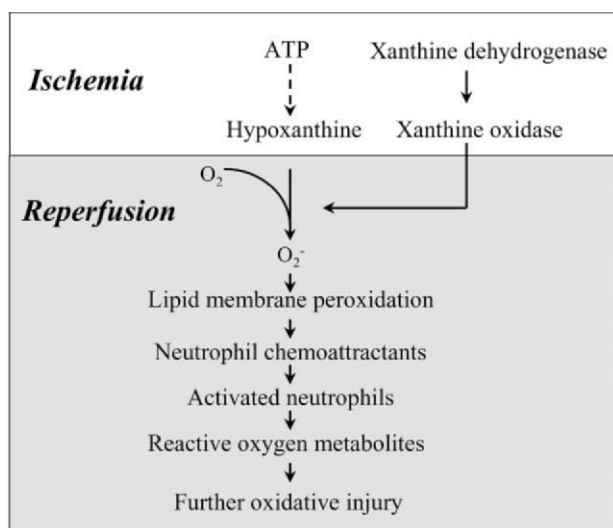
Figure 13.5-2   Intestinal reperfusion injury cascade. Reperfusion injury is initiated by elaboration of superoxide by metabolism of hypoxanthine by xanthine oxidase and subsequent infiltration of neutrophils.

xanthine oxidase rapidly degrades hypoxanthine in the presence of oxygen, producing the superoxide radical as a by-product.[57] The superoxide radical contributes to oxidative tissue damage and, most importantly, activates neutrophil chemoattractants.[84,85] Thus inhibition of xanthine oxidase in feline studies of intestinal ischemia-reperfusion injury prevents infiltration of neutrophils and subsequent mucosal injury.[83,84] However, inhibition of xanthine oxidase has had no effect on ischemia-reperfusion injury in equine small intestine[87] and colon,[95] suggesting that reperfusion injury is simply a continuation of injury initiated during ischemia, as suggested in some equine studies,[63] or that the classic reperfusion injury pathway is activated by alternate sources of reactive oxygen metabolites. The latter has been suggested by studies in feline models of ischemia-reperfusion injury in which the source of a significant proportion of reactive oxygen metabolites is unknown and is independent of xanthine oxidase and neutrophils.[83]

A veterinary review of the pathogenesis of intestinal reperfusion injury in the horse suggested the concept of a therapeutic window wherein treatment of reperfusion injury would be beneficial.[57] The basis of this concept is that certain conditions exist under which ischemic injury is minimal and that tissues are damaged severely during reperfusion.[88] Thus under conditions of low-flow ischemia, little injury is demonstrated during 3 hours of ischemia, but remarkable injury occurs during 1 hour of reperfusion.[83-85] However, a therapeutic window may not exist under conditions of strangulating obstruction in which severe injury occurs during ischemia and

minimal injury occurs during reperfusion.[96] This in turn greatly reduces clinicians' ability to ameliorate ischemia-reperfusion injury with treatments such as antioxidants at the time of reperfusion.

Mechanisms of Gastrointestinal Mucosal Repair

GASTRIC REPARATIVE MECHANISMS
Mechanisms of gastric repair depend greatly on the extent of injury. For instance, superficial erosions can be covered rapidly by migration of epithelium adjacent to the wound; a process termed *epithelial restitution*. However, ulceration (full-thickness disruption of mucosa and penetration of the muscularis mucosa) requires repair of submucosal vasculature and extracellular matrix. The formation of granulation tissue initiates repair and supplies connective tissue elements and microvasculature necessary for mucosal reconstruction. Connective tissue elements include proliferating fibroblasts that accompany newly produced capillaries that form from proliferating endothelium. Recent studies indicate that nitric oxide is critical to both processes,[40,97] which likely explains the reparative properties of nitric oxide in the stomach.[98]

Once an adequate granulation bed has formed, newly proliferated epithelium at the edge of the wound begins to migrate across the wound. In addition, gastric glands at the base of the ulcer begin to bud and migrate across the granulation bed in a tubular fashion.[99] Repairing epithelium expresses epidermal growth factor, which appears to facilitate these processes.[100] In addition, a mucoid cap facilitates these events and retains reparative factors and serum adjacent to the wound bed.[51] Once the ulcer crater has been filled with granulation tissue and the wound has been reepithelialized, the subepithelial tissue remodels by altering the type and amount of collagen. Despite the remodeling process, ulcers tend to recur at sites of previous ulceration, and the concern is that this remodeling can result in excessive deposition of collagen and fibrosis.[26]

INTESTINAL REPARATIVE MECHANISMS
Reparative mechanisms are similar in the intestine, except that in the small intestine, mucosal villi contribute to mucosal repair. Once intestinal epithelium is disrupted, two events occur almost immediately to reduce the size of the denuded portion of the villus: contraction of the villus and epithelial restitution (Figure 13.5-3). For example, in porcine ileum subjected to 2 hours of ischemia, villi were 60% of their former height and 50% of the denuded villous surface area was covered in flattened epithelium within 6 hours.[42] Enteric nerves appear to regulate villous contraction, because inhibition of enteric nerve conduction prevents villous shortening following

injury. The contractile component of the villus is a network of myofibroblasts distributed throughout the lamina propria of the villus and along the central lacteal. Inhibition of villous contraction results in retarded epithelial repair because of the larger denuded surface that remains to be covered by migrating epithelium compared with similarly injured villi that have contracted.[43] PGE_2 also has been implicated in regulating villous contraction, because application of PGE_2 resulted in villous contraction when perfused through normal rat ileum.[101] As villi contract, assuming the basement membrane is intact, epithelium from the margins of the wound migrates centripetally to resurface toward the tip of the villus.[43] The process of restitution is similar in denuded colonic mucosa, except that it may proceed more rapidly because of the lack of villi.[41] Epithelial restitution is solely a migratory event that does not depend on provision of new enterocytes by proliferation. Cellular migration is initiated by extension of cellular lamellipodia that receive signals from the basement membrane via integrins. Intracellular signaling converges on the actin cytoskeleton, which is responsible for movement of lamellipodia. Specific components of the basement membrane appear to be critical to the migratory process. For example, application of antibodies to collagen types III and IV, which are important components of intestinal mucosal basement membrane, impeded epithelial restitution.[102,103] Other elements of the basement membrane, including proteoglycans, hyaluronic acid and noncollagenous proteins such as fibronectin and laminin also may provide important signals.[104] These subepithelial matrix components that facilitate restitution may form the basis for clinical treatments designed to speed up the repair process, analogous to administration of matrix components to horses with articular cartilage damage.

Although epithelial restitution results in gross closure of previously denuded regions of gastrointestinal mucosa, closure of interepithelial spaces ultimately is required to restore normal epithelial barrier resistance. Because the tight junction is principally responsible for regulating the permeability of the interepithelial space, repair and closure of this structure likely is critical to restore intestinal barrier function. Recent research indicates that prostaglandins play a vital role in recovery of tight junction resistance,[105] indicating that administration of nonselective COX inhibitors to horses with colic, particularly those recovering from strangulating obstruction, may be deleterious. Therefore judicious use of NSAIDs is appropriate until more selective drugs that allow continued production of reparative prostaglandins are available for use in horse.[56]

After restoration of the epithelial barrier, the epithelium must reestablish normal mucosal architecture to allow normal gut absorptive and digestive function. In porcine ileum subjected to 2 hours of ischemia, the epithelial barrier was restored within 18 hours, but villi were contracted and covered in epithelium with a squamous appearance. Restoration of normal villous architecture required another 4 days.[42] Newly proliferated crypt epithelium replaces the flattened villous epithelium that characterizes restitution. Under normal circumstances the dividing stem cells, of which the base of each mucosal crypt has approximately four, form new enterocytes. Newly divided enterocytes migrate from the crypt onto the villus.[106] During migration, enterocytes differentiate and acquire specific absorptive and digestive functions. Fully differentiated enterocytes reside on the upper third of the villus for 2 to 3 days and then are sloughed into the intestinal lumen.[107] This process accelerates during mucosal repair and requires increased proliferative rates. A variety of locally available gut-derived factors, including luminal nutrients, polyamines, and growth factors, may stimulate increased proliferation within 12 to 18 hours.[42] The return of the normal leaflike shape of the villus occurs following the appearance of normal columnar epithelium.

Mediators of Repair

PROSTAGLANDINS
Although prostaglandins have been implicated in mucosal cytoprotective function, few studies have assessed their importance in mucosal repair. One study implicated prostaglandins in growth factor-stimulated restitution,[108] but a more prominent role of prostaglandins in mucosal repair is their ability to close interepithelial tight junctions.[105,109,110] For instance, ischemic-injured small intestine rapidly recovers barrier function (as measured in vitro as transepithelial resistance) in the presence of PGI_2 and PGE_2, despite the fact that these prostanoids had little effect on villous contraction and epithelial restitution. However, electron microscopic examination of tissues reveals dilation of tight junctions in tissues treated with NSAIDs,[110] whereas those additionally treated with prostaglandins have closely apposed tight junctions (Figures 13.5-3 and 13.5-4). Prostaglandins stimulate closure of tight junctions via the second messengers cyclic adenosine monophosphate and Ca^{2+},[105] which interestingly were among the first mediators found to modulate tight junction permeability.[111,112] Such tight junction closure is of importance to patients with intestinal injury that are treated with NSAIDs, because reduced prostaglandin levels may result in increased intestinal permeability. For example, in a study on ischemic-injured porcine ileum, treatment with the NSAID indomethacin resulted in a significant increase in intestinal permeability to inulin and lipopolysaccharide compared with tissues that were treated additionally with PGI_2 and PGE_2.[105]
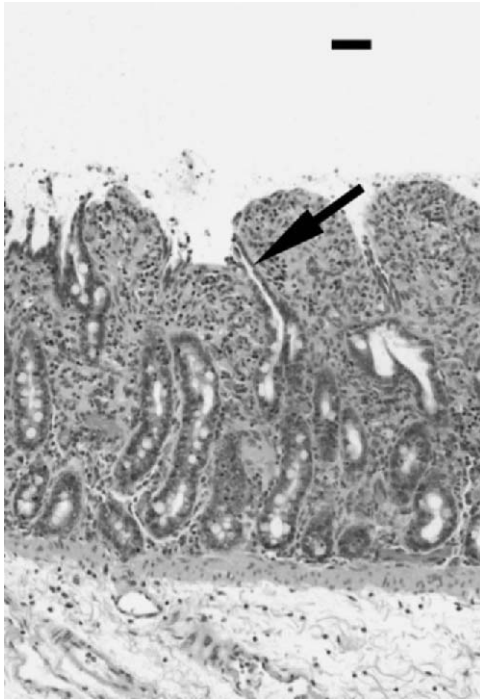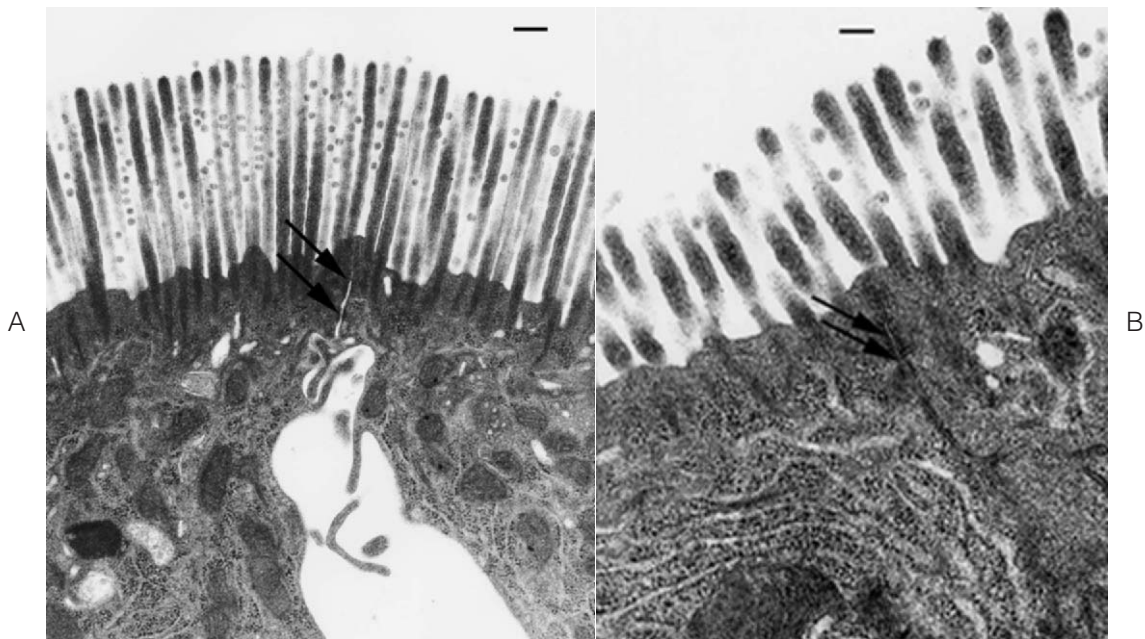
Figure 13.5-3   Histologic appearance of repairing intestinal mucosa 6 hours following a 2-hour ischemic episode. Blunting of the villi, attributable to villous contraction, and evidence of epithelial restitution *(arrows)* are notable. 1-cm bar = 100 μm.

POLYAMINES

The process of restitution absolutely depends on a group of compounds called polyamines.[113,114] The rate-limiting enzyme in the formation of the polyamines spermine, spermidine, and putrescine is ornithine decarboxylase. In rats with stress-induced duodenal ulcers, systemic administration of the ornithine decarboxylase inhibitor α-difluoromethylornithine significantly reduced polyamine levels and greatly reduced epithelial restitution. Furthermore, intragastric treatment of these same rats with putrescine, spermidine, and spermine prevented the delayed mucosal repair induced by α-difluoromethylornithine.[113] Interestingly, gastric tissue levels of ornithine decarboxylase increased in rats with stress-induced gastric ulcers, suggesting that tissue injury enhances polyamine production, which may contribute to the normal rapid rate of epithelial restitution.[115]

The mechanisms whereby polyamines stimulate epithelial restitution are not clear. McCormack, Wang, Viar, et al. hypothesized that polyamines increase transglutaminase activity, an enzyme that catalyzes the cross-linking of cytoskeletal and basement membrane proteins.[116] Further investigation of the role of polyamines in IEC-6 cell migration showed that depletion of polyamines resulted in disruption of the cytoskeleton and reduced the physical extension of

Figure 13.5-4   Ultrastructural appearance of repairing ischemic-injured mucosa. **A,** Restituting epithelium 2 hours following a 1-hour ischemic episode in the presence of the nonselective cyclooxygenase inhibitor indomethacin. Dilation of the interepithelial space and the apical tight junction *(arrows)* correlates with a leaky intestinal barrier, **B,** Similar restituting epithelium had been treated additionally with prostaglandins E_2 and I_2. The close apposition of the tight junction *(arrows)* and the interepithelial space correlate with normalization of intestinal barrier function. 1-cm bar = 6 μm.

lamellipodia.[117] More recent studies have clarified this pathway. In particular, polyamines have been shown to regulate cytoskeletal cellular migration via activation of the small guanosine triphosphatase-Rho-A by elevating intracellular Ca^{2+} levels. These elevations in Ca^{2+} result from polyamine regulation of expression of voltage-gated K^+ channels and altered membrane electric potential.[118]

Polyamines also play a role in the normal physiologic regulation of crypt cell proliferation and differentiation.[119,120] Polyamines are produced by fully differentiated enterocytes at the tip of the villus and may reach the crypt within sloughed luminal epithelium or via local villous circulation.[121] Following intestinal injury, polyamines appear to stimulate enhanced proliferation by increasing the expression of protooncogenes, which control the cell cycle.[122] The mechanism whereby polyamines influence gene expression likely relates to the cationic nature of these compounds, which may influence the tertiary structure of negatively charged DNA and RNA.[113]

GROWTH FACTORS

Locally produced growth factors—including epidermal growth factor (EGF), transforming growth factor α (TGF-α), TGF-β, and hepatocyte growth factor—have the ability to modulate mucosal recovery. The most important of these growth factors in early mucosal repair events is TGF-β, which is a potent stimulus of epithelial restitution and modulator of the extracellular matrix.[26] Neutralization of TGF-β retards epithelial migration in vitro, and TGF-β apparently may serve as a point of convergence for mediators of restitution, because neutralizing TGF-β also inhibits the effects of other peptides. However, TGF-β paradoxically inhibits epithelial proliferation, thereby reducing the supply of new enterocytes for mucosal repair. Conversely, EGF, produced by the salivary glands and duodenal Brunner's glands, and the related TGF-α, produced by small intestinal enterocytes, are potent stimulants of enterocyte proliferation. These growth factors share approximately 30% of their amino acid structure, bind to the same receptor on the basolateral surface of enterocytes, and are not related to TGF-β.[123] The physiologic role of EGF is difficult to discern because it is present in the intestinal lumen, with no apparent access to its basally located receptor. However, EGF has been proposed to act as a "surveillance agent" that gains access to its receptor during epithelial injury (when the EGF receptor likely would be exposed) to stimulate proliferation.[124] TGF-α presumably has a similar role, but it is present in greater concentrations in the small intestine because it is produced by differentiated villous enterocytes. The mature peptide is cleaved from the extracellular component of the transmembrane TGF-α precursor and released into the lumen.[123]

TREFOIL PEPTIDES

Another group of proreparative peptides produced within the gastrointestinal tract are the trefoil peptides. Under physiologic conditions, trefoil peptides are secreted by mucus-producing cells at distinct anatomic sites. For example, gastric epithelium produces the trefoil peptide pS2, whereas the small and large intestine mucosa produce intestinal trefoil peptide.[125] However, any of the trefoil peptides may be upregulated within repairing epithelium regardless of anatomic site.[26,126] In addition, trefoil peptides have the ability to induce their own expression, amplifying the level of these reparative factors at sites of mucosal repair.[127] Trefoil peptides are the most potent stimulants of epithelial migration in vitro, and their effects are independent of growth factors, including TGF-β.[128] However, recent evidence suggests that EGF receptor activation is required for induction of pS2 and another of the trefoil peptides, termed *spasmolytic peptide,* in gastric epithelium in vitro. The importance of trefoil peptides to the mucosal repair response in vivo is illustrated by gene knockout studies, in which mice deficient in intestinal trefoil factor have greatly reduced ability to repair intestinal injury.[129] In fact, detergent-induced mucosal injury was lethal because of a lack of restitution compared with wild-type mice that fully recovered from similar mucosal injury. The fact that administration of intestinal trefoil factor restored restitution has important therapeutic implications. The mechanism whereby trefoil peptides stimulate epithelial migration is yet to be characterized fully but appears to involve translocation of the adherens junction protein E-cadherin, thereby allowing cells to become untethered from neighboring cells.[26]

INTESTINAL NUTRIENTS

The principal metabolic fuel of enterocytes is glutamine and of colonocytes, butyrate. However, recent studies suggest that glutamine and butyrate have more specific proliferative actions aside from their role as nutrients. For example, in the piglet IPEC-J2 enterocyte cell line, glutamine enhanced gene transcription by increasing mitogen-activated protein kinase activity.[130,131] Similarly, butyrate stimulated mucosal growth following colonic infusion in the rat.[132] Because of such growth-promoting actions, glutamine was shown to prevent intestinal mucosal atrophy and dysfunction that accompanies starvation[133,134] and long-term total parental nutrition.[135,136] Additionally, glutamine improves function of transplanted small intestine[137,138] and protects intestinal mucosa from injury if administered before chemotherapy[139] and radiation therapy.[140,141] Intestinal nutrients also may synergize with other proliferative agents. For example, administration

of glutamine and TGF-α to porcine ileum that had been subjected to 2 hours of ischemia resulted in a synergistic increase in mitogen-activated protein kinase activity, enterocyte proliferation, and villous surface area.[42] Although concern has arisen that such early return to normal surface area may result in dysfunctional mucosal digestive and absorptive function because of resurfacing denuded mucosa with immature epithelium, nutrients and growth factors also appear to promote early differentiation. In the case of glutamine and TGF-α restoration of postischemic small intestine, rapid recovery of digestive enzymes also was documented.[142]

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13.6—Gastrointestinal Ileus

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Effective gastrointestinal motility involves a complex interaction between the enteric nervous system, muscular wall, and luminal contents. Additional factors that influence the net transit of digesta include gravity, the volume and viscosity of the contents, and pressure gradients created by simultaneous contraction and relaxation of adjacent segments of bowel. Casual use of the term *intestinal motility* in veterinary medicine often underestimates the complexity of the processes involved in the transit of intestinal contents. This is particularly true when the term is used to describe the frequency and or intensity of intestinal sounds, or borborygmi. The existence of borborygmi does not always equate with progressive movement of intestinal contents.

Disruption to normal motility occurs commonly in horses for a variety of reasons. Examples of diseases in which altered motility may be present include gastroduodenal ulceration, intraluminal obstruction or impaction, excessive wall distention, strangulating obstructions, peritonitis, and inflammatory bowel diseases such as duodenitis proximal jejunits or colitis. Ineffective intestinal motility is also a feature of several neonatal diseases, including prematurity, systemic sepsis, and perinatal asphyxia. Certain parasitic infections, electrolyte derangements, and endotoxemia can modify digesta transit in horses of all ages. General anesthesia and specific sedatives, such as xylazine, romifidine, or detomidine, also disturb motility.

Postoperative Ileus

The inhibition of propulsive bowel activity usually is referred to as ileus. Ileus is ascribed most frequently to the condition that occurs after laparotomy and is termed *simple* or *uncomplicated postoperative ileus* (POI). The

term *complicated* or *paralytic ileus* describes intestinal motility disturbed for longer periods after surgery. POI in horses is associated most commonly with surgery of the small intestine, particularly after resection and anastomosis,[1,2] is a common complication of small intestinal surgery, and can have a negative effect on short-term postoperative survival.[3,4] Motility dysfunction likely is present in all horses after laparotomy, but many are affected subclinically and require minimal or no specific intervention. In symptomatic animals, clinical signs are apparent shortly after recovery and include colic, tachycardia, dehydration, decreased borborygmi and fecal output, and sequestration of fluid within the stomach. Rectal examination and ultrasound reveal small intestinal distention with rare or absent wall movement. The severity and duration of intestinal stasis varies, lasting from minutes to days.

Cecal Emptying Defect

A specific motility disorder involving the cecum or ileocecocolic region occurs sporadically in horses.[5-7] The condition most commonly occurs after general anesthesia and extraabdominal surgery, particularly orthopedic and upper airway procedures, and therefore often is categorized as a form of POI. Anecdotally, horses at greatest risk are young male performance animals. Other cases occur spontaneously, often in animals with painful primary conditions such as uveitis or septic tenosynovitis. The syndrome is frustrating in that clinical signs are often subtle unless cecal perforation has occurred. In horses with a cecal emptying defect after anesthesia, overt signs are usually apparent 3 to 5 days after the procedure. The earliest detectable signs include depression and a reduction in feed intake and fecal output. Ineffective emptying results in overfilling of the cecum with moist contents, which is manifest by signs of mild to moderate colic. If the condition is recognized late or untreated, the cecum may rupture and result in fatal peritonitis.

Physiology

The inherent rhythmicity of electric activity in the intestine is controlled by the interstitial cells of Cajal, specialized cells that are electrically coupled to myocytes via gap junctions.[8] These cells are responsible for generating and propagating slow-wave activity and may be critically involved in a range of motility disorders. The enteric nervous system primarily controls and coordinates intestinal contraction. A combination of central and autonomic innervation influences events, but contraction does not require external neural input. The parasympathetic supply to the gastrointestinal tract is via the vagus and pelvic nerves, and the sympathetic supply is through postganglionic fibers of the cranial and caudal mesenteric

plexuses. A complex network of interneurons within each plexus integrates and amplifies neural input; the intensity and frequency of resultant smooth muscle contractions are proportional to the amount of sympathetic and parasympathetic input. Additional binding sites for a number of other endogenous chemicals, including dopamine, motilin, and serotonin exist within the enteric nervous system and on smooth muscle cells.[9] Acetylcholine is the dominant excitatory neurotransmitter in the gastrointestinal tract and exerts its action through muscurinic type 2 receptors on smooth muscle cells. Sympathetic fibers innervating the gastrointestinal tract are adrenergic, postganglionic fibers with cell bodies located in the prevertebral ganglia. Activation of α_2-adrenergic receptors on cholinergic neurons within enteric ganglia inhibits the release of acetylcholine and therefore reduces intestinal contraction.

β_1-, β_2-, and β-atypical receptors are directly inhibitory to the intestinal smooth muscle.[10] Inhibitory nonadrenergic, noncholinergic neurotransmitters include adenosine triphosphate, vasoactive intestinal peptide, and nitric oxide.[11,12] These neurotransmitters are critical for mediating descending inhibition during peristalsis and receptive relaxation. Substance P is a nonadrenergic, noncholinergic neurotransmitter that may be involved in contraction of the large colon.[13,14]

The rate and force of intestinal contractions along the small intestine and large colon of the horse are important determinants of intestinal motility; of even greater importance to the net propulsion of digesta are the cyclical patterns of contractile activity. These patterns are known as the small intestinal and colonic migrating motility (or myoelectric) complexes (MMCs).[15,16] The colonic complex usually originates in the right ventral colon and variably traverses the ascending and descending colons. Many of these complexes are related temporally to a specialized motility event of the ileum, the migrating action potential complex.

Pathophysiology

INFLAMMATION

Local inflammation within the intestinal muscularis and inhibitory neural events are important initiators of intestinal ileus.[17,18] Intestinal inflammation not only is important in primary intestinal diseases in horses, such as duodenitis-proximal jejunitis and colitis but also is induced after simple intestinal handling during laparotomy. Experimental data from other species suggests that handling of the small or large intestine at the time of surgery activates resident macrophages with resultant increased expression of P-selectin and intercellular adhesion molecule 1 on endothelial cells within the vasculature of the muscularis. The upregulation of

associated ligands on leukocytes leads to sequential "sticking and rolling," followed by neutrophil migration into the interstitium. The subsequent release of neutrophil products interferes with cell signaling and results in reduced intensity of smooth muscle contraction. Furthermore, the inflamed intestine fails to contract normally in response to putative prokinetic agents.

Another key factor in the development of intestinal stasis after inflammation is the local overproduction of nitric oxide caused by the upregulation of inducible nitric oxide synthase (iNOS) by resident macrophages. Nitric oxide is a key inhibitory neurotransmitter of the nonadrenergic, noncholinergic system.[12] Nitric oxide synthase inhibition has been a pharmacologic target in the treatment of experimental ileus.

DRUGS

The inhibitory effects of α_2-agonists such as xylazine and detomidine on cecal and large colon motility are well described.[19-24] Intravenously administered xylazine inhibits cecal and large colon motility for 20 to 30 minutes without seriously disrupting small intestinal myoelectric activity, and detomidine can reduce large intestinal myoelectric activity for up to 3 hours. The α_2-antagonist yohimbine has a weak but positive effect on cecal emptying in normal ponies, suggesting that normal motility is under constant α_2-adrenergic tone.[24]

Atropine is a postganglionic blocking agent that binds to muscarinic receptors. When administered at 0.04 mg/kg, atropine inhibits individual small intestinal, cecal, and colonic contractions for about 120 minutes but supresses small intestinal and colonic migrating complexes for up to 8 hours.[25]

NEURAL REFLEXES

Neural reflexes also may mediate inhibition of motility associated with peritoneal inflammation.[26,27] The afferent segment is composed partly of capsaicin-sensitive visceral afferent C fibers that terminate in the dorsal horn of the spinal cord, where they can activate inhibitory sympathetic fibers or synapse directly on the sympathetic ganglia. Consequently, the efferent limb of the reflex expresses increased sympathetic outflow, primarily mediated through stimulation of α_2-adrenoreceptors, and inhibition of acetylcholine release, which provides the rationale for α_2-blockade in treating ileus. Intraluminal infusion of capsaicin before abdominal surgery ameliorated the severity of POI in experimental rats. This finding highlights the importance of visceral afferent fibers in the development of POI.[28]

DISTENTION

Ileus also can occur in association with intestinal obstruction or displacement. Mild to moderate distention of the bowel, such as that occurring in the early stages of an intraluminal obstruction, evokes an increase in local contractile activity.[29,30] Excessive distention results in inhibition of motility within the distended segment of bowel. Intestinal stasis is not always detrimental and under certain conditions may be protective.

ENDOTOXINS

Endotoxemia is a clinical feature of many diseases of the equine gastrointestinal tract, and endotoxins independently can exert a negative effect on intestinal motility and transit.[31] A variety of mediators likely are involved, but activation of α_2-adrenoreceptors and production of prostanoids appear to be important, for pretreatment with yohimbine or nonsteroidal antiinflammatory drugs (NSAIDs; phenylbutazone or flunixin), respectively, ameliorates the inhibitory effects of experimental endotoxin infusion.[32,33] Endotoxin infusion induced an inflammatory response in the intestine of rats that mimicked the response induced by handling during laparotomy.[34] The similarity of the responses were highlighted in a recent study that demonstrated that prior exposure of the muscularis to endotoxin protected the intestine from the effects of manipulation.[35]

The pathophysiology of cecal emptying defect is not known. This syndrome may best mimic POI in human beings and generally is considered a large intestinal disorder. An important difference in horses is that laparotomy is a rare predisposing factor, and most cases occur in horses undergoing routine extraabdominal surgical procedures. General anesthesia itself is a potent inhibitor of gastrointestinal motility in horses, but these effects are short-lived and reversible within hours of anesthetic withdrawal.[15] The return of normal motility in horses after experimental ileus was most delayed in the cecum, suggesting that this may be a common site of ileus in horses.[36] A link between routine postoperative medications, such as phenylbutazone and aminoglycoside antibiotics, has been suspected but not established. An inhibitory effect of NSAIDs on large colon contractility has been demonstrated using in vitro techniques.[37] Primary sympathetic overstimulation could be involved, for many of the affected animals are young, male horses or animals with painful diseases.

The duration of surgery influences the development of small intestinal POI, but not cecal emptying dysfunction.[7,38] Technique may have a weak influence on small intestinal POI after jejunojejunostomy. The duration of intestinal ileus was shorter in animals that received a side-to-side stapled anastomosis than those that had a hand sewn end-to-end procedure.[3] The duration of ileus after stapled end-to-end anastomosis was not different from that after either procedure.

Reported risk factors for the development of POI in horses include age (>10 years), small intestinal resection

and anastomosis, breed (Arabians had a greatest risk than other breeds), and duration of surgery.[38] Interestingly, performing a pelvic flexure enterotomy and emptying the colon had a protective effect against POI.

Diagnosis

The diagnosis of ileus is based on history and physical examination findings. Important tests include determination of pulse rate and rhythm, auscultation and percussion of the abdomen, rectal palpation, and passage of a nasogastric tube. A complete blood count with fibrinogen estimation and cytologic analysis of peritoneal fluid may improve the accuracy of diagnosis. Affected animals may be colicky because of accumulation of fluid in the upper gastrointestinal tract (classical POI) or cecal contents (cecal emptying defect). Decompression of the stomach is important diagnostically and therapeutically in horses with POI after small intestinal surgery. Failure to relieve pain with gastric decompression could point toward mechanical obstruction, severe inflammation of the intestine, or peritonitis. Most animals with ileus are depressed and have reduced fecal output and intestinal borborygmi. One should interpret intestinal sounds with caution, however, because the presence of borborygmi does not always equate to progressive intestinal motility and merely may reflect local, nonpropagated contractions.

Rectal palpation findings in cases of persistent POI or duodenitis-proximal jejunitis are usually nonspecific but may reveal dilated, fluid-filled loops of small intestine. The clinician occasionally can palpate roughened peritoneal surfaces if peritonitis is present. One can palpate cecal distention with digesta in horses with advanced cecal dysfunction.

Distinguishing functional ileus from mechanical obstruction is important and can be difficult, but horses with mechanical obstruction typically have sustained high volumes of gastric reflux that vary little over time.

Treatment

The management of intestinal ileus depends on the segment of gastrointestinal tract involved. Therapy for ileus of the proximal gastrointestinal tract involves a combination of gastric decompression, fluid and electrolyte therapy, and antiinflammatory drug therapy. Electrolyte therapy is critical, particularly for maintaining adequate extracellular concentrations of potassium, calcium, and magnesium. Calculation of the volume of fluid to be administered should include maintenance requirements (40 to 60 ml/kg/day) plus an estimate of losses, especially those lost through gastric decompression. One should consider parenteral provision of calories when feed has been withheld for more than 96 hours, particularly after

the horse has had surgery. A combination of amino acids and dextrose with or without lipids effectively provides these calories. Hand walking also may provide some benefit to these animals but is not likely to have a direct effect on intestinal motility.

One should avoid drugs that may impair normal intestinal motility, including the anticholinergics such as atropine and opiate receptor agonists such as morphine and meperidine. Butorphanol appears to have little or no adverse effect on small or large intestinal motility.[39,40] One should use α_2-agonists sparingly because of their inhibitory effects on large intestinal motility.

Fluid therapy is the key component in managing cecal emptying defect, usually in combination with lubricants or laxatives, such as mineral oil or magnesium sulfate, and with careful use of antiinflammatory drugs. Horses with primary cecal impaction or impaction caused by an emptying defect frequently require surgery to prevent fatal rupture. The surgical management of these cases is controversial and may include typhlotomy alone, typhlotomy with a bypass procedure such as ileocolic or jejunocolic anastomosis, or a bypass without typhlotomy.[41] Most horses that undergo simple typhlotomy have an uneventful recovery,[42] although a small number experience impaction again and require a second laparotomy.

Experimental and anecdotal evidence provides a strong rationale for using antiinflammatory drugs to prevent and treat gastrointestinal ileus, particularly in animals that may have endotoxemia.[43] Flunixin meglumine is used widely in equine practice as an analgesic and antiinflammatory agent, and it ameliorates many of the adverse systemic effects of endotoxin, particularly those on the cardiovascular system. A potential negative effect of NSAIDs on large intestinal contractility has been suggested.

Broad-spectrum antimicrobials are indicated when one suspects sepsis or for the compromised immune system, as in cases of moderate to severe endotoxemia. Theoretical concerns have been raised regarding the use of aminoglycoside antibiotics in animals with ileus. High concentrations of aminoglycoside antimicrobials inhibited intestinal contractions in exposed sections of intestine in vitro, but this inhibitory effect is unlikely to occur at clinically relevant doses.[44]

Motility-enhancing drugs have been advocated to treat gastrointestinal ileus. Unfortunately, information directly pertinent to horses is limited and must be extrapolated cautiously from that of other species because of the differences in intestinal anatomy and physiology. Prokinetic drugs potentially can shorten the length of hospitalization, thereby reducing the cost of treatment and the number of potential complications such as weight loss, thrombophlebitis, and laminitis. Experimental evidence indicates that prokinetic drugs can minimize the

development of postoperative abdominal adhesions.[45] Most prokinetic drugs require a healthy gut wall to enhance intestinal contraction. Therefore one should not assume that many of these drugs would be effective in the presence of an inflammatory injury such as that which can occur after intestinal manipulation at surgery or that associated with duodenitis-proximal jejunitis.

Bethanechol is a parasympathomimetic agent that acts at the level of the myenteric plexus and directly on intestinal smooth cells through muscarinic receptors. Bethanechol is a synthetic ester of acetylcholine and is not degraded by anticholinesterase. Bethanechol has cholinergic side effects, including abdominal discomfort, sweating, and salivation, although these are minimal when the drug is administered at 0.025 mg/kg body mass subcutaneously or orally. Bethanechol has efficacy in diseases that involve abnormal gastric emptying and delayed small intestinal transit and has been shown to increase gastric contractility and hasten the emptying of liquid and solid phase markers from the stomach of normal horses.[46-47] Bethanechol also increases the strength and duration of wall contractions in the cecum and right ventral colon and consequently speeds up cecal emptying. Neostigmine increases receptor levels of acetylcholine by inhibiting cholinesterase. The drug (0.022 to 0.025 mg/kg intravenously) promotes cecal and colonic contractile activity and hastens the emptying of radiolabeled markers from the cecum.[24] Neostigmine has been used to manage small intestinal ileus, but it significantly delayed the emptying of 6-mm beads from the stomach of normal adult horses.[48]

Metoclopramide acts principally as a 5-hydroxytryptamine 4-receptor (5HT-4) agonist and 5HT-3–receptor antagonist. In contrast to newer generation benzamides, metoclopramide is also an antagonist at dopamine 1 (DA_1) and 2 (DA_2) receptors. Antagonism of prejunctional DA_2 receptors facilitates acetylcholine release and smooth muscle contraction. Metoclopramide crosses the blood-brain barrier, where its antagonist properties on central DA_2 receptors can result in extrapyramidal signs, including seizure. These signs were responsible for poor acceptance of the drug in equine practice. Most investigators have failed to demonstrate significant effects of metoclopramide in experimental animals, but constant intravenous infusion (0.04 mg/kg/hr) in a population of postoperative horses significantly decreased the volume and duration of gastric reflux over control and intermittent drug infusion groups.[49] Infusion was well tolerated and appeared to be superior to intermittent infusion or no treatment at all.

Cisapride is a second-generation benzamide that acts as a 5HT-4 agonist and 5HT-3 receptor antagonist but is without antidopaminergic action. Stimulation of 5HT-4 receptors within the enteric nervous system enhances release of acetylcholine from the myenteric plexus. Several reports suggest the efficacy of cisapride in managing intestinal disease in horses, including the resolution of persistent large colon impaction, treatment of equine grass sickness, and as a preventative for POI in horses after small intestinal surgery (0.1 mg/kg body mass intramuscularly during the postoperative period).[50-53] The horse erratically absorbs tablets administered rectally, but a method for preparing a parenteral form of the drug from tablets has been described.[54] Cisapride has the potential to cause adverse cardiac side effects mediated through blockage of the rapid component of the delayed rectifier potassium current that include lengthening of the QT interval and development of torsades de pointes, a potentially fatal arrhythmia. These adverse effects have resulted in withdrawal of the drug in the United States.

Domperidone acts as a competitive antagonist at peripheral DA_2 receptors. The drug is a therapeutic agent (1.1 mg/kg/day) for mares grazing endophyte-infected tall fescue, principally because of drug-enhanced prolactin release. The potential prokinetic effects of domperidone have not been studied extensively in horses, but a modest efficacy of domperidone (0.2 mg/kg intravenously) has been demonstrated in experimental ileus in two ponies.

Erythromycin is a direct motilin receptor agonist on smooth muscle cells and also may act within the enteric nervous system to facilitate the release of acetylcholine and motilin. Erythromycin enhances gastric emptying in normal horses but has a more pronounced effect on the hindgut.[47,55] Erythromycin lactobionate (1.0 mg/kg intravenously) hastens cecal emptying in normal animals and induces colonic MMC-like activity across the colon. Administration often is associated with defecation and abdominal discomfort. The drug may help prevent cecal impaction in horses after anesthesia, although its effectiveness on cecal motility in the immediate postoperative period may be reduced.[36] High doses, constant infusion, or prolonged use of erythromycin induces receptor downregulation and inhibition of activity. Erythromycin can induce diarrhea in adults, therefore one should avoid dosing over many days.

Naloxone (0.05 mg/kg intravenously) induces contractile activity in the cecum and left colon.[56] Defecation commonly follows administration of naloxone within 15 to 20 minutes.

α_2-Adrenoreceptor antagonists such as yohimbine or tolazoline counteract increased sympathetic outflow in response to nociceptive stimulation. Yohimbine infusion (75 µg/kg) also may attenuate the negative effects of endotoxin on motility.[32]

Intravenous infusion of lidocaine may suppress primary afferent neurons, thereby limiting reflex efferent inhibition of motility. An infusion dose of 15 to 20 mg/min over 5 to 6 hours has been recommended for horses.

Lidocaine infusion is associated with reversible side effects that include muscle fasciculations, ataxia, and seizure. Consequently, the rate of infusion requires close monitoring.

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13.7—Endotoxemia

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Introduction and Definitions

Endotoxemia is defined as the presence of endotoxin in the bloodstream. Most often, however, the term is used to refer to the associated clinical manifestations caused by an overshooting inflammatory reaction. In its pathophysiologic consequences the innate immune response to endotoxin (lipopolysaccharide) is similar to the response to other stimuli; for example, overwhelming bacterial infection, viral infection, or severe trauma. The term *systemic inflammatory response syndrome* therefore was introduced to describe a general systemic inflammatory process independent of cause. *Sepsis* is defined as the "systemic inflammatory response to infection," and *septic shock* as "sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction."[1] According to these definitions the diagnosis of sepsis requires documentation of infection by culture in addition to two or more of the following findings: hypo- or hyperthermia, tachycardia, tachypnea or hypocapnia, and leukocytosis, leukopenia, or an increased proportion of immature leukocyte forms. Organ failure is a common sequela of endotoxic or septic shock, and the term *multiple organ dysfunction syndrome* describes insufficiency of two or more organ systems, as evident by clinical or clinicopathologic changes. In horses one should include the laminae of the feet in the list of organs susceptible to failure.

Endotoxin

German scientist Richard Pfeiffer (1858-1945), in working with *Vibrio cholerae*, first described endotoxin as a toxin "closely attached to, and probably integral of, the bacterial body."[2] He observed this toxin to be distinct from the actively secreted, heat-labile, and proteinaceous bacterial exotoxins. Endotoxin later was found to be a heat-stable lipopolysaccharide structure, and the terms *endotoxin* and *lipopolysaccharide* now are used interchangeably.

Lipopolysaccharide is a major structural cell wall component of all gram-negative bacteria, including noninfectious species (Figure 13.7-1). With 3 to 4×10^6 molecules per cell, lipopolysaccharide makes up about 75% of the outer layer of the outer cell membrane and is a key functional molecule for the bacterial outer membrane, serving as a permeability barrier against external noxious agents. The lipopolysaccharide molecule
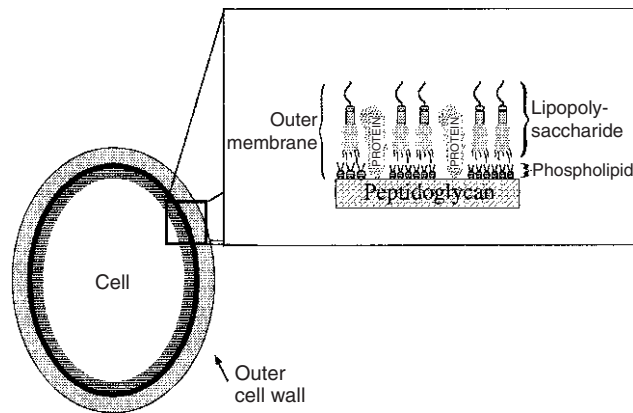
Figure 13.7-1

consists of four domains, which are essential for the virulence of gram-negative bacteria.[3] Three of the domains (inner core, outer core and O-specific chain) represent the hydrophilic polysaccharide portion of the molecule, whereas the lipid A portion represents the hydrophobic lipid portion (Figure 13.7-2). Combined, these domains confer the overall amphiphilic properties of the molecule that lead to the formation of micellar aggregates in aqueous solutions.

O-specific chains (also called O-antigen polysaccharides or O-chains) are characteristic of any given type of lipopolysaccharide and show enormous structural variability between bacterial serotypes.[4] O-chains are synthesized by addition of preformed oligosaccharide blocks to a growing polymer chain and therefore have a repetitive structure. O-specific chains determine part of the immunospecificity of bacterial cells[5] and, on interaction
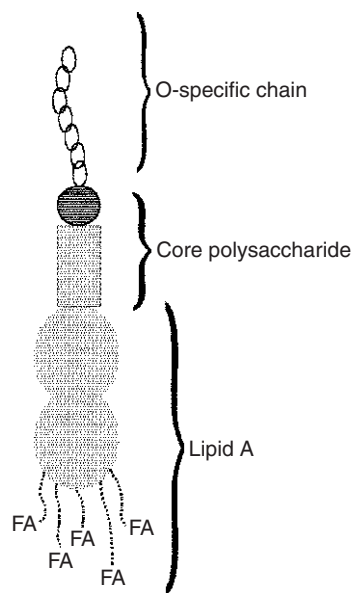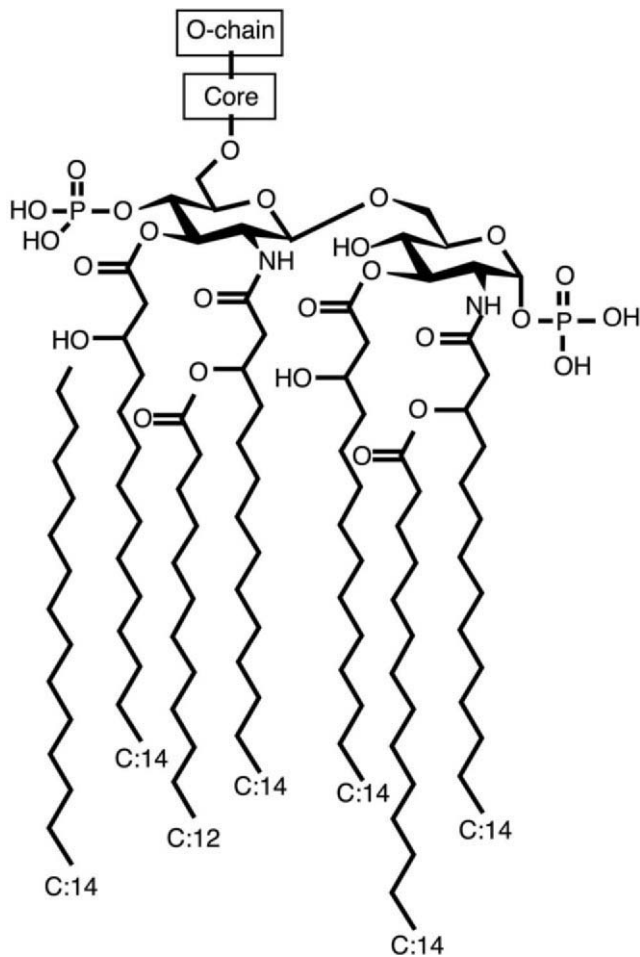

Figure 13.7-2

with the host immune system, serve as antigens for the production of species-specific antibodies.[6] O-specific chains are further responsible for the smooth appearance of gram-negative bacterial colonies on culture plates,[3] and lipopolysaccharide molecules containing an O-chain are termed *smooth lipopolysaccharide.*

The inner (lipid A-proximal) and outer (O-chain-proximal) core oligosaccharide portion is more conserved between different strains of gram-negative bacteria than the O-specific chain.[4] The core of all lipopolysaccharide molecules contains the unusual sugar KDO (3-deoxy-D-manno-oct-2-ulopyranosonic acid), which links the core region to the lipid A molecule. Synthesis of a minimal core is essential for the survival of bacteria,[7] and the smallest naturally occurring lipopolysaccharide structure consists of lipid A and KDO.[8] In contrast to the S-form colonies, colonies of gram-negative bacteria with lipopolysaccharide molecules that lack the O-specific chain but contain a core region show a rough appearance on culture plates. Rough lipopolysaccharide molecules are denoted further as Ra, Rb, etc. to indicate the length of the core region. In Re-lipopolysaccharide (also called deep rough lipopolysaccharide), the core region is reduced to a KDO residue. Remutants often are used to raise antibodies against the core region in an attempt to provide cross-protection against a variety of bacterial species.

The lipid A portion serves to anchor the lipopolysaccharide molecule in the bacterial outer membrane and has been identified as the toxic principle of lipopolysaccharide,[9] and its structure is highly conserved among gram-negative bacteria. The common structure shared by lipid A molecules is a 1,4'-bisphosphorylated β1,6-linked D-glucosamine disaccharide backbone (lipid A backbone), which is acylated by up to six fatty acids.[4] Figure 13.7-3 shows the acylation pattern for *Escherichia coli* lipopolysaccharide. Variation in the lipid A structure between gram-negative bacteria affects the number, length, and position of fatty acids and the backbone structure and the substitution of phosphate by other polar groups.[6]

Causes of Endotoxemia in Horses

According to its nature as a structural cell wall component, the presence of endotoxin implies the presence of gram-negative bacteria as a source. Depending on the nature of the underlying disease, these bacteria may circulate in the bloodstream in their intact form (i.e., bacteremia), may be confined to a localized infectious process, or may be part of the endogenous bacterial flora colonizing the gastrointestinal tract. In any of these scenarios, endotoxin molecules are released as a by-product of bacterial growth and in large numbers on bacterial cell death.[10] Common infectious conditions associated with endotoxemia in horses include neonatal gram-negative

Figure 13.7-3 Chemical structure of the lipid A backbone. *C:14,* Myristic acid, *C:12,* lauric acid.

sepsis, bacterial pneumonia and pleuropneumonia, endometritis, peritonitis, and infectious colitis with bacteria such as *Salmonella* spp., that are not part of the normal intestinal flora. In one study, for example, endotoxin was detectable in plasma of 50% of foals evaluated for presumed sepsis.[11]

The term *translocation* describes entry of endogenous bacteria and bacterial products from the gastrointestinal tract into tissues and the systemic circulation.[12] The natural intestinal flora of horses consists mainly of gram-negative, anaerobic bacteria, and thus large amounts of endotoxin normally exist in the lumen of the equine intestinal tract.[13] Even in health, small amounts of endotoxin cross the intact mucosal barrier and reach the portal circulation and the liver. These molecules are cleared, however, by the mononuclear phagocytic system in the liver and only lead to a localized and restricted activation of the host immune system. For endotoxin translocation to become detrimental, excessive amounts have to cross the intestinal barrier and overwhelm the mononuclear phagocytic system or the capacity of the liver to detoxify

lipopolysaccharide must be compromised. The latter may be a concern in conditions such as hepatitis, cholangio-hepatitis, or portosystemic shunting of blood.

Permeability of the intestinal mucosal barrier frequently increases in cases of acute gastrointestinal disease. Colic patients are prime candidates to development endotoxemia, and plasma endotoxin was detectable in 10% to 40% of colic patients on admission.[14,15] A higher percentage of horses tested positive for endotoxin when only patients presented for surgical intervention were evaluated.[15] Aside from gastrointestinal rupture, increased permeability to intact bacteria or free endotoxin molecules is thought to be associated most commonly with ischemic insults such as strangulating obstruction and bowel infarction, severe inflammation as in proximal enteritis and colitis, bacterial overgrowth, and intraluminal acidosis, which occurs with grain overload.[16,17] One study, however, found no difference in plasma endotoxin detection between disease groups, therefore emphasizing the fact that any disease of the abdominal cavity can induce endotoxemia in horses. In the same study, endotoxin was approximately 3 times more likely to be detected in peritoneal fluid as opposed to plasma samples. Similarly, higher cytokine concentrations have been measured in peritoneal fluid than in plasma. The likely explanation for these findings is a local inflammatory response in the peritoneal cavity elicited by translocated bacteria and/or lipopolysaccharide molecules before their absorption into the systemic circulation.[14]

Although certainly the most important factor in horses, conditions other than gastrointestinal disease may result in translocation of endotoxin and bacteria. In experimental studies using laboratory animals, entry of gut-associated bacteria into the lymphatic system was demonstrated after hypovolemic shock, burn injuries, trauma, malnutrition, and starvation.[18-20] Furthermore, endotoxin itself caused bacterial translocation into mesenteric lymph nodes after intraperitoneal administration to mice.[21] These findings have received much attention in the literature concerning human patients because they serve to explain cases of endotoxic shock in the absence of demonstrable bacterial infection. One should keep in mind the possibility of translocation when evaluating cases of presumed systemic inflammatory response syndrome in horses, in which one cannot demonstrate bacterial infection or gastrointestinal disease. Endotoxin translocation also may be associated with strenuous exercise, which results in reduced splanchnic blood flow, hypoxemia, and a higher body temperature. In fit racehorses a significantly increased mean plasma lipopolysaccharide concentration was found after racing, whereas antilipopolysaccharide immunoglobulin G levels were decreased. Fit horses showed significantly higher antilipopolysaccharide immunoglobulin G concentrations

at rest than sedentary controls, suggesting leakage of small amounts of endotoxin from the intestinal lumen during training and racing.[22] The clinical significance of these findings requires further investigation.

Mechanisms of Cellular Activation by Lipopolysaccharide

The initiating event in the pathophysiology of endotoxemia is the activation of lipopolysaccharide-responsive cells by endotoxin, resulting in altered cellular functions and increased expression of inflammatory mediators. Immune cells such as macrophages, which are the first to encounter endotoxin, respond to minute amounts of lipopolysaccharide, which usually allows them to eliminate gram-negative bacteria and free lipopolysaccharide molecules efficiently. An important factor in the exquisite sensitivity to lipopolysaccharide is the presence of lipopolysaccharide-binding protein (LBP).[4] LBP is an approximately 60-kd plasma glycoprotein[23] synthesized by hepatocytes[24] and belongs to the group of acute phase proteins. Under the control of inflammatory agents and cytokines, LBP concentration in plasma increases approximately 100-fold within 24 hours of an inflammatory stimulus.[25] The main function of LBP is to transfer lipopolysaccharide to endotoxin-responsive cells, which include mononuclear phagocytes, neutrophils, lymphocytes, and endothelial cells. The importance of a highly sensitive response to lipopolysaccharide for protection against gram-negative bacterial infection is demonstrated in experiments using LBP "knock-out" mice (mice that lack the LBP gene and are therefore unable to synthesize LBP). Although these animals are resistant to the effects of isolated lipopolysaccharide, they are unable to control bacterial infection and rapidly succumb.[26] Despite its crucial importance for an effective host defense, LBP is not essential for lipopolysaccharide-receptor interaction per se, because high concentrations of lipopolysaccharide can activate cells in the absence of LBP.[27]

Aside from its role as a catalyst of cellular activation by lipopolysaccharide, LBP has opsonizing activity[28] and participates in the phagocytosis of lipopolysaccharide by macrophages and neutrophils.[29,30] Although phagocytosis of lipopolysaccharide is receptor dependent, it appears to be uncoupled from intracellular signaling events and occurs in the absence of cell activation.[31] LBP further catalyzes transfer of lipopolysaccharide to lipoproteins such as high-density lipoprotein, which neutralizes lipopolysaccharide activity.[32] This detoxifying effect may become important when large amounts of lipopolysaccharide are present. A protective effect of LBP against lipopolysaccharide challenge and infection has been demonstrated in a murine model.[33]

The most important lipopolysaccharide receptors known to date are cluster differentiation antigen 14 (CD14)[27] and Toll-like receptor 4 (TLR4).[34] Both are classified as pattern recognition receptors,[35] which means that they recognize lipopolysaccharide as a pattern common to all gram-negative bacteria. CD14 is a 53-kd protein that in its membrane-bound form (mCD14) is inserted into the cell membrane via a glycosyl-phosphatidyl-inositol anchor.[36] CD14 is expressed primarily on monocytes and tissue macrophages and to a lesser extent on neutrophils.[37] CD14 also is found in a free, or soluble, form (sCD14)[38] that can bind to cell types lacking CD14, such as endothelial cells, and make them lipopolysaccharide-responsive. In addition to this proinflammatory effect, high concentrations of sCD14 can sequester and neutralize lipopolysaccharide.[39] The amount of circulating sCD14 greatly increases during inflammation, which makes it a useful marker of acute and chronic inflammation.[37]

Although CD14 is known to be crucial for cellular activation, it cannot transmit signals to the inside of the cell because it lacks a transmembrane domain. The missing link between CD14 and the cytosolic environment is a Toll-like receptor in association with a molecule named MD-2.[40] The name *Toll-like receptor* stems from the homology of the mammalian receptor with a receptor type in *Drosophila* (Toll) that is important for dorsoventral orientation and immune responses in the fly. A number of Toll-like receptors have been identified in mammalian species so far, but TLR4 appears to be the receptor subtype most important for lipopolysaccharide signaling.[34] The importance of CD14 and TLR4 in the cellular response to lipopolysaccharide has been demonstrated in a number of experiments. Mice deficient in CD14 are incapable of mounting a normal inflammatory response to lipopolysaccharide,[39] whereas mutation or deletion of the gene encoding for TLR4 causes lipopolysaccharide hyporesponsiveness.[41-43]

After binding of lipopolysaccharide to cellular receptors, a multitude of signaling events takes place within the cell and results in the alterations of cellular metabolism known as cell activation. Signaling pathways are characterized by sequential phosphorylation and thereby activation of enzymatic activities. A typical end result of intracellular signaling is the activation of transcription factors; for example, proteins that bind to DNA and promote gene transcription. Translational mechanisms are activated in a similar manner. Among the best-characterized pathways in endotoxin-induced cell signaling are the mitogen-activated protein kinase (MAPK) pathways and the activation of transcription factor nuclear factor κB (NFκB) (Figure 13.7-4).[44,45] In the NFκB pathway the intracellular domain of TLR4 associates with the adapter protein myeloid differentiation factor 88 and

recruits interleukin-1 receptor-associated kinase to the complex. Activation of interleukin-1 receptor-associated kinase, tumor necrosis factor receptor-associated factor, NFκB-inducing kinase, and IκB-kinase follow, and lastly, IκB is phosphorylated. IκB is an inhibitor protein complex that sequesters and inactivates NFκB in the cytoplasm. On phosphorylation, IκB is ubiquinated and degraded, and NFκB is translocated to the nucleus where it unfolds its activity.[46] NFκB is a dimeric protein complex with several isoforms of which the p65/p50 heterodimer is the most important inducible complex in mammals.[47] Proteins of importance for the pathogenesis of septic
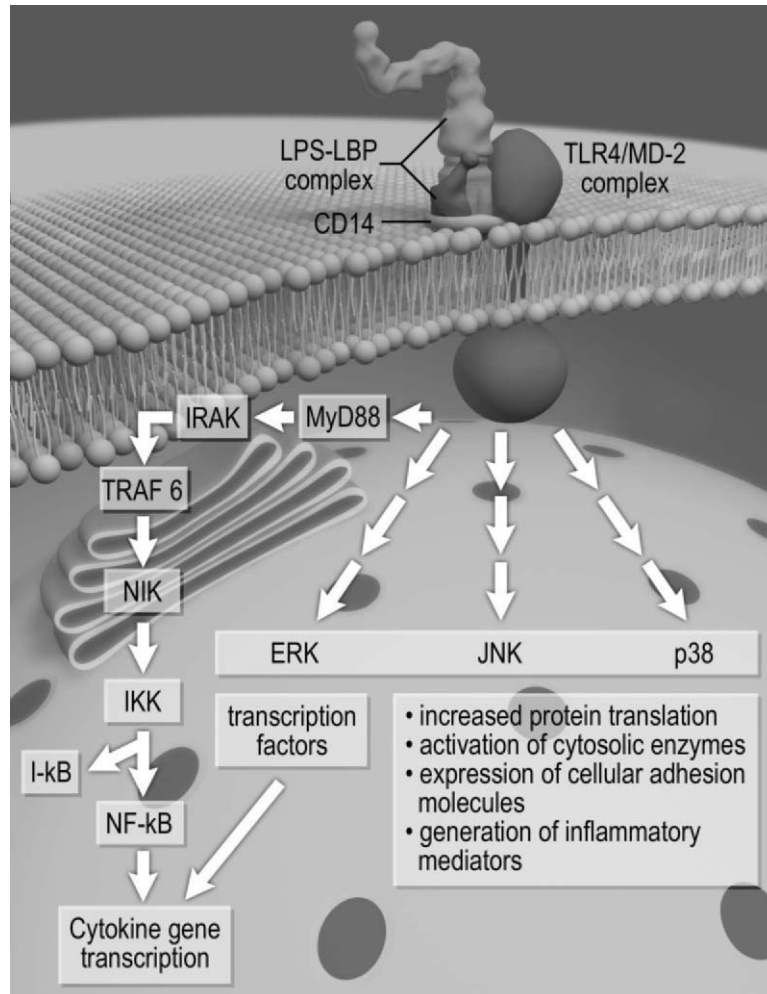
Figure 13.7-4 Mechanisms of cell activation by endotoxin. Lipopolysaccharide-binding protein *(LPB)* associates with lipopolysaccharide (*LPS,* endotoxin) and transfers it to the cellular surface, where lipopolysaccharide interacts with a receptor complex comprising CD14, Toll-like receptor 4 *(TLR4),* and MD-2. Toll-like receptor 4, but not CD14, possesses a transmembrane portion and allows signal transduction to the cytosol. Signaling via the mitogen-activated protein kinases including extracellular signal-regulated kinase *(ERK),* c-Jun-terminal kinase *(JNK),* and p38 results in numerous alterations of cellular metabolism. Activation of IκB-kinase *(IKK)* via sequential phosphorylation of myeloid differentiation factor 88 *(MyD88),* interleukin-1 receptor-associated kinase *(IRAK),* tumor necrosis factor receptor–associated factor *(TRAF 6),* and NFκB-inducing kinase *(NIK)* leads to phosphorylation, ubiquination, and degradation of IκB and release of NFκB. Transcription factors such as NFκB translocate to the nucleus and promote gene transcription. See the text for further details and alternative pathways of cellular activation.

shock, the genes of which contain promoter elements for NFκB, include cytokines, inducible nitric oxide synthase, and cyclooxygenase 2 (COX-2).[44]

Three groups of MAPKs known to be crucially important for lipopolysaccharide-induced signal transduction are extracellular signal-regulated kinase, c-Jun-terminal kinase, and p38. Final effects of signaling through MAPK pathways include the activation of several transcription factors, translation initiation factors, and cytosolic enzymes such as phospholipase A_2, as well as an increase in the expression of adhesion molecules on the cell surface.[44] Despite the characterization of seemingly separate pathways, one should recognize that interaction and synergy between pathways is likely to occur. For example, simultaneous activation of p38, c-Jun-terminal kinase, and extracellular signal-regulated kinase results in much higher levels of tumor necrosis factor (TNF) reporter expression than activation of a single pathway.[44,48] Aside from the mechanisms described here, pathways involving atypical protein kinase C[49,50] and receptor-independent integration of lipopolysaccharide into the cell membrane and ceramide-like second messenger activity of lipopolysaccharide[37] have been proposed. Additional pathways are likely to be uncovered in the ongoing investigation of intracellular signaling mechanisms and their in vivo significance.

Inflammatory Mediators

Although endotoxin can exert some direct effects, cytokines are a primary mediator of lipopolysaccharide effects. Cytokines are glycoprotein molecules that regulate inflammatory and immune responses by acting as a signal between cells.[51] Cytokines of major interest in the pathogenesis of endotoxemia include TNF, the interleukins, chemokines, and growth factors such as granulocyte-monocyte colony-stimulating factor. TNF is thought of as the most "proximal" cytokine released in response to lipopolysaccharide. Studies corroborate this by showing that administration of recombinant TNF mimics the effects of lipopolysaccharide,[52] and that antibodies directed against TNF protect against the lethal effects of endotoxin.[53] Increased plasma activity of TNF is associated with increased mortality in equine patients with acute gastrointestinal disease and in septic neonates.[14] Despite being a structurally diverse group of proteins, cytokines share several characteristics that allow them to execute their complex functions in the inflammatory response.[51] Any individual cytokine generally is produced by several different cell types, can act on different cell types, and has multiple effects on any given cell. Furthermore, cytokine effects are redundant, meaning that different cytokines can share the same effect. In endotoxemia, this is particularly true for the effects of interleukin-1 (IL-1) and TNF.[54] Many of the biologic

activities of cytokines in vivo result from synergistic or antagonistic actions involving two or more cytokines.[55] Within itself the cytokine response is highly regulated: cytokines induce or suppress synthesis of other cytokines including their own (feedback regulation), regulate expression of cytokine receptors, and regulate cytokine activities. Additional regulatory mechanisms include the release of specific cytokine inhibitors such as soluble IL-1 and TNF-α receptors, cytokine receptor antagonists such as IL-1 receptor antagonist, and antiinflammatory cytokines including IL-10, IL-4, IL-13, and transforming growth factor β. Glucocorticoids also are produced increasingly in response to endotoxin and inhibit the production of cytokines.[56] During a controlled inflammatory response, therefore, cytokine secretion is a self-limited event, whereas excessive stimulation of cytokine release can lead to the perpetuation of the inflammatory response even after the initial stimulus has been removed. Conversely, the compensatory antiinflammatory reaction can become severe enough to cause anergy of the immune system and increased susceptibility to infection, which has been termed the *compensatory antiinflammatory response syndrome*. Overall, excessive and unbalanced stimulation of the immune system therefore may result in predominantly proinflammatory (systemic inflammatory response syndrome), antiinflammatory (compensatory antiinflammatory response syndrome), or combined (mixed antagonist response syndrome) responses.[57]

Interestingly, tolerance to endotoxin develops after repeated exposure to lipopolysaccharide.[58] Tolerance can be demonstrated in vitro and in vivo and encompasses decreased production of cytokines and a diminished clinical response.[58,59] Mechanisms that likely are responsible for the development of endotoxin tolerance include receptor downregulation and inhibition of intracellular signaling pathways.[60,61] Cytokines such as TNF are important mediators in the development of endotoxin tolerance.[62] The development of endotoxin tolerance in horses has been reported.[63,64]

Aside from cytokines, a number of other molecules function as inflammatory mediators in the pathogenesis of endotoxemia, the synthesis and release of which are stimulated by endotoxin and by cytokines. These mediators include the arachidonic acid metabolites or prostanoids, platelet-activating factor (PAF), oxygen-derived free radicals, nitric oxide (NO), histamine, kinins, and complement components. Table 13.7-1 summarizes the origins, targets, and effects of the most important inflammatory mediators involved in the pathogenesis of endotoxemia. Figure 13.7-5 shows the pathways of arachidonic acid metabolism by COX and lipoxygenase. COX products are the prostaglandins (PGs), prostacyclin (PGI_2) and thromboxanes, and the lipoxygenase produces the leukotrienes.

TABLE 13.7-1

Important Mediators of the Systemic Inflammatory Response to Endotoxin

MEDIATOR	ORIGIN	EFFECTS
Tumor necrosis factor	Macrophages	Induces synthesis of TNF, IL-1, IL-6, and GM-CSF.*
	Monocytes	Activates neutrophils.
	Neutrophils	Activates fibrinolysis and coagulation.
	CD4+ T cells	Activates contact and complement system.
	Natural killer cells	Induces a catabolic state.
		Induces insulin resistance.
		Is a pyrogen (direct action and via IL-1 induction).
		Induces synthesis of TNF, IL-1, IL-6, PGI$_2$, PAF, and GM-CSF.
Interleukin-1	Activated macrophages	Activates pyrogen.
	Endothelial cells	Induces malaise.
	Fibroblasts	Activates neutrophils and chemotaxis.
	Dendritic cells	Activates fibrinolysis and coagulation.
	Lymphocytes	Activates contact and complement system.
	Keratinocytes	Induces acute phase response.
		Increases activity of lipoprotein lipase.
		Mobilizes amino acids.
		Induces muscle proteolysis.
Interleukin-6	Activated macrophages	Induces acute phase response.
	Fibroblasts	Induces stress response.
	Keratinocytes	Is a weak pyrogen.
	T lymphocytes	
Interleukin-8	Macrophages	Activates neutrophils and chemotaxis.
	Endothelial cells	
Thromboxane A$_2$	Platelets	Induces vasoconstriction.
		Activates platelet aggregation.
Prostaglandin E$_2$	Most nucleated cells	Induces vasodilation.
		Activates platelet aggregation.
		Induces fever.
Prostaglandin I$_2$	Vascular endothelial cells	Induces vasodilation.
		Inhibits platelet aggregation.
Platelet-activating factor	Macrophages	Activates platelet aggregation.
	Platelets	Activates macrophages and neutrophils.
	Neutrophils	Induces hypotension.
	Mast cells	Increased vascular permeability.
	Eosinophils	Aids recruitment of leukocytes.
		Induces visceral smooth muscle contraction.
		Is a negative inotrope and arrhythmogenic.
		Induces ileus.
Prostaglandin F$_{2\alpha}$	Most nucleated cells	Induces vasoconstriction.
		Activates luteolysis.
Leukotriene B$_4$	Most nucleated cells	Is a chemoattractant.
		Promotes neutrophil interaction with endothelial cells.
Leukotrienes C$_4$, D$_4$, E$_4$	Most nucleated cells	Increase vascular permeability.
		Induce bronchoconstriction.
		Induce vasoconstriction.
Kinins	Produced from serum precursors	Increase vascular permeability.
		Induce smooth muscle contraction.
		Cause pain.
Complement components (C3a, C5a)	—	Activate neutrophils and chemotaxis.
		Induce smooth muscle constriction.
		Induce mast cell degranulation.
		Induce release of histamine and serotonin.
		Increase vascular permeability.
Oxygen-derived free radicals	Macrophages	Damage cell membranes.
	Neutrophils	Inactivate enzymes.
		Damage tissues.
Granulocyte-monocyte colony-stimulating factor	—	Induces rebound neutrophilia.

*TNF, Tumor necrosis factor; IL, interleukin; GM-CSF, granulocyte-monocyte colony-stimulating factor; PG, prostaglandin; PAF, platelet-activating factor.
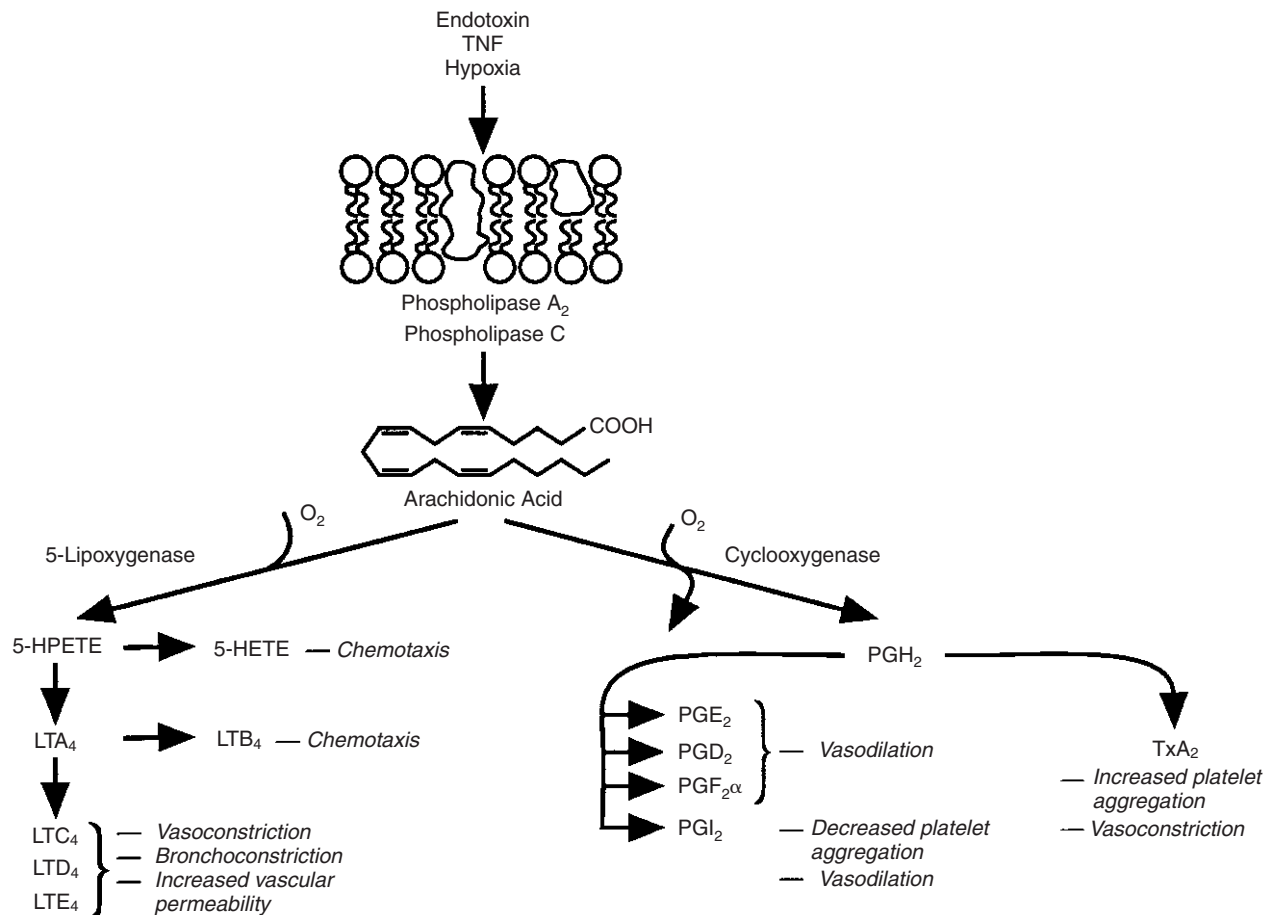
Endotoxin
TNF
Hypoxia

Phospholipase A_2
Phospholipase C

COOH

Arachidonic Acid

O_2 5-Lipoxygenase

O_2 Cyclooxygenase

5-HPETE ⟶ 5-HETE — *Chemotaxis*

LTA$_4$ ⟶ LTB$_4$ — *Chemotaxis*

LTC$_4$ — *Vasoconstriction*
LTD$_4$ — *Bronchoconstriction*
LTE$_4$ — *Increased vascular permeability*

PGH$_2$

PGE$_2$
PGD$_2$ } — *Vasodilation*
PGF$_{2}\alpha$

PGI$_2$ — *Decreased platelet aggregation*
    ---- *Vasodilation*

TxA$_2$
— *Increased platelet aggregation*
--- *Vasoconstriction*

Figure 13.7-5

Pathogenesis

The innate immune response to lipopolysaccharide is an efficient defense mechanism that provides maintenance of homeostasis and therefore health in the face of an almost continuous exposure to microorganisms and their products.[65] Detrimental consequences of this immune response only occur if excessive and uncontrolled mediator output results in endothelial damage, neutrophil-mediated tissue damage, and uncontrolled activation of the coagulation and fibrinolytic cascades and the complement system. Ultimately, the combination of these events culminates in cardiovascular instability, impaired hemostasis, organ failure, shock, and death. The following discussion addresses the various pathophysiologic events in the development of endotoxemia and shock and the role of inflammatory mediators.

ENDOTHELIAL DYSFUNCTION AND DAMAGE
Normal endothelium plays an important role in regulating blood pressure and regional tissue perfusion and provides an anticoagulant surface. Endothelial dysfunction and

damage result in a decreased responsiveness to vasoactive agents (vasoplegia), increased vascular permeability, and a tendency for clot formation in the microvasculature. If the basement membrane and underlying matrix are compromised, further microvascular hemorrhage can occur. Endothelial cell damage is primarily neutrophil-mediated. More specifically, damage is caused by oxygen-derived free radicals, which are produced within endothelial cells via reactions involving neutrophil-derived elastase and hydrogen peroxide molecules, endothelial cell enzymes such as xanthine oxidase, and endothelial cytosolic iron. The hypochloric anion radical (HO·) is thought to be responsible most directly for endothelial cell cytotoxicity. NO· produced by constitutively expressed nitric oxide synthase in endothelial cells may afford protection from oxygen radical–induced endothelial cell damage. NO is able to scavenge superoxide radicals and react with them to form peroxynitrite. Variations in the ability to produce NO may explain why vascular beds in different organs vary in their susceptibility to neutrophil-mediated damage.[66] Excessive production of NO by an inducible form of nitric oxide synthase (iNOS),

however, contributes to tissue damage, and increased peroxynitrite concentrations may be responsible in part for PAF-induced increases in vascular permeability.[67] In addition to oxygen-derived free radicals, activated neutrophils release matrix metalloproteinases, which contribute to tissue damage.[56] Vascular endothelial cells are further susceptible to direct effects of various cytokines, most prominently TNF-α and IL-1. These cytokines are thought to cause damage via the induction of COX activity and production of prostanoids and through generation of free radicals.

NEUTROPHIL ACTIVATION, MARGINATION, AND TRANSMIGRATION

Neutrophil activation by lipopolysaccharide and cytokines results in stimulation of phagocytosis and the respiratory burst, release of lysosomal enzymes and inflammatory mediators, and expression of adhesion molecules. Perhaps the single most specific clinicopathologic indicator of endotoxemia is pronounced neutropenia,[68] which temporally correlates with peak plasma concentrations of TNF.[69] Neutropenia is caused primarily by margination of neutrophils in the vasculature, whereas significant loss through active migration into peripheral tissues likely is limited to the presence of a localized source of infection. Margination is made possible by adhesion molecules on endothelial cells and leukocytes that interact and allow sticking of leukocytes to the endothelial lining of blood vessels. Endotoxin or cytokines such as TNF and IL-1 can initiate expression of adhesion molecules.[70] Subsequent transmigration of cells into tissue spaces is aided by the production of leukocyte collagenase, which allows enzymatic destruction of the vascular basement membrane. Margination and transmigration of neutrophils occurs in three phases.[70,71] In the first phase of tethering and rolling, endothelial cells are stimulated to express P-selectin and E-selectin, which bind to P-selectin glycoprotein ligand-1 and sialylated Lewis-X–like structures on leukocytes, respectively. Whereas P-selectin is stored preformed in Weibel-Palade bodies of endothelial cells, E-selectin is expressed only following stimulation by cytokines. Additionally, constitutively expressed L-selectin on neutrophils can bind to endothelial glycoproteins and glycolipids. During the second phase, firm adhesion is mediated by binding of neutrophil integrins (LFA-1 and Mac-1, also known as CD11a/CD18 and CD11b/CD18) to intercellular adhesion molecule 1 (an immunoglobulin structure) on endothelial cells. Although integrins are expressed constitutively on the leukocyte surface, activation signals are necessary to induce a high-affinity state and interaction with the endothelial surface. Transmigration finally requires the expression of yet another adhesion molecule, namely platelet/endothelial cell adhesion molecule 1, which is located at the intercellular junction

of endothelial cells.[71] Chemotactic factors including activated complement factor C5a and the CXC chemokines control transmigration.[66] The latter group includes IL-8, which is expressed by endothelial cells in response to activation. Rebound neutrophilia, which is observed frequently following episodes of endotoxemia, is caused by neutrophil release from the bone marrow reserve pool and by stimulation of myeloid cell proliferation via granulocyte-macrophage colony-stimulating factor and is mediated primarily by TNF and IL-1.[54]

COAGULOPATHY AND DISSEMINATED INTRAVASCULAR COAGULATION

In health, coagulation and fibrinolysis underlie stringent control mechanisms that allow appropriate clot formation and their resolution. Coagulopathies frequently are observed in horses with colic[16,72,73] and foals with sepsis[11] and are likely attributable to endotoxemia. Disseminated intravascular coagulation (DIC) results from a widespread activation of the coagulation and fibrinolytic systems and failure of their control mechanisms. Ultimately, this leads to disseminated fibrin deposition in the microvasculature, consumption of platelets and clotting factors, and accumulation of fibrin degradation products (FDPs). Depending on the underlying disease process and the impairment of the systems, DIC can manifest as a diffuse thrombotic syndrome leading to ischemic organ failure, a fibrinolytic syndrome with uncontrolled hemorrhage, or a combination of both.[74] A procoagulant state in which one can detect clinicopathologic abnormalities precedes DIC.

Activation of the coagulation cascade culminates in the cleavage of fibrinogen to fibrin by the serine protease thrombin. Thrombin deposition on endothelial cell surfaces leads to platelet adherence and their activation by surface-bound PAF.[56] The intrinsic and extrinsic arms of the coagulation cascade are activated in endotoxemia. The intrinsic pathway is initiated by activation of coagulation factor XII (Hageman factor), prekallikrein, and high-molecular-weight kininogen, which compose the contact system.[75] Although direct activation of coagulation factor XII by endotoxin has been demonstrated,[76] the extrinsic pathway likely is more important for the development of coagulopathy in endotoxemia and sepsis.[75] Activation of the extrinsic pathway depends on the interaction of coagulation factor VII with tissue factor, which is the only coagulation factor not constitutively present in blood. Tissue factor is present in subendothelial tissues and is exposed on vascular injury but also is expressed on endothelial cells and mononuclear phagocytes in response to lipopolysaccharide.[77,78] Increased expression of monocyte tissue factor (also described as increased procoagulant activity) was found to be associated significantly with coagulopathy and poor prognosis in horses with colic.[79]

Furthermore, lipopolysaccharide-induced tissue factor expression by equine peritoneal macrophages may be associated with the development of intraabdominal adhesions.[63]

Regulatory mechanisms of the coagulation cascade include tissue factor pathway inhibitor, antithrombin III (AT III), and the protein C system.[75] Protein C acts as an anticoagulant by inactivating clotting factors V and VIII and promotes fibrinolysis by inactivating plasminogen activator inhibitor (PAI).[80] Protein C activation by thrombin-thrombomodulin complexes is important for the anticoagulative properties of normal endothelium,[75] and downregulation of endothelial thrombomodulin expression by TNF and IL-1 and decreased expression of AT III and tissue factor pathway inhibitor by damaged endothelial cells contribute to the procoagulant state in endotoxemia and sepsis.[81-83] In addition, activation of vascular endothelial cells leads to a loss of prostacyclin and NO production and an increased release of thromboxane A_2 (TXA_2). As a result, platelets are stimulated to aggregate and release TXA_2 and PAF, thereby further promoting clot formation.[17]

The crucial step in the fibrinolytic cascade is the conversion of plasminogen to plasmin, a fibrin-degrading enzyme.[75] Tissue-type (tPA) and urokinase-type (uPA) plasminogen activator are the major initiators of fibrinolysis, whereas PAI and α_2-antiplasmin are the main regulatory components.[84,85] TNF and IL-1 have been shown to induce the release of uPA and tPA and the synthesis of PAI.[75] Activation of fibrinolysis leads to consumption of α_2-antiplasmin and accumulation of FDPs, which if present in high concentrations can interfere with platelet aggregation, fibrin polymerization, and thrombin formation and can promote bleeding. Additionally, FDPs mediate an increase in vascular permeability. Lipopolysaccharide infusion in rabbits[86] and human beings[87] resulted in an early increase in plasma tPA activity, followed by a later profound rise in PAI activity and fall in tPA activity. Increased plasma PAI concentrations also were found in horses with colic compared with controls.[88,89] Thus although fibrinolysis may compensate initially for accelerated coagulation, its subsequent inhibition contributes to clot formation.

COMPLEMENT ACTIVATION

Activation of the complement system in endotoxemia occurs via the alternative pathway through interaction with lipopolysaccharide. Increased concentrations of plasmin and kallikrein (caused by activation of the fibrinolytic and contact system) further promote this pathway by directly activating complement factors C3a and C5a. Aside from being key molecules in the complement cascade, C3a and C5a are anaphylatoxins and cause an increase in vascular permeability via mast cell degranulation. C5a further activates the lipoxygenase pathway in neutrophils and monocytes, acts as a chemotaxin for leukocytes and monocytes, and promotes neutrophil adhesion to endothelial cells.

ACUTE PHASE RESPONSE

In response to acute inflammation, synthesis and secretion of a number of proteins called the acute phase proteins increases in hepatocytes, whereas synthesis of albumin decreases. The primary function of this acute phase response may be to suppress and contain inflammatory responses.[56] IL-6 and IL-1 are the most important cytokines that induce the acute phase response,[90] which typically begins within a few hours of the insult and subsides within 24 to 48 hours,[91] unless the initiating cause persists. In horses, fibrinogen (the most commonly evaluated), haptoglobin, transferrin, ferritin, ceruloplasmin, coagulation factor VIII:C, serum amyloid A protein, C-reactive protein, α_1-acid glycoprotein, and phospholipase A_2 are considered part of the acute phase response.[92] One must consider the effect of acute inflammation on the serum concentration of several coagulation factors when evaluating coagulation profiles. Serum fibrinogen concentration is determined primarily by the acute phase response, although fibrinogen is consumed increasingly on activation of the clotting cascade.

HEMODYNAMIC CHANGES, DEVELOPMENT OF SHOCK, AND ORGAN FAILURE

Shock is characterized by a loss of homeostasis attributable to breakdown of hemodynamic control mechanisms, decreases in cardiac output and the effective circulating volume, and inadequate perfusion of vital organs. Shock caused by endotoxemia is classified as distributive shock[93] and is largely initiated by vascular dysfunction in the periphery. Peripheral vascular beds are of major importance for the regulation of local tissue perfusion and affect systemic blood pressure by regulating total peripheral resistance. Normally, vascular smooth muscle tone is regulated by endothelin-1 (vasoconstriction), NO, and prostacyclin (vasodilation) released from vascular endothelial cells.[94] As mentioned before, detrimental effects of NO are attributable to induction of iNOS in macrophages and other cell types, rather than endothelial-derived NO. Peripheral vasomotor effects of endotoxin manifest as vasodilation and vasoplegia and are mediated by PGI_2, NO, and mediators such as bradykinin. Widespread vasodilation leads to vascular blood pooling, decentralization of blood flow, decreased venous return, and in effect decreased effective circulating volume and cardiac output.[93] Compensatory responses in the form of an initial hyperdynamic phase include tachycardia, increased cardiac output and central venous pressure, pulmonary hypertension, peripheral vasoconstriction, and increased peripheral vascular resistance.[93,95,96]

The early vasoconstrictive phase corresponds to an increased serum concentration of TXA_2,[17] but additional vasoconstrictors such as arginine vasopressin, angiotensin II, serotonin, endothelin, and norepinephrine likely are implicated in the pathogenesis of shock and organ failure.[56] With progression of disease, the animal enters a stage of decompensated shock and progressive systemic hypotension, which correspond to increased plasma concentrations of prostacyclin, PGE_2 and bradykinin.[17,56] Inadequate blood flow and oxygen delivery to tissues caused by hypotension is confounded by direct myocardial suppression via NO,[93] increased vascular permeability,[17] intravascular microthrombosis, and impaired tissue oxygen extraction[93] and results in progressive metabolic acidosis and inhibition of normal cellular metabolism.

Clinical Signs and Diagnosis

Quantification of endotoxin in plasma samples is possible. The *Limulus* amebocyte lysate assay is an activity assay based on the endotoxin-sensitive hemolymph coagulation cascade in the horseshoe crab *Limulus polyphemus.* In *Limulus* this reaction is thought to be a defense mechanism against gram-negative infection.[97] Although frequently used as a research tool, the assay is not convenient enough to become a routine clinical test. The clinician therefore must appreciate the primary disease processes associated with a high risk of endotoxemia and rely on clinical signs and clinicopathologic data to achieve a diagnosis. In some cases, endotoxemia may be the first indication of disease or may be the most overt of otherwise subtle clinical manifestations. With colitis or proximal enteritis, for example, one may detect signs of endotoxemia before the development of colic, diarrhea, or gastric reflux, which more specifically indicate the nature of the primary illness. Diseases such as peritonitis or pleuritis, however, may show nonspecific clinical findings including fever, anorexia, and depression. Findings such as neutropenia, which indicate endotoxemia, should urge the clinician to search for a septic process.

In vivo experiments in horses clearly show that many of the clinical signs associated with acute gastrointestinal disease and sepsis are attributable to the activities of lipopolysaccharide and cytokines such as TNF. On administration of sublethal doses of lipopolysaccharide the clinical response can be divided into the early hyperdynamic and the later hypodynamic or shock phases. Clinical signs during the first phase, which begins within 15 to 45 minutes after lipopolysaccharide administration, include anorexia, yawning, sweating, depression, evidence of abdominal discomfort, muscle fasciculation, and recumbency. Heart and respiratory rates increase, and

decreased borborygmi suggest ileus. Hyperemia of the mucous membranes and an accelerated capillary refill time indicate the hyperdynamic state.[68] If one administers large amounts of lipopolysaccharide or if exposure is ongoing, depression worsens progressively, anorexia persists, and feces develop diarrheic character. Signs of colic typically abate after the initial stage. Fever develops as a result of direct action of TNF on the thermoregulatory center and IL-1-induced local production of PGE_2 in or near the hypothalamus.[98,99] Because of compromised peripheral perfusion, mucous membrane color changes to brick red or purple, a dark "toxic" line appears, and capillary refill time is prolonged.[68] Inadequate peripheral perfusion and compromised organ function finally characterize the hypodynamic shock phase. Body temperature may become subnormal and the skin, especially on extremities, is cool to the touch. The arterial pulse weakens and venous fill is decreased. Vascular endothelial damage and increased capillary permeability result in a muddy mucous membrane color and diffuse scleral reddening.

Hemostatic abnormalities can manifest in the form of thrombosis, such as of the jugular vein, or increased bleeding tendency with mucosal petechiation or ecchymoses and prolonged bleeding from venipuncture sites.[74] Bleeding also may occur in spontaneous epistaxis or prolonged hemorrhage after nasogastric intubation.[17] Additional clinical signs typically reflect the development of organ failure. Renal failure and laminitis appear to be common complications of endotoxemia in horses. Renal failure results from ischemic cortical necrosis and acute tubular necrosis caused by coagulopathy-induced afferent arteriolar obstruction. Clinical signs may include oliguria, anuria, or hematuria caused by renal infarction. Laminitis may lead to lameness, increased digital arterial pulsation, increased warmth of the hoof wall, and sensitivity to hoof tester pressure. Other signs of organ failure include icterus, anorexia and depression caused by liver failure,[74] tachypnea and dyspnea caused by pulmonary failure, colic and bleeding caused by ischemia-induced gastrointestinal ulceration and abnormal motility patterns,[17] and persistent tachycardia or cardiac arrhythmia in cases of cardiac failure. In pregnant mares, fetal death and abortion can occur because of increased production of $PGF_{2\alpha}$ and decreased serum progesterone concentrations.[100,101]

Alterations in the Hemogram and Serum Biochemistry Profile

Alterations in the hemogram and serum biochemical profile are nonspecific and mainly reflect the underlying disease process and the occurrence of organ failure. Leukopenia caused by neutropenia may be the most

specific indicator of acute bacterial sepsis or endotoxemia.[68] In prolonged cases, an increased proportion of immature neutrophil forms (bands) and toxic changes are observable. Toxic changes resulting from neutrophil activation include vacuolation, cytoplasmic granulation, basophilic cytoplasm, and Döhle's bodies. Because neutropenia occurs early in the development of endotoxemia, it also may be a useful parameter for monitoring horses at risk.[68] On recovery, neutropenia typically is followed by a pronounced rebound neutrophilia.

An elevated hematocrit and total serum protein concentration are evidence of dehydration; however, splenic contraction caused by increased sympathetic stimulation and protein losses also influence these parameters. A normal or only slightly decreased serum protein and albumin concentration in the face of an elevated hematocrit and clinical signs of dehydration should alert the clinician to the possibility of protein loss. Hypoproteinemia and hypoalbuminemia can occur because of loss via the gastrointestinal or urinary tract or with pleural or peritoneal cavity effusion. Increased vascular permeability and edema formation contribute to hypoproteinemia.

Serum electrolyte abnormalities primarily depend on the nature and duration of underlying disease processes and need to be evaluated individually. Common sources of electrolyte loss are gastrointestinal secretions, urine, and sweat; however, severe effusion into body cavities may contribute. In anorexic patients, lack of dietary intake is a confounding factor that warrants consideration. In human patients, gram-negative sepsis frequently is associated with hypocalcemia, more specifically a decrease in serum ionized calcium concentration. Endotoxin is thought to be a causative factor, and proposed mechanisms include acquired parathyroid gland insufficiency, dietary vitamin D deficiency, impaired calcium mobilization, and renal 1α-hydroxylase insufficiency leading to decreased 1,25-hydroxylation of vitamin D. Hypocalcemia in septic human patients was found to be associated with hypotension and poor outcome.[102] In horses with surgically managed gastrointestinal disease, decreased serum ionized calcium concentration was a common finding and was most severe in patients with strangulating or nonstrangulating infarctions. In some horses, ionized calcium concentration decreased further throughout surgery. Treatment with calcium gluconate resulted in normalization of serum ionized calcium concentrations in all cases.[103]

Septic neonatal patients are frequently hypoglycemic. Aside from decreased oral intake and generally increased metabolism, glucose use by the infecting bacteria, inhibition of gluconeogenesis by endotoxin, and insulin-like activity produced by macrophages are responsible for hypoglycemia.[17] Interestingly, experimental endotoxin administration results in transient hyperglycemia in adult horses,[95] whereas profound hypoglycemia occurs in foals.[104]

One should evaluate coagulation parameters if coagulopathy is suspected. The most significant changes can be expected with severe inflammatory disease such as colitis,[72,73] devitalized intestine as with strangulating obstruction,[73,105] and with increased duration of disease. In 30 horses with acute gastrointestinal disease, coagulation profiles were considered normal in only 2 horses.[72] Although coagulation times may be shortened during the procoagulant state, commonly observed abnormalities with developing DIC include an increased concentration of FDPs and soluble fibrin monomer, prolonged prothrombin time indicative of factor VII consumption, prolonged activated partial thromboplastin time indicative of factor VIII:C and IX consumption, prolonged thrombin time, decreased AT III activity, thrombocytopenia, and decreased protein C and plasminogen activities. Fibrinogen concentration frequently increases and reflects the acute phase response rather than coagulation abnormalities.[79] Some clinicians make a diagnosis of DIC if three or more coagulation parameters (specifically AT III, FDPs, platelet count, prothrombin time, and activated partial thromboplastin time) are abnormal,[105] whereas others require overt clinical signs of hemorrhage and concomitant thrombosis in addition to classic laboratory findings.[73] The prognostic value of coagulation parameters has been evaluated.[16,73,89] Overall, persistence or worsening of abnormalities in the face of treatment appears to be more indicative of poor outcome than alterations in any specific parameter. In one study, decreased serum AT III concentration was the parameter most commonly associated with fatal outcome in mature horses with colic.[72]

One should further evaluate the serum biochemical profile regarding compromise or failure of specific organ systems. Increases in serum creatinine and urea nitrogen concentration can have prerenal, renal, or postrenal causes. In cases of endotoxemia and sepsis, prerenal azotemia caused by dehydration and decreased renal blood flow and renal azotemia caused by organ failure are most likely to occur. One can use urine specific gravity and the response to fluid therapy to differentiate renal from prerenal causes of azotemia. Although ideally one should perform urinalysis before initiating fluid therapy, one should never delay treatment to obtain a sample and instead should use the first available urine sample. With prerenal azotemia, urine specific gravity is increased, urinalysis is normal in other respects, and azotemia resolves with adequate fluid therapy. Azotemia in the face of normal or decreased urine specific gravity, however, indicates compromised renal function. Depending on the extent of renal damage, proteinuria and hematuria also may be

present. Bacteriuria and an elevated urine leukocyte count may occur if urinary tract infection is the underlying cause for the development of endotoxemia. In these cases, urine culture and sensitivity testing are indicated to aid appropriate antimicrobial therapy.

Increased serum activity of liver enzymes (aspartate aminotransferase, γ-glutamyltransferase, sorbitol dehydrogenase, alkaline phosphatase) are common in endotoxemic patients; however, liver failure caused by endotoxemia is rare. Sorbitol dehydrogenase is the most liver-specific of the enzymes and a sensitive indicator of acute hepatocellular necrosis; however, sorbitol is unstable and routine assays may not be available. One should evaluate liver enzymes and function tests (serum indirect and direct bilirubin concentration, serum bile acids and blood ammonia) in cases of prolonged and profound depression to rule out hepatoencephalopathy.

One should evaluate arterial blood gases in patients with primary respiratory disease or with clinical evidence of respiratory failure and in profoundly depressed, recumbent patients, especially neonates. Hypoxemia observed in response to endotoxin infusion is thought to be caused by an increase in ventilation-perfusion mismatch rather than pulmonary edema as occurs in human patients with acute respiratory distress syndrome. The lung is not a major shock organ in horses; however, pulmonary edema may occur in patients with associated sepsis or complications such as DIC.[106]

Management

The ideal treatment for endotoxemia is prevention. If one possibly can recognize and closely monitor patients at risk, one can provide treatment proactively and may reverse the effects of endotoxin before the inflammatory response has developed a dynamic of its own. Unfortunately, endotoxemia can develop rapidly, and horses are exquisitely sensitive to the effects of endotoxin; therefore, many equine patients are not evaluated until reaching more severe stages of endotoxemia or shock. Prognosis and patient outcome then frequently depend on the severity of complications associated with endotoxemia.[17]

Treatment of endotoxemia involves multiple aspects, and the following strategies have been proposed[107]:

- Inhibition of endotoxin release into the circulation
- Scavenging of lipopolysaccharide molecules to prevent direct effects and interaction with inflammatory cells
- Inhibition of cellular activation by lipopolysaccharide
- Inhibition of mediator synthesis
- Interference with the effects of inflammatory mediators
- General supportive care

In addition, complications such as renal failure, one also must address liver failure, cardiac failure, laminitis, and abortion in pregnant mares.

When evaluating reports concerning the efficacy of any one treatment, one should keep in mind differences in underlying disease processes and the complexity of the inflammatory cascade. A "one for all" treatment most likely will not be found, and similarly, any one treatment can only address one or few pathophysiologic aspects of endotoxemia. Understanding the rationale for different treatment strategies is important to be able to tailor treatment to the needs of the patient.

INHIBITION OF ENDOTOXIN RELEASE INTO THE CIRCULATION

Inhibition of endotoxin release requires identification and removal of its source. Therefore whenever endotoxemia is evident, the clinician should strive to reach a diagnosis of the underlying disease and ascertain whether ischemic or inflamed bowel or a gram-negative septic process is present. Aside from history, physical examination, and routine laboratory tests, evaluation may include exploratory laparotomy in colic patients, roentgenologic and ultrasonographic evaluation of the pleural and peritoneal cavity and organs, ultrasonographic evaluation of umbilical remnants in neonatal foals, evaluation of passive transfer and calculation of a sepsis score in foals, and repeated culturing of blood or other specimens. If one suspects an infectious process, one should pursue identification of the responsible microorganisms and their antimicrobial sensitivity spectrum; however, one should not delay treatment to obtain culture results. Specimen containers with removal devices for antimicrobials are available and are useful in cases for which one has initiated treatment before specimen collection. Once one reaches a diagnosis, one must take appropriate measures to correct the primary disease process. Examples are removal of devitalized sections of bowel or infected umbilical remnants, drainage of infected pleural or peritoneal fluid, and gastric lavage followed by administration of mineral oil and/or activated charcoal in cases of grain overload to prevent further absorption of endotoxin. One must address any septic process with appropriate antimicrobial therapy. Initially, broad-spectrum coverage of the most likely organisms is recommended; one then should specify therapy according to results of culture and sensitivity testing. Sepsis in foals is caused predominantly by gram-negative organisms, of which *E. coli, Actinobacillus* spp., *Klebsiella* spp., *Salmonella* spp. and *Pasteurella* spp. frequently are identified.[108] The reader is referred to other texts for review of general principles of antimicrobial therapy. Regarding endotoxemia specifically, antimicrobial therapy has been suggested to increase the amount of circulating

endotoxin by inducing endotoxin release on cell death of gram-negative bacteria. A recent in vitro study compared endotoxin release and inflammatory mediator activity between antimicrobials commonly used to treat *E. coli* septicemia in foals and specifically evaluated amikacin, ampicillin, amikacin plus ampicillin, ceftiofur, and imipenem. Although these antimicrobials showed no difference in the ability to kill bacteria, amikacin and the amikacin/ampicillin combination resulted in the lowest and ceftiofur in the greatest release of endotoxin. Endotoxin release appeared to be dose-dependent in that lesser amounts were released at higher antimicrobial concentrations.[109] Based on these results and clinical experience, combining antimicrobial therapy with endotoxin-binding agents such as polymyxin B may be beneficial, especially when using β-lactam antimicrobials.

Antimicrobials frequently are given perioperatively to colic patients to lower the risk of peritonitis, incisional infection, and generalized sepsis and endotoxemia. Because antimicrobial therapy has been implicated in the development of colitis, the duration of treatment should be minimal. Unless evidence of sepsis, such as fever or changes in the leukogram, is present, perioperative administration of antimicrobials should not exceed a 24 to 48 hours. Conversely, antimicrobial therapy frequently is used in cases of infectious colitis to treat the inciting cause and to prevent sepsis from translocation of bacteria.

SCAVENGING OF LIPOPOLYSACCHARIDE MOLECULES

Endotoxin typically has a short plasma half-life and is removed rapidly by mononuclear phagocytes or neutralized by binding to serum proteins and lipoproteins. Many conditions responsible for the development of endotoxemia in horses, however, are associated with an ongoing release of endotoxin. Examples include severe gastrointestinal inflammation as in proximal enteritis or colitis, grain overload, or uncontrolled sepsis. Therapy directed against endotoxin itself may be able to interrupt the continuous activation of the inflammatory cascade in these cases. Further benefits of antiendotoxin treatment may be derived if large amounts of endotoxin have been released before the inciting cause can be addressed.

Immunotherapy

An important consideration regarding the efficacy of immunotherapy is the region of the lipopolysaccharide molecule against which antibodies are raised. The O-chain of lipopolysaccharide acts as a potent antigen on infection with gram-negative bacteria[6]; however, antibodies directed against the O-chain are serotype specific and cannot afford significant cross-protection against heterologous bacterial strains. The core and lipid A region, both of which show a much higher degree of homology between lipopolysaccharide derived from different bacterial strains, offer a more promising target for immunotherapy. Active immunization against endotoxin has been reported for horses. Vaccination with a bacterin/toxoid vaccine prepared from rough mutants of *Salmonella typhimurium* or *S. enteritidis* protected horses against homologous and heterologous endotoxin challenge[110,111] and carbohydrate overload.[111] Despite these encouraging results and the current availability of a vaccine for use in horses (Endovac-Equi, Immvac Inc., Columbus, Missouri), active immunization against endotoxin does not appear to be a common practice. In comparison, passive immunization with antilipopolysaccharide antibodies is used widely. Rough bacterial mutants, most commonly J5 of *E. coli* O111:B4 and *S. minnesota* Re595, are used to immunize donor horses and subsequently prepare serum or plasma products. Proposed mechanisms of action after binding of the antibodies to lipopolysaccharide include steric blockade of lipid A interaction with cellular receptors and enhanced bacterial clearance by opsonization.[112-114] Studies concerning the efficacy of antibody administration in equine patients vary in their results. Beneficial effects have been described in experimental models of endotoxemia, acute gastrointestinal disease, and neonates with sepsis,[111,115-117] whereas in other studies, antibodies failed to protect foals and horses against endotoxin effects.[118-120] Furthermore, administration of a *S. typhimurium* antiserum to foals was associated with an increased respiratory rate and higher serum activities of IL-6 and TNF.[118]

Various equine serum and plasma products are currently commercially available. An antiserum raised against the lipopolysaccharide-core of *S. typhimurium* (Endoserum) is available for administration to endotoxemic horses at a recommended dose of 1.5 ml/kg body mass. Diluting the serum ten- to twentyfold in crystalloid intravenous solutions, administering it slowly over 1 to 2 hours, and monitoring the patient for adverse reactions is advisable. Although the product is marketed for use in foals with failure of passive transfer, adverse effects have been reported,[118] and one should use caution when administering it to neonates. Plasma from donors inoculated with J5 *(E. coli)* and *S. typhimurium* (Re mutant) is available under a restricted license (Polymune-J, Vet Dynamics, Inc., San Louis Obispo, California). The manufacturer recommends administration of at least 1 to 2 L in cases of endotoxemia. In addition, hyperimmune plasma, which has a guaranteed minimum immunoglobulin G content but does not contain specific antiendotoxin antibodies (Hi-Gamm Equi, Lake Immunogenics, Inc., Ontario, New York; Polymune and Polymune-Plus, Vet Dynamics, Inc.), is marketed for treatment of failure of passive transfer, and many clinicians use it to treat endotoxemia and sepsis. In addition to antibodies and protein,

plasma contains active constituents such as complement components, fibronectin, clotting factors, and AT III[116] and therefore may be particularly useful in patients with endotoxemia-induced coagulopathy. Volumes of 2 to 10 ml/kg body mass of hyperimmune plasma have been recommended for use in endotoxemic patients.[56,121]

Polymyxin B

Polymyxin B is a cationic polypeptide antibiotic that binds to the anionic lipid A portion of lipopolysaccharide and neutralizes its endotoxin capacity.[122] At dosages required for antimicrobial activity, polymyxin B carries the risk of respiratory paralysis and ototoxic, nephrotoxic, and neurotoxic side effects; however, a much lower dose is required for endotoxin-binding activity. The effects of polymyxin B in horses have been evaluated in different experimental models.[118,122,123] In an in vivo study in foals, treatment with polymyxin B at a dosage of 6000 U/kg body mass before infusion with *S. typhimurium* lipopolysaccharide resulted in significantly less severe elevations of body temperature, respiratory rate, and serum activities of TNF and IL-6 compared with untreated controls.[118] Similarly, polymyxin B treatment of adult horses given endotoxin significantly ameliorated clinical signs and decreased plasma TNF activity.[124] In the latter study, benefits of treatment were also evident at lower dosages of polymyxin B (1000 and 5000 U/kg body mass) and administration of polymyxin B 1 hour after the start of endotoxin infusion. Conversely, polymyxin B failed to ameliorate clinical signs of endotoxemia or prevent the development of coagulopathy, acidosis, lameness, and shock in experimental carbohydrate overload.[125] Side effects suggestive of neurotoxicity appeared after repeated administration of 5 mg/kg body mass (36,000 U/kg) and in milder form, 2.5 mg/kg body mass (18,000 U/kg) polymyxin B. Nephrotoxicity was not observed. Currently, use of polymyxin B in equine patients is recommended at dosages of 1000 to 5000 U/kg body mass every 8 to 12 hours.[126] One should initiate treatment as early in the disease process as possible, because the beneficial effects of lipopolysaccharide scavenging are limited to the first 24 to 48 hours after the onset of endotoxemia, before tolerance develops. Side effects in the form of neuromuscular blockade and apnea, which necessitate slow infusion of the drug in human patients, have not been observed in horses. One therefore can administer the entire dose as a slow bolus. If one uses polymyxin B in horses with hypovolemia, dehydration, or azotemia, one should attempt to improve peripheral tissue perfusion, minimize the polymyxin B dose, and closely monitor patients for nephrotoxicity. Close monitoring is also important if one administers medications such as aminoglycoside antibiotics, which share a similar spectrum of potential side effects, concurrently. Azotemic neonates have been reported to be more susceptible to the nephrotoxic effects of polymyxin B than adult horses.[124]

In an attempt to decrease the risk for adverse effects while preserving lipopolysaccharide-neutralizing ability, a conjugate of polymyxin B with dextran has been developed.[127] In conjugated form, polymyxin B is prevented from extravasation into tissues, where it exerts toxic effects by interaction with cell membranes. In addition, conjugation increases the residence time of polymyxin B in the circulation and therefore should prolong the antiendotoxic effect. The polymyxin B–dextran combination was evaluated at a total dose of 5 mg/kg body mass of polymyxin B in 6.6 g/kg body mass dextran given 15 minutes before administration of endotoxin in horses.[128] Treatment was found to block the development of tachycardia, tachypnea, fever, and neutropenia completely and to prevent increases in serum concentrations of TNF, IL-6, TXB_2 (a TXA_2 metabolite), and the prostacyclin metabolite 6-keto-$PGF_{1\alpha}$. Although mild adverse effects in the form of tachypnea, sweating, and increased systolic blood pressure were observed, these were transient and could be prevented by pretreatment with ketoprofen. The polymyxin B–dextran combination is not commercially available at this time.

Natural Endotoxin-Binding Substances

Natural endotoxin-binding proteins such as LBP, lipoproteins, and sCD14 have been evaluated experimentally. Results of these studies are controversial, and detrimental effects occurred in some cases.[129] A protein receiving much attention regarding potential therapeutic efficacy is the bactericidal permeability-increasing protein (BPI). This protein is structurally similar to LBP but is expressed exclusively in myeloid precursors of polymorphonuclear leukocytes.[130] BPI is stored in primary granules of mature neutrophils and during inflammation is expressed on their cell membranes and secreted into the extracellular environment.[131] BPI has an even higher affinity for lipopolysaccharide than LBP[132] and shows antibacterial activity specific for gram-negative bacteria.[65] Binding of BPI to the gram-negative bacterial membrane results in growth arrest and is an important factor in the antibacterial activity of intact neutrophils. Furthermore, BPI binding disrupts normal membrane organization and makes bacteria more susceptible to hydrophobic substances, including antimicrobials.[133] Experimentally, recombinant BPI has been shown to protect against the toxic and lethal effects of isolated lipopolysaccharide and intact gram-negative bacteria, and clinical trials in human patients show promising results concerning its therapeutic use.[134] The biology and potential use of BPI in horses has not been evaluated.

INHIBITION OF CELLULAR ACTIVATION BY LIPOPOLYSACCHARIDE

Treatments aimed at inhibiting lipopolysaccharide interaction with cells or turning off intracellular signaling pathways are under investigation. Nontoxic lipopolysaccharide or lipid A structures can act as endotoxin antagonists, if they competitively inhibit binding to LBP or cellular receptors or inhibit cellular activation by other mechanisms. Of the potential antagonists that have been evaluated experimentally, lipopolysaccharide and lipid A from the phototrophic bacterium *Rhodobacter sphaeroides,* and a synthetic compound (E5531) the structure of which is based on *R. sphaeroides* lipopolysaccharide, have been most promising.[135-139] Unfortunately, species differences exist regarding cellular response to these structures, and *R. sphaeroides* lipopolysaccharide acts as a potent inducer of cytokine expression in equine cells.[140] Based on results of receptor transfection studies in other species,[141,142] TLR4 is likely responsible for this phenotypic variation. Additional compounds including lipopolysaccharide derived from nitrogen-fixing plant bacteria of the species *Rhizobium* are being evaluated to reveal further insight into structural requirements for endotoxin antagonists in horses.

INHIBITION OF MEDIATOR SYNTHESIS
Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) are probably the most commonly used drugs to treat endotoxemia. The rationale for their use is inhibition of prostaglandin endoperoxide H synthase, that is, COX, and thereby inhibition of prostanoid production (see Figure 13.7-5). Additional beneficial effects may include scavenging of oxygen-derived free radicals and iron chelation; however, side effects may occur at dosages required to achieve these effects.[143] Prostanoids have been identified as important mediators in the inflammatory response in a number of studies, and inhibition of their synthesis is associated with beneficial effects. Two COX isoforms are recognized: constitutively expressed COX-1 and inducible COX-2. Upregulation of COX-2 expression results from various proinflammatory stimuli, including lipopolysaccharide, TNF-α, and IL-1.[144] Constitutively expressed COX products are likely important for maintenance of homeostasis, whereas increased production of prostanoids by COX-2 is thought to be responsible for detrimental effects during inflammation and shock. Research has focused on the development of selective COX-2 inhibitors; however, none of these products are currently available for use in horses. In horses the most commonly used NSAID to treat endotoxemia is flunixin meglumine. Beneficial effects of flunixin meglumine have been described in experimental models of endotoxemia[145-147] and in clinical cases.

In equine colic patients, treatment with flunixin meglumine before exploratory surgery resulted in reduced plasma concentrations of TXB_2 and PGE_2 and had a favorable effect on cardiovascular parameters.[148] Flunixin meglumine was shown further to maintain cardiac output and systemic arterial blood pressure, improve blood flow to vital organs, reduce pulmonary endothelial damage, and improve survival on endotoxin challenge.[149-152]

NSAID use in horses carries the risk of side effects, most importantly the development of gastrointestinal ulceration and renal papillary necrosis (renal crest necrosis). In a study comparing the side effects of flunixin meglumine (1.1 mg/kg body mass), phenylbutazone (4.4 mg/kg body mass), and ketoprofen (2.2 mg/kg body mass) given 3 times daily for 12 days, lesions of the gastric glandular mucosa occurred most commonly. Phenylbutazone resulted in the most severe side effects, which included small intestinal edema, erosions, and ulcers in the large colon and decreased serum albumin concentration. Renal crest necrosis occurred more frequently in horses treated with phenylbutazone but also occurred with flunixin meglumine treatment.[153] Despite the higher risk of side effects, use of phenylbutazone has been suggested for certain cases. In colic patients, phenylbutazone may provide analgesia and ameliorate endotoxin-induced ileus without masking cardiovascular effects of endotoxin, which are used to determine the necessity of surgical exploration.[154] For similar reasons and to minimize side effects a reduced dose of flunixin meglumine (0.25 mg/kg body mass) has been suggested and is used widely in horses.[155] At this dosage, flunixin meglumine was shown to inhibit eicosanoid synthesis efficiently in an in vivo model of endotoxemia.[156] Reduction of clinical signs, however, was dose dependent, and therefore one should choose the appropriate dose based on the circumstances of each case.

Ketoprofen has been suggested to have superior effects because of a proposed dual inhibitory effect on COX and lipoxygenase and may carry a decreased risk of side effects compared with flunixin meglumine and phenylbutazone. A comparison of cytokine and eicosanoid production by lipopolysaccharide-stimulated isolated monocytes in vitro, however, showed no significant difference between horses pretreated with flunixin meglumine (1.1 mg/kg body mass) or ketoprofen (2.2 mg/kg body mass), respectively.[157]

Eltenac has been evaluated in an experimental endotoxemia model in horses.[158] Given 15 minutes before lipopolysaccharide infusion, eltenac at a dose of 0.5 mg/kg protected against changes in clinical, hemodynamic, and hematologic parameters and blunted the lipopolysaccharide-induced rise in plasma cytokine concentrations in comparison with controls. Some parameters, however, including heart rate, leukocyte count, lactate

concentration, and plasma TNF activity, were not improved.

Ibuprofen may have beneficial effects superior to the other NSAIDs, because it may be possible to achieve tissue concentrations safely that allow iron chelation to occur. According to a study in healthy foals, dosages of ibuprofen up to 25 mg/kg every 8 hours can be given safely for up to 6 days.[143]

Corticosteroids

The use of corticosteroids for antiinflammatory therapy in sepsis and endotoxemia has been controversial in human and equine patients, and beneficial effects superior to the ones achieved by NSAIDs have not been demonstrated consistently overall. Corticosteroids inhibit the activity of phospholipase A_2 and the release of arachidonic acid from cell membrane phospholipids, as well as the production of TNF, IL-1, and IL-6 in response to a lipopolysaccharide stimulus. Experimentally, beneficial effects of dexamethasone in equine endotoxemia have been demonstrated.[159,160] To inhibit TNF production by equine peritoneal macrophages, however, the required concentration of dexamethasone was high and corresponded to an in vivo dosage (approximately 3 mg/kg body mass) greatly exceeding current recommendations.[159] Although single doses of corticosteroids are unlikely to carry a disproportionate risk of side effects, one should consider the suggested association of laminitis with corticosteroid use in horses. In cases of sepsis, further immunosuppressive effects could be detrimental.

In human patients with certain types of septic shock, dysfunction of the hypothalamic-pituitary-adrenal axis has been recognized and successfully treated with hydrocortisone replacement therapy.[161] Use of corticosteroids for this indication has not been evaluated in horses.

Pentoxifylline

Pentoxifylline, a methylxanthine derivative and phosphodiesterase inhibitor, has been suggested for use in endotoxemia because of its effects on neutrophil function and its ability to inhibit the production of various cytokines, interferons, and thromboplastin. Decreased production of TNF, IL-6, TXB_2, and thromboplastin in response to endotoxin was shown in an equine ex vivo model.[162] In horses given endotoxin followed by treatment with pentoxifylline (7.5 mg/kg body mass followed by continuous infusion of 3 mg/kg/hr for 3 hours), however, only minimal beneficial effects were observed.[163] Treatment significantly improved body temperature, respiratory rate, and whole blood recalcification time, but no effect was observed regarding heart rate, blood pressure, leukocyte count, plasma fibrinogen concentration, and serum cytokine concentrations. The conclusion was that benefits of treatment with pentoxifylline might be restricted to

administration of high bolus doses or continuous infusion early in the pathophysiologic process. In an in vivo endotoxemia model in horses, combination of pentoxifylline (8 mg/kg body mass) and flunixin meglumine (1.1 mg/kg body mass) was found to have greater benefit than each treatment on its own.[164] The currently recommended dosage for oral administration of pentoxifylline is 8 mg/kg every 8 hours. Because of its rheologic properties, that is, the ability to increase erythrocyte deformability and microvascular blood flow, pentoxifylline may be particularly useful in endotoxemic patients showing evidence of laminitis. An intravenous preparation of pentoxifylline is not commercially available.

Antioxidants

Dimethyl sulfoxide (DMSO) is used frequently in an attempt to scavenge oxygen-derived radicals. The treatment may be most appropriate in cases of ischemia-induced intestinal damage and associated reperfusion injury. However, DMSO failed to show beneficial effects in an experimental model of intestinal ischemia when administered on reperfusion of the ischemic intestine.[165] DMSO at the commonly used dose of 1 g/kg body mass was shown to increase mucosal loss after ischemia and reperfusion of the large colon,[166] and hence a reduced dose of 0.1 g/kg body mass has been proposed for cases of intestinal ischemia. For intravenous administration, DMSO needs to be diluted in polyionic solutions to a concentration not exceeding 10%. Oral administration of a 10% to 20% solution via nasogastric intubation is also possible. Aside from DMSO the xanthine oxidase inhibitor allopurinol has been suggested as a treatment to prevent oxygen radical–induced tissue damage. During periods of ischemia, tissue xanthine dehydrogenase is converted to xanthine oxidase, which on reperfusion catalyzes the generation of superoxide radicals.[167,168] Evaluation in horses showed beneficial effects of 5 mg allopurinol per kilogram body mass administered 12 hours before endotoxin challenge.[169] In another study, mucosal damage attributable to oxygen-derived free radicals was not attenuated by allopurinol in an experimental ischemia-reperfusion model.[166]

Lidocaine

Lidocaine given intravenously has been suggested as an antiinflammatory, analgesic, and prokinetic agent, and some clinicians use it to treat colic and laminitis in horses. In an experimental endotoxemia model in rabbits, lidocaine was found to inhibit hemodynamic and cytokine responses to endotoxin profoundly if given immediately following lipopolysaccharide infusion.[170] Use of lidocaine therefore may have additional merit in endotoxemic patients. A common regimen for lidocaine use in horses is administration of an initial bolus (1.3 mg/kg body mass)

followed by continuous infusion at a rate of 0.05 mg/kg/min. One should monitor patients for toxic neurologic effects associated with a lidocaine overdose.

ω-3 Fatty Acids

High concentrations of ω-3 fatty acids can alter the phospholipid composition of cellular membranes toward a decreased ratio of ω-6 to ω-3 and thereby can affect membrane functions such as phagocytosis, receptor binding, and activities of membrane-bound enzymes.[68] Most importantly for the treatment of endotoxemia, ω-3 fatty acid incorporation into cell membranes decreases the availability of arachidonic acid (an ω-6 fatty acid) for eicosanoid synthesis[171] and provides alternative substrates. Metabolism of ω-3 fatty acids via the COX and lipoxygenase pathway leads to the production of 3-series prostaglandins and 5-series leukotrienes, which have less biologic activity than their 2-series and 4-series counterparts derived from arachidonic acid. Aside from these mechanisms, ω-3 fatty acids prevent lipopolysaccharide-induced upregulation of CD14 in monocytic cells and therefore may be able to block transmembrane signaling of lipopolysaccharide.[172] Cells from horses given linseed oil (high in ω-3 fatty acids) for 8 weeks before blood collection showed significantly decreased expression of procoagulant activity, TXB_2, and TNF in response to lipopolysaccharide stimulation.[173,174] In an in vivo experimental model of endotoxemia in horses, treatment resulted in prolonged activated partial thromboplastin time and whole blood recalcification time, suggesting an anticoagulant effect; however, a significant beneficial effect on clinical response and serum eicosanoid concentrations was not observed.[175] Because dietary addition of ω-3 fatty acids requires several weeks of treatment, intravenous infusion was evaluated and shown to alter the composition of cell membrane phospholipids rapidly.[176] Further evaluation of this treatment for use in horses is necessary before dosage recommendations can be made.

INTERFERENCE WITH THE EFFECTS OF SPECIFIC INFLAMMATORY MEDIATORS
Antibodies Directed Against Tumor Necrosis Factor

Monoclonal and polyclonal antibodies against equine TNF have been evaluated.[177-179] Administration of a monoclonal antibody preparation before lipopolysaccharide infusion resulted in significantly reduced plasma TNF-activity, improved clinical abnormality scores, lower heart rate, and higher leukocyte count compared with controls.[178] Furthermore, plasma concentrations of lactate and 6-keto-$PGF_{1\alpha}$ were reduced significantly, whereas TXA_2 production was not affected.[177] In another study,[179] administration of a rabbit polyclonal antibody

against recombinant human TNF was unable to improve clinical and hematologic parameters when given shortly (15 minutes) after lipopolysaccharide infusion, although inhibition of TNF activity was present in vitro.[179,180] Findings in horses are in agreement with studies in other species and suggest that beneficial effects of TNF inhibition may be limited to administration before lipopolysaccharide exposure. Widespread clinical use therefore is unlikely to become feasible. Clinical trials in human patients have not shown significant benefits of TNF antibody treatment.[181,182]

Platelet-Activating Factor Receptor Antagonists

The effects of selective PAF receptor antagonists have been evaluated. PAF is implicated in the development of systemic hypotension,[183] lipopolysaccharide-induced platelet aggregation,[184] ileus,[185] and increased vascular permeability[186] and may mediate recruitment of leukocytes to inflamed tissues.[187,188] A study in horses using the PAF receptor antagonist SRI 63-441 before lipopolysaccharide infusion showed significant decreases in heart rate and shorter elevation of lactate concentrations in response to the treatment. Although not statistically significant, additional beneficial effects included delayed onset of fever, a shortened period of neutropenia, and reduced maximal platelet aggregation.[189]

SUPPORTIVE CARE
Fluid Therapy and Cardiovascular Support

Whenever possible, the clinician should correct volume and electrolyte deficits, or at least improve them, before anesthetizing a patient for a surgical procedure. For initial resuscitation, polyionic solutions such as lactated Ringer's solution given at rates of 10 to 20 ml/kg/hr are appropriate. Patients with severe hypovolemia and shock may require higher fluid volumes. A viable alternative to large-volume resuscitation with isotonic fluids is the use of small volumes of hypertonic solutions, which transiently raise plasma osmolality, thereby causing a fluid shift from the interstitial space into the vasculature and rapidly restoring circulating volume. Hypertonic saline solution (7.5% sodium chloride) is the most commonly used hypertonic solution and has been shown to have beneficial effects in endotoxemic horses.[190] A dose of 4 ml/kg is recommended, which one should give as a bolus infusion over 10 to 15 minutes, followed by administration of an isotonic solution to restore total body fluid volume. One should use hypertonic saline with caution in patients with sodium and/or chloride derangements and should monitor serum electrolyte concentrations in the case of repeated administration. Improvement of the cardiovascular status in response to fluid therapy is indicated by normalization of heart rate, mucous membrane color, and capillary refill time. Failure of urination

to occur despite appropriate fluid resuscitation should result in critical evaluation of renal function.

Once one has stabilized the patient, one should choose a maintenance fluid rate to maintain adequate hydration and plasma volume. For adult horses, the maintenance fluid rate is approximately 2 ml/kg/hr, whereas neonatal foals that are not nursing may require larger volumes (4 ml/kg/hr). One should monitor fluid administration carefully in endotoxemic patients, because lowered plasma oncotic pressure caused by hypoproteinemia along with an increased vascular permeability increase the risk of tissue edema formation. Furthermore, a rapid increase in total body fluid volume may be detrimental in patients with compromised cardiac and peripheral vasomotor function and may increase the severity of vascular pooling in peripheral organs. In these patients, hypertonic saline or colloids may be more appropriate means of stabilization than large volumes of crystalloid solutions.

Plasma is an ideal colloid and should be administered to maintain a serum total protein concentration above 4.2 g/dl.[121] To raise plasma protein concentration and colloid osmotic pressure significantly, however, horses often require large volumes of plasma (7 to 10 L or more in a 450-kg horse), and one should consider alternative colloids. Furthermore, high-molecular-weight polymers are thought to provide superior oncotic effects in cases of sepsis and endotoxemia, when vascular permeability is increased. Hetastarch, or hydroxyethyl starch, (Hespan) is commercially available as a 6% solution in 0.9% sodium chloride. Hetastarch molecules have very high molecular weight, and degradation must occur before renal excretion.[191] These properties result in a longer plasma half-life and prolonged oncotic effects compared with other colloids; persistence of the oncotic effect for 24 hours was found in hypoproteinemic horses.[192] A dosage of 5 to 15 ml/kg given by slow intravenous infusion along with an equal or greater volume of crystalloid fluids is recommended.[191,193] In human patients, prolonged activated partial thromboplastin time, decreased factor VIII activity, and decreased serum fibrinogen concentration have been described in association with hetastarch use.[194] In the limited number of equine studies, bleeding times were not affected[195,196]; however, one should monitor patients treated with hetastarch for coagulopathy.

One should base correction of serum electrolyte concentrations on the results of laboratory evaluation. Ideally, one should evaluate serum electrolyte concentrations of patients receiving fluid therapy daily. One should take ongoing losses and lack of dietary intake into account, especially when serum concentrations, as in the case of potassium, poorly reflect total body electrolyte stores. Potassium supplementation is recommended in patients experiencing prolonged (greater than 48 hours) periods of anorexia. One can add calcium in the form of calcium

gluconate, which is available as a 23% solution. Based on a study in healthy horses, rates of administration for calcium gluconate in the range of 0.1 to 0.4 mg/kg/min are recommended,[197] and as a guideline, one should administer 0.5 to 1 ml/kg body mass per day of a 23% solution. One can add potassium in the form of potassium chloride or potassium gluconate to intravenous solutions at a dose of 20 to 40 mEq/L given at a maintenance rate. Administration of potassium should not exceed a rate of 0.5 to 1 mEq/kg/hr.

Metabolic acidosis in endotoxic shock is attributable to lactic acidemia and inadequate tissue perfusion.[198] Acid-base balance often improves considerably after fluid resuscitation (preferably with alkalinizing solutions such as lactated Ringer's solution) alone; however, additional sodium bicarbonate may be required in cases in which serum bicarbonate concentration remains below 15 mEq/L. For adult horses, the bicarbonate deficit (in mEq HCO_3) is calculated as $0.3 \times$ body mass (kg) $\times$ base deficit, whereas for foals one should use a factor of 0.5. As a general rule, one should administer half the required amount as a bolus followed by the remaining half over 12 to 24 hours. Because endotoxemia is a dynamic process and losses are ongoing, one should reevaluate acid-base status at least once daily.

Foals with sepsis are frequently hypoglycemic, and 5% dextrose solutions are useful as initial resuscitation fluids. One should reduce the glucose concentration of intravenous solutions according to the blood glucose concentration to avoid prolonged hyperglycemia. Administration of hyperimmune plasma (20 to 40 ml/kg body mass) is highly recommended in foals with evidence of partial or complete failure of passive transfer.

One should consider positive inotropic and vasomotor agents in patients with persistently inadequate tissue perfusion. Lower dosages of dopamine (0.5 to 2 μg/kg/min) result in vasodilation of the renal, mesenteric, coronary, and intracerebral vasculature via dopaminergic effects, whereas higher dosages (up to 10 μg/kg/min) also exert stimulation of β_1-adrenergic receptors, resulting in increased myocardial contractility and heart rate.[199] Dobutamine is a direct β_1-adrenergic agonist and does not appear to have significant vasodilator properties. Dosages for dobutamine of 1 to 5 μg/kg/min as continuous intravenous infusion have been recommended for use in horses. In addition, norepinephrine was evaluated in hypotensive critically ill foals that were refractory to the effects of dopamine and dobutamine.[200] At dosages up to 1.5 μg/kg/min administered concurrently with dobutamine, six out of seven foals showed an increase in mean arterial pressure, and all foals had increased urine output. Because of the risk of cardiac side effects, close monitoring of heart rate and rhythm should accompany infusion of inotropes. Indirect blood

pressure measurements using a tail cuff may be used to monitor the effects of treatment.

Management of Coagulopathy

More frequently than overt thrombosis or bleeding attributable to DIC, hemostatic abnormalities occur in the form of alterations in the coagulation profile. A procoagulant state with shortened bleeding times or prolonged bleeding times caused by consumption of clotting factors may be evident. One should address abnormalities in the coagulation profile as early as possible but especially if they persist more than 24 hours after initiation of therapy. Because of the complex interactions of coagulation and fibrinolysis during endotoxemia, one should combine anticoagulant therapy with the administration of fresh frozen plasma to replace clotting and fibrinolytic factors. Heparin acts as an anticoagulant by activation of AT III and subsequent inhibition of thrombin, release of tissue factor pathway inhibitor from endothelial cells, and inhibition of platelet aggregation.[201] Because endogenous AT III levels frequently are decreased in patients with coagulopathy, addition of heparin to fresh frozen plasma may be the most effective route of administration. An initial dose of 100 IU/kg body mass followed by 40 to 80 IU/kg body mass 3 times daily has been recommended.[121] Anemia caused by erythrocyte agglutination occurs in some patients during therapy with unfractionated heparin[202,203] but typically resolves within 96 hours if therapy is discontinued.[121] Because of the risk of microthrombosis associated with erythrocyte agglutination, use of low-molecular-weight heparin (50 IU/kg body mass subcutaneously every 24 hours) has been recommended[204] but may be cost-prohibitive. One may give aspirin orally (10 to 20 mg/kg body mass, every 48 hours), which irreversibly inhibits platelet COX activity, to inhibit platelet aggregation and microthrombosis. Platelet hyperaggregability has been implicated in the pathogenesis of carbohydrate-induced laminitis,[205] and heparin and aspirin have been recommended to prevent development of laminitis. In an in vitro study, however, aspirin did not inhibit endotoxin-induced platelet aggregation.[206]

Prevention of Abortion in Pregnant Mares

Luteolysis caused by increased concentrations of $PGF_{2\alpha}$ leads to pregnancy loss in endotoxemic mares before day 55 of pregnancy.[207] Daily administration of altrenogest (Regu-Mate, Hoechst-Roussel Agri-Vet, Somerville, New Jersey) at a dose of 44 mg orally consistently prevented fetal loss in mares if administered until day 70 of pregnancy.[100] Treatment with flunixin meglumine, by blockade of $PGF_{2\alpha}$ release,[101] also may contribute to the maintenance of pregnancy in endotoxemic mares. The pathogenesis of fetal loss and abortion caused by endotoxemia, surgery, or systemic disease later in gestation is not understood completely. Proposed mechanisms include direct effects on the fetus, placental function, or placental progesterone production.[208]

Laminitis

The pathophysiology of laminitis caused by endotoxemia is understood incompletely; however, decreased digital blood flow[209,210] and intravascular microthrombosis have been implicated. Decreased NO production by vascular endothelial cells in response to endotoxin has been suggested as a mechanism for vasoconstriction and decreased blood flow[211]; however, use of NO donors remains controversial. Maintenance of adequate peripheral perfusion and anticoagulant and antiinflammatory therapy may be helpful in preventing and treating laminitis caused by endotoxemia.

Summary

Although the innate immune response to endotoxin (lipopolysaccharide) is crucially important for the preservation of homeostasis and health, large amounts of endotoxin can evoke an excessive and uncontrolled inflammatory response and result in a dysfunction of hemostatic and circulatory control mechanisms, loss of vascular integrity, and finally tissue damage. Conditions commonly associated with the development of endotoxemia in horses are acute gastrointestinal diseases, especially of ischemic and severe inflammatory nature, and localized or generalized infections. Although measuring endotoxin concentrations in equine plasma is possible, this is not feasible in a clinical setting, and one typically reaches a diagnosis of endotoxemia based on clinical signs and clinicopathologic data. Successful treatment of endotoxemia requires resolution of the primary disease process in addition to neutralization of circulating endotoxin, interference with the activities of inflammatory mediators, and general supportive care. Newer treatments, such as blockade of endotoxin-interaction with cells or interruption of cell signaling pathways, are under investigation. Possible sequelae of endotoxemia include DIC, multiple organ failure, circulatory failure, and death. Frequently, the outcome of conditions associated with endotoxemia in horses depends on the severity of associated complications; for example, renal compromise, laminitis, and abortion.

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13.8—Oral Diseases

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The word *mouth* is used commonly to signify the first part of the alimentary canal or the entrance to it.[1] The mouth is bounded laterally by the cheeks, dorsally by the palate, and ventrally by the body of the mandible and by the mylohyoideus muscles. The caudal margin is the soft palate. The mouth of the horse is long and cylindric, and when the lips are closed, the contained structures almost fill the cavity. A small space remains between the root of the tongue and the epiglottis and is termed the *oropharynx.* The cavity of the mouth is subdivided into sections by the teeth. The space external to the teeth and enclosed by the lips is termed the *vesicle of the mouth,* and in the resting state the lateral margins of the vesicle, that is, the buccal mucosa, are in close contact with the cheek teeth. Caudally, the external space communicates with the pharynx through the aditus pharyngis. The mucous membrane of the mouth is continuous at the margin of the lips with the skin and during life is chiefly pink but can be more or less pigmented, depending on the skin color and the breed type.

Morphology and Function

The lips are two muscular membranous folds that unite at angles close to the first cheek teeth. Each lip presents an outer and an inner surface. The upper lip has a shallow median furrow (philtrum); the lower lip has a rounded prominence or chin (mentum). The internal surface is covered with a thick mucous membrane that contains small, pitted surfaces that are the openings of the ducts of the labial glands. Small folds of the mucous membrane called the frenula labii pass from the lips to the gum. The free border of the lip is dense and bears short, stiff hairs. The arteries of the mouth are derived from the maxillary, mandibular, labial, and sphenopalatine arteries of the major palatine artery. The veins drain chiefly to the lingual facial vein. Sensory nerves originate from the trigeminal nerve (cranial nerve V) and the motor nerves from the facial nerve (VII). The cheeks spread back from the lips and form both sides of the mouth and are attached to the alveolar borders of the bones of the jaws. The cheeks are composed of skin and muscular and glandular layers and then the internal mucous membrane. The skin is thin and pliable. In contrast, the oral mucous membrane is dense and in many areas of the oral cavity is attached firmly to the periosteum so that construction of oral mucosal flaps can be achieved only by horizontal division of the periosteal attachment. Such a feature is important in reconstructive techniques applied to the oral cavity. The blood supply to the cheeks comes from the facial and buccal arteries and the sensory nerves from the trigeminal and motor nerves from the facial nerve.

The hard palate (palatum durum) is bounded rostrally and laterally by the alveolar arches and is continuous with the soft palate caudally. The hard palate has a central raphe that divides the surface into two equal portions. From the line of the rostral cheek tooth, the hard palate is concave to the line of the caudal cheek tooth. Paired transverse ridges (about 18) traverse the concavity and have their free edges directed caudally. The incisive duct is a small tube of mucous membrane that extends obliquely through the palatine fissure. The dorsal component communicates by a slitlike opening in the rostral portion of the ventral nasal meatus and its palatine end is blind and lies in the submucosa of the palate. When stallions display their flehmen response, watery secretions

enter the nose from the glands of the vomeronasal duct. To what extent these secretions aid in pheromone reception is not known.[2]

That portion of the palatine mucosa immediately behind the incisor teeth frequently is swollen (lampas) during eruption of the permanent teeth. This swelling is physiologic and not pathologic.

The tongue is situated on the floor of the mouth between the bodies of the mandible and is supported by the sling formed by the mylohyoideus muscles. The root of the tongue is attached to the hyoid bone, soft palate, and pharynx. The upper surface and the rostral portion of the tongue are free; the body of the tongue has three surfaces. The apex of the tongue is spatulate and has a rounded border. The mucous membrane adheres intimately to the adjacent structure and on the dorsum is dense and thick. From the lower surface of the free part of the tongue, a fold of mucous membrane passes to the floor of the mouth forming the lingual frenulum. Caudally, a fold passes on each side of the dorsum to join the soft palate, forming the palatoglossal arch. Dorsally from the soft palate the palatopharyngeal arch attaches and circumvents the aditus laryngis and attaches to the roof of the nasopharynx. The mucous membrane of the tongue presents four kinds of papillae:

1. *Filiform papillae* are fine threadlike projections across the dorsum of the tongue. They are absent on the root of the tongue and are small on the rostral portion of the tongue.
2. The *fungiform papillae* are larger and easily seen at the rounded free end. They occur principally on the lateral portion of the tongue.
3. *Vallate papillae* are usually two or three in number and are found on the caudal portion of the dorsum of the tongue. The free surface bears numerous small, round secondary papillae.
4. Foliate papillae are situated rostral to the palatoglossal arches of the soft palate where they form a rounded eminence about 2 or 3 cm in length marked by transverse fissures.

Foliate, vallate, and fungiform papillae are covered with taste buds and secondary papillae.

The lingual and sublingual arteries supply the tongue from the linguofacial trunk and matching veins. The linguofacial trunk drains into the linguofacial vein. The lingual muscles are innervated by the hypoglossal nerve (XII) and the sensory supply is from the lingual and glossopharyngeal (IX) nerves.

Equine Dentition

The formula for the deciduous teeth of the horse is 2 times I3-3 C0-0 P3-3 for a total of 24. The permanent dental formula is 2 times I3-3 C1-1 P3-3 or P4-3 M3-3

for a total of 40 or 42. In the mare the canine teeth are usually small or do not erupt, hence reducing the number to 36 or 38. The first premolar tooth (wolf tooth) is often absent and has been reported as occurring in only 20% of the upper dentition of Thoroughbred horses.[3] The teeth of the horse are complex in shape and are compounded of different materials (dentin, cementum, and enamel). They function as grinding blades to masticate and macerate cellulose food in the important first stage of the digestive process. The cheek teeth in the horse are a well-documented feature of the evolution of *Equus caballus.*

DECIDUOUS TEETH

The first incisor is present at birth or the first week of life. The second incisor erupts at 4 to 6 weeks of age; the third incisor, at 6 to 9 months of age; the first and second premolars, at birth to 2 weeks of age; and the third premolar, 3 months of age.

PERMANENT TEETH

The eruption times for the permanent teeth are as follows: first incisor, 2½ years of age; second incisor, 3½ years of age; third incisor, 4½ years of age; the canine tooth, 4 to 5 years of age; the first premolar (wolf tooth), 5 to 6 months of age; the second premolar, 2½ years of age; the third premolar, 3 years of age; the fourth premolar, 4 years of age; the first molar, 10 to 12 months of age; the second molar, 2 years of age; and the third molar, 3½ to 4 years of age. This eruption sequence clearly indicates that the eruption of the second and third permanent premolar teeth give the potential for dental impaction.

The modern horse has six incisor teeth in each jaw that are placed close together so that the labile edges form a semicircle. The occlusal surface has a deep enamel invagination (infundibulum) that is filled only partially with cementum. As the incisor teeth wear, a characteristic pattern forms in which the infundibulum is surrounded by rings of enamel, dentin, enamel, and crown cementum in a concentric pattern. Each incisor tooth tapers from a broad crown to a narrow root so that as the midportion of the incisor is exposed to wear, the cross-sectional diameters are about equal; that is, at 14 years of age, the central incisor tooth of the horse has an occlusal surface that is an equilateral triangle. Observations on the state of eruption, the angles of incidence of the incisor teeth, and the pattern of the occlusal surfaces are used as guides for aging of horses. The canine teeth are simple teeth without complex crowns and are curved. The crown is compressed and is smooth on its labial aspect but carries two ridges on its lingual aspect. No occlusal contact occurs between the upper and lower canine teeth.

When erupted, the six cheek teeth of the horse function as a single unit in the mastication of food. Each arcade consists of three premolar and three molar teeth. The maxillary arcade is slightly curved, and the teeth have a square occlusal surface. The occlusal surfaces of the mandibular teeth are more oblong, and each arcade is straighter. The horse is anisognathic, that is, the distance between the mandibular teeth is narrower (one-third) than the distance between the upper cheek teeth. This anatomic arrangement affects the inclination of the dental arcade as the jaws slide across each other in the food preparation process. The unworn upper cheek tooth presents a surface with two undulating and narrow ridges, one of which is lateral and the other medial. On the rostral and lingual side of the medial style is an extra hillock. The central portion of these surfaces is indented by two depressions that are comparable with, but much deeper than, the infundibula of the incisor teeth. When the teeth have been subjected to wear, the enamel that closed the ridges is worn through and the underlying dentin appears on the surface. Thus after a time the chewing surface displays a complicated pattern that may be likened to the outline of an ornate letter *B,* the upright stroke of the *B* being on the lingual aspect. Dentin supports the enamel internally, cementum supports the enamel lakes, and the peripheral cementum fills in the spaces between the teeth so that all six teeth may function as a single unit, that is, the dental arcade. Transverse ridges cross each tooth so that the whole maxillary arcade consists of a serrated edge. The serrations are formed so that a valley is present at the area of contact with adjacent teeth. These serrations match fitting serrations on the mandibular arcade.

The true roots of the cheek teeth are short compared with the total length of the tooth. Cheek teeth have three roots: two small lateral roots and one large medial root. By custom, that portion of the crown embedded within the dental alveolus is referred to as the *reserve crown,* and the term *root* is confined to that area of the tooth that is comparatively short and enamel free. Wear on the tooth gradually exposes the reserve crown, and the roots lengthen. In an adult 1000-lb horse the maxillary cheek teeth are between 8.0 and 8.5 cm in length. Dental wear accounts for erosion and loss of tooth substance at a rate of 2 mm/yr.

The pulp chambers of the teeth are also complex. The incisors and canines have a single pulp chamber. The mandibular cheek teeth have two roots and two separate pulp chambers. The maxillary cheek teeth, although they have three roots, have in fact five pulp chambers. As occlusal wear proceeds, deposition of secondary dentin within the pulp chambers protects the chambers (e.g., the dental star, medial to the infundibulum on the incisor teeth).

In the mandibular cheek teeth the transverse folding of the enamel anlage (during morphogenesis of the tooth) does not take place, and the occlusal surface is a simple surface of central dentin surrounded by enamel. Each tooth then is conformed to a single arcade by the presence of peripheral crown cementum.

Mouth Diseases

The oral cavity and oropharynx are subject to a variety of diseases. However, many conditions affecting the first portion of the alimentary system produce the same clinical signs, regardless of their cause. The clinical signs may include inappetance or reluctance to eat, pain on eating or swallowing, oral swelling, oral discharge, and fetid breath. Affected animals may show some interest in food but hesitate to eat it. Salivation may be excessive and may be contaminated with purulent exudate or blood. The occurrence of bruxism (i.e., grinding of teeth) can indicate discomfort in other areas of the alimentary tract; for example, bruxism and frothing oral saliva are characteristic features of gastric ulceration in the horse.

The clinician needs to be aware that considerable weight loss can occur rapidly with inability to feed and swallow. Diseases that result in denervation of the pharynx and inappropriate swallowing can have the complication of inhalation pneumonia.

EXAMINATION AND CLINICAL SIGNS

After a complete physical examination and ascertaining the history, the clinician should approach examination of the mouth systematically in all cases. One can examine a considerable portion of the mouth and teeth from the outside by palpation of the structures through the folds of the cheek. Most horses allow an oral examination without sedation or the use of an oral speculum. In many cases, however, one best achieves the detailed oral examination by sedation and the use of an oral speculum and a light source. One should irrigate the mouth to wash out retained food material so as to be able to inspect and palpate the lips, cheeks, teeth, and gums.

The classic signs of dental disease in the horse include difficulty and slowness in feeding, together with a progressive unthriftiness and loss of body condition. In some instances, the horse may quid, that is, it may drop poorly masticated food boluses from the mouth, and halitosis may be obvious. Additional problems reported by owners include bitting and riding problems and head-shaking or head shyness. Facial or mandibular swelling may occur. Nasal discharge can result from dental disease associated with maxillary sinus empyema. Mandibular fistulae frequently are caused by lower cheek tooth apical infections. Some correlation exists between the age of the animal and clinical signs (Table 13.8-1).

TABLE 13.8-1
Correlation Between Dental Disease and Dental Therapy

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From Baker GJ: Diseases of the teeth. In Colohan PT, Mayhew IG, Merritt AM et al, editors: *Equine medicine and surgery,* ed 4, vol 1, Goleta, Calif, 1991, American Veterinary Publications.

ANCILLARY DIAGNOSTIC TECHNIQUES

Ancillary aids for a complete examination of the oral cavity of the horse may include radiology, endoscopic examination, fluoroscopy, biopsy, and culture. One should take care always during endoscopic evaluation of the oral cavity using a flexible endoscope. The author recommends sedation and the use of an oral speculum to prevent inadvertent mastication of the endoscope. If one uses general anesthesia as part of the diagnostic workup, then endoscopic evaluation of the oral cavity is much easier. In selected cases, advanced imaging technologies such as computed tomography, magnetic resonance imaging, or nuclear scintigraphy may be beneficial.

Dysphagia

CLINICAL SIGNS AND DIAGNOSIS

The lips of the horse are mobile and prehensile. In many ways they function like the tip of the elephant's trunk in that they test, manipulate, and sample the environment for potential nutritive value. Consequently, loss of motor function (e.g., facial palsy) affects the efficiency of the prehensile system. The lips grasp food in grazing or browsing, and the incisor teeth section the food. With mastication and lubrication with saliva, the bolus of food forms and is manipulated from side to side across the mouth, assisted by the tight cheeks of the horse and the palatine ridges. Swallowing begins as the food bolus contacts the base of the tongue and the pharyngeal walls.

During swallowing, the soft palate elevates to close the nasopharynx, the base of the tongue elevates, and the hyoid bone and the larynx move rostrally following contraction of the hyoid muscles. During this process, the rima glottidis closes and the epiglottis tilts dorsally and caudally to protect the airway so that food is swept through lateral food channels around the sides of the larynx into the laryngoesophagus. Fluoroscopic studies in nursing foals in the dorsoventral view showed that contact occurs between the lateral food channels in the midline so that in outline the food bolus achieves a bow tie shape.[4]

Dysphagia is defined as a difficulty or inability to swallow. Anatomic classifications for dysphagia include prepharyngeal, pharyngeal, and esophageal (postpharyngeal) dysphagias. The site of the cause for dysphagia influences the clinical signs. Prepharyngeal dysphagia is characterized by dropping food (quidding) or water from the mouth, reluctance to chew, hypersalivation, or abnormalities in prehension. Pharyngeal and esophageal dysphagias are characterized by coughing; nasal discharge containing saliva, water, or food material; gagging; anxiousness; and neck extension during attempts to swallow. The following section describes esophageal dysphagia in more detail. Causes of dysphagia can be divided into four types: painful, muscular, neurologic, or obstructive (Table 13.8-2). Pain and obstruction cause dysphagia by interfering with the mechanics of prehension, bolus formation and transfer to the pharynx, and deglutition.

TABLE 13.8-2
Differential Diagnoses for Dysphagia

CLASS OF DYSPHAGIA	DIFFERENTIAL DIAGNOSES		
Painful	Tooth root abscess or periodontal disease	Obstructive—cont'd	Pharyngeal abscess or foreign body
	Broken teeth		Dorsal displacement of the soft palate or rostral displacement of the palatopharyngeal arch
	Abnormal dentition or wear		
	Stomatitis, glossitis, or pharyngitis		
	Nonsteroidal antiinflammatory drug toxicity		Cleft palate
	Chemical irritation		Guttural pouch tympany or empyema
	Thrush (candidiasis)		Follicular pharyngitis
	Influenza		Esophageal obstruction
	Streptococcus equi		Pharyngeal cicatrix
	Vesicular stomatitis virus		Retropharyngeal abscess or neoplasia
	Actinobacillus lignieresii	Neurologic	Guttural pouch empyema, mycosis, or neoplasia
	Buccal, gingival, or glossal trauma (bits or chains)	forebrain disease;	
		generalized	Stylohyoid osteopathy
	Foreign bodies	neuropathy;	Lead poisoning
	Retropharyngeal lymphadenopathy or abscess	disorders of	Petrous temporal bone osteomyelitis or fracture
	Mandibular trauma	cranial nerves	
	Stylohyoid osteopathy	V, VII, IX, X,	Retropharyngeal abscess
	Temporomandibular osteopathy	or XII	Botulism
Muscular	Hyperkalemic periodic paralysis		Yellow star thistle toxicity
	Nutritional myopathy (white muscle disease)		Viral encephalitis
	Polysaccharide storage disease		Cerebral edema
	Glycogen branching enzyme deficiency		Cerebral or brainstem hemorrhage
	Masseter myositis		Intracranial masses (hematoma, neoplasia, abscess)
	Hypocalcemia tetany or ecclampsia		
	Myotonia		Meningitis
	Rectus capitis ventralis rupture		Verminous encephalitis
	White snakeroot toxicity		Equine protozoal myeloencephalitis
	Megaesophagus		Equine herpesvirus 1
Obstructive	Retropharyngeal abscess and lymphadenopathy		Equine dysautonomia
	Oral, pharyngeal, retropharyngeal, laryngeal, or esophageal malformations, injury, edema, or neoplasia		Hepatoencephalopathy
			Tetanus
	Pharyngeal or epiglottic cysts		Polyneuritis equi

Muscular and neurologic causes of dysphagia impede prehension and swallowing by affecting the motor function of the lingual or buccal musculature, muscles of mastication (temporal and masseters), and pharyngeal and cranial esophageal muscles. Sensory loss to the lips, buccal mucous membranes, pharynx, or tongue also may cause dysphagia. Neurologic causes of dysphagia may affect the forebrain, brainstem, or peripheral nerves that control prehension (cranial nerves Vm, Vs, VII, and XII), transfer of the food bolus to the pharynx (cranial nerves Vs and XII) and swallowing (cranial nerves IX and X).

Diagnosis of the cause of dysphagia is based on physical examination including a careful oral examination, neurologic examination, clinical signs, and endoscopy of the pharynx, esophagus, and guttural pouches. Radiology may be useful to assess the bony structures of the head and throat. Ultrasonography is valuable for examining the retropharyngeal space and esophagus to detect and evaluate masses. One may detect pharyngeal or esophageal

causes of dysphagia with routine endoscopic examination or with contrast radiography. Although one also can use endoscopy to assess deglutition, one must remember that sedation adversely affects the deglutition mechanism. One may assess deglutition using fluoroscopy[4] or manometry,[5] but these techniques require specialized equipment. Specific diagnostic procedures for nonalimentary causes of dysphagia are covered elsewhere in this text (see Chapter 3).

MANAGEMENT
Specific treatments aimed at resolving the underlying disorder causing dysphagia are discussed in detail elsewhere. One should avoid feeding roughage with long fiber length (hay or grass) to most horses with dysphagia. Dietary modifications that promote swallowing such as feeding slurries made from complete pelleted feeds may be sufficient to manage some cases of partial dysphagia. One must take care to prevent or avoid aspiration

pneumonia in horses with pharyngeal or esophageal dysphagia. One can manage foals by feeding mare's milk or a suitable substitute through a nasogastric tube. One also may administer pellet slurries or formulated liquid diets via nasogastric tubes to older horses. Prolonged nutritional management of dysphagic horses may require extraoral feeding using a tube placed through an esophagostomy.[6]

Formulated pelleted diets are often easy to administer through a tube as slurry and are balanced to meet the nutritional requirements for healthy horses. One must feed sufficient quantities to deliver adequate calories (16 to 17 Mcal/day for a 500-kg horse). Adjustments may be necessary for horses that are cachectic or have extra metabolic demand (such as pregnancy). Adding corn oil to the ration (1 cup every 12 or 24 hours) is a common method of increasing fed calories. Liquid diets also have been used for enteral feeding[7] but may not be tolerated as well as pelleted diets. Regardless of the method of nutritional management, one must monitor and replace salivary losses of electrolytes. Saliva contains high concentrations of Na, K, and Cl. A group of ponies with experimental esophagostomies[8] and a horse with esophageal squamous cell carcinoma[9] were fed a complete pelleted diet through esophagostomy tubes but developed metabolic acidosis, hyponatremia, and hypochloremia apparently because of salivary losses. Surprisingly, salivary losses of potassium did not result in hypokalemia in these cases, presumably because of replacement in the diet. However, if the diet is deficient in potassium, hypokalemia may result. One often can accomplish electrolyte replacement by adding NaCl and KCl to the diet. One can maintain horses for months with frequent feedings through an esophagostomy tube.[9] Parenteral nutrition (total or partial) may be useful in the short term but is not often feasible for long-term management.

Dental Diseases

ERUPTION DISORDERS

Tooth eruption is a complex phenomenon involving the interplay of dental morphogenesis and those vascular forces responsible for creating the eruption pathway. These changes are responsible for osteitis and bone remodeling within the maxilla and mandible. Young horses frequently show symmetric bony swelling resulting from these eruption cysts. In some cases, additional clinical signs of nasal obstruction with respiratory stridor or nasal discharges may be apparent.

Pathologic problems associated with maleruption include a variety of dental diseases. Oral trauma can displace or damage erupting teeth or the permanent tooth buds. As a result, teeth may be displaced and erupt in abnormal positions or may have abnormal shapes. Supernumerary teeth, incisors and molars, can develop, as well as palatal displacement of impacted teeth (maxillary P3-3, or third cheek tooth). In almost all of these conditions some form of surgical treatment is necessary.

Significant evidence from the location of apical osteitis in diseased teeth (Table 13.8-3) confirms that dental impaction is a major cause of dental disease in the horse. In a series of 142 extracted teeth, 63 were P3-3 or P4-4 (cheek tooth 2 or 3, respectively).[10] Early observations had indicated that the first molar (M1, or cheek tooth 4) was the most commonly diseased tooth, and an "open infundibulum" in this tooth has been suggested as the cause.[11] Studies on cementogenesis of the maxillary cheek teeth have shown, however, that in fact most maxillary cheek teeth have a greater or lesser degree of hypoplasia of cementum within the enamel lakes and that this "lesion" rarely expands into the pulp. The central infundibular hole is the site of its vascular supply to the unerupted cement lake. On those occasions in which

TABLE 13.8-3
Sites of Apical Infections in Diseased Cheek Teeth

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caries of cementum occurs, that is, secondary inflammatory disease and acid necrosis of the cementum, apical osteitis may develop.

DENTAL DECAY

Pulpitis is key to the pathogenesis of dental decay in the horse. The initiation of inflammatory pulp changes may be a sequela to dental impaction or dental caries or may result from fracture of a tooth. If the onset of the inflammatory process is slow, then formation of secondary dentin within the pulp chambers may protect the pulp and the tooth. Secondary dentin formation occurs from stimulation of odontoblasts within the pulp chamber. Such changes are the normal process of protection during dental wear and attrition as crown substances wear away and the reserve crown comes into wear. In acute disease, however, this defense mechanism is ineffective, and the changes that occur and that are sequelae to pulpitis reflect the location of each affected tooth. For example, pulpitis and apical osteitis of the third mandibular cheek tooth most commonly results in the development of a mandibular dental fistula. Pulpitis of the third maxillary cheek tooth, however, results in an inflammatory disease within the rostral maxillary sinus and in development of chronic maxillary sinus empyema (Figure 13.8-1).

Oblique radiographs greatly assist the diagnosis of dental decay by demonstrating sinus tract formation, sequestration of bone, mandibular osteitis, hyperplasia of cementum, and new bone formation (so-called alveolar periosteitis).[12]

The management of dental decay in the horse usually involves surgical extraction of the diseased tooth. In some cases one can use apicoectomy and retrograde endodontic techniques to save the diseased tooth. One must take care, however, in selection of patients. In most cases of apical osteitis in the horse that result from dental impaction, immature root structures make achieving an apical seal of the exposed pulp difficult.

Periodontal Disease

Gingival hyperemia and inflammation occur during the eruption of the permanent teeth and are common causes of a sore mouth in young horses (particularly 3-year-olds as the first dental caps loosen). Such periodontal changes usually resolve as the permanent dental arcade is established. During normal mastication, the shearing forces generated by the occlusal contact of the cheek teeth essentially clean the teeth of plaque and effectively inhibit deposition of dental calculus. Wherever occlusal contact is ineffective, periodontal changes and calculus buildup occur; for example, the deposition of calculus on the canine teeth of mature geldings and stallions is common. Routine dental prophylaxis forms an important component of maintaining normal occlusal contact, and for this reason one should remove arcade irregularities that result in enamel point formation on the buccal edges of the maxillary cheek teeth and the lingual edges of the mandibular cheek teeth. One should remove these edges annually in horses that are at grass and twice yearly in young horses, aged horses, and stabled horses. Horses at grass have been shown to have a greater range of occlusal contact and therefore better periodontal hygiene than stabled horses. In stabled horses the range of occlusal contact is narrower and the formation of enamel points occurs more frequently with subsequent buccal ulceration and the initiation of a cycle of altered occlusal contact and hence irregular arcade formation. This process leads to severe forms of periodontal disease and wave mouth formation.

Periodontal disease occurs with abnormal occlusal contact and initiation of the cycle of irregular wear and abnormal contact. Such changes progress to loss of alveolar bone, gross periodontal sepsis, and loss of tooth support. In this sense periodontal disease truly is the scourge of the equine mouth and results in tooth loss.[13]

Congenital and Developmental Abnormalities

CLEFT PALATE

Palatine clefts may result from an inherited defect and are caused by failure of the transverse palatal folds to fuse in the oral cavity. Harelip accompanies few palatine clefts in the horse. The degree of palatine clefting depends on the stage at which interruption in the fusion of the

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Figure 13.8-1   Possible sequelae to pulpitis in the horse.

(From Baker GJ: Disease of the teeth. In Colohan PT, Mayhew IG, Merritt AM et al, editors: *Equine medicine and surgery,* ed 4, vol 1, Goleta, Calif, 1991, American Veterinary Publications.)

palatopalatal folds occurs. Toxic or teratogenic effects are documented in other species, but little data are available in the horse.

In recent years, treatment for repair of uncomplicated palatine defects has been recommended but prognosis is generally poor because of the considerable nursing care required and the high incidence of surgical failures. One should emphasize early surgery and the use of mandibular symphysiotomy in affording surgical exposure. The combination of mandibular symphysiotomy and transhyoid pharyngotomy to approach the caudal margins of the soft palate affords surgical access, and one can construct mucosal flaps to repair the defects. However, the incidence of surgical breakdown is high, and healing by first intention is the exception rather than the rule. A recent surgical report documented the successful closure of a median cleft of the lower lip and mandible in a donkey.[14]

CAMPYLORHINUS LATERALIS

Foals born with a severely deviated premaxilla and palate have a wry nose. One can achieve surgical correction of the deviated premaxilla by submucosal division of the premaxilla across the nose at the line of the first cheek tooth. Circumstantial evidence indicates that such a defect has a genetic cause, and the defect occurs most frequently in the Arabian breed.

CYSTS

Other developmental abnormalities are subepiglottic cysts resulting from cystic distortion of remnants of the thyroglossal duct, which may cause dyspnea and choking in foals. Surgical removal of these cysts results in normal function.

PARROT MOUTH

The most significant developmental defect of dental origin is a maxilla that is longer than the mandible, that is, the horse is parrot-mouthed. An overbite of 2 cm in the incisor arcade may be present in a horse with a mismatch of less than 1 cm between the first upper and lower cheek teeth. Parrot mouth and monkey or sow mouth are thought to be inherited conditions. Some correction of minor incisor malocclusion occurs up to 5 years of age.

Recognition and detection of parrot mouth are important in the examination of potential breeding stock. Surgical attempts to inhibit overgrowth of the premaxilla by wiring or by the application of dental bite plate procedures have been documented in recent years.[15]

Oral Wounds

As has been indicated, the horse is by nature a curious animal and uses its lips as a means of exploring a variety of objects. Wounds of the lips, incisive bone, and the mandibular incisor area occur commonly in the horse and usually result from the horse getting the lips, jaw, or teeth caught in feeding buckets, in fence posts, or in halters or having a segment of tongue encircled with hair in tail chewing. As the horse panics and pulls away from its oral entrapment, considerable trauma can occur to the lips, teeth, and gums.

Most wounds repair satisfactorily, provided one finds them early and observes the basic principles of wound hygiene, excision of necrotic tissue, and wound closure. One must ensure that oral mucosal defects are closed and that effective oral seals are made before external wounds are closed. In some cases, offering specially constructed diets or even feeding the horse by nasogastric tube or esophagostomy during the healing processes may be necessary.

Stomatitis and Glossitis

Foreign body penetration of the tongue, cheek, or palate has been reported in grazing and browsing horses and in particular in horses that have certain hay sources that contain desiccated barley awns or yellow bristle grass.[16] Other plant material and grass awns also occasionally may penetrate the tongue, gingiva, or cheek, causing inflammation or abscesses. Ulcerative stomatitis also results from the toxicity of phenylbutazone therapy.[17] Vesicular stomatitis is a highly contagious viral blistering disease described in more detail elsewhere. Treatment of glossitis and stomatitis primarily aims at removing the inciting cause.

Actinobacillus lignieresii, the causative agent of actinobacillosis, has been isolated and identified from ulcers on the free border of the soft palate and oral and laryngeal granulomata. The bacterium also was reported in a sublingual caruncle in a horse with a greatly swollen tongue.[18] Therapy with 150 ml of 20% sodium iodide and 5 g of ampicillin every 8 to 12 hours effected a clinical cure.

Salivary Glands

FUNCTION

Saliva is important for lubricating and softening food material. The horse has paired parotid, mandibular, and polystomatic sublingual salivary glands. The parotid gland is the largest of the salivary glands in the horse and is situated in the space between the ramus of the mandible and the wing of the atlas. The parotid duct is formed at the ventral part of the gland near the facial crest by the union of three or four smaller ducts. The duct leaves the gland above the linguofacial vein, crosses the tendon of the sternocephalicus muscle, and enters the mouth obliquely in the cheek opposite the third upper

cheek tooth. The parotic duct orifice is small, but some dilation of the duct and a circular mucous fold (the parotid papillae) exist at this point. The mandibular gland is smaller than the parotid gland and extends from the atlantal fossa to the basihyoid bone. For the most part, the mandibular gland is covered by the parotid gland and by the lower jaw. The mandibular duct is formed by union of a number of small duct radicles that emerge along the concave edge of the gland and run rostral to the border of the mouth opposite the canine tooth. The orifice is at the end of a sublingual caruncle. The mandibular gland possesses serous, mucous, and mixed alveolar glandular components. The parotid gland is a compound alveolar serous gland. The parotid salivary gland can secrete saliva to yield rates of 50 ml/min, and a total daily parotid secretion can be as much as 12 L in a 500-kg horse. Parotid secretion only occurs during mastication, and administration of atropine or anesthesia of the oral mucosa can block secretion. Parotid saliva is hypotonic compared with plasma, but at high rates of flow, concentrations of sodium, chloride, and bicarbonate ions increase.

SALIVARY GLAND DISORDERS

Parotid saliva of the horse has a high concentration of calcium, and occasionally calculi (sialoliths) form within the duct radicles of the parotid salivary gland.[19] Congenital parotid duct atresia, acquired stricture from trauma to the duct, or obstruction by plant material (sticks or foxtails and other seeds) also may occur. The clinical signs of sialolithiasis or other forms of ductule obstruction include a fluid swelling in the form of a mucocele proximal to the stone and occasionally inflammation of the parotid gland. Ultrasonography is useful to diagnose salivary mucoceles and to detect foreign bodies or sialoliths. Measurement of electrolyte concentrations in aspirates from suspected mucoceles might be helpful to distinguish them from hematomas. Salivary potassium and calcium concentrations are higher than plasma. Treatment may require surgical removal of the stone or plant material in the case of sialolithiasis or foreign body obstructions. Other causes of obstruction may require resection of the affected portion of the duct or chemical ablation of the gland.[20]

Primary sialoadenitis is unusual but can occur in one or both glands. The condition is painful and may be associated with a fever and anorexia. Secondary sialoadenitis is more common and usually is associated with trauma. Infectious sialoadenitis from *Corynebacterium pseudotuberculosis*[21] or other bacterial pathogens also may occur. Diagnosis is by physical examination and by finding an enlarged edematous parotid gland tissue on ultrasonographic examination. Culture and cytologic examination of aspirates may be useful for diagnostic

purposes. Treatment in usually palliative, consisting of nonsteroidal antiinflammatory drugs. Appropriate antibiotic therapy is indicated as directed by culture and sensitivity results.

Chemical irritation, glossitis, stomatitis, or other causes of prepharyngeal dysphagia cause ptyalism or excessive salivation in horses. Specific therapy for the ptyalism usually is not required as long as salivary losses are not excessive, resulting in dehydration and electrolyte imbalances. Ingestion of the fungal toxin slaframine also causes hypersalivation in horses.[22] The fungus *Rhizoctonia leguminicola*, which produces slaframine, causes black patch disease in red clover. Slaframine is a parasympathomimetic compound that stimulates exocrine secretion in the parotid gland. Slaframine toxicosis most commonly occurs in the spring or early summer and rarely requires treatment other than removal from the pasture. Mowing removes the source in most cases because regrowth in pastures often has less fungal contamination.[23]

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13.9—Esophageal Diseases

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Anatomy and Function

The esophagus is a musculomembranous tube that originates from the pharynx dorsal to the larynx and terminates at the cardia of the stomach.[1] In adult Thoroughbred horses the esophagus is approximately 120 cm long. The cervical portion is approximately 70 cm long; the thoracic portion, approximately 50 cm long; and the short abdominal portion, only approximately 2 cm long. The cervical esophagus generally lies dorsal and to the left of the trachea in the cervical region. In the thorax the esophagus courses through the mediastinum lying dorsal to the trachea and crosses to the right of the aortic arch dorsal to the heart base.

The esophagus has no digestive or absorptive functions and serves as a conduit to the stomach for food, water, and salivary secretions. The esophageal mucosa is a keratinized stratified squamous epithelium.[1] The submucosa contains elastic fibers that contribute to the longitudinal folds of the esophagus and confer elasticity to the esophageal wall. A transition occurs in the muscle type composing the tunica muscularis from striated skeletal muscle in the proximal two thirds of the esophagus to smooth muscle in the distal third. In the proximal esophagus the skeletal muscle layers spiral across one another at angles. Within the smooth muscle layers of the distal esophagus the outer layer becomes more longitudinal, whereas the inner layer thickens and becomes circular. The wall of the terminal esophagus can be 1 to 2 cm thick. Deep cervical fascia, pleura, and peritoneum contribute to the thin fibrous tunica adventitia of the esophagus.

Motor innervation to the striated skeletal muscle of the esophagus includes the pharyngeal and esophageal branches of the vagus nerve, which originate in the nucleus ambiguus of the medulla oblongata. Parasympathetic fibers of the vagus nerve supply the smooth muscle of the distal esophagus. Sympathetic innervation of the esophagus is minimal.

Passage of ingesta through the esophagus can be considered part of the swallowing process, which consists of oral, pharyngeal, and esophageal stages. The oral stage is voluntary and involves transport of the food bolus from the mouth into the oropharynx. During the involuntary pharyngeal stage the food bolus is forced through the momentarily relaxed upper esophageal sphincter by simultaneous contractions of the pharyngeal muscles. In the esophageal phase of swallowing the upper esophageal sphincter closes immediately, the lower esophageal sphincter opens, and esophageal peristalsis propels the bolus into the stomach.[2] Unlike a food bolus, liquids do not require peristalsis to reach the lower esophageal sphincter and may precede the food bolus during swallowing.

The upper esophageal sphincter prevents esophagopharyngeal reflux during swallowing and air distention of the esophagus during inspiration. Upper esophageal pressure increases in response to pressure from a food bolus and to increased intraluminal acidity, as would occur with gastroesophageal reflux. The lower esophageal sphincter is a smooth muscle located at the gastroesophageal junction that is morphologically ill defined but forms an effective functional barrier.[2] Normally the lower esophageal sphincter is closed in response to gastric distention to restrict gastroesophageal reflux. Relaxation of the lower esophageal sphincter permits passage of ingested material from the esophagus to the stomach. Distention of the stomach with ingesta mechanically constricts the lower esophageal sphincter. Gastric distention also triggers a

vagal reflex that increases lower esophageal sphincter tone, a safety mechanism against gastroesophageal reflux. The mechanical and vagal mechanisms that promote lower esophageal sphincter tone prevent spontaneous decompression of the stomach, which along with a lack of a vomiting reflex in the horse, increases the risk of gastric rupture during episodes of severe distention.

Esophageal Obstruction

Esophageal obstruction has many causes (Table 13.9-1) and most often is manifested clinically by impaction of food material and resulting esophageal dysphagia. Esophageal obstruction may be caused by primary impactions (simple choke) of roughage, particularly leafy alfalfa hay, coarse grass hay, bedding, and even grass. Prior esophageal trauma or poor mastication caused by dental abnormalities may predispose horses to primary esophageal impaction.[3] Wolfing or gulping food may precipitate primary impactions, particularly if the horse is exhausted or mildly dehydrated after a long ride or is weakened from chronic debilitation. Impactions also may result from disorders that physically impede the passage of food material and fluid by narrowing the luminal diameter, reduce the compliance of the esophageal wall, or alter the conformation of the esophageal wall such that food material accumulates in a pocket or diverticulum. Foreign bodies, intra- or extramural masses, or acquired or congenital anomalies cause these so-called secondary impactions. Intramural causes of esophageal obstruction include tumors (squamous cell carcinoma), strictures, diverticula, and cysts.[3-10] Mediastinal or cervical masses (tumors or abscesses) may cause extramural obstructions. Congenital anomalies are covered in detail later.

CLINICAL SIGNS AND DIAGNOSIS

The clinician must perform a thorough physical examination, including complete oral and neurologic examination, to help rule out causes of dysphagia and nasal discharge other than esophageal obstruction. The clinical signs associated with esophageal obstructions are related primarily to regurgitation of food, water, and saliva caused by esophageal (postpharyngeal) dysphagia.[11] Horses with esophageal obstruction are often anxious and stand with their neck extended. One may note gagging or retching, particularly with acute proximal obstructions. Bilateral frothy nasal discharge containing saliva, water, and food material; coughing; odynophagia; and ptyalism are characteristic clinical signs, the severity of which varies with the degree and location of the obstruction. Distention in the jugular furrow may be evident at the site of obstruction. One may observe other clinical signs related to regurgitation of saliva, water, and food material, such as dehydration, electrolyte or acid-base imbalances, weight loss, and aspiration pneumonia. In extreme cases, pressure necrosis from the impaction or trauma to the esophagus may cause esophageal rupture. If the rupture is in the cervical esophagus, crepitus or cellulitis may be evident along with signs of systemic inflammation. Thoracic auscultation is important to determine whether aspiration pneumonia is present. Intrathoracic esophageal rupture may result in pleuritis and its associated clinical signs.

Passage of a nasogastric tube is an effective way to detect and localize an obstruction but provides little information about the nature of the obstruction or the condition of the esophagus. The most direct method for diagnosis of esophageal obstructions is endoscopic examination. Most cases of esophageal obstruction occur at sites of natural narrowing of the esophageal lumen, such as the cervical esophagus, the thoracic inlet, base of the heart, or the terminal esophagus, thus one may need an endoscope longer than 1 m for complete evaluation. Endoscopic evaluation is useful before relief of an impaction to localize the obstruction and to investigate the nature of the impaction if one suspects a foreign body. Foreign bodies may be retrievable via transendoscopic tethering.[12] One can obtain critical diagnostic and prognostic information following resolution of the impaction. Assessing the affected esophagus for mucosal ulceration, rupture, masses, strictures, diverticula, and signs of functional abnormalities is important (Figure 13.9-1).

Ultrasonography of the cervical region is useful not only to confirm a cervical esophageal impaction but also

TABLE 13.9-1

Causes of Complete or Partial Esophageal Obstruction in the Horse

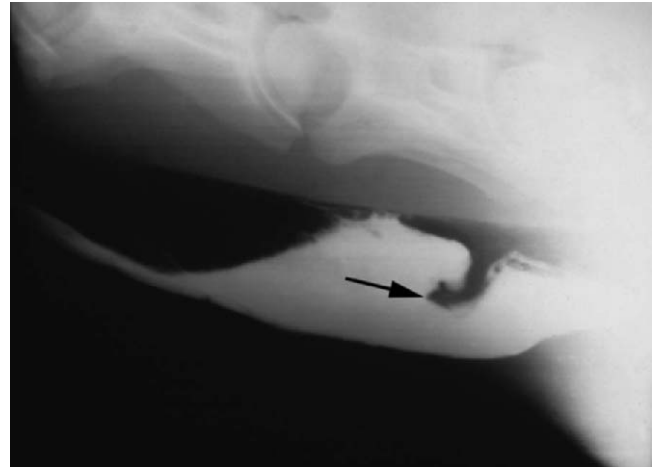| CATEGORY	DIFFERENTIAL
Intraluminal	Foreign body
	Feed material (simple impaction)
Extramural	Neoplasm (squamous cell carcinoma, lymphoma)
	Vascular ring anomaly (persistent right aortic arch)
	Granuloma
Intramural	Esophageal abscess
	Granuloma
	Neoplasm (squamous cell carcinoma, leiomyosarcoma)
	Cysts (intramural cysts, duplication cysts)
	Diverticulum
	Stenosis
Functional disorders	Dehydration
	Exhaustion
	Pharmacologic (acepromazine, detomidine)
	Primary megaesophagus (congenital ectasia)
	Esophagitis
	Autonomic dysautonomia
	Vagal neuropathies
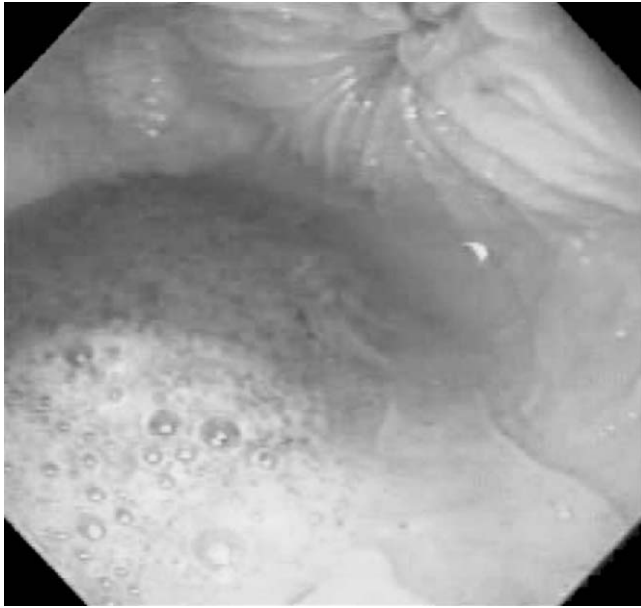
Figure 13.9-1 Endoscopic view of the cervical esophagus in an adult horse 6 months after an episode of choke that caused circumferential ulceration of the esophageal mucosa. The area of luminal narrowing (stricture) is at the upper right of the image, and the proximal dilation forms an outpouching of the esophageal wall. A contrast esophagram revealed that the outpouching was a pulsion diverticulum.

Figure 13.9-2 Contrast esophagram in a horse with circumferential esophageal stricture *(arrow)* and a pulsion diverticulum proximal to the stricture.

to provide critical information about the location and extent of the impaction and esophageal wall thickness and integrity. Ultrasonography may provide information about the cause.[13] Radiographic assessment of the esophagus can confirm the presence of esophageal obstruction in cases in which one cannot view the affected area adequately using endoscopy. One can detect impacted food material in the esophagus by a typical granular pattern and often can observe gas accumulation proximal to the obstruction. Air or barium contrast radiographic studies are most useful for evaluating the esophagus following relief of the impaction if one suspects a stricture. One often can detect esophageal dilation, diverticula, rupture, functional disorder (megaesophagus), or luminal narrowing caused by extraluminal compression more easily using contrast radiographic studies instead of endoscopy (Figure 13.9-2).[14-16] One should take care when interpreting radiographic studies in sedated horses, particularly after passage of a nasogastric tube or other esophageal manipulations that may contribute to esophageal dilation.[17]

TREATMENT

The primary goal of treatment for esophageal impaction is to relieve the obstruction. Parenteral administration of acepromazine (0.05 mg/kg intravenously), xylazine

(0.25 to 0.5 mg/kg intravenously) or detomidine (0.01 to 0.02 mg/kg intravenously), oxytocin (0.11 to 0.22 IU/kg intramuscularly), and/or esophageal instillation of lidocaine (30 to 60 ml of 1% lidocaine) may reduce esophageal spasms caused by pain or may decrease esophageal tone.[17-20] Some clinicians advocate parasympatholytic drugs such as atropine (0.02 mg/kg intravenously) to reduce salivary secretions and lessen the risk of aspiration. However, undesirable effects of atropine including excessive drying of the impaction and inhibition of distal gastrointestinal motility may preclude its use.

Resolution of an impaction may require physical dispersal of the material.[18] One can use a nasogastric tube to displace the impacted material along with external massage if the obstruction is in the cervical region. Often, carefully lavaging the esophagus with water via an uncuffed or a cuffed nasogastric tube while the head is lowered is necessary to aid in breaking up the impaction. Some clinicians advocate a dual tube method whereby a tube is placed through each nasal passage into the esophagus for ingress and egress of the lavage fluid. Because of the risk of aspiration of water and food material, esophageal lavage sometimes is done under general anesthesia with a cuffed nasotracheal tube.

In refractory cases, intravenous administration of isotonic fluid containing 0.9% NaCl and KCl (10 to 20 mEq/L) for 24 hours at a rate of 50 to 100 ml/kg/day along with esophageal relaxants such as oxytocin may promote hydration and softening of the impaction and help prevent or alleviate any electrolyte or acid-base imbalances resulting from salivary losses of chloride, sodium, and potassium.[21] One should note that the effects of oxytocin on esophageal tone occur in the proximal two thirds of the esophagus and may not be effective for

distal obstructions.[19,20] Rarely, esophageal obstruction ultimately may require esophagotomy to relieve the impaction. One must enforce strict restriction of food and water, including access to bedding material, until the obstruction is resolved and the esophagus has regained function.

Systemic effects of dysphagia associated with esophageal impaction include dehydration, hyponatremia, hypochloremia, and metabolic alkalosis from prolonged loss of salivary free water and electrolytes.[21] If the duration of a complete esophageal obstruction is 48 hours or longer, one should correct dehydration and electrolyte and acid-base imbalances. One can restore fluid and electrolyte balance with oral electrolyte solutions if the patient is less than 6% to 7% dehydrated and the esophageal obstruction is resolved. Horses that are greater than 6% to 7% dehydrated or those that have a refractory obstruction or moderate to severe electrolyte imbalances may require intravenous fluid therapy with solutions containing 0.9% NaCl and KCl (10 to 20 mEq/L).

One should perform esophageal endoscopy after relief of the impaction to determine whether any complications of the impaction have developed or if a primary cause of the obstruction is present. Endoscopic examination is critical to determine the postobstruction treatment plan and for follow-up evaluation of esophageal healing. One should reevaluate the horse every 2 to 4 weeks following resolution of the impaction if one notes esophageal dilation or mucosal injury. Additional evaluation via radiography may be warranted to assess motility and transit times.

Dilation proximal to the site of obstruction, mucosal injury from trauma, stricture formation, formation of a diverticulum, megaesophagus, and esophagitis are sequelae to esophageal obstruction that predispose patients to reobstruction. The rate of reobstruction may be as high as 37%. Depending on the duration of the obstruction and the degree of trauma or dilation, the risk of reobstruction is high for 24 to 48 hours or longer, thus one should withhold food for at least 24 to 48 hours after resolution of the obstruction. Sucralfate (20 mg/kg orally every 6 hours) may hasten healing if esophageal ulceration is evident, but the efficacy of sucralfate for this purpose is not established. Some clinicians suggest that administration of a nonsteroidal antiinflammatory drug (NSAID) such as flunixin meglumine (1 mg/kg orally or intravenously every 12 hours) or phenylbutazone (1 to 2 mg/kg orally or intravenously every 12 to 24 hours) for 2 to 4 weeks after resolution of the impaction may reduce the development of strictures. Judicious use of NSAIDs is recommended to prevent NSAID-induced worsening of esophageal mucosal injury. One should avoid orally administered NSAIDs if esophagitis is present. After 48 to 72 hours or when the esophageal mucosa has recovered as assessed by endoscopy, one can feed the horse soft food (moistened pellets and bran mashes). One can return the patient gradually to a high-quality roughage diet over 7 to 21 days, depending on the degree of esophageal damage induced by the impaction and the nature of any underlying disease. The prognosis for survival is good (78%), but some horses may require permanent dietary modification if persistent chronic obstruction is a problem.[3]

Aspiration pneumonia and perforation are potential complications of severe or prolonged esophageal obstructions. If aspiration is suspected, administration of broad-spectrum antibiotics that are effective against gram-positive and gram-negative organisms, including metronidazole (20 mg/kg orally every 8 hours) for anaerobes is advisable. A subsequent section describes treatment of esophageal perforation or rupture.

Esophagitis

Esophagitis refers to a clinical syndrome of esophageal inflammation that may or may not be ulcerative. The major protective mechanisms of the esophageal mucosa include salivary and food material buffers, normal peristaltic motility, and the barrier formed by the gastroesophageal sphincter. Reflux esophagitis is caused by repeated episodes of gastric fluid regurgitation into the distal esophagus and subsequent chemical injury to the mucosa (Figure 13.9-3).[22] Esophageal mucosal ulceration also can occur if the clearance of gastric fluid from the
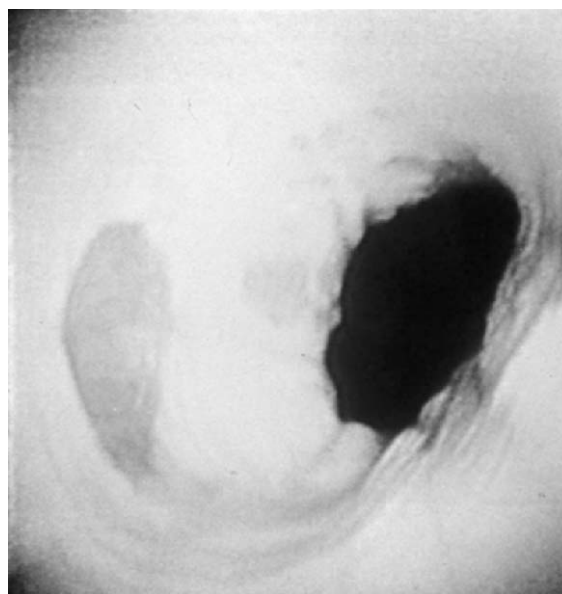
Figure 13.9-3   Endoscopic view of the distal esophagus in a 7-month-old foal with duodenal obstruction. The ulcerative lesions in the distal esophagus and the generalized hyperkeratosis of the esophageal mucosa are notable.
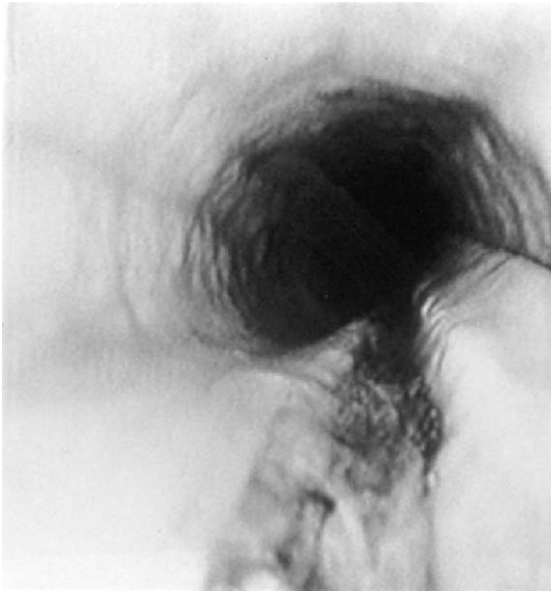
Figure 13.9-4 Endoscopic view of the cervical esophagus of a horse that had repeated passages of a stiff nasogastric tube. The deep, linear ulceration of the esophageal mucosa is notable.

esophagus is delayed, such as in functional disorders of the esophagus. Like ulceration of the squamous portion of the stomach in horses, gastric acid and bile salt chemical injury is a major mechanism of esophageal squamous epithelial ulceration.[22,23] Reflux esophagitis may occur along with gastric ulcer disease, motility disorders, increased gastric volume from gastric outflow obstructions, gastric paresis, intestinal ileus, or impaired lower esophageal sphincter function.[7,22] Other causes of esophagitis in horses include trauma (foreign bodies, food impactions, nasogastric tubes), infection (mural abscesses), or chemical injury (pharmaceuticals, cantharidin) (Figure 13.9-4).[24-27]

CLINICAL SIGNS AND DIAGNOSIS

The clinical signs of esophagitis are nonspecific and similar to esophageal obstruction and gastric ulcer diseases. Gagging or discomfort when swallowing may be evident, and hypersalivation and bruxism are signs of esophageal pain. Esophageal (postpharyngeal) dysphagia may be evident. One may note partial or complete anorexia such that horses with chronic esophagitis may have significant weight loss. Esophageal hypomotility dysfunction caused by the inflammatory process may result in esophageal impaction. Clinical signs of underlying diseases that predispose to esophagitis may predominate or mask the signs of esophagitis. Horses with gastrointestinal motility disorders such as proximal enteritis or gastric outflow obstruction are at a high risk of developing reflux esophagitis because of the presence of gastric acid and bile salts in the fluid reflux. Foals with gastric, pyloric, or

duodenal strictures caused by chronic ulceration commonly have reflux esophagitis.

Diagnosis requires endoscopic examination of the esophagus. One may note diffuse, patchy, linear, or coalescing erosion or ulcerations (see Figures 13.9-3 and 13.9-4). One also may observe significant edema or hyperemia. Determining whether an underlying disease, such as infection, neoplasia, esophageal strictures, or diverticula, is present is important. In addition, one must examine the stomach to determine whether the esophagitis is associated with gastritis, gastric obstruction, or gastric ulcer disease. Contrast radiography may be helpful to detect esophageal ulceration and is useful to assess esophageal motility and transit time.[14]

TREATMENT

The principles of therapy for reflux esophagitis include control of gastric acidity, mucosal protection, and correction of any underlying disorder contributing to gastroesophageal reflux. Reduction of gastric acid production with H_2 histamine receptor blockers such as ranitidine or proton pump antagonists such as omeprazole is critical for resolution of the esophagitis. Some clinicians advocate using sucralfate to promote healing of ulcerated esophageal mucosa. However, the ability of sucralfate to bind ulcerated esophageal mucosa is not proven, nor is the efficacy of sucralfate for hastening esophageal ulcer healing.

Horses with reflux esophagitis following delayed gastric outflow caused by gastroduodenal ulcer disease, gastric paresis, or proximal enteritis may benefit from prokinetic drugs that act on the proximal gastrointestinal tract. Metoclopramide (0.02 to 0.1 mg/kg subcutaneously every 4 to 12 hours) reduces gastroesophageal reflux by increasing lower esophageal sphincter tone, gastric emptying, and gastroduodenal coordination. One should exercise caution when giving metoclopramide to horses because they are prone to extrapyramidal neurologic side effects of the drug. Cholinergic drugs such as bethanechol (0.025 to 0.035 mg/kg subcutaneously every 4 to 24 hours or 0.035 to 0.045 mg/kg orally every 6 to 8 hours) may improve gastric emptying and are effective for treating reflux esophagitis. For esophagitis from trauma or pressure injury after esophageal impaction, judicious use of NSAIDs may be warranted to reduce esophageal inflammation and pain.

Dietary modification may be necessary for patients with esophagitis, depending on the degree of ulceration or if motility is impaired. One should feed horses with mild esophagitis frequent small meals of moistened pellets and fresh grass. Severe esophagitis may necessitate withholding food and complete esophageal rest for several days. Although the prognosis for esophagitis is good in the absence of underlying disease, the risk of

stricture formation is high if severe circumferential or coalescing ulcerations are present. Esophagitis from severe trauma or infection may be prone to stricture formation.

Motility Disorders

Motility dysfunction of the equine esophagus is caused most commonly by hypomotility resulting in esophageal dilation (ectasia) or megaesophagus. Although mega-esophagus in horses most commonly is acquired, reports indicate idiopathic megaesophagus in young horses may be congenital.[28-31] Acquired megaesophagus in horses may be a consequence of chronic or recurrent esophageal obstruction.[3,7] Esophageal impactions of a short duration cause a proximal dilation of the esophagus that is generally reversible.[14] However, if the duration of the obstruction is long enough, the motility of the esophagus proximal to the site of obstruction may be impaired permanently. Other causes of acquired megaesophagus include extraesophageal obstruction by tumors or abscesses, pleuropneumonia, and vascular ring anomalies.[3,8]

Acquired megaesophagus also may result from neurologic, neuromuscular, and muscular disorders. Neurologic diseases that cause vagal neuropathy—such as equine protozoal myeloencephalitis, equine herpesvirus myeloencephalitis, and idiopathic vagal neuropathy—have been associated with megaesophagus in horses. Pleuropneumonia may be associated with a vagal neuropathy resulting in megaesophagus. Megaesophagus is an early sign of equine dysautonomia[32] and may be observable in patients with botulism. Myasthenia gravis is a well-known cause of megaesophagus in nonequine species but has not been reported in horses. Also in other species, electrolyte disorders, cachexia, primary myopathies, myositis, and Addison's disease may affect esophageal motility but have not been associated with megaesophagus in horses. One can induce iatrogenic megaesophagus by the α_2-adrenergic agonist detomidine, but this is transient and reversible.[17,33] Nonetheless, the use of this drug may complicate clinical evaluation of esophageal motility.

Esophageal inflammation, particularly reflux esophagitis, may affect motility and cause megaesophagus. However, because esophageal hypomotility affects the tone and function of the lower esophageal sphincter, reflux esophagitis also may be a complication of a primary functional disorder. Thus assessing esophageal motility in horses with esophagitis that is not responding appropriately to treatment is important.

CLINICAL SIGNS AND DIAGNOSIS
Along with a complete physical examination one should include a careful neurologic examination to help rule out primary neurologic causes of megaesophagus. Because esophageal hypomotility is a functional obstruction, the clinical signs of esophageal hypomotility or megaesophagus are similar to esophageal obstruction. Unlike mechanical obstruction the onset of clinical signs is insidious rather than acute. The clinical signs include those associated with esophageal dysphagia.[7,8,28-31] The cervical esophagus may be dilated enough to be evident externally. Weight loss is a common sign. Signs attributable to an underlying disease may be evident.

Diagnosis of esophageal hypomotility requires transit studies. One can measure the transit time of a bolus from the cervical esophagus to the stomach by fluoroscopy or contrast radiography.[14,32] Other signs of esophageal hypomotility and megaesophagus include pooling of contrast material and an absence of peristaltic constrictions.[7,14,28,32] Endoscopy may reveal a dilated esophagus and an absence of peristaltic waves.[7,28] One may observe evidence of underlying disease causing obstruction or esophageal dilation.[3,7] One should evaluate the esophagus for evidence of esophagitis that is causing esophageal motility dysfunction or is a result of impaired esophageal clearance of gastric fluid. Esophageal manometry may be useful to document abnormal post-deglutition contraction pressures, contraction time, and propagation times but is not often available for routine clinical application.[28,34] One should perform other diagnostic tests such as a complete blood count and chemistry to help determine a possible underlying cause. Cerebral spinal fluid analysis may be indicated to rule out neurologic disorders. Specialized testing such as electromyography to detect neuromuscular disorders may also be indicated.

TREATMENT
Treatment of esophageal hypomotility or megaesophagus should aim at treating the underlying cause. Dietary modification should aim at improving esophageal transit of food. One should feed the horse slurries of pellets, and feeding from an elevated position to promote transit may be beneficial. Metoclopramide or bethanechol may benefit patients with reflux esophagitis associated with megaesophagus by increasing lower esophageal tone, gastric emptying, and reducing gastroesophageal reflux. The prognosis depends on the underlying cause and the degree of dilation. Although many cases of megaesophagus associated with reflux esophagitis respond well to treatment, many other forms of megaesophagus including congenital megaesophagus have a poor prognosis.

Esophageal Stricture

Strictures most commonly are caused by pressure necrosis from esophageal impactions that induce circumferential erosion or ulceration of the esophageal mucosa,

although esophageal injury caused by oral administration of corrosive medicinal agents and trauma to the neck may also result in stricture formation.[35] Congenital strictures also have been reported.[36] Strictures caused by mucosal and submucosal trauma are termed *esophageal webs* or *rings*. Strictures may also originate in the muscular layers and adventitia of the esophagus (mural strictures) or in all of the layers of the esophagus (annular stenosis).[36,37] Horses with these lesions have a presentation similar to those with simple obstructions, because strictures result in partial obstruction and impaction of food material in the lumen. One can detect esophageal webs or rings with endoscopy (see Figure 13.9-1), whereas identification of mural strictures or annular stenosis may require a double-contrast esophogram (see Figure 13.9-2).

In a retrospective study of horses with esophageal stricture following simple obstruction, maximal reduction in esophageal lumen diameter occurred within 30 days of the esophageal obstruction. Although surgery has been used to relieve such strictures, initial medical management is warranted because strictures may resolve with conservative therapy, and the esophagus continues to remodel for up to 60 days following ulceration. In one report, seven horses with esophageal obstruction-induced stricture were treated conservatively by feeding a slurry diet and administering antiinflammatory and antimicrobial medications, and five of seven were clinically normal within 60 days.[35] One of the five successfully treated horses had a 10-cm area of circumferential ulceration, suggesting that the potential exists for extensive mucosal injury to resolve without permanent stricture formation.

If resolution of strictures within 60 days is insufficient, one should investigate other methods to increase esophageal diameter. Bougienage has been used successfully in small animal patients and human beings. The technique involves passage of a tubular dilatable instrument down the esophagus and stretching of the stricture. One may perform the technique by passing a nasogastric tube with an inflatable cuff. However, one has to perform the procedure frequently to have any success, and horses do not tolerate it well.[36] Alternatively, a number of surgical techniques have been used to resolve strictures, including resection and anastomosis,[38,39] temporary esophagostomy with fenestration of the stricture,[37] esophagomyotomy for strictures of the muscularis and adventitia,[40,41] or patch grafting with local musculature.[42] However, such surgeries are fraught with complications, largely because of the propensity of the traumatized esophagus to restricture.[3,35] The esophagus lacks a serosal layer and does not rapidly form a fibrin seal as does the remainder of the intestinal tract, so anastomoses tend to leak.[38] In addition, tension on the esophagus during swallowing and movement of the neck impairs healing of anastomoses.[37,39] In spite of these difficulties, the

long-term prognosis for horses with chronic esophageal strictures treated surgically is better than for those treated nonsurgically.[3]

Esophageal Diverticula

Two types of diverticula are traction (true) diverticula and pulsion (false) diverticula. Traction diverticula result from wounding and subsequent contraction of peri-esophageal tissues, with resultant tenting of the wall of the esophagus. Pulsion diverticula arise from protrusion of esophageal mucosa through defects in the muscular wall of the esophagus and usually result from trauma or acute changes in intraluminal pressure.[36] Traction diverticula appear as a dilation with a broad neck on contrast esophagography, whereas pulsion diverticula typically have a flask shape with a small neck on an esophagram (see Figure 13.9-2).[10,43] Although traction diverticula are usually asymptomatic and of little clinical significance, pulsion diverticula may fill with feed material, ultimately leading to esophageal obstruction.[43-45] A movable mass in the midcervical region may be noticeable before onset of complete obstruction.[36] Pulsion diverticula may be corrected surgically by inverting or resecting prolapsed mucosa and closing the defect in the wall of the esophagus.[10,43,45] Inversion of excessive mucosa may reduce the diameter of the esophageal lumen and predispose horses to esophageal obstruction and therefore should be reserved for small diverticula.[10]

Congenital Disorders

Congenital disorders of the esophagus are rare. Reported congenital abnormalities include congenital stenosis,[46] persistent right aortic arch,[8] esophageal duplication cysts,[47-49] intramural inclusion cysts,[9,50] and idiopathic megaesophagus.[28,30,31] In the one report of congenital stenosis, double-contrast radiography revealed concentric narrowing of the thoracic esophagus in the absence of any vascular abnormalities at the base of the heart. Successful treatment included having the foal stand with the forelimbs elevated off the ground following each feeding.[46]

Persistent right aortic arch is a congenital anomaly in which the right fourth aortic arch becomes the definitive aorta instead of the left aortic arch, which results in constriction of the esophagus by the ligamentum arteriosum as it extends between the anomalous right aorta and the left pulmonary artery. Clinical signs may include those associated with esophageal (postpharyngeal) dysphagia, drooling, and distention of the cervical esophagus resulting from partial obstruction of the thoracic esophagus.[8,51] Endoscopic examination typically reveals dilation of the esophagus cranial to the obstruction

with evidence of diffuse esophagitis. Successful surgical treatment of persistent right aortic arch has been reported in one foal.[51]

Esophageal duplication cysts and intramural inclusion cysts cause typical signs of esophageal obstruction, including salivation, esophageal dysphagia, and swelling of the cervical esophagus as the cysts enlarge.[47,49,50] Such signs can make them difficult to differentiate from other forms of esophageal obstruction (choke). Endoscopic examination may reveal compression of the esophageal lumen and communication with the esophageal lumen if it exists. Ultrasonographic examination may be the most useful method of antemortem diagnosis if the cyst is in the cervical esophagus. Examination of an aspirate of the mass may aid in the diagnosis by revealing the presence of keratinized squamous cells.[47,50] Surgical treatments have included complete surgical resection and surgical marsupialization.[47,49,50] The latter appears to be more successful and results in fewer complications.[49,50] Complications of surgical resection have included laryngeal hemiplegia following surgical trauma to the recurrent laryngeal nerve in the region of the esophagus and esophageal fistula formation.[50]

ESOPHAGEAL PERFORATION

Perforation typically occurs in the cervical region in response to external trauma, necrosis of the esophageal wall caused by a food impaction, or rupture of an esophageal lesion such as an impacted diverticulum. The esophagus is particularly vulnerable to external trauma in the distal third of the neck because only a thin layer of muscle covers it at this point.[52] Iatrogenic perforation may occur in response to excessive force with a stomach tube against an obstruction or a compromised region of the esophagus.[24] Esophageal perforations may be open or closed and tend to cause extensive cellulitis and necrosis of tissues surrounding the wound because of drainage of saliva and feed material within fascial planes. Systemic inflammation associated with endotoxemia from septic cellulitis may occur. Closed perforations of the esophagus are particularly troublesome because food material, water, saliva, and air may migrate to the mediastinum and pleural space via fascial planes.[24,52] Because of the leakage of air into the tissues surrounding the rupture, extensive subcutaneous and fascial emphysema frequently develops and is usually evident clinically and on cervical radiographs. Pneumomediastinum and pneumothorax are potentially fatal complications of esophageal ruptures.

Treatment should include converting closed perforations to open perforations if possible,[53] extensive debridement and lavage of affected tissues, broad-spectrum antibiotics, tetanus prophylaxis, and esophageal rest. The clinician may achieve the latter by placing a feeding tube into the esophagus via the wound.

Alternatively, one may place a nasogastric tube using a small tube (12-F diameter).[24] For open perforations, once the wound has granulated and contracted to a small size, one may attempt peroral feeding.[52] Extensive loss of saliva via esophageal wounds may lead to hyponatremia and hypochloremia. In addition, transient metabolic acidosis occurs because of salivary bicarbonate loss, followed by progressive metabolic alkalosis.[21] Although reports of esophageal wounds healing well by second intention exist, healing takes a prolonged time.[54] In addition, some perforations never completely heal and form permanent esophagocutaneous fistulae that may require surgical correction. The development of esophageal strictures is not common because wounds are usually linear and not circumferential. However, traction diverticula may develop. Other complications of esophageal wounds include Horner's syndrome and left laryngeal hemiplegia.[52]

In a retrospective study on esophageal disorders, only 2 of 11 horses with esophageal perforations survived long-term[3]; in a report of esophageal trauma following nasogastric intubation, 4 of 5 horses were euthanized.[24] The prognosis is therefore poor in horses with esophageal perforations, largely because of the extent of cellulitis, tissue necrosis, shock, and local wound complications.

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13.10—Diseases of the Stomach

L. Chris Sanchez

Specialized endoscopic equipment allowing visual inspection of the entire adult equine stomach has become increasingly available to veterinarians in academia and private practice. Thus gastric disease in horses recently

has gained increasing awareness among veterinarians, owners, and trainers.

Gastroduodenal Ulceration

Peptic ulcer disease is defined as erosions or ulcers of any portion of the gastrointestinal tract normally exposed to acid.[1] Mucosal damage can include inflammation, erosion (disruption of the superficial mucosa), or ulceration (penetration of the submucosa). In severe cases, full-thickness ulceration can occur, resulting in perforation. The proximal (orad) portion of the equine stomach is lined by stratified squamous mucosa similar to the esophageal lining. The distal (aborad) portion of the stomach is lined with glandular mucosa, and the distinct junction between the two regions is deemed the *margo plicatus*. Ulceration can occur in either or both gastric regions, although different clinical syndromes and pathophysiologic mechanisms apply. As a result, the broad term *equine gastric ulcer syndrome* (EGUS) has been used to encompass the wide array of associated clinical syndromes. EGUS develops in horses of all ages and continues to be of major clinical and economical importance.[2]

PREVALENCE

The prevalence of gastric ulceration has been reported for a variety of breeds and types of horses; however, most current data involve Thoroughbreds in race training. The prevalence of squamous ulceration in horses in race training varies from 70% to 94%[3-8] and can be as high as 100% when limited to animals actively racing.[4] In a survey of 50 active show horses, 58% had gastric ulceration, with only 1 horse having ulceration of the glandular fundus.[9] In one large retrospective study (3715 adult horses from 1924 to 1996) evaluating incidence of gastric ulceration identified at necropsy, an overall prevalence of 10.3% was found. The highest prevalence was found in Thoroughbreds (including Arabians) and Standardbred trotters, and cold-blooded horses were affected significantly less. Lesions were located most commonly in the squamous mucosa along the margo plicatus, followed by the glandular body, proximal squamous mucosa, and antrum.[10]

Many studies investigating prevalence of gastric ulceration do not differentiate between squamous and glandular lesions or evaluate only squamous disease. In a recent study in which the gastric antrum and pylorus were evaluated in 162 horses in a hospital setting, 58% had antral or pyloric erosions or ulcerations, 58% had squamous mucosal lesions, and 8% had lesions involving the glandular body.[11] A correlation between the presence or severity of squamous disease and antral/pyloric disease was not identified.

The reported prevalence of gastric ulceration in foals varies from 25% to 57%.[12-14]

PATHOPHYSIOLOGY

An imbalance between inciting and protective factors in the mucosal environment can result in ulcer formation.[15,16] The major intrinsic factors promoting ulcer formation include hydrochloric acid, bile acids, and pepsin, with hydrochloric acid being the predominant factor. Various intrinsic factors protect against ulcer formation such as the mucus-bicarbonate layer, maintenance of adequate mucosal blood flow, mucosal prostaglandin E_2 and epidermal growth factor production, and gastro-duodenal motility. In human beings, extrinsic ulcerogenic factors include nonsteroidal antiinflammatory drugs, *Helicobacter pylori*, stress, changes in diet, or gastrointestinal disorders, especially those resulting in delayed gastric emptying.[1] In human neonates, physiologic stress associated with a major primary illness seems to be associated strongly with gastric ulcers.[17] Many of the other factors mentioned previously are believed to be important in horses, but clear evidence of an infectious agent has not yet been identified in horses or foals with EGUS.[18,19] Recently, the possibility of *Helicobacter* infection in horses has reemerged with the identification of polymerase chain reaction products from Urel, a proton-gated urea channel unique to gastric-dwelling *Helicobacter* species, in the squamous epithelium of three horses, two of which had squamous erosions.[20]

The specific factors involved in injury and the protective mechanisms vary between regions of the proximal gastrointestinal tract. The pathophysiology of squamous mucosal ulceration in the horse appears similar to that in gastroesophageal reflux disease in human beings and ulceration of the nonglandular mucosa in pigs. Excess acid exposure is the predominant mechanism responsible for squamous mucosal ulceration, although many details remain unclear.[21] Hydrochloric acid is secreted by parietal cells in the gastric glands via a hydrogen-potassium adenosine triphosphatase (H^+,K^+-ATPase) pump on the luminal side. Horses secrete acid continuously, and measured pH of equine gastric contents varies from less than 2 to greater than 6 depending on the dietary state of the horse (fed or fasted).[22,23] A protocol of repeated 24-hour periods of fasting and feeding has been shown to induce squamous erosion and ulceration.[24] Because this protocol results in periods of prolonged gastric acidity (pH <2.0) and because concurrent administration of the histamine$_2$ (H_2) receptor antagonist ranitidine reduces lesion severity, the protocol supports the role of acid exposure in the pathogenesis of squamous ulcer disease.

Several peptides can stimulate or inhibit parietal cell secretion of acid. The predominant stimuli for hydrochloric acid secretion are gastrin, histamine, and acetylcholine via the vagus nerve.[1] G cells release gastrin within the antral mucosa, whereas mast cells and enterochromaffin-like cells release histamine in the gastric

gland. Histamine binds to type 2 receptors on the parietal cell membrane, causing an increase in cyclic adenosine monophosphate and resulting in phosphorylation of enzymes that activate the proton pump. Gastrin and acetylcholine can act via calcium-mediated intracellular pathways and also stimulate histamine release directly.[25] Isolated equine parietal cells respond maximally to histamine stimulation and only minimally to carbachol and pentagastrin.[26] Gastrin release is controlled primarily by gastrin-releasing peptide, which is stimulated by gastric distention and increased luminal pH, but the interaction between gastrin and histamine has not been elucidated fully in the horse.

Somatostatin, released by fundic and antral D cells, is the primary inhibitor of gastric acid secretion by parietal cells. The inhibitory effect of somatostatin is primarily paracrine, but plasma levels of somatostatin negatively correlate with gastric luminal acidity.[27] Epidermal growth factor, a peptide produced in saliva, also inhibits gastric acid secretion.[28]

Foals can produce significant amounts of gastric acid by the second day of life, with consistent periods of acidity (pH <2.0) in clinically normal animals.[29,30] In one study, foals tended to have a high gastric pH at day 1 of age,[30] but in a study of critically ill foals, some foals demonstrated periods of gastric acidity on the first day of life.[31] Suckling was associated with an immediate rise in gastric pH, whereas periods of rest in which foals did not suck for more than 20 minutes were associated with prolonged periods of acidity.[29] Whereas premature human infants are capable of gastric acid production at 28 weeks of gestation,[32] only 1 of 7 premature foals demonstrated an acidic pH recording in a study of gastric pH profiles in critically ill foals.[31] However, multiple factors likely were involved in critically ill foals of this study, and the true ontogeny of gastric acid production in foals is currently unknown.

Equine squamous mucosa is thin at birth but becomes hyperplastic and parakeratotic within days.[33] The parallel between decreasing pH and proliferation of squamous epithelium correlates with that observed in other species.[34] The combination of a thin gastric epithelium with a high acid output may leave neonatal foals susceptible to ulcer formation at a young age. In addition, one must remember the difference in normal appearance of the squamous mucosa when interpreting gastric endoscopy in a neonatal population.

In esophageal squamous mucosa, intercellular tight junctions and bicarbonate secretion are the major factors involved in protection against acid injury in other species, although squamous bicarbonate secretion had not been documented in the horse.[35-37] The principal barrier is a glycoconjugate substance secreted by cells in the *stratum spinosum,* with a contribution from the tight junctions in the *stratum corneum*.[37] This barrier function is considered weak at best, and thus a functioning lower esophageal sphincter, normal salivary flow, and salivary mucins contribute to the prevention of acid injury in human gastroesophageal reflux disease. In horses a mechanical barrier like the lower esophageal sphincter is not available to protect the gastric squamous mucosa from acid exposure. The normal gastric fill line rests just below the cardia, so only the squamous mucosa along the lesser curvature adjacent to the margo plicatus should receive exposure to acidic gastric contents regularly. Not surprisingly, this correlates with the most common location of squamous mucosal ulceration.

Bile salts and pepsin have been implicated as contributing factors to ulcer disease in many species. In rabbit esophageal mucosa, bile salt absorption occurs and is correlated directly with mucosal barrier disruption. The unconjugated bile salts cholate and deoxycholate have a pK_a (negative logarithm of the ionization constant of an acid) of 5 and 5.3, respectively, and therefore cannot remain in solution and cause mucosal damage in the presence of acid. Alternatively, the conjugated bile salt taurocholate (pK_a 1.9) can cause mucosal injury in the ionized salt form at pH 7 or the un-ionized acid form at pH 1 to 2.[38] In the pig, bile salts or acid alone cause squamous mucosal damage, whereas a combination of the two result in extensive damage in vitro.[39] In the horse a similar synergistically damaging effect was found with the addition of bile salts and acid (pH 2.5) to stratified squamous mucosa in vitro in one study.[40] In addition, the investigators were able to document levels of bile salts and acid sufficient to cause mucosal damage in gastric contents within 14 hours of feed deprivation. This is not surprising, given that duodenogastric reflux occurs normally in the horse.[41] In a separate in vitro study of equine squamous mucosa, prolonged exposure to acid alone (pH 1.5) had a damaging effect, and synergism with exposure to a combination of acid and pepsin or taurocholate was not found.[42] The lack of synergism likely is caused by the lower pH used in this study and stresses the importance of acid exposure in squamous ulcer disease.

Pepsinogens are secreted primarily by chief cells, although secretion by neck cells, cardiac glands, and antral pyloric glands also occurs.[43] In an acidic environment (pH <3.0), pepsinogen is converted to the active pepsin. Although the proteolytic activity of pepsin normally is directed toward dietary protein, it also can act on the gastric mucosa.[44] Thus acid remains the major contributing factor to squamous mucosal damage, although other factors such as pepsin and bile salts may play an important role as well in the initiation or perpetuation of disease.

Several mechanisms help protect the glandular mucosa from acid injury. The mucus-bicarbonate layer

serves to titrate H^+ ion from the gastric lumen to CO_2 and H_2O. Cellular restitution and prostaglandins of the E series, which enhance mucosal blood flow and secretion of mucus and bicarbonate in the glandular mucosa have not been documented in squamous epithelium.[21,36] Of these mechanisms, mucosal blood flow is likely the most important contributor to overall gastric mucosal health. Nitric oxide is a key regulator of mucosal blood flow and prostaglandin synthesis and thus may play a role in mucosal protection.[45]

Dietary factors also have been implicated in ulcer disease. Horses in race training have a high incidence of gastric ulceration and frequently are fed high-concentrate, low-roughage diets. In one study, higher volatile fatty acid (acetic, propionic, and isovaleric acid) concentrations, higher gastric juice pH, and lower number and severity of nonglandular ulceration were documented after feeding an alfalfa hay-grain diet compared with a bromegrass hay diet.[46] However, many factors differed between the diets, such as digestible energy, bulk, crude protein, and mineral content (especially calcium). Thus dietary factors represent an important area of further investigation in the pathophysiology of EGUS, particularly squamous ulceration.

The pathophysiologic correlation between exercise and squamous ulcer disease has not yet been defined despite the high prevalence of ulceration in performance horses. Preliminary work suggests that gastric compression occurs during treadmill exercise, presumably because of an increase in intraabdominal pressure.[47] Such contracture could result in increased acid exposure to the squamous mucosa by raising the fill line of gastric contents. Further studies in this laboratory have provided support for this theory by demonstrating a high pH in the proximal stomach, immediately distal to the lower esophageal sphincter, during resting conditions that decreases during treadmill exercise (M. Lorenzo-Figueras and A.M. Merritt, personal communication, 2002).

Risk factors associated with gastric ulceration include gender and age, and the reported prevalence of gastric ulcers has increased over time. In one study, ulcers were found more commonly in stallions, and the prevalence of gastric ulceration decreased with age, independent of gender, although this trend was only significant in the population of Standardbred trotters.[10] Interestingly, the frequency of gastric ulceration increased from less than 6% before 1945 to approximately 18% after 1975. In a study of Thoroughbred horses in race training, an increase in squamous ulcer severity was noted in horses 3 years old or older and in those horses that had raced.[4] In the same study, severity of glandular lesions did not change between examinations, and age (>3 years) was the only factor associated with glandular lesion severity.

Several studies have failed to document a correlation between nonsteroidal antiinflammatory drug (NSAID) administration and naturally occurring ulcer disease.[3,4,6,7,10] However, NSAID administration is a well-known cause of gastric ulceration under experimental conditions.[48-52] NSAID-related ulceration typically is described as predominantly glandular, although nonglandular ulceration also can occur by a mechanism that has not yet been characterized fully. NSAIDS cause a decrease in prostaglandin E_2 synthesis because of inhibition of the cyclooxygenase pathway. Therefore a resultant decrease in glandular mucosal protection, most notably via decreased mucosal blood flow and mucus production, is the most likely mechanism of action. In one study, however, phenylbutazone administration resulted in ulceration of the glandular mucosa at the pyloric antrum but did not alter mucosal prostaglandin E_2 concentration significantly.[52]

CLINICAL SYNDROME: NEONATAL FOALS

Clinical signs typically associated with gastric ulceration in foals include poor appetite, diarrhea, and colic. Many foals probably never exhibit clinical signs, and some do not exhibit clinical signs until ulceration is severe or fatal perforation has occurred. Glandular ulceration typically is considered the most clinically significant type of disease in this population.

The physiologic stress of a concurrent illness has been associated with gastric ulceration in foals. Retrospectively, 14 (23%) of 61 foals up to 85 days of age with a clinical disorder were found to have lesions in the gastric glandular mucosa,[13] and prospectively 8 (40%) of 20 foals up to 30 days of age with a clinical disorder had glandular ulceration.[53] By contrast, only 4% to 9% of clinically normal foals examined in endoscopic surveys had lesions observed in the gastric glandular mucosa.[14,54]

Critically ill neonatal foals can have a greatly different pH profile compared with that in clinically normal foals, potentially because of alterations in gastric motility and acid secretion.[31] Gastric ulceration was not identified in any animals at necropsy in that study; however, ulceration has been documented in a similar population.[12] Thus factors other than acid exposure, most notably mucosal blood flow, may play an important role in the stress-related ulceration in neonates. Subjectively, gastric ulceration and rupture in the hospitalized neonatal population occurs less commonly now than in previous reports. Advances in overall neonatal care, especially supportive care, likely have contributed to this decline.

CLINICAL SYNDROME: SUCKLINGS/WEANLINGS

In suckling foals less than 50 days old, lesions typically originate in the squamous mucosa adjacent to the margo plicatus along the greater curvature. Such lesions can occur in foals as young as 2 days of age and have been

observed in 50% of foals less than 50 days old. Histologic examination of these lesions has revealed disruption of the epithelial layers of the mucosa and a neutrophilic infiltration. Another phenomenon that occurs in young foals is the shedding, or desquamation, of squamous epithelium, which appears as flakes or sheets of epithelium. Desquamation occurs without ulceration in up to 80% of foals less than 35 days of age, and this process typically is not associated with clinical signs.[13,14,54]

In older foals, lesions become more prevalent in the squamous mucosa, particularly along the lesser curvature.[53] Lesions also are found in the squamous mucosa of the fundus and adjacent to the margo plicatus. These lesions can be severe and often are associated with clinical signs such as diarrhea, poor appetite, and poor growth and body condition. Diarrhea is the most frequent sign in symptomatic foals with squamous mucosal lesions and is associated with more diffuse erosion or ulceration of the squamous mucosa than that which occurs in asymptomatic foals. In some foals, poor growth, rough hair coat, a potbelly appearance, or all of those occur along with moderate to severe squamous mucosal ulceration. In horses with severe or diffuse squamous ulceration, bruxism or colic may occur.

Gastroduodenal ulcer disease occurs almost exclusively in suckling and early weanling foals. Clinical signs of duodenal ulceration are similar to those described for gastric ulceration (bruxism, colic, salivation, diarrhea), but the consequences are often more severe. Lesions occur primarily in the proximal duodenum and range from diffuse inflammation to severe ulceration. Foals with duodenal ulceration often have delayed gastric emptying and may have gastroesophageal reflux. Complications can include gastric or duodenal rupture, duodenal stricture, and ascending cholangitis. Severe squamous and esophageal ulceration and aspiration pneumonia can occur following gastroesophageal reflux.[15,55-58]

The gastroduodenal ulcer disease syndrome can occur in outbreaks and most commonly is identified in intensive breeding operations. The cause of duodenal lesions in foals is not known. One theory is that the problem begins with diffuse duodenal inflammation that can coalesce down to a focal area of ulceration (G.D. Lester and A.M. Merritt, personal communication, 2002). A temporal relationship between gastroduodenal ulcer disease and rotaviral diarrhea has been suggested, but an infectious cause remains unproven. Although lesion location and severity associated with rotaviral infection varies among species, duodenal ulceration has not been reported.[59]

CLINICAL SYNDROME: YEARLINGS AND ADULT HORSES

Clinical signs attributable to EGUS in older horses vary and classically include anorexia and chronic or intermittent colic of varying severity.[60] Many horses with endoscopic

evidence of disease may appear to be clinically normal or have vague signs that include decreased consumption of concentrates, postprandial episodes of colic, poor performance or failure to train up to expectations, poor-quality hair coat, and decreased condition or failure to thrive. Diarrhea typically is not associated with gastric ulceration in adult horses, although ulceration can occur concurrently with other causes of diarrhea. Horses actively racing are more likely to have squamous ulceration than those solely in training.[4]

Lesions occur predominantly in the squamous mucosa, particularly adjacent to the margo plicatus (Figure 13.10-1). In more severe cases, lesions can extend dorsally into the squamous fundus. Clinically relevant lesions typically affect a greater portion of the squamous mucosa and can be deep enough to cause bleeding. However, bleeding from ulcers in the gastric squamous mucosa typically is not associated with anemia or hypoproteinemia.

According to a recent study, the incidence of glandular lesions, particularly within the pyloric region, may be higher than previously reported,[11] which emphasizes the importance of a thorough endoscopic examination and proper documentation of lesion location when reporting or discussing EGUS, especially the differentiation between squamous and glandular disease.
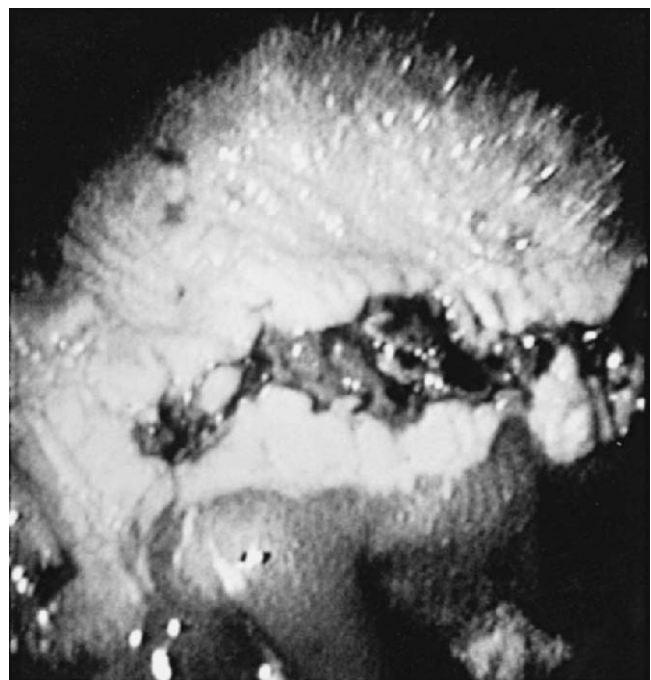
Figure 13.10-1 Endoscopic view of the right side of the stomach of a horse with recurrent colic and poor appetite. The large area of ulceration on the squamous mucosa adjacent to the margo plicatus is notable.

	TABLE 13.10-1
	Equine Gastric Ulcer Syndrome Lesion Scoring System

LESION GRADE	DESCRIPTION
0	Intact epithelium with no appearance of hyperemia or hyperkeratosis
1	Intact mucosa with areas of reddening or hyperkeratosis (squamous)
2	Small single or multifocal lesions
3	Large single or multifocal lesions or extensive superficial lesions
4	Extensive lesions with areas of deep ulceration

From Andrews FM, Bernard WV, Byars TD et al: Recommendations for the diagnosis and treatment of equine gastric ulcer syndrome (EGUS), *Equine Vet Educ* 1:122-134, 1999.

DIAGNOSIS

Although one may suspect a diagnosis of EGUS based on clinical signs and response to treatment, the only current method of confirmation is via gastroendoscopy, which one can perform easily in the standing horse or foal with mild sedation. In adult horses a 3-m endoscope allows for visual inspection of the entire stomach, pylorus, and proximal duodenum. Shorter scopes permit examination of the gastric body and fundus, but not the pyloric antrum in most cases. One should use an endoscope with a maximum external diameter of 9 mm for neonatal foals. Numerous scoring systems for lesion severity have been described, but a recent consensus has been published by the Equine Gastric Ulcer Council (Table 13.10-1).[2]

Duodenal ulceration can be difficult to confirm. Duodenoscopy is the most specific means of diagnosis, although the procedure is more difficult than gastroscopy. Additionally, an endoscope at least 200 cm in length is needed for foals up to 5 to 7 months old, and a longer endoscope usually is required for older animals. Diffuse reddening or inflammation may be the only recognizable lesion in cases of early duodenal disease.

Excessive enterogastric reflux of bile through the pylorus suggests duodenal dysfunction. However, the pylorus frequently appears open, and some degree of enterogastric reflux is common under normal conditions. Ulceration at the pylorus or pyloric antrum also suggests the presence of a duodenal lesion. If one can perform gastroendoscopy, but not duodenoscopy, the severity of lesions, particularly in the glandular mucosa and in the squamous mucosa of the lesser curvature dorsal to the pyloric antrum, usually will be severe when duodenal ulcers are present.

TREATMENT

Multiple pharmacologic treatments have been suggested for treating EGUS. Because acid has been implicated as the most important pathophysiologic component of squamous ulcer disease, most antiulcer therapy centers on suppression or neutralization of gastric acid. Severity and location of gastric lesions and severity and duration of clinical signs, as well as medication cost, can play a role in the therapeutic management of EGUS (Table 13.10-2).

If gastroendoscopy is unavailable, some guidelines to therapy can be used, but the efficacy of the treatment is based on clinical signs, which are often vague or nonspecific. Signs of colic or diarrhea that result from gastric ulcers often resolve within 48 hours. One can note improvements in appetite, bodily condition, and attitude within 1 to 3 weeks. If one does not observe improvement in clinical signs, treatment has not been effective or gastric ulceration was not the primary problem.

The principal therapeutic options for ulcer treatment include H_2 antagonists (cimetidine, ranitidine, famotidine, nizatidine), proton pump blockers (omeprazole, pantoprazole, rabeprazole, esomeprazole), the mucosal adherent sucralfate, and antacids.

The H_2 antagonists suppress hydrochloric acid secretion through competitive inhibition of the parietal cell histamine receptor that can be overcome partially with exogenous pentagastrin.[61] Use of H_2 antagonists has been successful in raising gastric pH and resolving gastric lesions in foals and adult horses.[29,55,62]

Clinical and experimental evidence has demonstrated greater individual variability with lower dosages of H_2 antagonists.[63] Thus dosage recommendations are based

	TABLE 13.10-2		
	Therapeutic Options for Treating Equine Gastric Ulcer Syndrome		
DRUG	DOSE (mg/kg)	DOSING INTERVAL (HOURS)	ROUTE OF ADMINISTRATION
Ranitidine	6.6	8	Orally
Ranitidine	1.5-2	6-8	Intravenously or intramuscularly
Cimetidine	20-25	8	Orally
Cimetidine	6.6	6-8	Intravenously or intramuscularly
Omeprazole	2-4	24	Orally
Sucralfate	20-40	8	Orally
Aluminum/magnesium antacids	0.5	4	Orally

on levels necessary to increase gastric pH and promote ulcer healing in a majority of horses. Commonly recommended dosages are 20 to 30 mg/kg orally every 8 hours or 6.6 mg/kg intravenously every 6 hours for cimetidine and 6.6 mg/kg orally every 8 hours or 1.5 to 2 mg/kg intravenously every 6 hours for ranitidine. Famotidine has been used less extensively in the horse, but a dose of 10 to 15 mg/kg/day has been recommended.

Because gastric perforation caused by glandular ulcer disease has been reported in hospitalized neonates, many clinicians routinely use prophylactic antiulcer therapy in this population. Although clinically normal foals respond predictably to ranitidine,[29] sick neonates have shown variability in pH response to intravenously administered ranitidine, with a much shorter duration of action and in some cases no noticeable response.[31] Thus currently used dosing schedules for hospitalized foals may be inadequate. Because some critically ill foals have a predominantly alkaline gastric pH profile and because gastric acidity may be protective against bacterial translocation in neonates, the need for prophylactic ulcer therapy is controversial. In critically ill human neonates, intravenous administration of ranitidine raises gastric pH and gastric bacterial colonization but does not increase the risk of sepsis.[64] In a retrospective study of 85 hospitalized foals less than 30 days of age, no difference in the frequency of gastric ulceration at necropsy was found between those foals that received prophylactic treatment for gastric ulcers and those that did not.[65] Because the study was retrospective, specific details regarding lesion location and severity were not available; however, none of the foals in the study died because of gastric ulcer disease.

H$_2$ antagonist therapy should continue for 14 to 21 days, but complete ulcer healing may take 30 to 40 days. If an animal is kept in race training during therapy, clinical signs may resolve but the lesions may not. Currently, cimetidine and ranitidine are available in injectable, tablet, and liquid forms. Famotidine and nizatidine are available in tablets.

Proton pump inhibitors block secretion of H$^+$ at the parietal cell membrane by irreversibly binding to the H$^+$,K$^+$-ATPase proton pump of the cell. These agents have a prolonged antisecretory effect, which allows for once-daily dosing. Omeprazole, the first proton pump inhibitor to be developed, is the only currently approved agent for the treatment of EGUS.

Several studies have documented the safety of orally administered omeprazole in foals and adult horses.[66,67] Omeprazole has demonstrated efficacy in the healing of NSAID-induced ulcers in horses and in naturally occurring cases of EGUS.[68,69] More importantly, omeprazole has been shown to eliminate or reduce the severity of gastric ulcers in Thoroughbreds maintained in race training.[70]

The available equine preparation of omeprazole (GastroGard, Merial, Ltd., Duluth, Georgia) is recommended at a dose of 4 mg/kg orally every 24 hours. Initial reports suggested that 3 to 5 days of omeprazole therapy were necessary to achieve maximum acid suppression; however, an increase in gastric pH and a decrease in acid output are evident 5 to 8 hours after omeprazole paste administration.[71] After initial treatment (28 days), treatment with 2 or 4 mg/kg every 24 hours has been shown to decrease or prevent the recurrence of disease in animals maintained in training.[72] The powder form of omeprazole degrades rapidly in an acidic environment, thus one must use an enteric-coated capsule (as used in the human preparation) or a specially formulated paste (such as GastroGard) to allow delivery of the active drug to the small intestine for absorption. Many compounding pharmacies prepare omeprazole in liquid or paste formulation for use in horses, but their efficacy has not been evaluated to date.

Other proton pump inhibitors have been developed recently for use in human beings, including rabeprazole, lansoprazole, esomeprazole, and pantoprazole. In gastroesophageal reflux disease treatment in human beings, esomeprazole has demonstrated a higher rate of healing at 4 and 8 weeks compared with omeprazole, but rabeprazole, lansoprazole, and pantoprazole have similar efficacy.[73] An intravenous formulation of pantoprazole recently became available commercially and may prove beneficial for patients in need of antiulcer therapy that cannot be treated orally. Research regarding the pharmacokinetics and efficacy of other proton pump inhibitors in horses is not currently available.

Sucralfate is effective in treating peptic ulcers and preventing stress-induced ulcers in human beings. The mechanism of action likely involves adherence to ulcerated mucosa, stimulation of mucus secretion, enhanced prostaglandin E synthesis, and increased concentration of growth factor at the site of ulceration, although the prostaglandin effects may not play an important role in ulcer healing.[74] These are factors relevant to glandular mucosa, and the efficacy of sucralfate in treating ulcers in the equine gastric squamous mucosa remains undetermined. Sucralfate may be effective in preventing stress-induced ulcers in neonatal foals, because these occur in the glandular mucosa, although no clinical evidence directly supports this concept. In human beings, sucralfate provides protection against stress-induced ulcers with a decreased risk of pathogenic gastric colonization.[75] One should give sucralfate at a dosage of 10 to 20 mg/kg every 6 to 8 hours. The efficacy of sucralfate in an alkaline pH is controversial but appears likely.[76-78] Moreover, at the time of administration of an

H_2 antagonist, the gastric pH likely will have returned to an acidic pH since the last dosage and will remain so for 30 to 60 minutes depending on the route of administration; thus one likely can administer the agents simultaneously if so desired.

The use of antacids to treat gastric ulcers has not been examined critically in the horse. Research in horses has shown that 30 g aluminum hydroxide per 15 g magnesium hydroxide results in an increase in gastric pH above 4 for approximately 2 hours.[79] Thus although antacids may be useful for treating ulcers in horses, a dose of approximately 180 to 200 ml at least every 4 hours is necessary for a standard adult horse.

The use of synthetic prostaglandin E_1 analogs, such as misoprostol, has been effective in treating gastric and duodenal ulcers in human beings, and the proposed mechanism of action involves inhibition of gastric acid secretion and mucosal cytoprotection.[80] Frequently reported adverse effects of intestinal cramping and diarrhea in human beings have precluded the use of misoprostol in horses.

One should consider prokinetic drugs in foals with duodenal disease and gastroesophageal reflux and when one suspects delayed gastric emptying without a physical obstruction. The cholinergic drug bethanechol has been shown to increase the rate of gastric emptying in horses.[81] In cases of acute gastric atony, bethanechol 0.025 to 0.030 mg/kg administered subcutaneously every 3 to 4 hours has been effective in promoting gastric motility and emptying, followed by oral maintenance dosages of 0.35 to 0.45 mg/kg 3 to 4 times daily. Adverse effects can include diarrhea, inappetance, salivation, and colic, but at the dosages stated, adverse effects have been infrequent and mild. A complete review of ileus and prokinetic therapy is available in Chapter 13.6.

For foals with severe gastroduodenal ulcer disease that have developed duodenal stricture, surgical therapy is necessary.[57,82] These animals require a serious financial commitment because intensive perioperative medical therapy is critical for a successful outcome. Even with surgical therapy, these foals often warrant a guarded prognosis.

Other Disorders of the Stomach

PYLORIC STENOSIS AND DELAYED GASTRIC EMPTYING

Pyloric stenosis is a structural resistance to gastric outflow. Congenital pyloric stenosis has been reported in foals and one yearling and results from hypertrophy of the pyloric musculature.[83-85] Acquired pyloric stenosis can result from neoplasia or duodenal ulceration.[86-89] Clinical signs depend on the degree of obstruction and

include abdominal pain, salivation, and teeth grinding. Complete or near complete obstruction can result in gastric reflux and reflux esophagitis. In foals with congenital pyloric hypertrophy, clinical signs may begin with the consumption of solid feed. In foals one can make a presumptive diagnosis via gastric endoscopy and radiography (plain and contrast studies). Depending on the cause and severity of disease, gastric endoscopy may provide a presumptive diagnosis in the adult horse. Measurement of gastric emptying can aid the diagnosis. Several methods of measurement are currently available, including nuclear scintigraphy, acetaminophen absorption, and postconsumption [^{13}C] octanoic acid blood or breath testing.[81,90,91] Exploratory laparotomy shows a distended stomach and thickened pylorus accompanied by a relatively empty intestinal tract.

If complete obstruction is not present, medical therapy with a prokinetic such as bethanechol can increase the rate of gastric emptying.[81] Phenylbutazone and cisapride also have been shown to attenuate the delay in gastric emptying caused by endotoxin administration.[90,92] Surgical repair is necessary for definitive treatment of complete or near-complete obstruction and consists of gastroenterostomy or pyloroplasty.[57,82]

GASTRIC DILATION AND RUPTURE

Gastric dilation can be classified as primary, secondary, or idiopathic. Causes of primary gastric dilation include gastric impaction, grain engorgement, excessive water intake after exercise, aerophagia, and parasitism.[86,93] Secondary gastric dilation occurs more commonly and can result from primary intestinal ileus or small or large intestinal obstruction. Time to development of gastric reflux is proportional to the distance to the intestinal segment involved, with duodenal obstruction resulting in reflux within 4 hours.[94] Clinical signs of gastric dilation include those associated with acute colic and in severe cases, ingesta appearing at the nares. Associated laboratory abnormalities include hemoconcentration, hypokalemia, and hypochloremia.[86]

The most common reported cause of gastric rupture in horses varies between reports. In a retrospective study of 54 horses, gastric rupture occurred most commonly as a secondary phenomenon (65%), usually because of small intestinal obstruction, with primary gastric dilation and idiopathic rupture occurring almost equally (15% and 17%, respectively).[93] In another retrospective study of 50 horses in combination with a search of the Veterinary Medical Database (VMDB), 60% of the gastric rupture cases were classified as idiopathic.[95] Risk factors for gastric rupture include feeding grass hay, not feeding grain, gelding, and a nonautomatic water source.[93,95] Nasogastric intubation does not preclude the possibility of gastric rupture, and the amount of reflux

obtained before rupture varies greatly.[93] Because these reports were retrospective, one cannot rule out confounding factors with certainty.

Regardless of the initiating cause, gastric rupture usually occurs along the greater curvature. In horses with rupture caused by gastric dilation, tears in the seromuscular layer are frequently larger than the corresponding tears in the mucosal layer, indicating that the seromuscularis likely weakens and tears before the mucosa.[93,95] In contrast, horses with gastric rupture following gastric ulceration usually demonstrate full-thickness tears of equal size in all layers. Gastric rupture is usually fatal because of widespread contamination of the peritoneal cavity, septic peritonitis, and septic shock. Initial clinical signs vary with the primary disease; however, when rupture occurs, a previously painful animal can exhibit signs of relief. Subsequent signs are consistent with peritonitis and shock, including tachypnea, tachycardia, sweating, and muscle fasciculations. Surgical repair is thus limited but has been reported for partial-thickness tears,[96] and in one case of a combined tear of the mucosa and muscularis with only a focal serosal tear, a full-thickness repair was performed with a favorable outcome.[97]

GASTRIC IMPACTION

Gastric impaction can result in acute or chronic signs of colic in the horse. Although a specific cause is not always evident, ingestion of coarse roughage (straw bedding, poor-quality forage), foreign objects (rubber fencing material), and feed that may swell after ingestion or improper mastication (persimmon seeds, mesquite beans, wheat, barley, sugar beet pulp) have been implicated. Possible predisposing factors include poor dentition, poor mastication and rapid consumption of feedstuffs, and inadequate water consumption. Clinical signs can vary from anorexia and weight loss to those consistent with severe abdominal pain. In severe cases, spontaneous reflux may occur, with gastric contents visible at the nares. In cases of acute severe abdominal pain, one often makes a diagnosis during exploratory celiotomy. In animals not exhibiting signs of colic warranting surgical intervention, an endoscopic finding of a full stomach after a normally adequate fast (18 to 24 hours) often can confirm the diagnosis. Abdominal radiographs are reserved for smaller horses and ponies. In addition to pain management, specific treatment consists of gastric lavage via nasogastric intubation or massage and injection of fluid to soften the impaction during laparotomy.[98-100]

MISCELLANEOUS CAUSES OF GASTRITIS

Nonulcerative gastritis rarely occurs in the horse; however, a single case of emphysematous gastritis caused by *Clostridium perfringens* has been reported.[101]

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13.11—Duodentitis–Proximal Jejunitis (Anterior Enteritis, Proximal Enteritis)

Rebecca S. McConnico

Duodenitis–proximal jejunitis (DPJ) is an inflammatory condition affecting the upper small intestine and resulting in distention, abdominal pain, gastric reflux caused by excessive fluid and electrolyte secretion, and increased peritoneal fluid protein concentration without a significant elevated nucleated cell count. Clinical signs of DPJ

mimic that of a strangulating or nonstrangulating small intestinal obstruction, so distinguishing between the two syndromes is important because appropriate treatment of small intestinal obstruction usually requires surgical intervention. Studies suggest that the survival rate for horses with DPJ that endured surgical exploratory laparotomy was poor compared with those treated medically, although differences in disease severity may have accounted for the results in these early reports.[1,2] The clinical syndrome of DPJ was well described in the 1980s, and although recognized by its classical presentation, varying degrees of focal intestinal and systemic illness may occur.[1-4] DPJ usually occurs alone but can occur along with gastritis, ileitis, typhlitis, and or colitis.

Pathophysiology

Typical pathologic findings in horses with DPJ include involvement of the duodenum and usually the proximal jejunum.[3] The ileum and large colon usually are determined to be grossly normal. Gastric distention is a common finding and is thought to be caused by hypersecretory mechanisms in the proximal small intestine and a functional ileus of affected enteric segments. The small intestine may be 5 to 7 cm in diameter because of fluid distention with malodorous, red to brown-red intralumenal fluid accumulation. Duodenal (and jejunal) serosal surfaces may have varying degrees and distribution of bright-red to dark-red petechial and ecchymotic hemorrhages and yellow to white streaks. The enteric mucosal surfaces are usually hyperemic and have varying degrees of petechiation and ulceration.

Microscopically, the most severe lesions have been located in the duodenum and proximal jejunum but may extend proximally to the gastric mucosa and aborally to the large intestinal mucosa and submucosa.[3] Microscopic lesions consist of varying degrees of mucosal and submucosal hyperemia and edema. More severe lesions include villus degeneration with necrosis and more severely, sloughing of villous epithelium. The lamina propria, mucosa, and submucosa may have varying degrees of granulocyte infiltration (predominantly neutrophils), and the muscular layers and serosal surfaces contain small hemorrhages. Proximal small intestinal serosal fibrinopurulent exudate is a common finding in the more severe cases; therefore the term *hemorrhagic fibrinonecrotic duodenitis–proximal jejunitis* has been suggested as a more descriptive name for this syndrome.

Horses with DPJ often have evidence of multiple organ involvement such as hepatic changes including congestion and varying degrees of biliary duct hyperplasia. Additional systemic involvement likely is caused by endotoxin absorption, metabolic imbalances such as acidemia, and circulatory changes.

The cause of this syndrome remains an enigma (much like the cause of other inflammatory conditions affecting the intestinal tract). Several microorganisms have been implicated as playing a role in triggering DPJ, including *Clostridium* spp., *Salmonella* spp., and some mycotoxins, but efforts to reproduce the syndrome experimentally have been futile.[5] A recent dietary change with an abrupt increase in dietary concentrate level has been suggested to predispose a horse to developing DPJ because of intraluminal microbial imbalances.

Two intracellular processes control intestinal secretion, the cyclic nucleotide (cyclic adenosine monophosphate and cyclic guanosine monophosphate) and the calcium systems.[6] Agents (inflammatory mediators, microorganisms, toxic agents) can activate adenyl cyclase (vasoactive intestinal peptide, prostaglandin E$_2$) or guanyl cyclase (bacterial enterotoxins) and induce increases in cyclic adenosine monophosphate and cyclic guanosine monophosphate, respectively. This reaction causes phosphorylation of specific protein kinases, which induce the actual mucosal membrane transport events. Increases in intracellular free calcium may arise from cyclic nucleotide–dependent release of stored calcium within the cell or from increased calcium entry across the cell membrane.[7] Calcium may act through calmodulin, which then can activate membrane-phosphorylating protein kinases. The net effect is increased movement of sodium and chloride into the mucosal cell from the interstitium, with secretion of sodium and chloride into the intestinal lumen. Water follows the directional flux of sodium and chloride through highly permeable intercellular spaces. Several bacterial toxins and endogenous mediators can cause active secretion and contribute to a synergistic mucosal secretory response. Passive secretion of protein-rich fluid into the lumen occurs following damage to the mucosal epithelium, capillary endothelium, and submucosal inflammation in the proximal small intestine. The clinically relevant events that result from active and passive fluid secretion are proximal small intestinal distention and nasogastric reflux, dehydration, and circulatory shock.

The concentration of protein in the peritoneal fluid from horses with DPJ is usually higher than in horses with small intestinal obstruction. A disproportionate increase in total protein concentration relative to nucleated cell count occurs probably by leakage of blood or plasma into the peritoneal cavity without a significant stimulus for leukocyte chemotaxis. Suggested mechanisms for increased abdominal fluid protein concentration include serositis associated with inflamed intestine and small intestinal distention causing passive congestion and increased capillary hydrostatic pressure of visceral peritoneal vessels.[8]

Small intestinal ileus is another hallmark sign of DPJ and the pathophysiology is complicated, involving

primary and secondary dysfunction of the central, autonomic, and enteric nervous systems and their purported roles in governing intestinal motility.[9] Primary role-players in DPJ-associated ileus include peritoneal inflammation, inflammatory cell migration/activation within the muscularis, small intestinal mechanical distention, and effects of endotoxin absorption. The use of prokinetic agents for treating ileus and gastric/small intestinal distention in horses with DPJ is becoming more common, but veterinarians should realize that a potential restriction on their use is the need for normal intestinal integrity. In spite of that, one may use motility modifiers judiciously.

Clinical and Clinicopathologic Signs

The veterinarian has the challenge of differentiating horses with DPJ from horses with small intestinal obstructive lesions so as to avoid surgical intervention (Table 13.11-1). Horses with DPJ typically show signs of acute abdominal pain initially, and then after gastric decompression, volume replacement, and analgesic therapy, the colic signs subside, but signs of lethargy and malaise become more apparent. In contrast, horses with obstructive lesions of the small intestine usually show signs of abdominal pain until the affected viscus is repaired via surgical intervention or the viscus ruptures.

Another differentiating characteristic is the large volume (>4 to 20 L with each decompressive effort) of nasogastric reflux that is often malodorous and orange-brown or red-brown. DPJ-affected horses have moderate to severe small intestinal distention palpated on rectal examination, temperature of 38.6° to 39.1° C (101.5° to 102.5° F), dehydration, brick-red mucous membranes, lethargy and absent borborygmi, prolonged capillary refill time, tachycardia (>60 beats/min), and tachypnea. Although the signs of abdominal pain usually resolve after gastric decompression, most horses remain severely lethargic. Without periodic removal of the fluid that accumulates in the proximal intestinal tract, signs of abdominal pain usually recur. Horses with DPJ often require gastric decompression at 2-hour intervals, with 2 to 10 L of fluid recovered each time. Nasogastric tubes left in place for long periods of time cause varying degrees of pharyngitis, laryngitis, and esophagitis.

Typical clinical laboratory findings include an increased packed cell volume and total plasma protein reflective of volume depletion, a metabolic acidosis (with elevated anion gap) in longstanding or severe cases, an increased peritoneal fluid protein concentration (often >3.5 g/dl), and a mild to moderate elevation of the peritoneal white blood cell count, although the count usually is less than 10,000 cells per microliter.[3,4] The

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TABLE 13.11-1

Physical and Laboratory Examination Findings in Horses With Duodenitis–Proximal Jejunitis (DPJ) and an Operable Small Intestinal Lesion

EXAMINATION	DPJ	STRANGULATING OBSTRUCTION	NONSTRANGULATING OBSTRUCTION
Abdominal pain	Acute onset	Acute onset	Acute onset
Attitude	Depressed, painful	Painful	Painful
Heart rate (beats/min)	40-80	≥80	40-80
Respiratory rate (breaths/min)	16-28	24-40	15-35
Rectal temperature (°F)	101.5-102.5	≤101	99-101
Capillary refill time	>3 seconds	≥3 seconds	1.5-3.0 seconds
Intestinal sounds	Mildly to greatly depressed	Greatly depressed to absent	Mildly depressed to absent
Nasogastric reflux	3-4 gallons orange-brown	2-4 gallons, ± malodorous	2-3 gallons with ingesta character, ± malodorous
Rectal examination	Dilated to moderately distended	Moderately to greatly distended	Mild to moderately distended, ± ileal impaction
Response to nasogastric decompression	Depressed, quiet	Temporary to no pain relief	Temporary to no pain relief
Complete blood count	± Increased white blood cells; mature neutrophilia	± Increased white blood cells; slight neutrophilia	Normal to increased white blood cells
Peritoneal fluid protein	>3.0 g/dl and may be >4.5 g/dl	2.5-4.5 g/dl	2.5-3.5 g/dl
Peritoneal fluid nucleated cell count	≤5000/µl	3000 to >20,000/µl	3000 to 12,000/µl

*Findings in which differences between DPJ and obstructive disorders are often present are italicized.

peritoneal fluid is usually yellow and turbid, but in severe cases diapedesis occurs resulting in a serosanguinous color. The white blood cell count in the peripheral blood may be normal, decreased, or increased. In addition, hyponatremia, hypochloremia, hypokalemia, and acid-base alterations (elevated anion gap) are often evident. The loss of enteric bicarbonate through evacuation of enterogastric reflux and poor tissue perfusion from hypovolemia can lead to metabolic acidosis. One makes a definitive diagnosis of DPJ in most cases by gross examination of the duodenum and proximal jejunum at surgery or at necropsy. Some equine practitioners have observed an apparent geographic relationship in the incidence and severity of the syndrome, with more cases occurring in the southeastern United States.

Treatment

Horses with DPJ appear to share a common characteristic clinical presentation, and the mechanisms leading to electrolyte imbalances, fluid loss, ileus, and endotoxemia and septicemia are similar. Treatment regimens are supportive and aim at plasma volume replacement (usually in the form of crystalloid fluid replacement), analgesia and antiinflammatory therapy, gastric decompression, antiendotoxin therapy, antimicrobial therapy if indicated, nutritional support, and nursing care.

FLUID THERAPY

One should institute aggressive intravenous polyionic fluid therapy immediately in a horse with DPJ. One should calculate the total fluid deficit based on clinical assessment of dehydration (e.g., for 8% or moderate dehydration, 0.08×450 kg body mass = 36 L) and should administer replacement fluids rapidly (up to 6 to 10 L per hour per 450-kg adult horse). Administering intravenous hypertonic saline (7%) may be useful to treat hypovolemic shock in horses with severe circulatory shock. The use of 1 to 2 L of hypertonic saline (7% NaCl) improved systemic blood pressure and cardiac output in horses with hemorrhagic shock and in a model of equine endotoxemia.[10] If one chooses this treatment option, intravenous administration of replacement isotonic fluids must follow immediately to maintain tissue integrity. One should not allow horses with significant volumes of gastric reflux to ingest foodstuffs or liquids orally.

Once one has administered replacement fluids and the horse is well hydrated, one should administer maintenance fluid amounts, which may be as high as 120 ml/kg/day. Unfortunately, the intravenous fluid therapy itself may accelerate the flux of fluid from the vasculature into the intestinal lumen because of a reduction in intravascular oncotic pressure and an increased capillary perfusion pressure, which can result in an increased volume of gastrointestinal reflux. However, the veterinarian should not consider reducing the volume of intravenous fluid therapy because excessive fluid losses continue to occur. One should monitor plasma protein concentration, overall hydration, and the volume of reflux and then determine the rate of intravenous fluid administration. During the initial hours of therapy, even aggressive intravenous fluid administration results in only moderate clinical improvement. The clinical response, as evidenced by improved hydration status, decreased nasogastric reflux, improved attitude, and improvement in values reflecting kidney function (decreased blood urea nitrogen and creatinine), correlates with improvement of intestinal damage.

HYPOPROTEINEMIA

Horses with DPJ that continue to reflux large volumes of enterogastric fluid frequently for more than 36 to 48 hours most likely will experience protein loss from the inflamed and disrupted intestinal mucosal barrier and from systemic protein catabolism. Decreased colloid oncotic pressure leads to decreased effective circulating fluid volume and edema. Total plasma protein may decline to below 4 g/dl and the albumin may decrease to below 2.0 g/dl. Fresh or thawed frozen plasma is ideal for replacement of functional proteins. One should consider treatment with intravenous plasma therapy or a combination of plasma and synthetic colloid (e.g., synthetic amylopectin) as soon as one sees evidence of a consistent decline in total plasma protein or albumin (<2.0 g/dl) or if the horse is developing dependent edema. Fresh plasma (preferred) or fresh frozen plasma is the treatment of choice if coagulation disorders accompany protein loss. An average-size horse (450 kg) requires 6 to 10 L of plasma (albumin 3.0 g/dl) or synthetic colloid to improve plasma oncotic pressure. Administration of additional aliquots of 2 to 10 L of a balanced colloidal solution may be necessary if the DPJ crisis continues. In addition to albumin (the major colloid component), plasma contains other components that provide overall systemic support (e.g., fibronectins, complement inhibitors, elastase and proteinase inhibitors, antithrombin III). One may administer a 6% solution of hydroxyethyl starch (Hetastarch (6%), Abbott Laboratories, North Chicago, Illinois), a synthetic colloid, at 5 to 10 ml/kg. Because of the large size of the starch molecules, this solution is an effective plasma volume expander, resulting in sustained dose-dependent decreases in packed cell volume and plasma protein concentration with increased oncotic pressure. The cost of an appropriate amount of commercial plasma or synthetic colloid solution for treatment of adult horses with DPJ may be prohibitive but can be life-saving.

ANTIENDOTOXIN THERAPY

Horses with enteritis frequently absorb large amounts of endotoxin from the disrupted intestinal mucosal barrier, therefore putting these horses at a high risk for laminitis. One should monitor digital pulses every 4 to 6 hours until systemic signs of enteritis have abated (fever, leukopenia, etc.). Treatment to combat endotoxemia is critical, and several therapeutic approaches are available. Choice of treatment options is based on severity of disease, renal function, hydration status, and economics. The reader is referred to Chapter 13.7 for a thorough discussion of endotoxemia pathophysiology, treatment, and prevention.

ANTIINFLAMMATORIES AND ANALGESIA

Nonsteroidal antiinflammatory drugs are the most frequently used group of drugs for treatment of abdominal pain in horses (flunixin meglumine 1.1 mg/kg intravenously every 12 hours or phenylbutazone 2.2 mg/kg orally or intravenously every 12 hours). The clinician must weigh the benefit of the analgesic effect of nonsteroidal antiinflammatory drugs with the possibility of further damage to the intestine by potentially blocking the protective effects of intestinal mucosal prostaglandins.

One should consider other classes of drugs for treating colic associated with DPJ. Butorphanol (Torbugesic; an opioid analgesic) at 0.06 to 0.1 mg/kg with detomidine (Dormosedan; an α-agonist) at 0.01 to 0.02 mg/kg given intramuscularly every 6 to 8 hours is a useful combination that has minimal effects on gastrointestinal motility.

ANTIMICROBIAL THERAPY

Because *Clostridium* spp. are suspected as a causative agent of DPJ, penicillin often is administered to affected horses. However, one should consider broad-spectrum antimicrobial coverage for horses with DPJ. One can add an aminoglycoside (gentamicin, amikacin) or third-generation cephalosporin (ceftiofur [Naxcel], Upjohn Co., Kalamazoo, Michigan) to the penicillin therapy, keeping in mind the potential adverse effects of these drugs on renal function.

ANTISECRETORY THERAPY

Effective antisecretory medications targeting the equine small intestine have not been identified.

MANAGEMENT OF NUTRITION

One should consider the nutritional needs of horses with DPJ. Most horses have a total body protein loss from cachexia and a protein-losing enteropathy. Total parenteral nutrition may be indicated in horses that remain anorectic for more than 3 to 4 days. Parenterally administered solutions containing glucose, balanced amino acid solutions, lipid emulsions, balanced electrolyte and trace minerals, and vitamins have been administered to adult horses with small intestinal ileus or enterocolitis. Based on a small number of horses, this therapy has proved promising in terms of minimizing protein losses and decreasing the duration of illness. Providing for part of the nutritional requirements of the horse (8000 to 12,000 kcal/day) is possible with glucose–amino acid solutions, which are of moderate cost. One may suppose reasonably that providing nutritional support to an anorectic, severely ill horse will facilitate the healing process and even shorten the duration of illness. Thus the overall cost of providing parenteral nutritional supplementation to horses with DPJ may well be offset by quicker recovery and diminished requirements for other, expensive treatments.

INTESTINAL MOTILITY MODIFIERS

Normal (healthy) intestine is necessary for optimum performance of prokinetic agents in horses. Many motility-modifying agents likely are ineffective in cases of DPJ. However, some benefit may come of the judicious use of prokinetic agents in inflammatory conditions of the equine intestine, particularly if the agent provides additional effects such as analgesia. For example, lidocaine infusion has several actions that may be beneficial in the treatment of ileus, including suppression of primary afferent firing, antiinflammatory properties, an observed analgesic effect, and direct stimulation of smooth muscle.[9] An infusion dose of 15 to 20 mg/min over 5 to 6 hours has been recommended. The reader is referred to Chapters 13.6 and 13.15 for a complete description of motility modifying agents.

NONRESPONSIVE CASES

Medical therapy is sufficient in most cases of DPJ, but in those cases in which the horse continues to produce copious enterogastric reflux, one may consider surgery as an option. Refractory cases have been observed to improve with surgical intervention; however, some horses with refractory DPJ have been observed to recover with supportive medical care alone even after 20 days of refluxing large amounts of fluid every 2 to 4 hours (personal observation). The decision of when to intervene surgically often is difficult. One may elect surgery to determine the extent of gross pathologic condition and intestinal distention and to perform intestinal bypass so as to direct enterogastric reflux toward the cecum and colon, where the fluid can be reabsorbed. Allen and Clark[5] have described two approaches for surgical therapy in such cases. A standing right flank laparotomy with resection of the last rib has been used to approach the duodenum and cecal base. Using this approach, one makes a small stoma between the duodenum and cecum using a

handsewn 1.0- to 1.5-cm side-to-side anastomosis. The stoma may act as a shunt to decompress the proximal small intestine and deliver the small intestinal fluid to the cecum for reabsorption. Following recovery, the stoma likely will close.

When a veterinarian is confronted with a horse exhibiting abdominal discomfort, with small intestinal distention palpable per rectum, and greater than 2 L of gastric reflux, the veterinarian should recommend referral of the horse to a facility capable of performing abdominal surgery. The chance that such a horse has an intestinal obstruction is too great to decide to treat it as if it may have DPJ. Surgery on such horses is not unusual, even though DPJ is possible, to rule out an obstruction. At present, the survival of horses with DPJ that undergo surgery is much greater than previously described, and certainly greater than that of horses with small intestinal obstruction that do not have surgery. Horses with DPJ that receive appropriate therapy have a reasonably good chance of making a full recovery. Horses that continue to have frequent episodes of voluminous nasogastric reflux and systemic signs of endotoxemia and septicemia have a poorer prognosis for recovery. Frequent complications of DPJ include laminitis, thrombophlebitis, and weight loss.

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13.12—Proliferative and Inflammatory Intestinal Diseases Associated With Malabsorption and Maldigestion

Malcolm C. Roberts

Malabsorption is associated with pathologic conditions of the small intestine characterized by substantial reduction of the available absorptive surface area. By virtue of the extent of the morphologic changes, interference with digestive processes occurs, although maldigestion may be difficult to confirm in the absence of assessment measures. The small bowel problem may alter the composition and availability of substrate presented for fermentation in the large intestine. Clinical signs may be modified or accentuated if involvement of the large intestine is concomitant. Diarrhea indicates significant alterations in bidirectional fluid and electrolyte fluxes and in large intestinal transit.

The clinical signs of chronic wasting and poor body condition, although nonspecific for a diagnosis of malabsorption antemortem, can be attributed to proliferative or inflammatory intestinal disorders, often collectively referred to as chronic inflammatory bowel diseases.[1] Clinical signs include alimentary lymphosarcoma, granulomatous enteritis, multisystemic eosinophilic epitheliotropic disease (MEED), and lymphocytic-plasmacytic enterocolitis—conditions affecting young and adult horses. Proliferative enterocolitis,[2] a transmissible disease of foals 3 to 7 months of age characterized by significant small intestinal pathologic changes, will be included in this group. However, several other primarily small intestinal conditions described from a morphologic perspective, such as chronic postinfarctive inflammation and mycobacterial infections,[3] will not be discussed. In addition, a single case of AA amyloid-associated gastroenteropathy in an 18- year-old Morgan stallion that had evidence of severe malabsorption based on poor D-xylose absorption is included.[4]

For comparative purposes, Table 13.12-1 lists the clinical and clinicopathologic features of the diseases, and Tables 13.12-2 and 13.12-3 present the gross morphologic and histopathologic findings, respectively. The extent of small intestinal disease is the key to determine whether one can demonstrate malabsorption based

TABLE 13.12-1

Predominant Clinical and Clinicopathologic Features of Horses With a Primary Problem of Chronic Wasting (or a More Rapid Weight Loss) Attributable to Proliferative and Inflammatory Bowel Diseases

CONDITION	AGE RANGE/ BREED	OTHER PRESENTING SIGNS	DERMATITIS/ CORONITIS	HEMATOLOGY	CHEMISTRY*	ABSORPTION TESTS
Alimentary lymphosarcoma	2 to aged Majority ≤4 years None*	Poor appetite, edema, depression, occasional fever, occasional diarrhea or colic, pain	+/– Scurfy skin	Anemia, neutrophilia; lymphocytosis is rare	Decreased albumin Total protein normal to increased Increased globulin	Reduced absorption; partial to complete malabsorption
Granulomatous enteritis	1-6 years Majority ≤3 years Standardbred	Severe wasting, edema, poor to ravenous appetite, depression, infrequent diarrhea, occasional slight fever	+/– Scurfy skin; severe lesions rare	Anemia Leucocytes normal to slightly decreased or increased	Decreased albumin Total protein normal to decreased GGT normal ALP normal to increased	Reduced absorption; partial to complete malabsorption
Multisystemic eosinophilic epitheliotropic disease	1-17+ years Majority ≤4 years Standardbred, Thoroughbred	Severe wasting, edema, appetite poor to often ravenous, slight fever, diarrhea or soft feces common; depression, colic rare, oral ulcers	++++/Severe skin lesions and ulcerative coronitis prominent	Anemia rare to slight; neutrophilia and eosinophilia rare	Decreased albumin Total protein normal to decreased GGT normal to increased ALP normal to increased	Slower absorption; reduced or normal peak concentration delayed (shifted to right)
Lymphocytic-plasmacytic enterocolitis	3-26 years None	Inappetance, depression diarrhea, colic, edema	—	Normal	Decreased albumin Decreased total protein Increased fibrinogen	Inadequate absorption or delayed peak
Proliferative enteropathy	3-7 months Arabian	Depression, colic, diarrhea, edema, appetite often normal, concurrent infection	+/– Scurfy skin	Anemia Leukocytosis	Decreased albumin Decreased total protein Increased CPK	Normal absorption in 3 of 3 foals tested

*GGT, γ-Glutamyltransferase; ALP, alkaline phosphatase; CPK, creatine phosphokinase; none, no predominant breed.

TABLE 13.12-2

Gross Morphologic Features of Proliferative and Inflammatory Bowel Diseases of Horses

CONDITION	SMALL INTESTINE	LARGE INTESTINE	OTHER ORGANS/SYSTEMS
Alimentary lymphosarcoma	**Constant;** extensive thickening, thickened mucosa, fissures, serosal plaques, nodules, congestion	**Infrequent;** unremarkable to thickened segments	Mesenteric lymph nodes (MLNs) massively enlarged Other lymph nodes involved in liver, spleen, stomach (rare)
Granulomatous enteritis	**Constant;** thickened wall, thickened mucosa, fissures, widespread ulceration (tiny ulcers)	**Common;** generally discrete	MLNs enlarged, edematous Stomach commonly affected (generally discrete) Liver, pancreas rare
Multisystemic eosinophilic epitheliotropic disease	**Common;** diffusely thickened, especially proximal duodenum and distal ileum; serosal nodules or granularity; ulceration	**Constant;** severe; segmental, or multifocal granulomata; mucosal (predominantly) and transmural thickening; extensive ulcers	MLNs (and other nodes) enlarged Stomach and esophagus commonly affected Liver/pancreas commonly affected; may be hyperkeratotic Skin: exudative dermatitis, ulcerative coronitis
Lymphocytic-plasmacytic enterocolitis	**Constant;** mucosal/submucosal edema, prominent folds	**Common;** edema, congestion, areas of mucosal ulceration	MLNs enlarged
Proliferative enteropathy	**Constant;** significant mucosal thickening, corrugated appearance from proximal jejunum to distal ileum	**Uncommon;** submucosal edema	MLNs unremarkable

TABLE 13.12-3

Significant Histopathologic Features of Proliferative and Inflammatory Diseases of Horses

CONDITION	SMALL INTESTINE	LARGE INTESTINE	OTHER ORGANS/SYSTEMS
Alimentary lymphosarcoma	Villous atrophy (partial to total); crypts disappear with hyperplasia; infiltrate of pleomorphic lymphoid cells, plasma cells; transmural	Nothing evident to diffuse mucosal infiltration	Mesenteric lymph nodes (MLNs): extensive infiltration; more moderate in other lymph nodes (hepatic, abdominal, inguinal, superficial)
Granulomatous enteritis	Villous atrophy (partial to total), crypt hyperplasia and abscesses, diffuse granulomatous inflammation; mononuclear cells (lymphoid), giant cells, epithelioid foci; lymphangiectasia	Similar infiltrate usually discrete; mucosa, submucosa	Similar infiltrate; stomach discrete MLNs: discrete to florid macrophage infiltration Diffuse cortical hyperplasia
Multisystemic eosinophilic epitheliotropic disease	Villous atrophy rare; lymphocytic and eosinophilic infiltration most severe in cranial duodenum, ileum, ileocecal junction; infiltrate more widespread than gross lesions	Segmental/multifocal lesions, severe infiltration, reactive fibrosis, tissue eosinophilia, walled off granulomata, central necrotic core of eosinophilic material	Similar infiltration with fibrosis of MLNs, liver, pancreas Skin: acanthosis, hyperkeratosis, diffuse infiltrate of eosinophils; lymphocytes in dermis; focal eosinophilic accumulations
Lymphocytic-plasmacytic enterocolitis	Villous blunting to atrophy; moderate to severe infiltration of lymphocytes, plasma cells; edema, dilated lymphatics	Similar infiltrate, less remarkable	Minimal evidence
Proliferative enteropathy	Villous shortening, severe hyperplasia of crypt epithelium, small curved bacteria in apical cytoplasm, mononuclear infiltrate	No evidence	No evidence

on abnormal carbohydrate absorption. As described in Chapter 13.4, this is not an all-or-nothing situation. In the same animal the staging of the pathologic changes differs in different regions of the small and large intestines, thus influencing severity of clinical signs and absorption findings. Furthermore, the extent of pathologic changes in different animals with ultimately the same morphologic diagnosis affects absorption studies and progress of the disease. Early diagnosis remains a challenge, and even multiple intestinal biopsies taken at exploratory laparotomy may prove unhelpful. By contrast, intestinal infiltration with the predominant cell types can be found in grossly normal appearing intestinal tissue.

Alimentary Lymphosarcoma

Alimentary lymphosarcoma of the horse may represent a primary neoplasia of the gut associated lymphoid tissue with significant cellular infiltration of the small intestine and associated lymph nodes with minimal large intestinal or systemic involvement. Case series and pathology reports indicate that young horses 2 to 4 years of age primarily are affected, although the age range can be broad.[5-7] No breed or sex predilection exists. Prevalence is unknown. Despite the progressive nature of lymphomata, onset of clinical signs can be rapid and the animal may become acutely ill. As with all adult cases of chronic inflammatory bowel disease, antemortem diagnosis is by a process of exclusion and usually is confirmed post mortem. Frequently, the horse has anemia, thrombocytopenia, neutrophilia or neutropenia, hypoalbuminemia, normal serum protein or hyperproteinemia, and hypergammaglobulinemia. Lymphocytosis is rare. One may palpate intraabdominal masses, mainly enlarged mesenteric lymph nodes, rectally. Abdominocentesis has been of diagnostic value. Carbohydrate absorption tests usually reveal partial to total malabsorption indicative of the severely reduced surface area resulting from significant villous atrophy and the extensive mucosal or transmural infiltration. Rectal biopsy has aided diagnosis. Early confirmation of a suspected diagnosis necessitates exploratory laparotomy to obtain multiple intestinal and lymph node biopsies. In the future, markers of cancer cells may become available and may be cost-effective to aid diagnosis. Prognosis is poor. Natural progress of the disease is unknown. Most horses are presented in an advanced state of disease. Immunosuppressive drugs or chemotherapy may afford temporary improvement. However, outcome is unaffected.

Granulomatous Enteritis

The chronic wasting condition granulomatous enteritis was first described in 1974[8]; 9 of 10 horses were young Standardbreds. Most affected horses are 2 to 3 years

of age. Case reports from many countries revealed a predominance of Standardbred over Thoroughbred horses by three to one.[9,10] Some of the Standardbreds were related, implicating a genetic predisposition. Prevalence is low. The condition is sporadic and has an insidious onset, and the course can be protracted. Significant diagnostic features include anemia, slight increases or decreases in white blood cell counts, hypoalbuminemia, normal serum protein or hypoproteinemia, occasional increases in serum alkaline phosphatase activity, normal serum γ-glutamyltransferase activity, and enlarged mesenteric lymph nodes on rectal palpation. Reduced carbohydrate absorption to the level of partial to total malabsorption is reported frequently, consistent with the severe morphologic changes throughout the small intestine. One can attribute the low proportion of horses exhibiting diarrhea[9,10] to the preferential distribution of inflammatory infiltration in the small intestine,[11] with lesser involvement of the large intestine. Rectal biopsy can be a useful aid to diagnosis.[12]

Treatment of horses with granulomatous enteritis with a variety of drugs, particularly corticosteroids, has not affected the outcome except in the short term.[13] One successful response has been reported. Prolonged corticosteroid administration produced clinical remission in a 6-year-old Standardbred gelding based on improvement in clinical signs and in D-xylose absorption.[14] Five months after cessation of approximately 5 months therapy, D-xylose absorption was normal and the horse was bright, alert, and resumed a level of athletic performance. Parenteral administration of dexamethasone sodium phosphate was tapered to achieve a minimal effective dose to reduce intestinal inflammation and abolish clinical signs. Adverse effects were not reported. The outcome of this single case is encouraging. Surgery may be indicated if the disease is localized. Two young horses underwent resection of the thickened terminal small intestine to confirm a diagnosis and provide a means of treatment; one horse died 4 months after surgery, and the other has remained clinically normal for at least 10 years.[10]

The cause of granulomatous enteritis is unknown. Several infectious agents have been implicated, including *Mycobacterium avium*.[15] The condition may represent a granulomatous hypersensitivity reaction. Immune-mediated responses to dietary, parasitic, or bacterial antigens may be important initiating factors.[1] Recently, six cases purported to represent granulomatous enteritis were linked to environmental contamination with aluminum.[16] Although the case definition was flawed and problems existed with the data and interpretation,[17] the report nevertheless raised the possibility that a toxicologic basis may exist for some equine inflammatory bowel disorders.

Multisystemic Eosinophilic Epitheliotropic Disease

MEED encompasses disorders characterized by a predominant eosinophilic infiltrate in the gastrointestinal tract, associated lymph nodes, liver, pancreas, skin, and other structures and accompanied by some degree of malabsorption and enteric protein loss. The disorders include chronic eosinophilic gastroenteritis,[18] eosinophilic granulomatosis,[9] chronic eosinophilic dermatitis,[19] and probably basophilic enterocolitis.[20] The condition differs from idiopathic eosinophilic enterocolitis,[10] in which segmental lesions in the small or large intestine induce signs of colic requiring surgical intervention[21,22] without evidence of malabsorption or multisystem involvement.

Although prevalence is low, MEED appears to be more common than granulomatous enteritis based on the accumulated published reports and personal experience in Australia and the United States. Most affected horses are 2 to 4 years of age, and Standardbreds and Thoroughbred are reported to predominate. The condition is sporadic and has an insidious onset, and the course is protracted with a duration of 1 to 10 months. Diarrhea is common in contrast to granulomatous enteritis. Severe skin lesions with exudative dermatitis and ulcerative coronitis are prominent and frequently are the principal reason for veterinary attention being sought. Despite extensive tissue eosinophilia, systemic eosinophilia is rare. Hematologic values are usually unremarkable. Notable features include hypoalbuminemia and normal serum protein or hypoproteinemia, and because of liver involvement, serum γ-glutamyltransferase and alkaline phosphatase activities may be increased. Most reports of carbohydrate absorption test findings (glucose or D-xylose) indicate retarded absorption and a reduced or normal peak concentration delayed to at least 180 minutes. One can interpret this pattern as the existence of sufficient small intestinal absorptive capacity to enable moderate absorption with possibly delayed gastric emptying or ileocecal ejection. Morphologic changes are less pronounced in the small intestine than in the large intestine,[9] and small intestinal lesions predominate segmentally in the proximal duodenum and distal ileum. Furthermore, significant hyperkeratosis of the fundic region may contribute to gastric muscle contractile disruption. Diarrhea can be a consequence of the severe segmental or multifocal granulomatous lesions in the large intestine with mucosal and transmural thickening and extensive ulceration. Abundant fibrosis is a feature of all affected tissues (see Table 13.12-3).

The cause of MEED is unknown and could represent a chronic ongoing immediate hypersensitivity reaction against undefined antigens ingested or excreted into the lumen from parasitic, bacterial, or dietary sources. Infectious agents have not been identified.[18,19] Widespread use of the avermectins has tended to reduce parasite loads and composition to favor small strongyles (cyathostomes). Eosinophilia is a feature of parasitism in the equine intestinal tract, although nematodes rarely have been identified in any lesions of MEED.[3,18] However, failure to detect larval structures in these lesions may be attributable to chronicity of the disease and destruction of the parasites in tissue.[10]

Biopsies of the rectal mucosa[12] or of the skin, liver, intestinal tract, and lymph nodes may assist in diagnosis. Treatment has been attempted with a variety of drugs, including antibiotics, corticosteroids, and anthelmintics with larvicidal activity. Immediate improvement has not been borne out in the long term. Prognosis is poor. The clinical objective is to reach a tentative diagnosis early in the course of the disease for intervention to be more than transient. Unlike the other conditions (see Table 13.12-1), MEED has definitive liver and pancreatic involvement, and thus maldigestion may make a significant contribution to the wasting disease. For example, the lowered albumin and protein could result in part from impaired pancreatic enzyme digestion, and the effects of inflammatory lesions in the liver and ileum may decrease bile salt concentrations.

Lymphocytic-Plasmacytic Enterocolitis

The morphologic findings in lymphocytic-plasmacytic enterocolitis reflect the predominant infiltrative cellular elements of this rarely encountered condition. A retrospective study of 14 horses[23] provided the information presented in the tables. No specific clinical or clinico-pathologic features differentiate this condition antemortem from other inflammatory diseases of adult horses. Carbohydrate absorption was abnormal or delayed in 9 of 12 horses, consistent with the predominance of small intestinal pathologic changes. Rectal biopsies were abnormal in 3 of 7 horses, two of which were reported as having lymphocytic-plasmacytic proctitis. Prognosis is poor. Treatment has been unsuccessful, probably because of the advanced nature of the condition at the beginning of treatment.

Proliferative Enteropathy

Proliferative enteropathy has not been associated with abnormal carbohydrate absorption based on three horses subjected to carbohydrate absorption tests. However, the florid mucosal lesions in the jejunum and ileum undoubtedly contribute to impaired digestive function and potential malabsorption of vitamins, minerals, and amino acids in the distal small intestine. The condition

affects foals 3 to 7 months of age, particularly those that have been weaned recently. The disease is caused by *Lawsonia intracellulare,* an obligate intracellular bacterium found in the cytoplasm of proliferative crypt epithelial cells of the intestine. The condition in a foal was described first as intestinal adenomatosis,[24] because of similarity to the swine disorder of the same name. Later, molecular studies showed that intestines from an affected foal contained *L. intracellulare* sequences as determined by polymerase chain reaction analysis and confirmed by Southern blot hybridization.[25] Recently, studies of a cluster of affected foals on three breeding farms in Canada provided much information on the clinical syndrome, laboratory investigations, and response to treatment.[2]

Two of the three farms bred Arabians, hence a demographic predominance of Arabian foals exists. Clinical signs included depression, rapid and significant weight loss, edema, diarrhea, and colic. Poor body condition, a rough hair coat, and potbelly appearance were common findings. Other problems often were concurrent, including respiratory tract infection, dermatitis, intestinal parasitism, and gastric ulceration. Significant laboratory findings were anemia, transient leucocytosis, hypoalbuminemia, hypoproteinemia, and elevated serum creatine kinase concentrations.

Diagnosis was confirmed by identifying characteristic intracellular bacteria within the apical cytoplasm of proliferating crypt epithelial cells using silver stains and by results of polymerase chain reaction analysis and immunohistochemical testing. Antemortem diagnosis relied on clinical signs, hypoproteinemia, and exclusion of common enteric infections. One can confirm diagnosis in live animals by fecal polymerase chain reaction analysis (positive in 6 of 18 foals tested) and serologic testing; 7 foals with proliferative enteropathy were evaluated serologically and had antibodies against *Lawsonia intracellulare.*[2]

Treatment is effective. Most foals received erythromycin estolate (15 to 25 mg/kg per os every 6 to 8 hours), alone or with rifampin (7 to 10 mg/kg per os every 12 hours) for 2 to 4 weeks. Foals frequently needed supportive therapy at the outset for stabilization. Response to therapy has been excellent.[2] Rapid improvement in clinical signs even within 24 hours preceded the rise in plasma protein concentration. The source of the infection was undetermined. No apparent link existed between the three farms and a swine operation or solid and liquid waste disposal on pasture. However, one cannot exclude airborne spread of dried fecal material over distances. Comparisons of epidemiologic findings from the swine disease indicated that overcrowding, feed changes, antibiotic usage, and mixing and transportation were potential risk factors at two of the farms.

Recent weaning appeared to be a key element in the pathogenesis.

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13.13—Inflammatory Diseases of the Gastrointestinal Tract Causing Diarrhea

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Equine Acute Diarrhea

Acute diarrhea caused by colitis in adult or young horses is a potentially life-threatening disorder of a variety of causes (Table 13.13-1) characterized by hypersecretion of fluid, motility disturbances, altered microbial flora in the colon, and an impaired mucosal barrier caused by direct injury or inflammation. Many of the clinical and clinicopathologic features are similar regardless of the cause. Severe dehydration with profound electrolyte abnormalities is common, as is systemic inflammation from absorption of endotoxin or other bacterial products through the compromised mucosa. Gastrointestinal protein loss may result in reduced colloid oncotic pressure from hypoproteinemia, leading to tissue edema. Colitis is a highly catabolic disorder, and weight loss may be rapid and severe. Some cases of colitis may be complicated by extensive mucosal ulceration, serosal inflammation, or mural ischemia/infarction extending from the inflammation or resulting from coagulopathies. Thus diagnostic measures aimed at determining the cause necessarily must be accompanied by clinical and laboratory assessment of hydration, electrolyte and acid-base balance, plasma protein concentration and colloid oncotic pressure, organ function, and evaluation of the degree of systemic inflammation and of the integrity of the intestinal wall.

Although therapeutic strategies are similar for many causes of colitis, consisting primarily of control of local and systemic inflammation, maintenance of fluid and electrolyte balance, promotion of tissue perfusion, replacement of plasma protein, preservation of colloid oncotic pressure, promotion of mucosal repair, restoration of the microbial ecology of the colon, and nutritional management, some causes of acute colitis have specific therapies aimed at eliminating the cause.

Infectious Diseases

A variety of infectious organisms has been identified as causes of acute colitis in adult horses. The clinical syndromes associated with these infections are indistinguishable in most horses. However, appropriate diagnostic tests including fecal bacterial culture, fecal bacterial toxin analysis, PCR, and/or serology may identify specific infectious organisms.

SALMONELLOSIS
Pathogenesis

Salmonella is a genus of gram-negative facultatively anaerobic bacteria that are common gastrointestinal pathogens in horses. Many serotypes of *Salmonella* have been reported to infect horses, but those classified in group B appear to be associated more commonly with disease than those in other groups. Group B includes *S. typhimurium* and *S. agona,* two of the species most frequently isolated from horses.[1-3] *S. typhimurium* is the most pathogenic serotype in horses and is associated with a higher case fatality rate than other species of *Salmonella.*[1] The number of horses that are infected inapparently with and actively shed *Salmonella* in their feces has been reported to be as high as 10% to 20%, but actual prevalence of *Salmonella*-shedding in the general horse population is likely to be much lower, less than 1% to 2%.[4] Horses shedding salmonellae are a potential source of infection to susceptible horses,[1,5] as are environmental reservoirs.[6-8] For these reasons, salmonellosis is one of the most common nosocomial diseases in horses. Nosocomial salmonellosis significantly affects morbidity and mortality in hospitalized horses.[9] The emergence of multidrug resistance in equine *Salmonella* isolates has been a cause of concern because of the importance of salmonellosis as a nosocomial disease and because *Salmonella* represents a significant zoonotic pathogen.[7,10-12]

The virulence of the bacteria varies tremendously with serotype and even among strains of the same serotype in part because of the important role of host susceptibility in the pathogenicity of particular organisms. The infective dose is generally millions of organisms inoculated orally, but various environmental and host factors can reduce the infective dose to a few thousand or even hundreds

	TABLE 13.13-1	
	Differentials and Diagnosis of Some Causes of Acute Diarrhea in Adult Horses	
CATEGORY	**DIFFERENTIALS**	**DIAGNOSIS**
Infectious	Salmonellosis	Fecal culture (five consecutive)
		Fecal polymerase chain reaction (PCR)
	Clostridium perfringens	Quantitative fecal culture
		Fecal toxin immunoassay or PCR
	Clostridium difficile	Fecal culture
		Fecal toxin immunoassay or PCR
	Lawsonia intracellulare	Serologic testing
		Fecal PCR
		Small intestinal ultrasound
	Ehrlichia risticii	Fecal or blood PCR
		Serologic testing
Parasitic	Strongylosis	Fecal egg counts
		Cranial mesenteric artery palpation
		Serum immunoglobulin G(T)
	Cyathostomiasis	Fecal egg count
		Rectal biopsy
		Cecal or colonic biopsy
Toxic	Nonsteroidal antiinflammatory drugs	History and clinical signs
		Right dorsal colon ultrasonography
		Laparoscopy or laparotomy
	Cantharidin	History of exposure
		Fecal or urine cantharidin concentrations
	Arsenic	History of exposure
		Fecal, blood, urine, or tissue arsenic concentrations
Miscellaneous	Carbohydrate overload	History of inappropriate ingestion of carbohydrates
		Blood lactate concentration
	Sand enteropathy	Auscultation of ventral colon
		Fecal sand content
		Abdominal radiography

of organisms.[13-15] Environmental factors or stresses that increase susceptibility to *Salmonella* infection are not well defined, but high ambient temperature, for example, is known to increase the prevalence of salmonellosis in horses greatly. Indeed, the peak incidence of salmonellosis in horses occurs in late summer and fall.[6,14,15] Other environmental and host factors that increase the risk of *Salmonella* infection include transportation, antibiotic administration, gastrointestinal surgery, general anesthesia, preexisting gastrointestinal disease, change in diet, and immunosuppression.[1,8,15]

Host factors that restrict gastrointestinal colonization and invasion by pathogens include gastric pH, commensal gastrointestinal flora, gastrointestinal motility, the mucosal barrier and mucosal immunity.[1,16] Gastric acidity is an important defense mechanism preventing live organisms from reaching the intestine. Altering the gastric pH with histamine$_2$ receptor antagonists, for example, may increase susceptibility to infection. Gastrointestinal flora inhibits the proliferation and colonization of *Salmonella* by secreting bacteriocins, short-chain fatty acids, and other substances that are toxic to *Salmonella*. In addition,

elements of the normal flora compete for nutrients and space, especially on the mucosa.[16] Being predominantly anaerobic, the normal flora maintain a low oxidation-reduction potential in the environment of the large intestine, which inhibits the growth of many bacterial pathogens.[17] The importance of normal host gastrointestinal ecology is illustrated by the fact that disturbances of the colonic flora with antibiotics, changes in feed, ileus, or other underlying gastrointestinal disease greatly increase the susceptibility of the host to infection by *Salmonella*, often resulting in serious disease.

The immune status of the host may be one of the most important factors determining not only the susceptibility to *Salmonella* infections but also the degree of invasion and subsequent outcome of the infection. Local immunity, such as mucosal antibody secretion and enterocyte-derived cationic peptides, prevents colonization of the mucosa.[16,18,19] Opsonizing antibodies and activation of the complement cascade are important in fighting systemic invasion by *Salmonella* by increasing the efficiency of phagocytosis and by direct bactericidal activity. Humoral immunity, however, is often ineffective in

preventing disease and dissemination once invasion occurs and *Salmonella* has established in its intracellular niche. Following invasion, *Salmonella* is capable of surviving and multiplying within macrophages, rendering humoral (noncellular) immune systems ineffective.[20,21] Specific cellular immunity may be the most effective defense mechanism in the host arsenal against dissemination and systemic infection by *Salmonella*.[21,22] Oral inoculation with small numbers of virulent organisms may induce protective immunity in horses and calves, but the duration of the immunity is not known.[23,24] Oral and parenteral vaccines using killed or attenuated organisms and bacterial products have been promising but are effective only against homologous organisms and are usually not cross-protective among different serogroups.[23-25]

In adult horses, *Salmonella* primarily infects the cecum and proximal colon, causing enterocolitis, and the ability to disseminate beyond the intestine and cause enteric fever is limited. In foals, however, salmonellosis often is associated with septicemia. The ability of *Salmonella* to cause enterocolitis depends on the ability of the bacteria to invade the gastrointestinal mucosa.[16,20] Invasion of the gastrointestinal mucosa occurs preferentially through specialized enterocytes called M cells that overlay intestinal lymphoid tissues such as Peyer's patches in nonequine species. A variety of enteric pathogens exploit M cells during infection of intestinal tissue.[26] Invasion of the epithelium occurs by self-induced uptake via the apical membrane of the M cell, often killing the cell in the process.[20] Salmonellae then invade neighboring cells via the basolateral membrane, eventually spreading the destruction of the epithelium beyond the principle area of attack. Virulent salmonellae have a well-developed invasion mechanism involving generation of an apparatus called a type III secretory system that enables virulence gene products to be injected directly into enterocytes.[27] Virulence proteins injected by salmonellae into enterocytes engage the cellular machinery and induce the cell to engulf the bacteria by macropinocytosis. *Salmonella* virulence gene products also induce enterocyte chloride and fluid secretion and upregulate enterocyte transcription of inflammatory cytokines (tumor necrosis factor α and interleukin-1β) and chemokines that trigger a mucosal inflammatory response.[20,27,28]

After salmonellae invade the mucosa, they are phagocytosed quickly by macrophages and dendritic cells in the lamina propria and lymphoid tissues. The ability of salmonellae to disseminate systemically and cause enteric fever is associated with the ability to survive and proliferate in macrophages. Indeed, phagocytes have an important role in dissemination of the pathogen to blood, lymph nodes, liver, and spleen. Most salmonellae in the blood and tissues of infected animals that are competent to cause enteric fever are within phagocytic cells.[29]

In adult horses with salmonellosis, dissemination appears to be limited to the intestine and mesenteric lymph nodes, and *Salmonella* rarely is cultured from blood. However, in foals and in some adults, *Salmonella* causes an enteric feverlike disease with dissemination to mesenteric lymph nodes, liver, spleen, and blood.

Salmonella organisms require specific virulence gene clusters encoded on the chromosome or on plasmids for intracellular survival in macrophages.[20] Some of these genes are sensors that signal the bacteria that it has entered an intracellular environment and turn on genes required for intracellular survival. Others, like invasion genes, are transported from the bacteria and injected into macrophage cytosol by a type III secretory system to prevent phagosome/lysosome fusion and subvert other essential macrophage killing mechanisms. Salmonellae also possess multiple genes that confer resistance to reactive oxygen and nitrogen metabolites, perhaps the most lethal antimicrobial mechanisms of macrophages.[30]

Diarrhea associated with salmonellosis has multiple causes. A *Salmonella* cytotoxin inhibits protein synthesis in mucosal cells, causing morphologic damage and altered permeability.[31] Virulent salmonellae also produce an enterotoxin similar to the heat-labile toxin (LT) produced by *Escherichia coli*.[32,33] The enterotoxin contributes to but is not required in the pathogenesis of diarrhea.[34,35] *Salmonella* enterotoxin increases secretion of chloride and water by colonic mucosal cells in many species, including horses, by increasing intracellular cyclic adenosine monophosphate concentrations.

The ability of virulent salmonellae to cause diarrhea appears to be associated most closely with the ability to invade enterocytes and to trigger an inflammatory reaction in the intestinal tissue.[20,36] Gene products injected into enterocyte cytosol by the type III secretory system of invading salmonellae stimulate chloride and fluid secretion.[27] *Salmonella* invasion of enterocytes is also a potent activator of inflammatory chemokine and cytokine production, resulting in the recruitment of leukocytes, particularly neutrophils, and activation of resident macrophages and mast cells. Products of these activated leukocytes, including prostaglandins, leukotrienes, reactive oxygen metabolites, and histamine, are potent stimulators of chloride secretion in the colon of many species.[16,37-39] The enteric nervous system integrates the diverse processes of pathogen recognition, triggering of the inflammatory response, and induction of enterocyte fluid secretion.[39]

Many of the inflammatory mediators studied stimulate colonic secretion by prostaglandin-dependent mechanisms, resulting in increased intracellular cyclic adenosine monophosphate or calcium concentrations or both in mucosal cells.[37] In addition, these mediators and the enteric nervous system may stimulate secretion by

prostaglandin-independent mechanisms, inhibit sodium and water absorption, cause motility disturbances, and potentiate tissue injury, all of which enhance the pathogenicity and dissemination of *Salmonella* and contribute to the pathogenesis of diarrhea.[37,39] Neutrophils recruited to the mucosa by signals generated by the infected enterocytes physically contribute to mucosal injury by producing a variety of products that are lethal to pathogens but are also toxic to host cells.[40,41] Moreover, neutrophils attracted to infected epithelial cells accumulate beneath the monolayer, lifting it off the basement membrane in sheets. Neutrophils also migrate across the epithelial monolayer in potentially massive numbers. Transepithelial migration of neutrophils increases the permeability to macromolecules, bacterial products, and even bacteria.[41] Potentially massive losses of electrolytes, water, and protein can occur depending on bacterial and host factors. Perhaps most devastatingly, mucosal injury and altered permeability allow systemic absorption of bacterial products and dissemination of bacteria, resulting in systemic inflammatory responses such as occur with endotoxemia and septicemia.

Clinical Signs and Diagnosis

Four syndromes of *Salmonella* infection have been described clinically and reproduced experimentally in horses: (1) inapparent infections with latent or active carrier states; (2) depression, fever, anorexia, and neutropenia without diarrhea or colic; (3) fulminant or peracute enterocolitis with diarrhea; and (4) septicemia (enteric fever) with or without diarrhea. Inapparent infections can be activated to clinical disease in compromised horses, such as horses with colic or horses being treated with antibiotics, causing mild to severe enterocolitis. In addition, latent infections (nonshedding) can become active infections (shedding) under certain conditions, such as transportation stress and antibiotic treatment. Horses with depression, anorexia, fever, and neutropenia without diarrhea generally have a good prognosis and recover in several days without specific treatment.[42] The septicemic form is restricted mostly to neonatal foals and is uncommon in adult horses. This discussion focuses on acute enterocolitis.

Acute enterocolitis is characterized by severe fibrinonecrotic typhlocolitis, with interstitial edema and variable degrees of intramural vascular thrombosis that may progress to infarction.[1] Severe ulceration of the large intestinal mucosa may occur with serosal ecchymoses and congestion. The earliest signs of enterocolitis are usually fever and anorexia.[1,15] Signs of colic may be apparent early in the course of the disease, especially if ileus is present. Clinical signs of endotoxemia are common and range from fever, elevated heart and respiratory rates, poor peripheral perfusion, and ileus to fulminant and rapidly

progressive signs of endotoxemic shock. Oral mucous membranes are often pale with perigingival hyperemia (a toxic rim) but may be brick red or cyanotic, with prolonged capillary refill time. One may note weakness, muscle fasciculations, cold extremities, and other signs suggestive of hypotensive shock; synchronous diaphragmatic flutter; abdominal pain; and significant metabolic and electrolyte abnormalities in severe cases of enterocolitis. One also may note signs of mild dehydration before diarrhea is apparent. Once diarrhea is evident, dehydration may become severe rapidly. Occasionally, horses die peracutely, without developing diarrhea.

Diarrhea may not be apparent for several days but usually occurs by 24 to 48 hours after the fever begins.[1,15] The duration of the diarrhea may be days to weeks. The character of the first diarrheal feces is usually watery with particles of roughage but may become fluid rapidly without solid material. Finding frank blood and fibrin in the feces is unusual. The volume of feces is often large, with frequent defecation. One may note straining or signs of colic when the patient is defecating, and rectal prolapse may occur occasionally. Persistent straining and rectal prolapse may be a sign of colonic infarction. Abdominal borborygmi are often absent early in the course of the disease because of ileus but become evident later, usually when diarrhea begins. Fluid and gas sounds are commonly audible, but normal progressive motility is less frequently audible than normally. Transrectal palpation may reveal edematous rectal mucosa and colon and fluid-filled colon and cecum. One may obtain gastric reflux, especially early in the course when ileus is evident.

Hematologic abnormalities early in the course of the disease include moderate to severe neutropenia, lymphopenia, and leukopenia, a mild to moderate left shift, and toxic changes in the neutrophils.[1,15] Thrombocytopenia, moderate to severe hemoconcentration, and hyperfibrinogenemia are also common. Neutropenia is an early but nonspecific indicator of salmonellosis, often occurring concurrently with the onset of fever.[1] Later in the course of disease, one may see neutrophilic leukocytosis, indicating recovery. A degenerative left shift, with metamyelocytes and myelocytes in the peripheral blood, is a poor prognostic sign.

Serum biochemical analysis may reveal azotemia, elevations in serum sorbitol dehydrogenase and γ-glutamine aminotransferase activity, and elevated serum lactic acid concentration. Azotemia is often prerenal, but acute hemodynamic renal failure may occur in severely dehydrated, endotoxemic, or septicemic patients. Indeed, elevation of creatinine concentration is a poor prognostic indicator in horses with acute colitis.[43] Hemodynamic renal disease may be complicated by toxic injury caused by administration of nephrotoxic drugs. Hyponatremia may also contribute to prerenal azotemia. Elevations

in hepatocellular enzymes are usually mild and reflect damage to the hepatocytes from absorbed toxins such as endotoxin and from poor perfusion caused by hypotensive shock or dehydration. Lactic acidemia may be present, reflecting poor tissue perfusion. Plasma protein rapidly drops as protein is lost in the gastrointestinal tract, causing moderate to severe hypoalbuminemia and hypoglobulinemia. Peripheral or organ edema (vascular leak syndrome) may occur if hypoproteinemia is severe, coupled with increases in endothelial permeability induced by systemic inflammation.

Hypokalemia, hyponatremia, hypochloridemia, and hypocalcemia are common electrolyte abnormalities in patients with enterocolitis. Metabolic acidosis also may be present. Coagulopathies, such as decreased antithrombin III activity and disseminated intravascular coagulation, may occur. Urinalysis may reveal isosthenuria, proteinuria, hematuria, cylindruria, and glucosuria if hemodynamic or toxic renal injury is present. The number of leukocytes in the feces usually is elevated, and occult blood may be detectable. Peritoneal fluid is usually normal except when severe mural inflammation or colonic infarction occurs.

Routine detection of salmonellae in feces involves five daily cultures of large samples (10 to 30 g) of feces using enrichment techniques.[1,44,45] However, the sensitivity of fecal culture can be as low as 30% to 50%, even if one cultures several fecal samples collected daily. Concurrent culture of rectal biopsy specimens and feces increases the sensitivity of culture techniques to 60% to 75%.[45] Currently, the polymerase chain reaction (PCR) is the most sensitive and rapid test for detecting *Salmonella* in feces. A single PCR test applied early in the course of disease is a more sensitive test for the presence of *Salmonella* than repeated fecal cultures.[46,47] Detection of salmonellae in feces does not prove a diagnosis of salmonellosis, but the positive predictive value of a positive PCR or culture results is high in horses with compatible clinical signs. Culture of peripheral blood may allow isolation of the organism if bacteremia or septicemia is present, but blood cultures are not a sensitive test for salmonellosis in adult horses. Although foals are more likely than adults to become septicemic, culture of blood is recommended in all cases with signs suggestive of septicemia. Increased numbers of fecal leukocytes suggest an invasive process in the colon but are not specific for salmonellosis.

Early in the course of the disease, dehydration, electrolyte and acid-base imbalances, endotoxemia, and sepsis may be life threatening. Aggressive treatment during the acute stages to replace fluids lost in the diarrhea and to control sepsis and endotoxemia is often effective in controlling the primary disease. Weight loss and hypoproteinemia are often severe. Complications such as multiorgan dysfunction, vascular leak syndrome with peripheral and organ edema, laminitis, acute renal failure, venous thrombosis and septic phlebitis, irreversible protein-losing enteropathy or chronic malabsorption, pulmonary aspergillosis, and gastrointestinal infarction can occur. In many instances, horses recover from acute salmonellosis with aggressive treatment, only to succumb to complications of the disease, partially explaining the high fatality rate of equine salmonellosis compared with human salmonellosis. Chronic, mild to moderate diarrhea occasionally occurs in horses after a bout of severe salmonellosis, usually with protein-losing enteropathy. If the chronic diarrhea persists beyond 4 to 5 weeks after the onset of signs, the prognosis for recovery is poor.[15]

POTOMAC HORSE FEVER
Pathogenesis
Potomac horse fever (equine monocytic ehrlichiosis) is caused by the obligate intracellular rickettsial organism *Neorickettsia risticii*.[48-51] The disease is most common from late summer to early fall, with a peak incidence in July and August. Potomac horse fever was described first in the Northeast but since has been diagnosed in most areas of the continental United States, with a particularly high prevalence in the Northeast and Midwest. The geographic distribution is characterized by a significantly higher percentage of cases found along waterways and rivers.[48,49] The disease occurs sporadically, temporally and geographically, and can affect any age group of horses. The case fatality rate is 5% to 30%.[48]

Transmission of *N. risticii* has been reproduced experimentally by oral, intramuscular, intradermal, subcutaneous, and intravenous routes.[48,52] However, the natural route of infection has remained a mystery until recently. The epidemiologic data, the fact that many other rickettsial diseases are transmitted by insect vectors, and the finding that the disease can be transmitted via whole blood have implicated insect vectors in the natural transmission of the organism. Attempts to transmit the disease experimentally with ticks *(Dermacentor variablis)* or biting flies *(Stomoxys calcitrans)* have been unsuccessful.[53,54] Recently, *N. risticii* has been found to infect virgulate cercariae larval stages of trematodes that use operculate freshwater snails (*Juga* spp.) as part of their life cycle in northern California.[55] Infected virgulate cercariae have been identified in aquatic snails collected in other parts of the country as well. Virgulate cercariae are part of the life cycle of trematodes that are common parasites of many species and use freshwater snails and aquatic insects as intermediate hosts. Although the trematode species infected with *N. risticii* remains to be identified definitively, at least two species are considered potential vectors.[52] During the trematode life cycle, aquatic snails release large numbers of infected cercariae into

water, where they seek their next intermediate host. Infected metacercaria have been identified in a variety of aquatic insects.[56] Preliminary studies suggest that *N. risticii* in fact may be transmitted via ingestion of mature caddis flies containing infected metacercariae.[57] Possibly horses are infected by drinking water containing infected cercaria released from snails or by ingesting infected metacercariae in other aquatic insects.[52] The number of PCR-positive snails in endemic regions corresponds to the seasonal incidence of Potomac horse fever and may be as high as 26%.[58]

The pathogenesis of *N. risticii* is not understood completely. The organism infects and survives in monocytes and monocyte-derived leukocytes and can be found in blood monocytes during natural infections, but the sequence of events resulting in enterocolitis remains speculative. The organism appears first to infect blood monocytes in experimentally infected horses, which may be the vehicle of organ infection.[50,59] However, in naturally infected horses, whether leukocytes of monocytic lineage or epithelial cells are infected first is unclear. The target organ is the gastrointestinal mucosa, with the most severe lesions found in the large intestine.[59,60] Infection of human colonic cells in vitro does not cause major cytopathologic effects for several days. Disruption of the microvilli in the region of the plasma membrane where sodium chloride channels are located has been observed in human colonic cell cultures.[61] Infection in horses is associated with variable degrees of morphologic damage.[59,60] Mild morphologic damage and mononuclear cell infiltration of the lamina propria occur early during the infection, but fibrinous, necrotizing typhlocolitis with severe mucosal ulceration and inflammation of the lamina propria may occur later in the disease. Vasculitis and intravascular coagulation are consistent features in the large intestine, with perivascular edema.[60] One can observe *N. risticii* in mucosal cells and macrophages and mast cells of the lamina propria.[59,60] *N. risticii* can survive and multiply in macrophages by inhibiting the production of reactive oxygen intermediates and by avoiding lysosomal digestion by blocking phagosome-lysosome fusion.[62-64]

Evidence of impaired sodium chloride absorption in the colon has been suggested to contribute to diarrhea in infected horses and may be related to destruction of the enterocyte membrane structure in the region of sodium chloride channels.[61,65] Direct injury to the mucosa by *N. risticii* and colonic inflammation are likely to be prominent features leading to diarrhea, especially later in the disease.[60] Fluid, protein, and electrolyte loss likely is caused by mucosal injury and effects on enterocyte fluid secretion caused by the inflammatory response. Like other inflammatory conditions of the colon, systemic inflammation caused by absorption of bacteria and bacterial products is a potential complication of *N. risticii* infections if

mucosal injury is severe, which contributes to the clinical signs seen during the disease.

Clinical Signs and Diagnosis
N. risticii infection is clinically similar to other forms of enterocolitis and is characterized by anorexia, depression, and fever.[48,60,66] Experimental infections produce a biphasic fever occurring 6 to 7 days apart. Decreased gastrointestinal motility, manifested as reduced borborygmi, occurs during the early stages before the onset of diarrhea. Diarrhea occurs in 75% of cases and occurs 2 days after the second fever episode during experimental infections.[66,67] The diarrhea can be moderate to severe and dehydrating. Ileus can develop at any stage of the disease and can cause signs of moderate to severe colic. Systemic signs of endotoxemia, shock, and peripheral edema may occur and are similar to those described for salmonellosis. Experimental and natural infection with *N. risticii* can cause abortion of infected fetuses in pregnant mares.[68,69] Laminitis is a complication in 20% to 30% of naturally occurring cases and is often severe. Other complications include protein-losing enteropathy, thrombosis, and renal failure, as described for salmonellosis.

Hematologic abnormalities reflect endotoxemia, dehydration, and sepsis and are essentially identical to those described for salmonellosis. Neutropenia with a left shift is a consistent feature and occurs concurrently with or soon after the onset of diarrhea. Thrombocytopenia is common and often severe.[67] Neutrophilic leukocytosis occurs later in the course of the disease. Hyperfibrinogenemia is usually more pronounced than that with salmonellosis. Serum electrolyte, acid-base, and biochemical abnormalities are also similar to those described for salmonellosis. Coagulopathies are common during *N. risticii* infection and reflect activation of coagulation pathways. Disseminated intravascular coagulation is common and may be related to the high frequency of laminitis associated with *N. risticii* infection.[70]

One cannot base diagnosis of *N. risticii* infection solely on clinical signs because the disease is clinically similar to other forms of enterocolitis. However, in endemic areas, acute colitis is likely to be caused by *N. risiticii,* and thus the clinical signs of acute inflammatory colitis in fact may have a high predictive value. Serologic evidence of infection, such as rising antibody titers to *N. risticii* detected by indirect immunofluorescence or enzyme-linked immunosorbent assay in paired serum samples may be helpful in establishing a diagnosis.[49,71] One should take care when interpreting the indirect immunofluorescence serologic test for *N. risticii* because the test appears to have a high false-positive rate.[72] Culture of the organism from blood is possible but is difficult and is generally useful only in the research laboratory. Recently developed polymerase chain PCR tests for *N. risticii*

DNA are rapid, highly sensitive (as sensitive as culture), and specific for *N. risticii* infection and can be applied to blood or feces.[73-75]

Prevention

Prevention of the disease by reducing exposure to the causative organism is difficult because the mode of transmission is not known. A killed vaccine has been developed that is effective in preventing clinical illness other than fever in 80% of experimentally challenged horses using the vaccine strain. However, field studies suggest the vaccine has limited benefit for prevention or decreasing the severity of natural infection. Vaccine failures have been attributed to strain differences in antigenicity or to poor antibody responses to the vaccine.[76,77]

EQUINE INTESTINAL CLOSTRIDIOSIS
Pathogenesis

Clostridiosis is an important cause of acute enterocolitis in foals and adult horses. *Clostridium perfringens* and *C. difficile* are associated most commonly with intestinal clostridiosis in horses, but other clostridial species, including *C. septicum, C. cadaveris,* and *C. sordellii* also have been isolated from horses with enterocolitis.[78-83] In horses of all ages, clostridial enterocolitis appears to be a common antibiotic-associated and nosocomial cause of enterocolitis.[82,84,85] However, clostridiosis in neonatal foals is a distinct clinical entity and is discussed in more detail elsewhere. This chapter focuses on adult intestinal clostridiosis.

Clostridia are obligate anaerobic to aerotolerant spore-forming gram-positive rods that are ubiquitous in the environment in the spore form.[83] Clostridia are elements of the normal flora of horses of all ages and are among the first bacteria acquired after birth. However, clostridia inhabiting the gastrointestinal tract normally are found in low numbers and do not produce enterotoxins. Clostridiosis is associated with an increase in the number of a particular species of clostridia in the gastrointestinal tract and, perhaps most importantly, exotoxin production. Although the conditions resulting in exotoxin production are not understood fully, several factors increase clostridial numbers in the gastrointestinal tract. Dietary factors are known to affect the numbers of *Clostridium* species shed in the horse feces.[78] Experimental induction of colic increases fecal shedding of *Clostridium* species in the absence of diarrhea.[86] Antibiotics, particularly administered orally or recycled via the enterohepatic system, are well documented to increase the recovery of clostridia colony-forming units (CFUs) in equine feces and may result in clinical clostridiosis.[79,81,87-90] Indeed, clostridiosis associated with *C. perfringens* or *C. difficile* is likely to be the most important cause of antibiotic-induced enterocolitis in the horse.

Clostridium perfringens *C. perfringens* is made up of many genetically distinct strains of variable virulence that produce one or more of a large group of exotoxins. The pattern of exotoxin production is used to classify *C. perfringens* into five types, A, B, C, D, and E. *C. perfringens* type A is the most common clostridium isolate from healthy horses of all ages and adults and foals with diarrhea worldwide. *C. perfringens* types A, B, C, and D have been associated with hemorrhagic enteritis in foals less than 10 days of age, with type C being the most common cause in North America.

The primary toxin produced by *C. perfringens* type A is α-toxin (phospholipase C), which interferes with glucose uptake and energy production and activates arachidonic acid metabolism and signaling pathways in enterocytes.[83] Oral administration of α-toxin does not cause tissue necrosis but causes increased secretion by small intestinal mucosal cells in human beings.[91,92] The β-toxin of types B and C is a cytotoxin that causes enterocyte necrosis, ulceration, and ultimately severe intestinal inflammation and hemorrhage.[93] A novel toxin designated β2 may also have a role in *C. perfringens* enterocolitis.[94] The biologic activity of the β2-toxin is similar to β-toxin, but β2-toxin is not related to β-toxin in sequence. The β2-toxin was prevalent in two groups of horses with acute enterocolitis but not in healthy horses.[95] The β2-toxin appears to be associated predominantly with *C. perfringens* that would have been classified otherwise as type A but that in fact may represent a previously undescribed type.

Virulent strains of *C. perfringens* type A and to a lesser extent type C also may produce enterotoxin. Enterotoxin is a cytotoxin that inserts into cell membranes to form pores, which alter permeability to water and macromolecules and ultimately lead to cellular necrosis.[96] Massive desquamation of the intestinal mucosa resulting from enterotoxin cytotoxicity triggers an inflammatory response, intestinal edema, mural hemorrhage, and systemic inflammation.[97] Enterotoxin also alters tight junction integrity, resulting in increased paracellular permeability by a noncytotoxic mechanism.[98]

Clostridium difficile *C. difficile* produces several toxins, but only two, toxin A and toxin B have been studied in detail. Toxin B is a potent cytotoxin in vitro, but its role in enterocolitis is less clear than the role of toxin A. Toxin B does not induce fluid secretion, inflammation, or characteristic alterations in intestinal morphology. *C. difficile* induces an inflammatory response with hypersecretory diarrhea that is induced in large part by the enterotoxin toxin A.[99] Toxin A induces neutrophil influx into intestinal tissue, mast cell degranulation, and secretion of prostaglandins, histamine, cytokines, and 5-hydroxytryptamine by these activated leukocytes.[100,101] The products of neutrophils and mast cells have a

prominent role in the vasodilatory and secretory responses in the intestine during *C. difficile* infection.

The enteric nervous system is central to the induction of intestinal inflammation and mucosal secretion by toxin A. A model for toxin A–induced secretory diarrhea has emerged in which toxin A stimulates substance P–containing afferent sensory nerve fibers, which in turn stimulate mast cell degranulation, recruitment and activation of polymorphonuclear leukocytes, and vasodilation.[102-104] Toxin A–induced stimulation of enterocyte secretion can occur via secretomotor neuronal stimulation by substance P–containing sensory neurons or products of mast cells and polymorphonuclear leukocytes. Neural blockade or depletion of substance P abolishes mast cell degranulation, polymorphonuclear leukocyte influx, and enterocyte secretion. How toxin A triggers the sensory component of the enteric nervous system is not known yet, but toxin A–induced necrosis of enterocytes likely exposes afferent neurons to the noxious milieu of the intestinal contents.

Clinical Signs and Diagnosis

Equine intestinal clostridiosis is clinically similar to other forms of acute enterocolitis in horses.[78,83] Although the clinical course is usually acute, peracute colitis with rapid death may occur. Occasionally, a milder, more prolonged clinical course occurs. One may note fever, anorexia, and depression before the onset of gastrointestinal signs, but more commonly no prodromal signs are apparent. Signs of endotoxemia and shock may accompany acute signs of colic and severe, dehydrating diarrhea. Diarrhea may not be profuse but is usually dark and foul smelling. Like the clinical signs, hematologic and serum biochemical abnormalities are similar to those associated with other forms of enterocolitis and reflect fluid, protein, and electrolyte loss and systemic inflammation from endotoxemia. Neutropenia, leukopenia, and hemoconcentration are common. Hypoproteinemia may be profound. One often may note hyponatremia, hypokalemia, hypochloremia, hypocalcemia, and a mixed prerenal/renal azotemia, as well as metabolic acidosis and coagulopathies. Serum concentrations of hepatocellular enzymes such as sorbitol dehydrogenase may be elevated, and liver function may be reduced.

Preliminary diagnosis of equine intestinal clostridiosis caused by *C. perfringens* is based on the isolation of greater than 100 CFUs of *C. perfringens* type A per gram of feces from patients with diarrhea and signs suggestive of toxemia. Similar criteria are used to screen human patients for *C. perfringens* type A infection. Normal horses shed fewer than 100 CFUs/g of feces, and usually horses with intestinal clostridiosis shed greater than 1×10^6 CFUs/g.[78,105] However, identification of increased numbers of *Clostridium* organisms in the feces does not prove infection. Detection of *C. perfringens* toxins in feces or intestinal contents in horses with increased numbers of fecal CFUs and clinical signs of enterocolitis is more conclusive evidence of an enterotoxigenic infection than culture alone. Immunoassays are available that are primarily designed to detect *C. perfringens* enterotoxin.[83] However, the reliability (specificity) of some immunoassays for diagnosis of *C. perfringens* infection has come into question. Recently, PCR multiplex and gene probe assays have been developed to detect the major lethal toxins in isolates or fecal samples to determine the pattern or toxin production and are currently the preferred methods of detection.[106-108]

As for *C. perfringens,* diagnosis of *C. difficile* infection consists of culture of the organism from feces and identification of toxins in the feces. Bacterial culture of *C. difficile* may be difficult and may be an insensitive test in horses.[109-110] Detection may require enrichment techniques and culture of multiple fecal samples.[110,111] Detection of toxins A and B in feces is regarded as the preferred test for diagnosis of *C. difficile* infection in human beings.[83] Commercial enzyme-linked immunosorbent assays are available for toxins A and B that are specific and appear to be more sensitive than a single culture for identifying *C. difficile* infection in adult horses.[109,110] One also may induce toxin production by *C. difficile* isolates. Sensitive PCR methods also have been developed for application to fecal samples and isolates to detect the genes for toxins A and B.[83]

PROLIFERATIVE ENTEROPATHY
Pathogenesis

Proliferative enteropathy is a chronic hyperplastic disorder of the small intestine and has been described in a variety of mammalian and avian species.[112,113] The only causative agent identified to date that induces proliferative enteropathy is the obligate intracellular pathogen *Lawsonia intracellulare*.[113,114] The pig is the most frequently naturally affected species. However, the reports of equine proliferative enteropathy associated with *L. intracellulare* have increased in recent years.[115-118] The relatedness of the strains of *L. intracellulare* causing proliferative enteropathy in pigs and horses or even among other affected species is not known. No host restriction is apparent because hamsters and other rodents can be infected with porcine strains of *L. intracellulare*. Before the year 2000, reports of proliferative enteropathy in the literature describing isolated cases were sporadic.[116-118] However, since 2000, outbreaks on breeding farms have been documented on farms in Canada, suggesting that a new strain has emerged.[115]

The mode of infection is fecal-oral, and infected animals can shed large numbers of organisms in feces.[113]

Affected animals shedding the organism in the feces serve as a source of infection for herdmates. Possibly nonequine species serve as reservoirs contributing to outbreaks on horse farms. Factors that increase the risk of proliferative enteropathy in pigs include overcrowding, ration changes, transport, and weaning.[113,114] Like pigs, horses are affected as weanlings. Factors associated with weaning and other stresses may affect immunity and increase susceptibility to infection. The incubation period is 2 to 3 weeks in nonequine species and is presumed to be similar in horses.

Experimental *L. intracellulare* infection produces characteristic pathologic lesions in pigs and hamsters that are identical to lesions in horses with proliferative enteropathy.[113,114] A profound hyperplasia of the mucosa predominantly caused by proliferation of crypt epithelium and crypt hyperplasia is induced locally in infected islands of tissue and eventually extends to the entire distal jejunum and ileum. *L. intracellulare* preferentially infects proliferating cells, thus the tropism for the crypt epithelium. Infected cells proliferate far more rapidly than uninfected cells, suggesting that *L. intracellulare* directly induced the proliferative response. However, the molecular basis for the enhanced proliferation is not known. *L. intracellulare* penetrates epithelial cells in a membrane-bound vesicle but eventually escapes the vacuole and is found free in the cytoplasm concentrated at the apical pole of the cell.

The gross pathologic lesions found in equine proliferative enteropathy are characteristic.[115-118] Lesions may be segmental and typically are found in the ileum and terminal jejunum in horses. However, lesions also may affect the duodenum. Severe mucosal hypertrophy often occurs but may wane during the chronic stages of the disease. The mucosa may become corrugated with focal erosions or ulcers. One often can identify submucosal edema easily on cut sections of affected segments. Moderate to severe crypt hyperplasia with atrophy of the intestinal villi is a consistent feature. The hyperplastic crypts are branched and may herniate into the submucosa. Necrosis, edema of the submucosal and lamina propria, hemorrhage, mononuclear inflammation and muscular hypertrophy have been reported in affected intestinal segments but are not consistent. Special stains such as silver stain are required to detect intracellular organisms. The organisms are curved or comma-shaped rods found clustered in the apical cytoplasm of hyperplastic crypt epithelium.

The proliferative response of the intestinal mucosa alters absorption of nutrients and fluid secretion by disrupting the architecture of the villi and by altering the maturation of epithelial cells into absorptive cells, accounting for the secretory diarrhea and often severe weight loss.[112,114] The combined effects of the inflammatory response and malabsorption may account for the protein-losing enteropathy.

Clinical Signs and Diagnosis

Proliferative enteritis most commonly affects weanling foals ages 4 to 6 months. The clinical signs of proliferative enteropathy include ill thrift, weight loss, peripheral edema, diarrhea, and colic.[115-118] The diarrhea is usually in the form of soft feces but may be profuse and watery. Some foals with mild diarrhea have black, tarry feces. Secondary complications such as gastric ulceration, bronchopneumonia, or parasitism may occur concurrently with the proliferative enteropathy. Clinicopathologic features include mild to moderate anemia, moderate to severe hypoalbuminemia (often <2 g/dl), hypoglobulinemia, neutrophilic leukocytosis, and hyperfibrinogenemia. Creatine kinase activities may be elevated in affected foals. Prerenal azotemia and electrolyte imbalances such as hyponatremia may be associated with diarrhea. Peritoneal fluid analysis is usually unremarkable. Ultrasonographic examination of the small intestine often reveals significant thickening of the intestinal wall (Figure 13.13-1). Intestinal edema may be evident as a hypoechoic appearance to one or more layers of the intestinal wall.

Methods for antemortem diagnosis include serologic analysis of *L. intracellulare* antibodies and PCR analysis of feces.[115] Serologic analysis using an indirect immunofluorescent antibody test may be the most useful single test available. The PCR test is specific but the sensitivity may be low. By the time clinical signs appear, 90% of pigs are serologically positive for anti–*Lawsonia intracellulare* immunoglobulin G (IgG). In contrast, only 37% of pigs had positive fecal PCR tests.[119] Of the seven foals tested in an outbreak of equine proliferative enteropathy,[115] four foals with confirmed disease and three with suspected
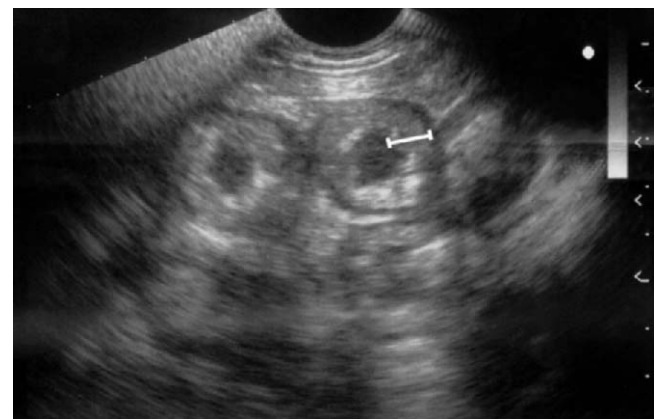
Figure 13.13-1   Ultrasonogram of the small intestine in a weanling foal with weight loss, diarrhea, and hypoproteinemia. The extreme mural thickening of the small intestine *(bar)* is typical of proliferative enteropathy.

proliferative enteropathy had serologic titers against *L. intracellulare* of 1:30 or greater. In contrast, serum samples collected from 72 foals before the outbreak were negative for *L. intracellulare* antibodies. Fecal PCR for *L. intracellulare* was positive in 6 of 18 foals tested, and half of the serologically positive foals had negative fecal PCR tests. Many clinicians combine serologic analysis with fecal PCR testing to increase the sensitivity and specificity of these diagnostic methods. Isolation and culture of the organism requires cell culture techniques that are not widely available. Thus no practical method exists for culturing the organism from feces or tissues that is available for clinical use.

Definitive diagnosis requires histopathologic examination of affected tissues.[112] Diagnosis is based on typical histopathologic findings of mucosal hypertrophy and submucosal edema and identification of small, curved, rod-shaped intracellular bacteria at the apical pole of epithelial cells in affected segments of intestine. Special stains such as Warthin-Starry silver stain are required to detect the bacteria in histopathologic specimens. PCR analysis of affected intestinal tissue is a specific test for the presence of *L. intracellulare* and, unlike fecal PCR analysis, appears to be sensitive.[120]

STRONGYLOSIS
Pathogenesis
Strongyle infections in horses are caused by two groups of nematodes: large and small strongyles (see the section Cyathostomiasis). Large strongyles that are pathogenic in horses include *Strongylus vulgaris, S. edentatus,* and *S. equinus.* Of these species, *S. vulgaris* is by far the most important cause of disease in the large intestine and in fact is the most pathogenic parasitic infection in horses. *S. vulgaris* infection in horses is manifested clinically by two forms: acute and chronic disease.[121] The age and resistance of the host, the infective dose, and the size and function of the affected arteries influence the type and degree of disease that occurs. Sudden ingestion of large numbers of infective larvae by a naïve host causes acute strongylosis, whereas ingestion of fewer infective larvae over a long period of time by an older, more resistant host causes chronic strongylosis. Acute strongylosis is more likely to cause colic than diarrhea and may be rapidly fatal. Chronic strongylosis tends to cause debilitation and signs of colic but may also cause diarrhea.

Diarrhea associated with acute strongylosis occurs within several days of infection and is likely to be caused by migration of the larvae through the intestinal wall. Fourth-stage larvae migrate through the mucosa and submucosa into the arterioles of the intestine, causing mural edema, hemorrhage, and infiltration with inflammatory cells into the intestinal wall.[121,122] Increased secretion and decreased absorption of fluid and electrolytes, stimulated by inflammatory mediators such as prostaglandins and histamine, may play a role in the diarrhea induced by *S. vulgaris.* Interstitial edema and damage to the interstitial matrix and mucosa may result from inflammation and migration of the parasites, causing increased secretion of fluid and albumin loss. Abnormal gastrointestinal motility also may play a role in the development of diarrhea. Migration of larvae through the intestinal wall early in the course of infection affects myoelectric activity and motility in the large intestine and may affect retention of ingesta and absorption of fluid.[123,124] The cause of death in acute strongylosis has not been addressed but may be related to massive migration through the vasculature, causing thrombosis with ischemia and infarction of the intestine.

Chronic strongylosis causes typical verminous arteritis and is associated more commonly with natural infections in horses than with acute strongylosis.[121] Lesions of the large intestinal vasculature caused by migration of larvae through the intima are characterized by thrombus formation, narrowing of the arterial lumen, fibrosis, and thickening of the arterial wall.[121,122] Embolization may occur, causing acute segmental infarction of the large intestine, but more commonly reduced blood flow without embolization causes ischemia and occasionally infarction.[122,125] Postmortem examination of horses with colonic infarction failed to reveal embolization as the cause in most cases.[125] Reduced blood flow in the tissues of the intestine usually results from narrowing of the arterial lumen by the thrombus and formation of microthrombi at sites independent of the parasites. Release of vasoconstrictive inflammatory mediators such as leukotrienes from platelets, neutrophils, and eosinophils and elaboration of parasitic antigens or toxins may cause vasoconstriction and ischemia.[126] Horses with experimental strongylosis were found to have a 50% reduction of blood flow in the colonic vasculature.[127]

Clearly, reduced blood flow is an important effect of chronic strongylosis, but the relationship between blood flow and diarrhea is unclear. Disrupted motility resulting from ischemia may lead to diarrhea by reducing the retention of ingesta and absorption of fluid. Acute infarction and mucosal ulceration have been found to cause severe chronic diarrhea in naturally infected horses.[128] Release of inflammatory mediators such as prostaglandins, histamine, and kinins from inflammatory cells associated with thrombi and inflamed intestine also may affect secretion, absorption, and motility, leading to diarrhea.

Clinical Signs and Diagnosis
The clinical signs of acute strongylosis caused by *S. vulgaris* infection are characterized by depression, moderate to severe colic, and fever.[129] Diarrhea is less often a feature

of acute strongylosis than is colic.[121] Most cases of acute strongylosis occur in young, naïve horses that are introduced to an infested environment or are inoculated experimentally with infective larvae. This form of strongylosis often is not recognized naturally. Chronic strongylosis, however, occurs most commonly as a natural syndrome. Weight loss or poor weight gain; chronic, intermittent colic; fever; poor appetite; and diarrhea are frequent signs.[121,122] Diarrhea may be profuse and watery, or the feces may be soft but of normal volume. Transrectal palpation may reveal thickening and fremitus in the cranial mesenteric artery. Young horses are most commonly affected, but older horses also may be affected. Horses with acute infarction or large intestinal ulceration following chronic strongylosis may have signs of severe abdominal pain, sepsis, and endotoxemia, and profuse, watery diarrhea is common.

Hematologic abnormalities associated with strongylosis include neutrophilic leukocytosis and eosinophilia.[129-131] Neutrophilia appears to be an early event during the course of the disease, and eosinophilia tends to appear later.[129,131] Hyperfibrinogenemia also may occur, especially later in the course of the disease. Serum α- and β-globulin and IgG(T) concentrations are characteristically elevated.[130-132] Horses with chronic ulcerative colitis following strongylosis may exhibit severe hypoalbuminemia.[128] Peritoneal fluid analysis may reveal an elevated protein concentration and eosinophilia.[130,131] Tentative diagnosis is based on clinical signs, hematologic abnormalities, and peritoneal fluid analysis. Elevated serum α- and β-globulin concentrations and IgG(T) concentration support the diagnosis.[132] Fecal analysis may reveal strongyle eggs, but fecal egg counts are often unreliable because nonpatent larvae cause the disease.

Prevention

Appropriate preventive measures are important in controlling this disease, including management procedures such as preventing overcrowding, reducing exposure of susceptible individuals, and instituting proper deworming schedules. Ivermectin is the preferred anthelmintic used to control strongylosis in horses. Monitoring fecal egg counts as a means of evaluating the efficacy of parasite control measures is recommended.

CYATHOSTOMIASIS
Pathogenesis

Infection with small strongyles (cyathostomiasis) is well recognized as a cause of diarrhea and large intestinal disease in horses of all ages.[133-138] Clinical disease is caused by intramural larval stages. The cyathostome life cycle requires migration by fourth-stage larvae through the mucosa of the large intestine and may include a period of hypobiosis during which the larvae remain encysted within

the mucosal layer of the large intestine. After a period of hypobiosis the larvae emerge in response to a largely unknown stimulus. Most cases occur when larval emergence takes place, classically in the late winter and spring in the northern temperate zones when larvae are expected to emerge and in the late fall or winter months in the southeastern United States and subtropical regions.[133] Sudden emergence of encysted larvae causes the mucosal injury, ulceration, and inflammatory reaction responsible in large part for the clinical disease.[133,139] However, migration of the larvae as they penetrate the mucosa affects motility patterns and can cause inflammation that may contribute to diarrhea.[139] Chronic, eosinophilic, granulomatous colitis and diarrhea with histopathologic evidence of hypobiotic cyathostome larvae in the large intestine have been reported in two horses during a period in which emergence of larvae would not be expected to occur (early winter).[133]

Natural emergence of cyathostome larvae causes fibrinous inflammation of the large intestine, focal necrosis, mural hemorrhage, and ulceration of the large intestinal mucosa, which even may result in bleeding into the lumen. Mild to moderate eosinophilic and mononuclear inflammation of the lamina propria occurs, and moderate to severe interstitial edema frequently occurs.[122,139] Colonic inflammation and interstitial edema may contribute to the diarrhea, along with the loss of the mucosal barrier, by causing increased active and passive secretion of fluid, electrolytes, and protein. Protein loss is often significant, resulting in profound hypoalbuminemia and interstitial edema of skin and other organs. Chronic, granulomatous colitis has been reported to occur in response to encysted larvae and may cause diarrhea by increased secretion following granulomatous inflammation or disruption of the interstitium by granulomatous infiltration. Administration of an anthelmintic to horses with a heavy load of encysted larvae also may cause rapid larval death and acute and often severe inflammation similar to natural emergence.

Clinical Signs and Diagnosis

Cyathostomiasis may be the most commonly identified cause of chronic diarrhea in the horse.[140-142] However, an acute syndrome also has been associated with cyathostomiasis.[138] Clinical signs of cyathostomiasis are characterized by moderate to severe weight loss or poor weight gain, ill thrift, ventral edema, intermittent fever, and intermittent, mild colic. Acute onset of diarrhea is typically profuse and progresses to chronic diarrhea that is often mild, is the consistency of bovine feces, and may be intermittent.[133-138,142] Appetite is usually normal, but affected horses occasionally have a ravenous appetite. Transrectal palpation usually does not reveal any abnormalities. Cyathostomiasis may affect any age of horse, and clinical

signs are more common during periods of emergence of larvae, corresponding to late winter and spring in northern temperate zones. The deworming history may appear to be adequate.

Neutrophilic leukocytosis is typically evident, but the white blood cell count may be normal.[133-138] Profound hypoalbuminemia is a characteristic feature of cyathostomiasis, manifested clinically by ventral edema. Plasma α- and β-globulin concentrations may be elevated, which can result in a normal total plasma protein concentration in spite of hypoalbuminemia.[134-136] The serum IgG(T) concentration, however, has been reported to be normal, which may help distinguish cyathostomiasis from *S. vulgaris* infection.[133,135,136] In addition, peritoneal fluid analysis does not usually reveal any abnormalities, in contrast to horses with *S. vulgaris* infection. Fecal analysis may be unrewarding because the infection is often not patent when clinical signs are apparent. Measurement of plasma fructosamine may provide a measure of protein catabolism or protein loss in the absence of hypoalbuminemia. Plasma fructosamine concentrations are significantly lower in horses with experimental cyathostomiasis than in normal controls,[142,143] suggesting that this test may be a useful diagnostic tool. However, the test has not yet been validated in naturally occurring cases, and neither the specificity nor the sensitivity is known. Rectal scrapings or rectal mucosal biopsies may reveal evidence of cyathostome larvae.[133,136] Definitive diagnosis usually requires microscopic examination of biopsy specimens of the cecum and ascending colon, collected by laparotomy. Examination of biopsy specimens collected from the small intestine is recommended to rule out other causes of weight loss and diarrhea. One should include appropriate diagnostic tests, such as culture of feces for pathogenic bacteria, in the workup to rule out other causes.

Prevention

Preventive measures are appropriate for other horses on premises known to have a problem with cyathostomiasis, particularly frequent deworming (every 6 weeks) during times of high infectivity (spring and summer in the north and fall, winter, and early spring in the south) to eliminate parasites before they become patent.[133] Because of high levels of resistance to benzimidazoles, avermectins (ivermectin or moxidectin) are the drugs of choice.[144-146] Resistance to ivermectin has been demonstrated, but the prevalence of ivermectin resistance appears to remain low.[144] Although daily pyrantel pamoate administration also has been reported to reduce worm burdens and pasture infectivity in young and mature horses effectively,[147] cyathostome resistance has been reported and is a concern for the use of this drug as a routine preventive anthelmintic.[145,148]

Toxicologic Diseases

Diarrhea in adult horses may also occur secondary to administration of antimicrobial or antiinflammatory medications or after ingestion of toxic compounds. Affected horses exhibit clinical signs that may be indistinguishable from signs exhibited by horses with diarrhea of infectious etiology.

ANTIBIOTIC-ASSOCIATED DIARRHEA
Pathogenesis
Antibiotic-associated diarrhea has been reported in many species, including horses.[149] Certain antibiotics—such as trimethoprim-sulfonamide combinations, erythromycin, penicillins, tetracyclines, clindamycin, and lincomycin—are associated with naturally occurring and experimental enterocolitis syndromes in horses.[79,149-152] In some cases, such as with trimethoprim-sulfonamide combinations, the geographic incidence of antibiotic-associated diarrhea appears to differ considerably.

Clostridium perfringens, C. difficile, and *Salmonella* spp. are apparently the most common causes of antibiotic-associated diarrhea in horses. Outbreaks of *C. difficile* have been reported in hospitalized horses being treated with antibiotics.[81,85] In Sweden, accidental erythromycin ingestion has been associated with *C. difficile* enterocolitis in mares in which their foals were being treated for *Rhodococcus equi*.[89,151,153] Interestingly, this phenomenon has not been reported in other areas of the world. Foals being treated with erythromycin are at a higher risk for diarrhea than foals being treated with other antibiotics. Tetracycline administration has been shown to be associated with an increase in the numbers of gram-negative enteric bacteria and *C. perfringens* in the feces of horses and reactivation of salmonellosis and prolongation of fecal shedding of *Salmonella*.[78,154]

The most common mechanism by which antibiotics cause diarrhea is by disrupting the gastrointestinal flora. The normal large intestinal flora, comprised of mainly obligate anaerobes and streptococci, protects the host from pathogenic bacteria by colonization resistance.[17] Ecologic factors play an important role in colonization resistance. For example, surface bacteria in the large intestine interact with receptors on the mucosal cells, facilitating adherence to the mucosa.[17,155] In doing so, the normal organisms compete more successfully for this important niche. Competition for space and nutrients is an important means of preventing colonization and proliferation of pathogenic bacteria. In addition, anaerobic bacteria produce short-chain fatty acids (SCFAs) and other metabolites that are toxic to facultative anaerobic bacteria, especially in the conditions of the large intestine.[16,17,155] Organisms of the normal flora also produce bacteriocins that inhibit growth of potential pathogens.[16]

Antibiotics that deplete the population of obligate anaerobes and streptococci efficiently decrease colonization resistance.[16] Production of fatty acids diminishes, thus reducing competition for space and nutrients. As a result, gram-negative enteric bacteria such as *Salmonella* are able to proliferate. In addition, pathogenic anaerobes normally found in low numbers can proliferate. Antibiotic-resistant strains of bacteria, especially gram-negative enteric bacteria and possibly clostridia, may be selected by antibiotic administration, allowing proliferation of pathogenic bacteria resistant to many antibiotics.[156] Obligate anaerobic commensal organisms, perhaps the most critical group of microbes for maintaining colonization resistance, are usually susceptible to macrolides, tetracyclines, β-lactams, and lincosamides, perhaps explaining the high incidence of diarrhea associated with the administration of these antibiotics.[83]

In addition to reduction of colonization resistance, depletion of the normal anaerobic microbial population in the intestine decreases carbohydrate fermentation and production of SCFAs, which contributes to the pathogenesis of antibiotic-associated diarrhea by decreasing absorption of sodium and water by the colonic mucosa.[157] Ampicillin decreases colonic fermentation of carbohydrates in human beings.[158] Human patients with antibiotic-associated diarrhea have greatly impaired colonic fermentation and low production of SCFAs. Erythromycin, ampicillin, or metronidazole treatment is associated with decreased production of SCFAs in patients with and without diarrhea.[88] Absorption of sodium and water is stimulated by absorption of SCFAs in the equine colon, suggesting that reduction of colonic SCFA content by antibiotic-induced depletion of anaerobic flora has similar effects in horses as in human beings.[157]

Broad-spectrum antibiotics exert a more profound effect on the gastrointestinal flora than narrow-spectrum antibiotics. Antibiotics administered orally, especially those that are poorly absorbed, are more likely to cause diarrhea than are parenterally administered antibiotics. For instance, clindamycin is less likely to cause diarrhea in human beings when administered intravenously than when administered orally. Antibiotics with extensive enterohepatic circulation, such as tetracyclines and erythromycin, are excreted in high concentrations in the bile and are associated more commonly with diarrhea than antibiotics that do not undergo enterohepatic circulation.[159]

Antibiotics may cause diarrhea by means other than by disrupting the normal flora. Direct toxic effects may play a role in producing irritation, increasing secretion, and disrupting motility patterns. Tetracyclines are irritating to the gastrointestinal mucosa and may cause inflammation and increase secretion.[159] Erythromycin has been shown to interact with smooth muscle cells, stimulating gastrointestinal motility.[159,160] Normal peristalsis plays an

important role in suppressing the population size of potentially pathogenic bacteria. Normally, bacteria that are prevented from adhering to the mucosa by colonization resistance are swept aborally by peristalsis and are excreted in the feces. Disruption of normal motility patterns may prevent clearance of pathogenic bacteria, contributing to the colonization of mucosal surfaces.

Clinical Signs and Diagnosis

Diarrhea induced by antibiotics usually occurs within 7 days of antibiotic administration or can occur several days after cessation of antibiotic treatment. The clinical syndrome of antibiotic-associated diarrhea can vary from mild diarrhea to fulminant enterocolitis with severe diarrhea. Mild cases of diarrhea are common, especially in foals receiving erythromycin, trimethoprim-sulfonamide combinations, or rifampin.[151,161] Mild cases of diarrhea are usually not clinically significant. However, acute, severe enterocolitis can occur in all ages of horses receiving antibiotics and can be life threatening. Clinical signs are identical to other causes of acute enterocolitis. Severe, dehydrating diarrhea, endotoxemia, sepsis, and shock may occur. Hemoconcentration, neutropenia, hypoproteinemia, and electrolyte and acid-base imbalances are common. Severe hyponatremia may occur in foals with antibiotic-associated diarrhea, especially if trimethoprim-sulfonamide and rifampin combinations are the cause.[161] More detailed descriptions of the clinical and laboratory findings were given previously. Diagnosis is presumptive, because definitive diagnosis of antibiotic-associated diarrhea is impossible. Fecal culture and PCR testing may reveal *Salmonella* or *Clostridium* infection.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS
Pathogenesis

Toxicity resulting from nonsteroidal antiinflammatory drug (NSAID) administration has been well documented in several species, including horses.[162-168] In horses and human beings, NSAID toxicity is manifested by renal and gastrointestinal disease. Elderly human patients are more susceptible to NSAID toxicity, but the effects of age on NSAID toxicity in horses are less well defined. Foals are considered to be more susceptible than adult horses to gastrointestinal disease following NSAID administration, and ponies may be more susceptible than horses. All NSAIDs are capable of inducing gastrointestinal and renal damage at toxic concentrations, and the toxicity is not significantly different among products. Aspirin is potentially more toxic than other NSAIDs because it irreversibly inactivates cyclooxygenase by acetylation, whereas other NSAIDs reversibly inhibit cyclooxygenase.[162] However, phenylbutazone is the drug most commonly reported to cause toxicity in horses, perhaps because of its widespread use by veterinarians

and horse owners. Phenylbutazone toxicity in horses is characterized by mucosal ulceration throughout the gastrointestinal tract, oral ulceration, renal papillary necrosis, vasculopathy, thrombosis, and protein-losing enteropathy with hypoalbuminemia.[164-166] This discussion focuses on the toxic effects of NSAIDs on the large intestine but necessarily includes elements of upper gastrointestinal and renal disease.

Horses with large intestinal disease resulting from NSAID toxicity generally are receiving inappropriately large doses. The dosage regimen recommended for phenylbutazone (4.4 mg/kg twice in 1 day and then 2.2 mg/kg twice daily) is considered to be safe. Experimental studies in horses, however, have shown toxicity to occur when greater than the recommended dosage (6.6 mg/kg/day) is administered for several days.[164,165] In most reported cases of phenylbutazone toxicosis horses were receiving higher than recommended dosages.[166,168,169] Regardless, administration of phenylbutazone at the recommended dosage has been reported to cause a significant decrease in plasma protein concentration and gastrointestinal disease.[165,170] Moreover, signs of NSAID toxicity have been reported in normovolemic horses treated with appropriate doses of phenylbutazone.[170,171] Dehydration, sepsis, and endotoxemia exacerbate the renal and gastrointestinal toxicity of NSAIDs.[162] Clearly, the margin of safety is narrow for phenylbutazone and probably for other NSAIDs used in horses as well.

Gastrointestinal disease induced by NSAIDs is manifested by mucosal ulceration, inflammation, bleeding, and protein-losing enteropathy.[164,165,168,170] In addition to direct effects on the mucosal barrier, NSAID administration has been shown to cause an acute relapse of preexisting colonic inflammatory disease and worsen colonic inflammation in human beings.[164,165,170] Whether this occurs in horses is not clear. The mechanism by which NSAIDs induce mucosal damage is probably multifactorial. Direct irritation may play a role in oral and gastric irritation and ulceration; however, parenteral administration of NSAIDs produces oral and gastric ulceration as well. Inhibition of prostaglandin synthesis by inhibition of cyclooxygenase 1 (the constitutive COX) and cyclooxygenase 2 (the inducible COX) appears to be the most important mechanism of mucosal injury. Prostaglandins, particularly PGE_2 and PGI_2, are critical for mucosal health.[172,173] PGE_2 has been shown to increase mucosal blood flow; increase secretion of mucus, water, and bicarbonate; increase mucosal cell turnover rate and migration; stimulate adenyl cyclase activity; and exert other protective effects in the gastric mucosa of several species.[162,172,173] Perhaps most importantly, PGE_2 and PGI_2 have a role in maintaining epithelial tight junction integrity, which is indispensable for mucosal barrier function and repair after mucosal injury.[172]

In spite of the overwhelming amount of information about the role of prostaglandins in maintaining the mucosal barrier in other species and clear clinical and experimental evidence that NSAIDs injure the equine colonic mucosa, the role of prostaglandins in mucosal protection in the equine colon is not yet well defined. Inhibition of COX-1 and COX-2 in equine colonic mucosa with flunixin meglumine resulted in reduced electric resistance of the mucosa and increased permeability to macromolecules in vitro (A.T. Blikslager and S.L. Jones, 2002), suggesting that flunixin treatment disrupts the epithelial tight junctions in the equine colon. Mucosal changes were correlated with a profound inhibition of PGE_2 and PGI_2 concentrations in the treated tissues. In other studies, administration of a PGE_2 analog prevented the gastrointestinal manifestations of phenylbutazone toxicosis in ponies.[165]

Recent development of NSAIDs specific for COX-2 have greatly reduced the frequency and severity of gastrointestinal side effects in human beings taking NSAIDs for chronic musculoskeletal conditions.[174] Thus COX-2–specific NSAIDs hold promise for use in horses to treat arthritis and reduce the incidence of toxicity. For example, the COX-2–specific inhibitor etodolac was less harmful to equine colonic mucosa than flunixin meglumine in vitro (A.T. Blikslager and S.L. Jones, 2002). Moreover, etodolac was significantly more permissive than flunixin for recovery of the mucosa in equine ischemic-injured intestinal tissues, and in fact, recovery was no different than control tissues.[175] However, their use is at present limited because the specificity of the so-called COX-2–selective inhibitors and their efficacy as analgesics have not been demonstrated in the horse.

NSAID-induced mucosal injury is associated with a significant inflammatory response to microbial products exposed to the lamina propria.[176] This inflammation exacerbates mucosal dysfunction and injury associated with NSAID toxicity. For example, depletion of neutrophils or blockade of neutrophil influx into gastrointestinal tissues or inhibition of neutrophil activation and release of toxic products prevents many of the pathophysiologic effects of NSAID toxicity in the gastrointestinal tract.[177-180] The inflammatory response alone may result in moderate to severe gastrointestinal ulceration, mural vascular thrombosis and edema, fluid secretion, protein-losing enteropathy, and mucosal hemorrhage.

Clinical Signs and Diagnosis

NSAID colitis manifests as two clinical syndromes: right dorsal colitis (RDC) and generalized NSAID toxicity. RDC is an ulcerative disorder isolated to the right dorsal segment of the large intestine.[167,168,171] The most prominent clinical signs of RDC are anorexia, lethargy, and colic. Anorexia, depression, diarrhea, fever, and signs of

endotoxemia also may be features. If the RDC is chronic, weight loss, intermittent colic, lethargy, anorexia, and ventral edema are common clinical signs, along with soft and unformed feces. Severe ulceration of the right dorsal colonic mucosa results in protein-losing enteropathy and significant hypoproteinemia attributable mainly to hypoalbuminemia. Hypoproteinemia may be severe enough to cause peripheral (usually ventral) edema.In some cases, one may note dehydration, electrolyte abnormalities, neutropenia or anemia, azotemia, and biochemical abnormalities if the ulceration and diarrhea are severe or if systemic inflammation is present.

Clinical signs of generalized NSAID toxicity may vary from mild diarrhea with no systemic signs to severe dehydrating diarrhea with anorexia, fever, depression, peripheral edema, oral ulceration, and colic.[165,166,169] Clinical signs of systemic inflammation caused by endotoxemia may occur, manifested as poor peripheral perfusion, tachycardia, tachypnea, weakness, trembling, and cyanotic or hyperemic oral mucous membranes. Hematuria or oliguria may be present if renal involvement is present. Complications associated with other forms of severe enterocolitis, such as laminitis, thrombophlebitis, and severe weight loss, may occur.

Hematologic abnormalities of generalized NSAID toxicity are nonspecific and include neutropenia with a left shift or leukocytosis and hemoconcentration. Serum biochemical analysis is characterized by profound hypoproteinemia, hyponatremia, and metabolic acidosis.[169,170] Hypocalcemia, hypokalemia, hypochloremia, and elevated hepatocellular enzyme activities also may occur. Hypoproteinemia may occur without signs of diarrhea. Azotemia may be prerenal from dehydration but frequently is caused by renal failure resulting from a combination of hemodynamic and toxic renal injury. Urinalysis frequently reveals hematuria, proteinuria, cylindruria, and isosthenuria. Fecal occult blood is frequently detectable.

Diagnosis of either form of NSAID colitis is often presumptive, with a history of overdose of NSAIDs being strong evidence of NSAID toxicity. But as discussed earlier, toxicity may occur with dosage regimens that are not considered inappropriate, particularly if the horse experiences a concurrent period of dehydration. One can use ultrasonographic examination of the right dorsal colon to confirm a diagnosis of RDC, but the sensitivity of this method is questionable. Ultrasonography (3.5- to 5-MHz transducer at the right twelfth to fifteenth intercostal spaces below the margin of the lung axial to the liver) may reveal a thickened right dorsal colon (>0.5 cm) and evidence of colonic edema in horses with RDC.[181] However, the sensitivity of this method of diagnosis is questionable. One can use nuclear scintigraphy of horses after infusion with technetium 99–labeled white blood cells to document inflammation of the right dorsal colon.[182] Diagnosis of RDC may require one to perform laparotomy or laparoscopic examination of the right dorsal colon. One must rule out other causes of enterocolitis, such as salmonellosis, Potomac horse fever, clostridiosis, and antibiotic-associated diarrhea.

CANTHARIDIN TOXICITY
Pathogenesis
Cantharidin is the toxic principle found in beetles of the genus *Epicauta,* commonly known as blister beetles.[183-185] Ingestion of the beetles in contaminated alfalfa hay causes release of the toxin from the tissues of the beetle and absorption through the gastrointestinal tract. Transcutaneous absorption may occur but appears to be rare in horses.[184] Blister beetles feed on the flowers of alfalfa and may be incorporated into processed alfalfa hay if the hay is cut and processed simultaneously, as by crimping.[183-185] The beetles often swarm, and one may find large numbers of beetles in small portions of hay. The lethal dose of cantharidin is less than 1 mg/kg, but the concentration of cantharidin varies from species to species of blister beetles and between sexes.[183,184] As many as 100 to as few as 6 to 8 beetles may be lethal. Usually, only one or a few horses fed contaminated hay ingest beetles because the beetles are concentrated in a small portion of the hay. However, outbreaks involving many horses on a farm have occurred. Most cases occur in Texas and Oklahoma, but horses in other states may be affected as well, especially if hay is imported from states where blister beetles are common. Peak incidence is in late summer and fall.[186] The fatality rate may be 50% or greater,[183,187] but if the patient survives several days, recovery is probable.

Cantharidin is absorbed from the gastrointestinal tract and excreted via the kidney. Cantharidin is a potent irritant, causing acantholysis and vesicle formation when applied topically.[183,185,187] The chemical is thought to disrupt oxidative metabolism in the mitochondria, causing mitochondrial swelling, plasma membrane damage, and changes in membrane permeability.[183] The mucosa of the gastrointestinal tract is affected most commonly in horses because they ingest the toxin. Cell swelling and necrosis occur, resulting in mucosal ulceration. Oral, esophageal, gastric, and small and large intestinal ulceration have been observed in natural and experimental canthariasis.[183,185,187] Severe fibrinous to pseudomembranous inflammation and submucosal edema of the intestine also have been reported. Diarrhea probably results from the severe ulceration and inflammation of the large intestine, causing increased secretion of water, electrolytes, and protein and decreased absorption of fluid. Large volumes of fluid and protein are lost in the gastrointestinal

tract, causing hemoconcentration and profound hypoalbuminemia in some cases.[183,184,187]

Cystitis and myocarditis occur in natural and experimentally produced cases of cantharidin toxicity.[183,185,187] Cystitis occurs because renal excretion of cantharidin results in high concentrations in urine. Occasionally, hemorrhagic cystitis may occur, with hematuria or frank hemorrhage into the bladder.[183] The cause of the myocarditis and myocardial necrosis is unknown but also may be a direct effect of the toxin on the myocardium. Elevated plasma creatine kinase activity often occurs and has been postulated to arise from the damaged myocardium.[183,184] Horses have a characteristically stiff gait, but histopathologic evidence of skeletal muscle injury that explains the elevated plasma creatine kinase activity has not been observed.[184] The kidneys are often pale, swollen, and moist, with occasional infarcts.[185]

Hypocalcemia and hypomagnesemia are biochemical features of cantharidin toxicity in horses that have not been explained.[183,184,187] Hypocalcemia may occur from hypoalbuminemia, but the ionized calcium concentration often is decreased along with the total calcium concentration, indicating that hypoalbuminemia is not responsible for the hypocalcemia.[184] In addition, clinical signs of hypocalcemia, such as synchronous diaphragmatic flutter, are often associated with hypocalcemia from cantharidin toxicity. Hypocalcemia associated with hypoalbuminemia alone does not produce clinical signs.

Clinical Signs and Diagnosis

Cantharidin toxicity can cause a range of clinical signs from mild depression and abdominal discomfort to fulminant signs of toxemia and rapid death, depending on the ingested dose of toxin. Most commonly, clinical signs include depression, sweating, irritability, abdominal pain, elevated heart and respiratory rates, fever, polyuria, polydypsia, and profuse diarrhea.[183,184,187] Blood is rarely visible in the feces. Affected horses frequently posture to urinate; indeed, stranguria and pollakiuria are characteristic of cantharidin toxicity.[183] Signs of hypocalcemia include synchronous diaphragmatic flutter and tremors. A stiff and stilted gait may be evident. One may note neurologic signs such as head pressing, swaying, and disorientation.[187] Signs of systemic inflammation from endotoxemia may be apparent in severe cases. Some horses develop severe depression and toxemia and may die within hours after ingestion of cantharidin without developing diarrhea.[183,187]

Hematologic abnormalities include hemoconcentration and neutrophilic leukocytosis. Occasionally, neutropenia and leukopenia may accompany endotoxemia. Serum biochemical analysis usually reveals elevated creatine kinase activity, hypocalcemia, and hypoalbuminemia.[183,184] Biochemical abnormalities include hypocalcemia (ionized

and total calcium concentrations), hypomagnesemia, and azotemia.[183,184,187] Urine specific gravity is characteristically in the hyposthenuric range.[183,184] Microscopic hematuria and mild proteinuria may be evident. Fecal occult blood is often present, but hematochezia is unusual.

One can make a tentative diagnosis based on clinical signs and the finding of blister beetles in the hay. Determining the species of the insects may be necessary to estimate the amount of cantharidin ingested. All species of *Epicauta* contain cantharidin, but some have small amounts. Definitive diagnosis requires the measurement of the cantharidin concentration in gastric or intestinal contents and urine.[183,186] Measurement of cantharidin concentration in the beetles is often done but is not necessary.

ARSENIC TOXICOSIS
Pathogenesis

Arsenic toxicosis is an unusual cause of diarrhea in horses, resulting from ingestion of arsenic-containing herbicides, insecticides, and other pest control products contaminating water or roughage used as a food source.[188] The toxicity of arsenic depends on the valence of the element.[188,189] Arsenate may be reduced to arsenite in mammalian systems, and arsenite is thought to be more toxic than arsenate and less rapidly excreted in urine. Arsenate and arsenite uncouple oxidative phosphorylation, leading to breakdown of energy metabolism in the cells of many tissues.[189] Widespread cellular injury and death occur rapidly during acute arsenic toxicosis. Multiorgan failure usually results. In fact, cardiomyopathy and pulmonary disease are common causes of death in human beings.[190] Damage to the large intestine is probably caused in part by direct cellular toxicity and corrosion by the compound. However, vasculitis is a hallmark of the disease in human beings and horses and is thought to be the most important mechanism of large intestinal disease in human beings.[181,191] Acute hemorrhagic colitis is a feature of arsenic toxicosis, with severe mural edema and mucosal ulceration.[188] Profuse, hemorrhagic diarrhea and abdominal pain result. Chronic arsenic toxicity can occur but appears to be rare in horses.

Clinical Signs and Diagnosis

Acute depression, weakness, abdominal pain, hemorrhagic diarrhea, and shock are characteristic of acute arsenic toxicosis in horses. Death may occur before diarrhea is evident. Initial clinical signs may be difficult to distinguish from other peracute forms of colitis and are related to endotoxic shock, metabolic disturbances, and dehydration. Later, cardiac arrhythmias, pulmonary edema, acute renal failure, and neurologic deficits (ataxia and stupor) may develop.[188] One may observe anuria or polyuria. Hemolytic anemia caused by preferential

binding of arsenic compounds to red blood cells is a feature of arsenic poisoning in human beings. Hematologic abnormalities may be apparent after the peracute stages from injury to bone marrow cells and ongoing hemolysis. Leukopenia and thrombocytopenia have been described in human patients.[190] Serum biochemical analysis may reveal azotemia, hepatocellular enzyme activities higher than generally attributed to endotoxemia, and elevated creatine kinase activity.[188] Urine specific gravity may be in the isosthenuric range, with hematuria, cylindruria, and proteinuria evident by urinalysis.

Diagnosis may be possible by measuring blood and urine arsenic concentration, but these tests may not be diagnostic. Postmortem diagnosis is by measuring the arsenic concentration in liver and kidney samples.[188] History of exposure and clinical signs remain the primary means of diagnosis.

Miscellaneous Disorders of the Large Intestine

Other disorders associated with diarrhea in adult horses include anaphylaxis, carbohydrate overload, and sand enteropathy. Careful evaluation of history, environment, and management will assist the clinician in arriving at an accurate diagnosis.

INTESTINAL ANAPHYLAXIS
Pathogenesis
Severe intestinal anaphylaxis is a syndrome in horses characterized by peracute, rapidly fatal colitis.[192] The severe syndrome is clinically and pathologically similar to other known causes of peracute colitis, such as salmonellosis, clostridiosis, and antibiotic-associated diarrhea. Some cases are less severe and manifest as mild to moderate diarrhea or colic. An IgE-mediated type I hypersensitivity or an IgE-independent anaphylactoid reaction can produce the syndrome of intestinal anaphylaxis.[193,194] Local gastrointestinal exposure to a food, environmental contaminant, drug, or other allergen usually induces intestinal anaphylaxis,[193,195] but anaphylaxis also may occur with systemic exposure to an allergen.[196-199] Massive mast cell degranulation, secretion of inflammatory mediators, and activation of enteric neural reflexes in the intestine causes profound alterations in blood flow, increased vascular permeability and interstitial edema, recruitment of neutrophils, altered motility, mucosal injury, absorption of microbial products, and mucosal hypersecretion.[200-204] Systemic signs may be caused by the anaphylactic reaction or may be associated with systemic inflammation triggered by microbial products (endotoxin) absorbed through the injured and hyperpermeable mucosa.

Intestinal anaphylaxis in horses may be a peracute, fulminant enterocolitis with endotoxemia that may be fatal.[192,205] This form is characterized by severe intramural edema and hemorrhagic inflammation of the large intestine, often producing submucosal thickening on the order of many centimeters. Vascular thrombosis may be widespread with mucosal and serosal petechia and ecchymoses. Less severe forms of intestinal anaphylaxis may manifest as patchy areas of intestinal edema and congestion.[196] Diarrhea results from intestinal inflammation initiated by the type I hypersensitivity response. Many of the mediators of type I hypersensitivity, such as histamine and 5-hydroxytryptamine, have well-documented stimulatory effects on mucosal secretory activity, vascular and epithelial permeability, and motility[200-202] in the intestine. Systemic inflammation from endotoxemia may be overwhelming once the mucosal barrier breaks down. Infarction of intestinal segments and other organs may occur from intravascular coagulation. Ileus, abdominal distention, and moderate to severe abdominal pain may result from motility disturbances and infarction of the large intestine.

Clinical Signs and Diagnosis
The clinical signs are similar to those described for other forms of peracute colitis. However, the severity may vary, manifesting as colic or moderate diarrhea. Characteristically, severe shock, signs of systemic inflammation from endotoxemia, and severe metabolic disturbances are observable.[192,205] Heart and respiratory rates may be elevated greatly, with other signs of cardiovascular collapse such as weak and thready peripheral pulses and peripheral vasoconstriction. However, peripheral vasodilation may occur later in the course of disease. Dark red, muddy, or cyanotic mucous membranes with a prolonged capillary refill time signify sepsis. Borborygmi are usually absent, and abdominal tympany may be heard on percussion, following ileus. Moderate to severe colic may accompany ileus. Severe diarrhea may occur, but death may occur before diarrhea is evident. Multiorgan failure from disseminated intravascular coagulation is not unusual. Rapid onset of weakness, staggering, and trembling commonly precedes death. The syndrome may cause death in 4 to 24 hours.

Hematologic abnormalities include severe neutropenia and leukopenia, thrombocytopenia, and hemoconcentration.[192] Serum biochemical alterations include hyponatremia, hypokalemia, hypocalcemia, and severe metabolic acidosis. Blood urea nitrogen and creatinine may be elevated from prerenal or renal azotemia. If acute renal failure accompanies the colitis, hyperkalemia may result. Hepatocellular enzyme activity may be elevated in the serum from endotoxemia. Severe coagulopathies are common, resulting in prolonged coagulation times,

elevated fibrinogen, decreased antithrombin III activity, and elevated plasma concentration of fibrin degradation products. Analysis of peritoneal fluid may be valuable because infarction of the large intestine is not unusual. Protein concentration and the white blood cell count may be elevated. Red blood cell counts are less likely to be elevated, because infarction and not strangulation of the intestine occurs.

Diagnosis is based on clinical signs, postmortem findings, and exclusion of other causes. Cultures and toxicologic analysis of fecal samples and gastrointestinal tissues fail to demonstrate a clear cause. Other diagnostic tests are also inconclusive. If an antigen is suspected as the trigger of the anaphylaxis, a Prausnitz-Küstner passive cutaneous anaphylaxis sensitization test can confirm the presence of antigen-specific IgE in the patient serum.[196]

CARBOHYDRATE OVERLOAD
Pathogenesis
Overeating of soluble carbohydrates, especially so-called hot grains such as corn, overwhelms the digestive capability of the small intestine, resulting in a high percentage of the soluble carbohydrates entering the large intestine. The amount of soluble carbohydrates that produce diarrhea varies according to the previous dietary history of the individual. Horses fed diets higher in soluble carbohydrates are more resistant to the deleterious effects of carbohydrate overload. Gradual accommodation to a diet high in carbohydrates can be accomplished over several weeks. However, horses fed an unusually large amount of grains or other form of soluble carbohydrates often develop diarrhea and may, depending on the amount ingested, develop severe colitis, systemic inflammation from endotoxemia, metabolic acidosis, and laminitis.[206-209]

The pathogenesis of colitis from carbohydrate overload is caused primarily by the toxic effects on the microbial flora in the large intestine.[207] A sudden delivery of soluble carbohydrates to the large intestine causes rapid fermentation by gram-positive lactic acid–producing bacteria and a sudden increase in organic acid production. The cecal pH rapidly decreases, and the lactic acid concentration rapidly increases. Rapid organic acid production overwhelms the buffering capacity of the large intestine not only by directly depleting the buffers found in the contents but also by reducing the efficiency of buffer secretion. Bicarbonate secretion is linked to absorption of volatile fatty acids, which are produced in low amounts by fermentation of soluble carbohydrates. The contents of the large intestine become profoundly acidic, resulting in unfavorable conditions for the microbial flora. Lactic acid–producing bacteria flourish, while the gram-negative bacteria, especially the Enterobacteriaceae, are killed in large numbers by the acids. Large quantities of endotoxin are released from the dying bacteria.[208]

The osmotic load from the lactic acid produced in the large intestine is an important factor in the development of diarrhea because organic acids such as lactic acid are absorbed poorly. Mild cases of carbohydrate overload may result purely from osmotic diarrhea. In more severe cases, the acidic contents of the large intestine are toxic to the mucosa, causing necrosis of the mucosal tissues, similar to that occurring in ruminal acidosis. Mucosal ulceration allows absorption of large quantities of endotoxin and lactic acid produced by the massive die-off of acid-intolerant microbes and fermentation of soluble carbohydrates, normally poorly absorbed by intact mucosa.[209] Systemic inflammation from endotoxemia may be overwhelming, and profound metabolic acidosis may occur. Secretory diarrhea caused by the direct effects of acid luminal contents on the mucosa, as well as the effects of inflammatory mediators on enterocyte secretion, worsens the acidosis and dehydration. Systemic inflammation from endotoxemia, along with intestinal inflammation, adversely affects intestinal motility, and ileus develops. Ileus and gas production from fermentation of the carbohydrates may cause severe distention of the large intestine and signs of abdominal pain. Laminitis is a frequent complication of endotoxemia and lactic acidosis. In fact, carbohydrate overload is used to induce laminitis as an experimental model because of the consistency of the laminitis produced.[207-209]

Clinical Signs and Diagnosis
Clinical signs of colitis from carbohydrate overload can vary according to the amount of carbohydrates ingested and accommodation of the flora to a high-carbohydrate diet. Mild cases may result in a transient osmotic diarrhea with no systemic effects. More severe cases are characterized by signs similar to those described for other forms of colitis, including abdominal pain, moderate to severe diarrhea, and dehydration. Signs of endotoxemia and sepsis are frequently present in severe cases. Elevated heart and respiratory rates are common, with peripheral vasoconstriction early in the disease, followed by peripheral vasodilation as the disease progresses. Depression may be profound from metabolic acidosis and endotoxemia. Abdominal auscultation and percussion may reveal ileus and intestinal tympany. Nasogastric intubation may yield significant gastric acidic reflux. One may note particles of grain in the gastric reflux and the feces, if grain overload is the source of the carbohydrate overload. Laminitis may complicate mild and severe cases of carbohydrate overload, especially if the animal has had previous bouts of laminitis.

Hematologic abnormalities include neutropenia and leukopenia. Severe dehydration may result in profound hemoconcentration. Protein loss later in the course of disease may result in hypoproteinemia. Serum biochemical

abnormalities include azotemia, elevated hepatocellular enzyme activity, hyponatremia, and hypokalemia. Severe hypocalcemia and metabolic acidosis are characteristic of the disease. Serum lactate concentrations are elevated in the absence of evidence of intestinal strangulation or infarction. Peritoneal fluid analysis often reveals no abnormalities.

SAND ENTEROPATHY

Sand enteropathy is described in more detail under the heading of obstructive diseases, because acute obstruction is often associated with abnormally large amounts of sand in the large intestine.[210] However, chronic sand-induced diarrhea is a distinct syndrome that can occur at any age from abnormal accumulation of sand in the large intestine.[211,212] Chronic diarrhea and signs of colic may occur without obstruction. The pathogenesis of sand accumulation in individual horses, other than simple ingestion of large quantities, is unclear. Presumably the sand causes irritation and may disrupt motility, leading to diarrhea. The diarrhea is usually not severe and dehydrating and may be intermittent. Weight loss is characteristic and can be severe in some cases. Complications may occur such as peritonitis and acute obstruction.[211]

Diagnosis usually is based on finding abnormal amounts of sand in the feces. Because sand-induced chronic diarrhea is associated primarily with sand accumulation in the ventral colon, auscultation of the ventral abdomen immediately behind the xiphoid process may reveal characteristic sand sounds.[213] This technique is only sensitive if peristalsis is present. Ultrasonography also may be useful to identify sand in the ventral colon but is not useful to quantitate the amount of sand. Occasionally, radiography may be required to detect sand in the colon.[211]

Principles of Therapy for Acute Diarrhea

The principles of therapy of acute diarrhea from colitis are similar regardless of the cause and include replacement of fluid and electrolyte losses, control of colonic inflammation and reduction of fluid secretion, promotion of mucosal repair, control of endotoxemia and sepsis, and reestablishment of normal flora. This section focuses on a review the principles of therapy with references to specific therapies for particular causes as they arise.

FLUID REPLACEMENT AND CIRCULATORY SUPPORT

Replacement of fluid and electrolyte losses is of primary concern in treating horses with salmonellosis. Depending on the severity of the disease, fluid losses may be minimal or massive. One can administer fluid and electrolytes orally or intravenously. Some horses with mild to moderate diarrhea may maintain hydration and electrolyte balance by consuming water and electrolytes voluntarily. Freshwater and water containing electrolytes should be available in all cases. In many instances, periodic nasogastric intubation and administration of water and electrolytes via the tube may be sufficient to maintain hydration.[214] In more severe cases, one can maintain indwelling nasogastric tubes and can administer up to 4 to 8 L of fluid by the tube every 20 to 30 minutes, if ileus is not evident. However, intravenous administration of fluids is preferred in most cases, requiring significant quantities of fluid to replace and maintain hydration and electrolyte balance.[215] For patients with severe diarrhea to require large volumes (50 to 100 L/day) of intravenous fluids to maintain hydration is not unusual. Frequent monitoring of packed cell volume, serum electrolyte concentration, venous blood gases or total serum carbon dioxide, blood urea nitrogen and creatinine, urine protein and cytologic findings, and body weight is important to monitor hydration, electrolyte and acid-base balance, and renal function.

Isotonic sodium chloride or lactated Ringer's solution frequently is used to restore and maintain fluid and electrolyte balance. One can add potassium chloride to the fluids and administer it at a rate up to 0.5 to 1.0 mEq/kg/hr. Generally, a rate of less than 0.5 mEq/kg/hr is used. Hypertonic NaCl solutions (1 to 2 L of 3% to 5% NaCl) have been used in horses that are severely hyponatremic (<120 mEq/dl). One should not administer hypertonic solutions to severely dehydrated horses, but such solutions have been used clinically without complication and with considerable beneficial effect in patients with endotoxemia. The beneficial effects of hypertonic NaCl are short-lived (30 to 60 minutes). One should administer isotonic solutions concurrently or immediately following administration of hypertonic NaCl solutions. Isotonic (1.3%) or hypertonic (5.0%) sodium bicarbonate solutions are used to correct metabolic acidosis. Prolonged administration of sodium-containing fluids may promote diuresis and renal water loss or accumulation of peripheral edema and should be used conservatively when one notes a free water loss. Administration of isotonic dextrose (5%) or 2.5% dextrose/0.45% NaCl solutions may be beneficial when free water loss (sodium excess) is evident.

Many horses with acute colitis are concurrently hypoproteinemic because of gastrointestinal losses and are absorbing bacterial products that induce a systemic inflammatory response. Thus plasma oncotic pressures are abnormally low in the face of increased vascular permeability. Interstitial edema formation is a clinical problem in these patients and contributes to organ dysfunction. Crystalloid fluids, although critical for replacing water

and electrolyte losses from diarrhea, actually may contribute to a drop in plasma oncotic pressure because of hemodilution.[216,217] Administration of colloid solutions are important for volume expansion and to maintain plasma oncotic pressures, which improve tissue perfusion and oxygenation and organ function in hypovolemic, hypotensive, and hypoproteinemic patients with or without systemic inflammatory response syndrome.[218] Colloids are more effective than crystalloid fluids at expanding plasma volume and thus require smaller volumes. Moreover, the effect of colloid volume expansion is longer lasting than crystalloid fluid volume expansion, because colloids are retained in the vasculature better.[217,218] Natural colloids, such as plasma and purified albumin are used commonly. In addition to its beneficial colloidal properties, plasma harvested from donor horses immunized with rough mutants of *Escherichia coli* (J5) or *Salmonella typhimurium* may have other benefits for treatment of endotoxemia from gastrointestinal disease.[219,220] The horse may require large volumes (6 to 8 L/day) to increase and maintain plasma protein concentration significantly. Synthetic colloids such as dextrans, starches, or polymerized hemoglobin are also available for use in the horse. Hetastarch (5 to 10 ml/kg of a 6% solution) increases colloidal oncotic pressures for up to 24 hours in hypoproteinemic horses and has beneficial effects on cardiac output and other cardiorespiratory parameters, vascular permeability, interstitial fluid content, and tissue perfusion in models of hypoproteinemia and systemic inflammatory response syndrome. When one administers synthetic or even natural colloids, monitoring plasma oncotic pressure may be more relevant than monitoring plasma protein concentrations as a means of assessing the need for plasma or other colloid administration.[216] Hetastarch may prolong bleeding times by altering von Willebrand's factor function; thus one should use this synthetic colloid cautiously in horses with suspected coagulopathies, active hemorrhage, or other bleeding problems.[217]

INFLAMMATION

Control of colonic inflammation and secretion is a difficult and poorly studied aspect of equine acute colitis. The role of inflammation and mediators such as prostaglandins as causes of fluid loss is well known for *Salmonella* and *Clostridium* infections. COX inhibitors (NSAIDs) have antisecretory effects in the equine colon and in models of salmonellosis that appear to extend to clinical management of salmonellosis.[16,36,221-223] Indeed, NSAIDs commonly are administered to horses with salmonellosis. However, prostaglandins such as PGE_2 and PGI_2 are also cytoprotective to gastrointestinal mucosa and critical for mucosal repair.[172] The doses of NSAIDs used pharmacologically to inhibit colonic inflammation

and secretion in fact may be detrimental to the mucosa if not used judiciously. NSAIDs have been shown to exacerbate colonic inflammation in human beings with inflammatory colitis, impede mucosal healing in several models of mucosal injury, and have well-documented detrimental effects on colonic mucosa in horses.[164,172,224] In addition to toxicity to the colonic mucosa, gastric ulceration is not unusual in horses with enterocolitis and may be related to treatment with NSAIDs.

In addition to NSAIDs, other drugs occasionally are used as antiinflammatory or antisecretory therapy. Metronidazole has beneficial effects in experimental models of gastrointestinal inflammation, including NSAID toxicity[176] and may be useful for treating horses with colitis, but evidence supporting its use is lacking. Bismuth subsalicylate solutions administered orally often are used to decrease inflammation and secretion in the colon. In adult horses the volume of solution necessary to be beneficial is large (3 to 4 L every 4 to 6 hours). Often the solution is administered twice daily instead of 4 to 6 times daily. If one does not achieve a beneficial effect within 3 to 4 days of treatment, one should discontinue administration of bismuth subsalicylate solution. One can administer the treatment more frequently in foals, and clinical improvement occurs more often in foals than in adult horses.

In light of the role of reactive oxygen metabolites in colonic inflammation, free radical scavengers have been advocated to reduce the effects of these molecules. Sulfasalazine metabolites have been shown to reduce reactive oxygen metabolite–induced colonic inflammation in other species,[176] and sulfasalazine has been used to treat chronic inflammatory disease in horses but has not been used to treat acute colitis. The only free radical scavenger used commonly in horses with colitis is dimethyl sulfoxide, which at a dosage of 0.1 to 1.0 g/kg intravenously every 12 to 24 hours in a 10% solution has been used in clinical cases of colitis, but evidence of efficacy has not been established.

Systemic inflammatory response syndrome associated with endotoxemia frequently occurs in patients with salmonellosis. The principles of therapy for endotoxemia are covered in detail elsewhere in this chapter. Oral administration of activated charcoal and mineral oil is used commonly to reduce absorption of endotoxin in horses with colitis. Low doses of NSAIDs (such as flunixin meglumine at 0.1 to 0.25 mg/kg intravenously every 6 to 8 hours) inhibit eicosanoid synthesis induced by endotoxin. In addition, administration of NSAIDs prevents laminitis from endotoxemia, a devastating complication of salmonellosis. One must remember that prostaglandins are important for mucosal healing and may worsen mucosal injury in colitis. Although the benefits of low doses of NSAIDs administered to

horses with systemic inflammatory response syndrome are believed to outweigh the risks of worsening gastrointestinal damage, judicious use is recommended.

MUCOSAL REPAIR AND PROTECTION

Sucralfate (20 mg/kg orally every 6 hours) has been advocated to aid in healing the colonic mucosa, but the efficacy in the large intestine is questionable.[94] Misoprostol (2 µg/kg orally 3 to 4 times daily) and other synthetic PGE analogs have been shown in several species including horses to enhance mucosal healing in the intestine and promote recovery in experimental models of colitis.[225] Misoprostol may be particularly useful for treating NSAID toxicity, the generalized form or RDC. However, the efficacy of misoprostil for hastening mucosal healing is clinically unproven in equine colitis. The primary drawbacks of prostaglandin analogs such as misoprostol are the side effects of the drug, including abdominal cramping, diarrhea, sweating, and abortion in pregnant mares.

One can add psyllium mucilloid to the diet (5 tablespoons once or twice daily) to increase the production of SCFAs in the colon. Amylase-resistant fermentable fiber such as psyllium is hydrolyzed by colonic bacteria to SCFAs such as butyrate, which represent a major energy source for colonocytes. Butyrate and other SCFAs hasten epithelial maturation and stimulate salt (and thus fluid) absorption in the colon, improve the clinical course of ulcerative colitis, and hasten colon healing.[226] Psyllium is itself a source of butyrate in the colon and also promotes the movement of amylase sensitive carbohydrates into the distal colon, which then are fermented to SCFAs. Thus psyllium is thought to be clinically useful for promoting mucosal healing in colitis.

PAIN CONTROL

Many horses with salmonellosis or other forms of colitis have mild to severe signs of abdominal pain from gas and fluid distention of the colon, colonic ischemia, or infarction. One can accomplish analgesia with NSAIDs such as flunixin, but the potential for worsening mucosal injury or nephrotoxicity may prevent the use of analgesic doses, especially in horses with suspected NSAID toxicity. Newer NSAIDs that specifically target COX-2 (the inducible COX) but have little activity against COX-1 (the constitutive COX) may be useful analgesics that spare the gastrointestinal mucosa. For example, etodolac (10 to 15 mg/kg intravenously or orally once daily) has analgesic properties in horses and may spare the intestinal mucosa from the detrimental effects associated with nonselective COX inhibitors (A.T. Blikslager, personal communication, 2002). However, the specificity for COX-2 in horses is unproven. Thus avoiding the use of any NSAIDs in horses with RDC or other forms of NSAID toxicity is advisable.

Xylazine or detomidine may provide temporary relief of pain. Butorphanol is a useful analgesic that one can administer intramuscularly (0.1 mg/kg every 6 hours) or as a continuous infusion. An infusion of 13.2 µg/kg/hr in isotonic crystalloid fluid such as lactated Ringer's solution has been suggested.[227] Continuous lidocaine infusions (1.3 mg/kg intravenous loading dose administered slowly over 5 minutes and followed by 3 mg/kg/hr infusion in isotonic crystalloid fluids) can provide profound visceral analgesia and may have added prokinetic benefits if ileus is present.

ANTIBIOTICS

Neutropenia

Broad-spectrum antibiotic treatment often is recommended in neutropenic horses or horses with signs of septicemia. Neutropenia is associated with an increased risk of septicemia and septic complications such as septic phlebitis and infection of surgical site.[1] Septicemia is a potentially life-threatening complication of enterocolitis and may be caused directly by *Salmonella, Clostridium,* other invasive enteric bacteria, or indirectly by toxic injury to the colonic mucosa that breaks down the barrier to luminal microbes. Neutropenia possibly may weaken host defenses enough to render horses susceptible to organisms that breach the mucosal barrier. Although most attempts to culture bacteria from the blood of adult horses with colitis fail to isolate organisms, no detailed studies have been undertaken to determine the prevalence of bacteremia or septicemia in these patients. Disseminated aspergillosis has been reported in horses as a complication of acute colitis, demonstrating the potential for systemic infections with rarely pathogenic organisms stemming from colonic mucosal injury in the face of potential immunosuppression from neutropenia.[228,229] Broad-spectrum antibiotics lessen septic complications in human patients. However, evidence supporting this principle in horses with colitis is lacking.

Salmonellosis

Treatment with antibiotics is controversial in horses with salmonellosis and is not thought to alter the course of the enterocolitis. Antibiotics directly targeted at the *Salmonella* are reserved for patients with the enteric fever (septicemia) form of salmonellosis, documented with positive blood cultures. Lipid-soluble antibiotics are suited ideally for *Salmonella* infections, because the bacteria persist intracellularly. Trimethoprim-sulfadiazine or other potentiated sulfa drugs, enrofloxacin, and chloramphenicol are preferred antibiotics for the enteric fever form of salmonellosis for this reason.

Equine Monocytic Ehrlichiosis

As with other causes of enterocolitis, the use of antibiotics for equine monocytic ehrlichiosis is controversial. Fear of inducing salmonellosis or other forms of

antibiotic-induced diarrhea and the difficulty of diagnosing the disease early have caused most authors to recommend judicious use of antibiotics.[49] However, in patients with a high suspicion of *Neorickettsia risticii* infection, treatment with antibiotics often is indicated before definitive diagnosis. Lipid-soluble drugs are desirable because the organism can live within cells. Oxytetracycline (6.6 mg/kg intravenously every 24 hours), doxycycline (10 mg/kg orally every 12 hours), trimethoprim-sulfadiazine (5 mg/kg trimethoprim orally or intravenously every 8 to 12 hours and 25 mg/kg sulfadiazine every 8 to 12 hours), or erythromycin-rifampin (30 mg/kg and 5 mg/kg, respectively, orally every 12 hours) have been used effectively to treat clinical cases.[49,230-232] The tetracyclines appear to be the most effective antibiotics for treatment of Potomac horse fever. Treatment is most successful if initiated before the onset of diarrhea.[49,231]

Clostridiosis

If one has administered antibiotics since the onset of enterocolitis, one should discontinue administration as soon as possible. Specific treatment with metronidazole (15 to 25 mg/kg orally every 8 hours) is effective for treating clostridiosis in human beings and appears to be effective in horses.[83,233] Metronidazole resistance in clinical isolates of *Clostridium difficile* has been reported in one outbreak but appears to be rare in most human and equine cases.[234] Metronidazole-resistant isolates were sensitive to vancomycin, which may be effective for treating clinical cases if one suspects metronidazole resistance. However, metronidazole remains the treatment of choice. Some authors describe the off-label use of *C. perfringens* type C antitoxin in cases of neonatal clostridiosis, described in more detail elsewhere.[235] Antitoxin preparations generally are not advocated for use in adult horses with clostridiosis.

Proliferative Enteropathy

Lawsonia intracellulare is susceptible to a variety of antibiotics in vitro, including chlortetracycline, erythromycin, penicillin, difloxacin, and ampicillin.[236] Lipid-soluble antibiotics with a large volume of distribution usually are chosen to treat proliferative enteropathy because *L. intracellulare* is an intracellular organism. Erythromycin estolate (15 to 25 mg/kg orally every 6 to 8 hours) alone or with rifampin (5 mg/kg orally every 12 hours) is the most commonly reported efficacious treatment for proliferative enteropathy. Chloramphenicol (50 mg/kg orally every 6 hours) has also been reported to be effective if erythromycin worsens the diarrhea.[115] Anecdotal reports suggest that oxytetracycline and doxycycline also may be effective. Supportive care including maintenance of hydration and electrolyte balance and plasma or colloid administration to

increase colloid oncotic pressure in hypoalbuminemic patients is also indicated. One should treat affected foals until clinical signs, hypoproteinemia, and ultrasonographic evidence of intestinal thickening resolve. The prognosis depends on the duration of the disease and the degree of fibrosis and destruction of the intestinal architecture.

ANTICOAGULATION

Hypercoagulability is a common complication of enterocolitis, associated with systemic inflammation from endotoxemia. Administration of heparin (20 to 80 IU/kg subcutaneously or intravenously every 6 to 12 hours) may prevent thrombosis in these patients, provided antithrombin III concentrations are adequate in the plasma. Concentrated sources of antithrombin III are not available for use in horses, but whole plasma may provide an important source. Treatment with heparin is thought to decrease thrombosis, especially of the jugular vein, a serious complication of salmonellosis. Low-dose aspirin treatment (15 mg/kg orally every 24 to 48 hours) along with heparin treatment may provide added benefit by irreversibly inhibiting platelet function.[237] Heparin and aspirin may have protective effects on the digital lamina.[237,238] Heparin also may enhance the phagocytic activity of the reticuloendothelial system by enhancing the efficiency of opsonins such as fibronectin and immunoglobulin, thereby stimulating phagocytosis of products of coagulation and possibly other particles, including bacteria.[239,240]

PROBIOTICS
Salmonellosis

Maintenance of the bacterial flora and antagonism of pathogenic bacteria such as *Salmonella* in the gastrointestinal tract are important defense mechanisms preventing colonization by pathogenic bacteria. The use of probiotic preparations containing beneficial bacteria has been shown to prevent colonization of pathogenic bacteria, including *Salmonella*, in poultry.[241] Little work has been done to investigate the efficacy of these products in preventing salmonellosis in horses, but ongoing studies may provide important information. Probiotic and other preparations designed to restore normal flora to the gastrointestinal tract, such as fecal suspensions, sour milk, and yogurt, have been used clinically to shorten the course of salmonellosis, with variable results. Therefore prevention of infection by using probiotic agents and other means is important. Exposure of susceptible horses to *Salmonella* should be avoided, but the task is difficult, especially because asymptomatic infections are common and the bacteria are ubiquitous in the environment. Prophylactic use of probiotic preparations, judicious use of antibiotics in susceptible horses, control of environmental conditions such as

temperature, and restricted exposure to pathogenic bacteria are important for control of salmonellosis.

Clostridiosis

Because altered large intestinal flora appears to play an important role in the pathogenesis of equine intestinal clostridiosis or any antibiotic-associated diarrhea, probiotic preparations have been advocated to treat affected horses. Sour milk, a product containing lactose-producing *Streptococcus* species, appears to improve the clinical course greatly in horses suspected of having *Clostridium perfringens* type A infection. Sour milk may benefit the patient by altering the flora and antagonizing enterotoxigenic *C. perfringens* type A but also is reported to be bactericidal against *C. perfringens* type A.[78] Preparations of *Saccharomyces boulardi* are effective for reducing diarrhea and the frequency of *C. difficile* recurrence in human beings.[83] However, whether relapse is a problem in horses with *C. difficile* colitis is not clear. *Lactobacillus* preparations have a protective effect in human beings and decrease the severity and duration of antibiotic-associated diarrhea.[242,243] However, evidence of their clinical usefulness in horses is lacking.

NUTRITION

Good nursing care and adequate nutrition are vital to the treatment of horses with salmonellosis. Salmonellosis is a severely catabolic disease, increasing caloric requirements greatly. Normal intake of roughage to provide energy may be inadequate; however, one should avoid feeding of grains to prevent carbohydrate overload. Dietary management usually consists of restricting or eliminating long-stem roughage (hay) from the diet and feeding exclusively a complete pelleted diet (at least 30% dietary fiber). The rationale behind this recommendation is to reduce the mechanical load on the colon. Frequent meals (4 to 6 times a day) are recommended. One can add corn oil (1 cup every 12 to 24 hours) to the pellets to increase the caloric intake without adding roughage or grain. One should note that if a horse with colitis refuses to eat pelleted feed, then one should feed good-quality grass hay. In anorectic or severely catabolic patients, enteral and parenteral nutrition (total and partial) has been used successfully to provide calories and nutritional support.

SPECIFIC THERAPIES
Strongylosis

Strongylus vulgaris infection requires treatment of the migrating parasite larvae and the lesions produced by the parasite. Fenbendazole (10 mg/kg orally every 24 hours for 3 days or 10 mg/kg orally every 24 hours for 5 days) and ivermectin (200 mg/kg orally) are effective in killing fourth-stage larvae.[121] Other anthelmintics also may be

effective when given at higher doses than those required to kill adult worms. The efficacy of these anthelmintics against larvae within thrombi is not known.

Thrombolytic and antithrombotic therapy has been advocated in horses with suspected strongylosis.[121,128] Heparin (20 to 80 IU intravenously or subcutaneously every 6 to 12 hours) is often administered as an anticoagulant. Aspirin (10 to 30 mg/kg orally every 12 to 48 hours) is usually combined with heparin to inhibit platelet adhesion. Aspirin also may inhibit release of platelet products such as thromboxane that affect the motility of the large intestine. Low-molecular-weight dextrans have been advocated as antithrombotics that act by inhibiting platelet function and coagulation.[128,218] The clinical efficacy of dextran administration appears to be good, but no controlled studies have been performed.

Cyathostomiasis

Anthelmintic administration is usually the only treatment necessary for mild to moderate cases of cyathostomiasis treated early in the course of the disease (within 1 to 3 weeks of onset). Fenbendazole is effective against many larval stages, but resistance is increasing. Although the reported efficacy of ivermectin varies against certain stages,[244] one study reported an overall efficacy of 75%.[245] Currently, fenbendazole (7.5 to 10 mg/kg orally every 24 hours for 5 days) followed on day 6 by ivermectin (200 mg/kg orally) is the most commonly advocated treatment regimen.[133,246] Moxidectin (400 µg/kg orally once daily) also may be effective against adults and L_3 and L_4 larval stages[247] and may be useful for treating cyathostomiasis. Antiinflammatory therapy also may be beneficial, especially in severe or refractory cases. NSAID administration may have limited value, but dexamethasone appears to be efficacious in refractory cases when used with larvicidal anthelmintics.[133,136] Pretreatment with dexamethasone or prednisolone is indicated before anthelmintic administration if heavy larval loads are suspected to prevent an acute exacerbation of the disease by rapid death of encysted larvae. Bismuth subsalicylate often is administered orally as an antisecretory agent in young animals. Supportive care may be necessary in severe cases, particularly if hypoproteinemia is severe. Horses occasionally require administration of intravenous crystalloid fluids and plasma or other colloids. Proper nutritional support is also important.

Cantharidin Toxicity

Supportive care is the most important principle of therapy for cantharidin toxicity. Intravenous fluid administration; maintenance of electrolyte balance, especially calcium; and prevention of further renal and urinary tract damage is important.[183,187] Diuresis by intravenous fluid administration is often sufficient to prevent renal

failure. Furosemide often is administered after rehydration of the patient to further promote diuresis and to decrease the concentration of the toxin in the urine, which may ameliorate some of the effects on the urinary tract mucosa. Diuresis also has been suggested to increase clearance of the toxin, but no evidence for this has been found. Judicious use of NSAIDs may be necessary to control abdominal pain but should be reserved until the patient is rehydrated and renal failure has been ruled out. Cantharidin is lipid-soluble; therefore oral administration of mineral oil may prevent further absorption of the toxin.[183] Activated charcoal often is administered with the mineral oil.

Arsenic Toxicity

To reduce arsenic absorption, one should initiate administration of cathartics such as mineral oil and magnesium sulfate slurries and activated charcoal by nasogastric tube immediately. Chelation therapy with sodium thiosulfate 20 to 30 g in 300 ml of water orally and dimercaprol (BAL) 3 mg/kg intramuscularly every 4 hours is indicated.[188] Dimercaprol is a specific antidote for trivalent arsenicals, but its efficacy in horses is questionable. Intravenous fluid administration may help treat shock, replace fluid lost in feces, and promote diuresis but should be monitored carefully because pulmonary edema is a frequent complication. The horse may require more specific treatment of renal, cardiac, pulmonary, or neurologic disease.

Intestinal Anaphylaxis

Treatment of intestinal anaphylaxis is in principle similar to treatment of other forms of colitis but is often unsuccessful because of the rapidly progressive nature of the syndrome. Inclusion of heparin in intravenous fluids (20 to 80 IU/kg intravenously every 8 to 12 hours) may help prevent vascular thrombosis. Administration of hypertonic saline solutions or colloids may prove to be useful during initial periods of shock. Early treatment with prednisolone succinate (10 to 20 mg/kg intravenously) or dexamethasone (0.1 to 0.2 mg/kg intravenously) may be essential for successful treatment.[192]

Carbohydrate Overload

Mild cases of carbohydrate overload may not require treatment other than exclusion of grains from the diet for several days to weeks and gradual reintroduction of grain into the diet later if the horse needs the extra energy. Patients showing signs of colic or diarrhea without other systemic signs may benefit from administration of mineral oil, charcoal, and fluids via nasogastric tube. One also may lavage residual carbohydrates from the stomach with the nasogastric tube. NSAIDs such as phenylbutazone (2.2 to 4.4 mg/kg/day intravenously)

or flunixin meglumine (1 mg/kg intravenously every 12 hours) often are administered to prevent laminitis. Phenoxybenzamine and heparin given before the onset of laminitis may prevent or decrease the severity of laminitis.[238,248]

More severe cases with dehydrating diarrhea, systemic signs of endotoxemia, or metabolic acidosis require intravenous fluid support to maintain water, electrolyte, and acid-base balance in addition to the previously mentioned treatments. Large amounts of bicarbonate-containing solutions may be required. One should take care when administering hypertonic bicarbonate solutions, because many patients already may be hyperosmotic from lactic acidemia. Isotonic sodium bicarbonate 1.3% may be useful in the hyperosmotic patient. Careful attention to calcium balance is also important, because severe hypocalcemia may occur. One should institute aggressive therapy for systemic inflammation from endotoxemia. One should administer broad-spectrum antibiotics intravenously to combat bacteremia and septicemia, which frequently complicate colitis induced by carbohydrate overload.

In extreme cases, especially if the patient has ingested a large quantity of grain, surgical removal of the grain from the large intestine may be indicated, especially if one can accomplish surgery before the onset of severe clinical signs. However, administration of oral cathartics, such as magnesium sulfate slurries or mineral oil, or a combination of these, is often sufficient to clear the carbohydrates from the large intestine before fermentation, mucosal damage, and absorption of endotoxin and lactic acid occur. Oral administration of activated charcoal may prevent absorption of endotoxin by binding the molecules in the lumen of the bowel. In any case, one should discontinue feeding of the source of the soluble carbohydrates, such as grains. One should feed the horse low-carbohydrate and low-protein roughage such as grass or oat hays until the microbial flora recovers. Oral administration of probiotic preparations containing *Lactobacillus* is contraindicated; however, other sources of normal equine large intestinal microbial flora, such as fecal extracts from normal feces, may be useful to reintroduce appropriate microorganisms. Complications from laminitis and sepsis are common and often cause death.

Sand Enteropathy

Treatment of sand enteropathy requires removal of the sand from the gastrointestinal tract using psyllium products and magnesium sulfate slurries administered orally. Analgesics may be required initially to relieve pain and stimulate appetite. A diet high in roughage often stimulates further passage of sand. Treatment may require several weeks to remove as much sand as

possible. Prevention of the disease is important, and recurrence is not unusual.

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13.14—Ischemic Disorders of the Intestinal Tract

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Strangulating Obstruction

Strangulating obstruction of the intestine is characterized by simultaneous occlusion of the intestinal lumen and its blood supply. Although strangulation of the intestinal

lumen results in clinical signs similar to those of simple obstruction, occlusion of the blood supply results in a more rapid deterioration of the intestinal mucosa and subsequent onset of endotoxemic shock. Although a great deal of interest in the relevance and treatment of intestinal reperfusion injury has arisen recently,[1-3] the lesion that develops during strangulation is often severe, leaving little viable bowel for further injury during reperfusion.[2] Although extensive lengths of strangulated small intestine may be resected, strangulation of the large colon presents a much greater treatment dilemma because strangulated intestine usually extends beyond the limits of surgical resection.[4] Therefore horses with large intestinal strangulation often recover with extensive intestinal injury left in place. Thus subtle degrees of reperfusion injury may be important in horses with large colon disease, warranting further work in this area in an attempt to reduce mortality.[3]

Strangulating obstruction may be divided into hemorrhagic and ischemic forms.[5,6] Hemorrhagic strangulating obstruction, which is most common, involves initial occlusion of veins before occlusion of arteries because of the greater stiffness of arterial walls. This lesion is characterized by a darkened appearance to affected bowel and increased thickness as blood is pumped into the lesion. Ischemic strangulating obstruction occurs if the intestine is twisted tightly enough to occlude arteries and veins simultaneously. In the case of the colon, such strangulation has been suggested to be determined by how much ingesta is in the colon, because intestinal contents may prevent the intestine from twisting tightly.[7] Tissue involved in ischemic strangulating obstruction appears pale and of normal or reduced thickness because of a complete lack of blood flow (Figure 13.14-1). Bowel peripheral to strangulating lesions also may become injured because of distention, which reduces mural blood flow once it reaches critical levels. Furthermore, as this intestine is decompressed, it also may undergo reperfusion injury.[8-10]

Small Intestinal Strangulation

CLINICAL SIGNS

Horses with small intestinal strangulating obstruction typically have moderate to severe signs of abdominal pain that are only intermittently responsive to analgesic medications. During the latter stages of the disease process, horses may become profoundly depressed rather than painful as affected intestine necroses. Horses have progressive signs of endotoxemia, including congested mucous membranes, delayed capillary refill time, and an elevated heart rate (>60 beats/min in most cases). In addition, one typically obtains reflux following passage of a stomach tube, and one usually can detect loops of distended small intestine on rectal palpation of the abdomen.[11] However, these latter findings vary depending on the duration and location of the obstruction. For example, horses with ileal obstructions tend to reflux later in the course of the disease process than horses with a jejunal obstruction. Furthermore, a horse that has an entrapment of small intestine in the epiploic foramen may not have palpable loops of small intestine because of the cranial location of these structures.[12] Abdominocentesis can provide critical information on the integrity of the intestine and is indicated in horses in which one suspects strangulation of the small intestine.[13] A horse that has signs compatible with a small intestinal obstruction and additionally has serosanguinous abdominal fluid with an elevated protein level (>2.5 mg/dl) is likely to require surgery, although one must differentiate these

Figure 13.14-1   Ischemic strangulating obstruction of the small colon by a mesenteric lipoma. **A,** The lipoma *(arrow)* has encircled a segment of small colon tightly. **B,** Following resection of the lipoma, a pale area of strangulated small colon clearly is demarcated *(arrows),* the appearance of which is consistent with ischemic strangulating obstruction.

cases from proximal enteritis. In general, horses with small intestinal strangulation show continued signs of abdominal pain, whereas horses with proximal enteritis tend to be depressed after initial episodes of mild abdominal pain. In addition, horses with small intestinal strangulation continue to deteriorate clinically despite appropriate medical therapy and will likely begin to show an increased white blood cell count (>10,000 cells/μl) in the abdominal fluid as the duration of strangulation increases. However, cases occur in which the differentiation between small intestinal strangulation and proximal enteritis is not clear, at which point one may elect surgery rather than risking delay of abdominal exploration of a horse with a potential strangulating lesion.[14]

PROGNOSIS

The prognosis for survival in horses with small intestinal strangulating lesions is generally lower than for most forms of colic.[15] However, recent studies indicate that in excess of 80% of horses with small intestinal strangulating lesions are discharged from the hospital.[16] Nonetheless, veterinarians should warn owners that the long-term survival rates are reduced substantially to below 70%,[17] in part because of long-term complications such as adhesions.[18,19] In addition, the prognosis is particularly low for some forms of strangulation, including entrapment of small intestine within a mesenteric rent.[20]

EPIPLOIC FORAMEN ENTRAPMENT

The epiploic foramen is a potential opening (because the walls of the foramen are usually in contact) to the omental bursa located within the right cranial quadrant of the abdomen. The foramen thus is bounded dorsally by the caudate process of the liver and caudal vena cava and ventrally by the pancreas, hepatoduodenal ligament, and portal vein. Intestine may enter the foramen from the visceral surface of the liver toward the right body wall or the opposite direction. Studies differ as to which is the most common form.[12,21] In the case of entrapments that enter the foramen in a left-to-right direction, the omental bursa ruptures as the intestine migrates through the epiploic foramen, which may contribute to intraabdominal hemorrhage often seen with this condition. Clinical signs include acute onset of severe colic with examination findings compatible with small intestinal obstruction. The condition tends to be more prevalent in older horses,[12] possibly because of enlargement of the epiploic foramen as the right lobe of the liver undergoes age-associated atrophy.[22] However, the disease also has been recognized in foals as young as 4 months of age.[23] One makes a definitive diagnosis at surgery, although ultrasonographic findings of distended loops of edematous small intestine adjacent to the right middle body wall suggest epiploic foramen entrapment.[12] In general,

thickened, amotile intestine on ultrasonographic examination is highly predictive for small intestinal strangulating obstruction.[24] Small intestine entrapped in the epiploic foramen may be limited to a portion of the intestinal wall (parietal hernia),[25] and the large colon may become entrapped within the epiploic foramen.[26] In treating epiploic foramen entrapment, one must not enlarge the epiploic foramen by blunt force or with a sharp instrument, because rupture of the vena cava or portal vein and fatal hemorrhage may occur. Prognosis has improved substantially over the last decade, with current short-term survival rates (discharge from the hospital) ranging from 74%[27] to 79%.[12] Preoperative abdominocentesis has been found consistently to be the most predictive test of postoperative survival.[12,27]

STRANGULATION BY PEDUNCULATED MESENTERIC LIPOMA

Lipomata form between the leaves of the mesentery as horses age and develop mesenteric stalks as the weight of the lipoma tugs on the mesentery. The stalk of the lipoma subsequently may wrap around a loop of small intestine or small colon causing strangulation. One should suspect strangulating lipomata in aged (>15 years old) geldings with acute colic referable to the small intestinal tract.[28,29] Ponies also appear to be at risk of developing disease,[29] suggesting alterations in fat metabolism may predispose certain horses to development of mesenteric lipomata. One usually makes the diagnosis at surgery, although on rare occasions one can palpate a lipoma per rectum.[30] Treatment involves surgical resection of the lipoma and strangulated bowel, although strangulated intestine is not always nonviable.[28] Studies indicate that approximately 50%[29] to 80%[28] of horses are discharged from the hospital following surgical treatment.

SMALL INTESTINAL VOLVULUS

A volvulus is a twist along the axis of the mesentery, whereas torsion is a twist along the longitudinal axis of the intestine. Small intestinal volvulus theoretically is initiated by a change in local peristalsis or the occurrence of a lesion around which the intestine and its mesentery may twist (such as an ascarid impaction).[11] Volvulus is reportedly one of the most commonly diagnosed causes of small intestinal obstruction in foals.[31,32] The theory is that young foals may be at risk of small intestinal volvulus because of changing feed habits and adaptation to a bulkier adult diet. Onset of acute, severe colic, a distended abdomen, and radiographic evidence of multiple loops of distended small intestine in a young foal suggest small intestinal volvulus. However, one cannot differentiate volvulus from other causes of small intestinal obstruction preoperatively. In adult horses, volvulus

frequently occurs in association with another disease process, during which small intestinal obstruction results in distention and subsequent rotation of the small intestine around the root of the mesentery. Although any segment of the small intestine may be involved, the distal jejunum and ileum are affected most frequently because of their longer mesenteries.[11] One makes the diagnosis at surgery by palpating a twist at the origin of the cranial mesenteric artery. Treatment includes resection of devitalized bowel, which may not be an option because of the extent of small intestinal involvement (similar to large colon volvulus). Prognosis is based on the extent of small intestine involved and its appearance following surgical correction of the lesion. In general, horses with greater than 50% of the small intestine devitalized are considered to have a grave prognosis.[33]

STRANGULATION VIA MESENTERIC OR LIGAMENTOUS RENTS

A number of structures, when torn, may incarcerate a segment of intestine (typically the small intestine), including intestinal mesentery,[20] the gastrosplenic ligament,[34] the broad ligament,[35] and the cecocolic ligament.[36] Horses with such incarcerations have signs typical of a horse with strangulating small intestine, including moderate to severe signs of abdominal pain, endotoxemia, absent gastrointestinal sounds, distended small intestine on per rectal palpation, nasogastric reflux, and serosanguinous abdominal fluid. However, the prognosis for many of these horses appears to be lower than for horses with other types of small intestinal strangulations. For example, in horses with small intestine entrapped in a mesenteric rent, only 7 of 15 horses were discharged from the hospital, and only 2 of 5 horses for which follow-up information was available survived long term (>5 months).[20] Poor outcome may result from the difficulty in unentrapping incarcerated intestine, the degree of hemorrhage, and the length of intestine affected.

INGUINAL HERNIA

Inguinal herniae are more common in Standardbred and Tennessee Walking horses that tend to have congenitally large inguinal canals.[11] Inguinal herniae also may occur in neonatal foals but differ from herniae in mature horses in that they are typically nonstrangulating. The nature of the hernia (direct versus indirect) is based on the integrity of the parietal vaginal tunic. In horses in which the bowel remains within the parietal vaginal tunic, the hernia is referred to as indirect, because strictly speaking the bowel remains within the peritoneal cavity. Direct herniae are those in which strangulated bowel ruptures through the parietal vaginal tunic and occupies a subcutaneous location. These direct herniae most commonly occur in foals and should be suspected when a congenital

Figure 13.14-2　Inguinal hernia in a horse with colic. The enlarged testicle has compromised venous drainage because of herniated small intestine within the inguinal canal.

inguinal hernia is associated with colic, swelling that extends from the inguinal region or the prepuce, and intestine that may be palpated subcutaneously.[37,38] Although most congenital indirect inguinal herniae resolve with repeated manual reduction or application of a diaper, surgical intervention is recommended for congenial direct herniae.[37]

Historical findings in horses with strangulating inguinal herniae include acute onset of colic in a stallion that recently had been used for breeding. A cardinal sign of inguinal herniation is a cool, enlarged testicle on one side of the scrotum (Figure 13.14-2).[39,40] However, inguinal herniae also have been reported in geldings.[41] One also can detect inguinal herniae on rectal palpation, and one can use manipulation of herniated bowel per rectum to reduce a hernia, but this is generally not recommended because of the risk of rectal tears. In many cases, the short segment of herniated intestine greatly improves in appearance after reduction and in some cases can be left unresected. The affected testicle will be congested because of vascular compromise within the spermatic cord, and although the testicle may remain viable, resection generally is recommended.[42] The prognosis in adult horses is good, with up to 75% of horses surviving to 6 months.[40] Horses that have been treated for inguinal herniae may be used for breeding. In these horses, the remaining testicle will have increased sperm production, although an increased number of sperm abnormalities will be noticeable following surgery because of edema and increased temperature of the scrotum.

STRANGULATING UMBILICAL HERNIAE

Although umbilical herniae are common in foals, strangulation of herniated bowel is rare. In one study, 6 of 147 (4%) horses with umbilical herniae had

incarcerated intestine.[43] Clinical signs include a warm, swollen, firm, and painful hernia sac associated with signs of colic. The affected segment of bowel is usually small intestine, but herniation of cecum or large colon also has been reported. In rare cases, one may find a hernia that involves only part of the intestinal wall, called a Richter's hernia. In foals that have a Richter's hernia, an enterocutaneous fistula may develop. In one study, 13 of 13 foals with strangulating umbilical herniae survived to discharge, although at least 3 died of long-term complications.[44]

INTUSSUSCEPTIONS

An intussusception involves a segment of bowel (intussusceptum) that invaginates into an adjacent aboral segment of bowel (intussuscipiens). The reason for such invagination is not always clear but may involve a lesion at the leading edge of the intussusception, including small masses, foreign bodies, or parasites. In particular, tapeworms *(Anoplocephala perfoliata)* have been implicated.[45] Ileocecal intussusceptions are the most common intestinal intussusceptions in the horse and typically affect young animals. In one study evaluating 26 cases of ileocecal intussusception, the median age of the horses was 1 year old. Acute ileocecal intussusceptions are those in which the horses has a duration of colic of less than 24 hours and involve variable lengths of intestine that ranged in one study from 6 to 457 cm long. In acute cases the involved segment of ileum typically has a compromised blood supply. Chronic ileocecal intussusceptions typically involve short segments of ileum (up to 10 cm long), and the ileal blood supply is frequently intact.[46] Abdominocentesis results vary because strangulated bowel is contained within the adjacent bowel. Obstruction of the small intestine often is evident, including nasogastric reflux and multiple distended loops of small intestine on rectal palpation. Horses with chronic ileocecal intussusceptions have mild, intermittent colic, often without evidence of small intestinal obstruction. In one study, a mass was palpated in the region of the cecal base in approximately 50% of cases.[45] Transabdominal ultrasound may be helpful in discerning the nature of the mass. The intussusception has a characteristic target appearance on cross section.[47] Other segments of the small intestine also may be intussuscepted, including the jejunum (Figure 13.14-3). In one study of 11 jejunojejunal intussusceptions, the length of bowel involved ranged from 0.4 to 9.1 m.[48] Attempts to reduce intussusceptions at surgery are usually futile because of intramural swelling of affected bowel. One should resect jejunojejunal intussusceptions.

For acute ileocecal intussusceptions, one should transect the small intestine as far distally as possible and perform a jejunocecal anastomosis. In horses with

Figure 13.14-3 Jejunojejunal intussusception in a horse presented for colic. The intussusceptum has become ischemic because of invagination of intestine and its mesenteric blood supply into the intussuscipiens.

particularly long intussusceptions (up to 10 m has been reported), one may attempt an intracecal resection.[49] For horses with chronic ileocecal intussusceptions, one should perform a jejunocecal bypass without small intestinal transection. The prognosis is good for horses with chronic ileocecal intussusceptions and guarded to poor for horses with acute ileocecal intussusceptions, depending on the length of bowel involved.[46]

DIAPHRAGMATIC HERNIAE

Herniation of intestine through a rent in the diaphragm is rare in the horse and may involve any segment of bowel, although small intestine is herniated most frequently. Diaphragmatic rents may be congenital or acquired, but acquired herniae are more common. Congenital rents may result from incomplete fusion of any of the four embryonic components of the diaphragm: pleuroperitoneal membranes, transverse septum, and esophageal mesentery. In addition, abdominal compression of the foal at parturition may result in a congenital hernia.[50] Acquired herniae are presumed to result from trauma to the chest or a sudden increase in intraabdominal pressure, such as might occur during parturition, distention of the abdomen, a sudden fall, or strenuous exercise.[51] Herniae have been found in a number of different locations, although large congenital herniae are typically present at the ventral most aspect of the diaphragm, and most acquired herniae are located at the junction of the muscular and tendinous portions of the diaphragm.[50] A peritoneopericardial hernia has been documented in at least one horse.[52]

Clinical signs usually are associated with intestinal obstruction rather than respiratory embarrassment.[51] However, careful auscultation may reveal an area of decreased lung sounds associated with obstructed intestine and increased fluid within the chest cavity.[53] Such signs may prompt thoracic radiography or ultrasound, both of which one can use to make a diagnosis. Auscultation also may reveal thoracic intestinal sounds, but differentiating these from sounds referred from the abdomen typically is not possible. In one report, two of three horses diagnosed with small intestinal strangulation by diaphragmatic hernia had respiratory acidemia attributable to decreased ventilation.[54] Treatment of horses with diaphragmatic hernia is fraught with complications because of the need to reduce and resect strangulated bowel and the need to repair the defect in the diaphragm.[55,56] Because dorsal defects in the diaphragm are among the common forms of diaphragmatic defect, closing the diaphragmatic hernia via the approach used for abdominal exploration may not be possible. However, because herniation is likely to recur,[55] scheduling a second surgery using an appropriate approach to resolve the diaphragmatic defect is appropriate.

Large Colon Volvulus

CLINICAL SIGNS

Horses with large colon volvulus have rapid onset of severe, unrelenting abdominal pain, most often in postpartum broodmares.[4] Once the large colon strangulates (≥270-degree volvulus), gas distention is significant, leading to gross distention of the abdomen, compromised respiration as the distended bowel presses up against the diaphragm, and visceral pooling of blood as the caudal vena cava is compressed. Horses with this condition are frequently refractory even to the most potent of analgesics. These horses may prefer to lie in dorsal recumbency, presumably to take weight off the strangulated colon. An abbreviated physical examination is warranted in these cases, because the time elapsed from the onset of strangulation to surgical correction is critical. Under experimental conditions, the colon is irreversibly damaged within 3 to 4 hours of a 360-degree volvulus of the entire colon.[57] Despite severe pain and hypovolemia, horses may have a paradoxically low heart rate, possibly related to increased vagal tone. In addition, results of abdominocentesis often do not indicate the degree of colonic compromise[4,58] and in many cases are not worth attempting because of extreme colonic distention.[59] Palpation per rectum reveals severe gas distention of the large colon, often restricting access to the abdomen beyond the pelvic brim. One may make the diagnosis tentatively based on signalment, severity of pain, and degree of distention.

SURGICAL FINDINGS

At surgery, the volvulus typically is located at the mesenteric attachment of the colon to the dorsal body wall and the most common direction of the twist is dorsomedial using the right ventral colon as a reference point. However, the colon may twist in the opposite direction, twist greater than 360 degrees (up to 720 degrees has been reported) or twist at the level of the diaphragmatic and sternal flexures.[4] In all cases, one should decompress the colon as much as possible, and in many cases a colonic evacuation via a pelvic flexure enterotomy greatly aids correction of the volvulus. One must determine after correction of the volvulus whether the colon has been injured irreversibly and should base the determination on mucosal color and bleeding (if an enterotomy has been performed), palpation of a pulse in the colonic arteries, serosal color, and appearance of muscular motility. If one judges the colon to be damaged irreversibly, one can consider the feasibility of a large colon resection. Although 95% of the colon can be resected (that part of the colon distal to the level of the cecocolic fold), damage from the volvulus usually exceeds that which can be resected. In these cases, surgeons may elect to resect as much damaged bowel as possible or may advise euthanasia.[7]

PROGNOSIS

The prognosis is guarded to poor because of the rapid onset of this disease. In one study the survival rate was 35%.[58] In a more recent report the survival rate was 36% for horses with 360-degree volvulus of the large colon compared with 71% for horses with 270-degree volvulus.[4] However, one study in central Kentucky documented a high success rate, possibly because of early recognition of the disease and the proximity of the hospital to the surgical caseload.[60] Postoperative complications include hypovolemic and endotoxic shock, extensive loss of circulating protein, disseminated intravascular coagulation, and laminitis. In addition, large colon volvulus has a propensity to recur. Although one study documented a recurrence rate of less than 5%,[58] some authors believe recurrence may be as high as 50%.[7] Therefore one should consider methods to prevent recurrence in patients at risk of recurrence, particularly broodmares that tend to suffer from the disease recurrently during the foaling season.[61,62]

Other Causes of Large Intestinal Ischemia

The most common intussusceptions of the large intestine are cecocecal and cecocolic intussusceptions.[63,64] Both are likely attributable to the same disease process, with variable inversion of the cecum. These conditions

tend to occur in young horses (63% were less than 3 years old in one study) and may be associated with intestinal tapeworms. Horses show highly variable clinical signs, including acute severe colic, intermittent pain over a number of days, or chronic weight loss.[64] These variable presentations likely relate to the degree to which the cecum has intussuscepted. Initially, the cecal tip inverts, creating a cecocecal intussusception, which does not obstruct flow of ingesta. As the intussusception progresses, the cecum inverts into the right ventral colon (cecocolic intussusception), obstructs flow of ingesta, and often causes severe colic. The cause of abdominal pain is often difficult to differentiate in these cases, although detecting a mass on the right side of the abdomen by per rectal palpation or ultrasound examination sometimes is possible.[63,64] Treatment involves manual surgical reduction by retracting the intussusceptum directly[63] or via an enterotomy in the right ventral colon.[65] However, a number of cases occur in which one cannot reduce the cecum readily because of severe thickening or in which surgical procedures result in fatal contamination. For example, one report stated that 8 of 11 horses were euthanized in the perioperative period because of complications,[63] and another report stated that 12 of 30 horses were euthanized before or during surgery. The latter included all of the horses with chronic disease because of irreversible changes to the cecum.[64] However, one recent report on cecocolic intussusceptions indicated that seven of eight horses that underwent right ventral colon enterotomy and cecal resection survived long-term,[65] suggesting that continued improvements in surgical techniques may improve the prognosis.

Colocolic intussusceptions are rare but have been reported to affect the pelvic flexure and the left colons.[66-69] Although the condition is reported to be more common in young horses,[67-69] the condition may affect older horses.[66] Clinical findings may include a palpable mass on the left side of the abdomen.[67] Ultrasonography also may be useful. Treatment requires manual reduction of the intussusception at surgery,[67,69] or resection of affected bowel.[66] Because the left colons may be exteriorized extensively and manipulated at surgery,[66-69] the prognosis is fair.

Rectal Prolapse

Rectal prolapse may occur following any disease that causes tenesmus, including diarrhea, rectal neoplasia, and parasitism,[70] or prolapse can occur following elevations in intraabdominal pressure during parturition or episodes of coughing.[71,72] Rectal prolapses are classified into four categories (Table 13.14-1) based on the extent of tissue prolapsed and the severity. Type I rectal prolapse is most common and is characterized by a

TABLE 13.14-1		
Classification of Rectal Prolapse		
GRADE	DESCRIPTION	PROGNOSIS
I	Prolapse of rectal mucosa	Good
II	Prolapse of full-thickness rectum	Fair
III	Grade II prolapse with additional protrusion of small colon	Guarded
IV	Intussusception of rectum and small colon through the anus	Poor

doughnut-shaped prolapse of rectal mucosa and submucosa. Type II prolapses involve full-thickness rectal tissue, whereas type III prolapses additionally have invagination of small colon into the rectum. Type IV prolapses involve intussusception of proximal rectum or small colon through the anus in the absence of prolapse of tissue at the mucocutaneous junction at the anus.[73] One can differentiate type IV from other forms of prolapse by their appearance and a palpable trench between prolapsed tissue and the anus.

Type I prolapses occur most frequently in horses with diarrhea, in which the rectal mucosa becomes irritated and protrudes intermittently during episodes of tenesmus. If tenesmus persists, rectal mucosa can remain prolapsed. Rectal mucosa rapidly becomes congested and edematous under these conditions, which one should treat with osmotic agents such as glycerin or magnesium sulfate and by massaging and reducing the prolapse.[74] A purse-string suture may be required to keep the mucosa inside the rectum. Topical application of lidocaine solution or jelly, epidural anesthesia, and sedation may help reduce tenesmus that incites and exacerbates rectal prolapse. One can apply similar treatments to type II rectal prolapses. However, these more severe prolapses may not be reducible without surgical resection of mucosa and submucosa from the prolapsed bowel.[70,74]

Type III and IV rectal prolapses are more serious injuries because of involvement of small colon.[75] In horses with type III prolapses, one should perform an abdominocentesis to determine if injured small colon has resulted in peritonitis. One should reduce the small colon component manually if possible, although prolapsed rectal tissue typically requires mucosal/submucosal resection. One should perform surgical exploration of the abdomen to determine the status of the small colon, although one can use serial abdominocenteses in lieu of surgery to detect progressive necrosis of bowel. Type IV prolapses occur most commonly in horses with dystocia.[73] These prolapses are almost always fatal because of stretching and tearing of mesenteric vasculature, with subsequent infarction of affected bowel. Therefore euthanasia usually is warranted

based on physical examination findings. However, confirmation of severe small colonic injury requires abdominal exploration via a midline approach or laparoscopy.[76] A horse with compromised small colon conceivably could undergo a colostomy of the proximal small colon, but the compromised small colon typically necroses beyond that which can be resected via a midline abdominal approach.[74]

Nonstrangulating Infarction

Nonstrangulating infarction occurs following cranial mesenteric arteritis caused by migration of *Strongylus vulgaris* and has become a rare disorder since the advent of broad-spectrum anthelmintics. Although thrombo-emboli have been implicated in the pathogenesis of this disease, careful dissection of naturally occurring lesions has not revealed the presence of thrombi at the site of intestinal infarctions in most cases.[77] These findings suggest that vasospasm plays an important role in this disease.[78] Clinical signs vary greatly depending on the extent to which arterial flow is reduced and the segment of intestine affected. Any segment of intestine supplied by the cranial mesenteric artery or one of its major branches may be affected, but the distal small intestine and large colon are more commonly involved. No clinical variables exist that one can use to differentiate this disease from strangulating obstruction reliably. In some cases, massive infarction results in acute, severe colic.[77] Occasionally, one may detect an abnormal mass and fremitus on palpation of the root of the cranial mesenteric artery per rectum. One should consider this disease a differential diagnosis in horses with a history of inadequate anthelmintic treatment and the presence of intermittent colic that is difficult to localize. Although one should perform fecal parasite egg counts, they are not indicative of the degree of parasitic infestation.

In addition to routine treatment of colic, dehydration, and endotoxemia, medical treatment may include aspirin (20 mg/kg every 24 hours) to decrease thrombosis.[78] Definitive diagnosis requires surgical exploration. However, these cases are difficult to treat because of the patchy distribution of the lesions and the possibility of lesions extending beyond the limits of surgical resection. In addition, further infarction may occur following surgery. The prognosis is fair for horses with intermittent mild episodes of colic that may be amenable to medical therapy but is poor in horses that require surgical intervention.[77,78]

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13.15—Obstructive Disorders of the Gastrointestinal Tract

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Approach to the Horse With Colic

Clinical management of colic is distinctly different from management of many other clinical syndromes because the initial focus is often not on defining the definitive diagnosis but rather on deciding whether a horse requires surgical exploration. Therefore the clinician must collect historical, physical examination, and clinicopathologic information and make a decision whether these findings warrant medical management or whether to perform surgical exploration of the abdomen because of a suspected obstructive or ischemic lesion. For example, one may examine a horse with signs of severe abdominal pain, poor cardiovascular status, and abdominal distention that may be compatible with an extensive list of differential diagnoses but that more importantly indicate the need for abdominal exploration to minimize the extent of intestinal injury. The speed with which one can make this clinical decision has a tremendous effect on the well-being of the patient,[1,2] because delaying surgical exploration of a horse with on-going intestinal injury exacerbates shock induced largely by endotoxin traversing damaged mucosa, and this in turn correlates with mortality.[3]

HISTORY

The initial clinical step in the workup of horses with colic is taking a thorough history. However, one may have to delay taking a complete history until after the physical examination and initial treatment, because management of abdominal pain may take precedence. If possible, one should obtain the vital components of the history before examination and treatment: the duration and severity of colic symptoms, analgesics already administered, and a history of any adverse drug reactions. The two most critical factors from a history that would support a decision to explore a horse with colic surgically are the duration of signs and the extent of pain. One deduces the latter from asking the owner about the presence and frequency of pawing, looking at the flanks, rolling, repeatedly going down and getting back up, posturing as if to lie down or urinate, among other clinical evidence of pain.[4] Table 13.15-1 lists other important components of the history one should obtain to try to ascertain why colic has occurred.

PHYSICAL EXAMINATION FINDINGS

Just as the history necessarily may need to be brief to allow rapid treatment of colic, so the clinician must be able to alter the extent of the physical examination to treat the horse in a timely fashion. The most critical examination finding is the heart rate of the horse, because it provides an excellent assessment of the cardiovascular status of the horse.[4] The heart rate is likely the single most reliable predictor of the need for surgery and survival.[4,5] Because analgesics can alter the heart rate dramatically, if possible, one should obtain the heart rate before administering analgesics. Other components of the examination are designed specifically to gather information about the cardiopulmonary status of the horse (quality of the pulse, mucous membrane color, capillary refill time, respiratory rate, and full auscultation of the chest), and the nature of the intestinal obstruction (auscultation of gastrointestinal sounds, per rectal palpation of the abdomen, and presence of nasogastric reflux). Although classic presentations exist for horses with obstructions of the small or large intestine (Table 13.15-2), clinical presentations of the various types of intestinal obstructions can vary. For example, a horse that has a small intestinal obstruction may have several loops of distended small intestine without any evidence of gasric fluid accumulation (assessed as nasogastric reflux), depending on the site (distal versus proximal), extent, and duration of the obstruction. Other examples include horses with large colon obstruction that may have

TABLE 13.15-1		
History Findings and Their Relevance to Colic and Its Prevention		
COMPONENT OF HISTORY	**RISK FOR COLIC**	**POTENTIAL MECHANISMS**
Feeding	Recent change in feed	Alteration in fluid flux or fermentation in the large colon
	Coastal Bermuda hay with a high fiber content	Obstruction of ileum by fine, fibrous hay
	Feeding round bales	Poor-quality hay
	Feeding off the ground	Horses may ingest sand in some regions of the country
	Excessive concentrate	Alteration in fluid flux or fermentation in the large colon
	Large, infrequent meals	Alteration in fluid flux or fermentation in the large colon
	Bolting feed	Large boluses of feed entering the esophagus and stomach
Environment	Excessive time in stall	Insufficient intake of roughage
		Insufficient exercise
	Insufficient access to water	Dehydration
Exercise	Exercise-induced exhaustion	Dehydration
		Reduced gastrointestinal motility
Preventive care	Insufficient dental care	Poor mastication of feed
	Insufficient anthelmintic treatment	Large parasite burden
Medication	Excessive administration of nonsteroidal antiinflammatory drugs	Mucosal damage, particularly in the stomach and colon
Previous medical history	Colic surgery	Adhesions
		Anastomotic obstruction

TABLE 13.15-2	
Indications for Surgery in Patients With Colic According to Their Clinical Signs	
INDICATION	**CLINICAL SIGNS**
Refractory pain	Repeated episodes of pain despite treatment with analgesics
	Violent episodes of pain
	Persistently elevated heart rate (>48 beats/min)
Endotoxemia in the face of colic	Persistently elevated heart rate
	Weak peripheral pulse
	Abnormal mucous membrane color (pale, hyperemic, purple)
	Delayed capillary refill time (>2 seconds)
Evidence of a refractory small intestinal obstruction	Refractory pain
	Nasogastric reflux
	Distended loops of small intestine on per rectum palpation
Evidence of a refractory large intestinal obstruction	Refractory pain
	Abdominal distention
	Distended large colon on per rectum palpation
	Tight band(s) on per rectum palpation
Evidence of devitalized bowel	Endotoxemia
	Abnormal abdominocentesis (total protein >2.5 g/dl, total nucleated cell count >10,000/μl)

gastric fluid accumulation because of direct compression of the small intestine by distended colon or via tension on the duodenocolic ligament. The most useful diagnostic test for determining the type of intestinal obstruction is rectal palpation of the abdomen.[4] However, one can reach only approximately one third of the abdomen via the rectum, and this percentage may be substantially less in large horses or heavily pregnant horses. Nonetheless, attempting to determine the type of obstruction present (small intestine versus large intestine, and simple obstruction versus strangulating obstruction) is worthwhile; this information directly affects prognosis. In one study, interns and residents at a veterinary teaching hospital were able to predict the type of lesion with a specificity exceeding 90%.[6] Findings from palpation are helpful in educating the client about the potential findings in surgery and the likelihood of survival for the horse.

MANAGEMENT OF ABDOMINAL PAIN

Before considering how to manage signs of colic, one should remember that such signs are poorly localized. Therefore although colic is most frequently associated with intestinal disease, one should consider dysfunction of other organ systems, including urinary obstruction,[7,8] biliary obstruction,[9] uterine torsion or tears,[10,11] ovarian artery hemorrhage,[10] and neurologic disease as differential diagnoses.[12] However, the duration and severity of colic

TABLE 13.15-3

Analgesics Commonly Used to Treat Colic in Horses

DRUG	DOSAGE	AMOUNT FOR AN ADULT HORSE
Butorphanol	0.025-0.05 mg/kg as needed	5-10 mg
Detomidine	10-20 µg/kg as needed	5-10 mg
Flunixin	0.25-1.1 mg/kg every 8 to 12 hours*	125-500 mg
Xylazine	0.3-0.5 mg/kg as needed	150-250 mg

*The longer treatment interval corresponds to the higher dose, whereas lower doses may be given more frequently.

signs are excellent predictors of whether a horse requires surgical exploration of the abdomen. In fact, refractory pain supersedes all other predictors of the need for surgery in the colic patient. Once signs of colic have been recognized and categorized as to their severity, rapidly and effectively relieving the pain is critical for the well-being of the horse and to reduce the owner's anxiety. In addition, pain is best managed before it becomes severe.[13] Several classes of analgesics are readily available to treat horses with colic (Table 13.15-3), including α_2-agonists (xylazine, detomidine), opiates (butorphanol), and nonsteroidal antiinflammatory drugs (NSAIDs, such as flunixin meglumine). Although much of this information is familiar to most practitioners, several principles deserve emphasis. The short-duration drugs xylazine and butorphanol, which provide analgesia for 30 to 45 minutes, allow the veterinarian to determine if pain is recurrent within the time period of the typical examination. In contrast, flunixin meglumine is not as potent as an analgesic but has a much longer duration of action. To avoid deleterious effects on gastrointestinal mucosa and the kidneys, one should not administer flunixin meglumine more frequently than recommended.[14,15] The recent discovery of two isoforms of cyclooxygenase (COX), the enzyme inhibited by NSAIDs, has resulted in discovery of drugs that can more selectively inhibit proinflammatory COX-2 while permitting continued constitutive production of prostanoids. Such specificity may be advantageous in horses with colic, particularly when one considers recent evidence of reduced intestinal recovery from an ischemic event with flunixin compared with a drug that is more selective for COX-2.[16] One should reserve the α_2-agonist detomidine for horses with severe, unrelenting pain because of its tremendous potency.[17] In addition, one should remember that α_2-agonists reduce the heart rate associated with a transient increase in blood pressure,[18,19] thereby reducing the predictive value of the heart rate and pulse pressure.

CLINICAL PATHOLOGY

The most immediately useful clinicopathologic information in horses with colic are the packed cell volume and total protein, because one can use them to substantiate clinical estimates of dehydration and they correlate strongly with prognosis.[20,21] A serum biochemical profile is useful for assessing electrolyte imbalances, tissue perfusion (anion gap or lactate), and kidney and liver function. One can use serum biochemical or blood gas analysis to assess acid-base status. Horses with colic most frequently show evidence of metabolic acidosis associated with poor tissue perfusion caused by hypovolemia or endotoxemia, but one may note other abnormalities such as metabolic alkalosis in association with extensive loss or sequestration of stomach chloride. Metabolic acidosis has been investigated further in horses with colic by measuring blood lactate, although this test is not offered routinely in many laboratories. Lactate levels also have been inferred from measurement of the anion gap, although one study noted that lactate in horses with colic did not account for the entire anion gap.[22] Lactate levels and anion gap closely correlate with prognosis for survival.[20,23,24]

Other key components of assessment of the horse with colic are abdominocentesis and complete blood count. The total white blood cell count and differential can provide crucial evidence of systemic inflammation associated with endotoxemia stemming from colic attributable to colitis (leukopenia, neutropenia, and a left shift) rather than an obstruction (highly variable complete blood count findings). Peritoneal fluid may be helpful in determining the integrity of the intestine. Specifically, as the intestine becomes progressively devitalized, the peritoneal fluid becomes serosanguinous as red blood cells leak into the abdomen, followed by an elevation in the total protein (>2.5 g/dl) and progressive increases in total nucleated cell count (>10,000 cells/µl). However, these findings do not always correlate well with the condition of the intestine, particularly in horses with large colon volvulus. For example, in a study of 57 horses with large colon volvulus, the average total protein (2.5 g/dl) and total nucleated cell count (1000 cells/µl) were normal despite the fact that only 36% with a 360-degree volvulus survived.[4,25] These measures may appear normal because the development of severe mucosal injury following large colon volvulus is rapid and may not allow enough time for protein and leukocytes to equilibrate with the abdominal fluid.[26]

Investigators have taken all the variables routinely assessed during evaluation of horses for colic and have attempted to develop models to predict accurately the need for surgery and the prognosis for life.[27-30] None of these predictor models has taken the place of clinical decision making, although these studies have added

tremendously to understanding of the importance of some prognostic factors, particularly those reflecting cardiovascular function.

Small Intestinal Simple Obstruction

Simple obstruction involves intestinal obstruction of the lumen without obstruction of vascular flow. However, because a tremendous volume of fluid enters the small intestinal lumen daily,[31,32] the obstructed intestine tends to become distended, which in turn may reduce mural blood flow.[33] Ultimately, such distention may result in necrosis of tissues, particularly in the immediate vicinity of the obstruction.[34] Few are the causes of simple obstruction in the small intestine, and the incidence of these obstructions is low (approximately 3% of all referred horses in one large hospital-based study).[5] However, in some geographic regions, this type of obstruction is prevalent. For example, in the southeastern United States, ileal impactions are common.[35,36]

ASCARID IMPACTIONS

Impactions caused by *Parascaris equorum* typically occur in foals under 6 months of age that have been on a poor deworming program and have a heavy parasite burden. Products that cause sudden ascarid death, including piperazine, organophosphates, and pyrantel pamoate, have been incriminated in triggering acute intestinal obstruction by dead parasites. Ascarids are particularly problematic because of the large size of the adult parasite (Figure 13.15-1). Clinical signs include acute onset of colic following administration of an anthelmintic and

Figure 13.15-1 Appearance of roundworms that have been retrieved within the nasogastric reflux from a foal with an ascarid impaction. The large size of these ascarids (bar = 1 cm) contributes to the risk of impaction following sudden kills of these parasites by broad-spectrum anthelmintics.

signs compatible with small intestinal obstruction, including nasogastric reflux. Occasionally, dead parasites are present in the reflux. The onset of the disease varies according to the degree of obstruction. One tentatively may base diagnosis on the history and signs referable to small intestinal obstruction. Abdominal radiographs may indicate the presence of multiple loops of distended small intestine but are not required if clinical signs indicate the immediate need for surgery. Initial medical treatment should include treatment of hypovolemic shock resulting from sequestration of fluid in the small intestine and systemic inflammation from absorption of endotoxin. Surgical treatment typically involves an enterotomy made over the intraluminal impaction and removal of ascarids. The prognosis is fair in horses that are rapidly and appropriately treated but poor in foals with evidence of hypovolemic and endotoxic shock.[37]

ILEAL IMPACTION

Ileal impactions most commonly occur in adult horses in the southeastern United States. Although feeding of coastal Bermuda hay has been implicated in the regional distribution of the disease, separating geographic location from regional hay sources as risk factors has been difficult. Nonetheless, feeding coastal Bermuda hay likely places horses at risk of ileal impaction, particularly if the coarse fiber content of the hay is high. Furthermore, sudden changes in feed from an alternate type of hay to coastal Bermuda hay likely places a horse at risk of ileal impaction.[38] Studies in England have revealed tapeworm infection as another important risk factor for ileal impaction. Based on risk analysis, the data suggested that in excess of 80% of the ileal impaction cases studied were associated with serologic or fecal evidence of tapeworm infection.[39] Because of the poor sensitivity of fecal analysis for tapeworms, Proudman and Trees have developed a serologic test (enzyme-linked immunosorbent assay) with a sensitivity of approximately 70% and a specificity of 95%.[40]

Clinical signs of horses with ileal impaction are typical for a horse with small intestinal obstruction, including onset of moderate to severe colic and loops of distended small intestine palpable per rectum as the condition progresses. Because the ileum is the distal most aspect of the small intestinal tract, nasogastric reflux may take a considerable time to develop and is found in approximately 50% of horses requiring surgical correction of impacted ileum.[35,41] One usually makes the diagnosis at surgery, although on occasion one may palpate an impacted ileum per rectum. Multiple loops of distended small intestine frequently make the impaction difficult to palpate. Ileal impactions may resolve with medical treatment[36] but frequently require surgical intervention (Figure 13.15-2). At surgery, one can infuse fluids directly

Figure 13.15-2 Intraoperative view of an ileal impaction. The distended appearance of the ileum as it courses toward the cecal base is notable.

into the mass, allowing the surgeon to breakdown the impaction. The surgeon may include dioctyl sodium sulfosuccinate in the infused fluid to aid in disruption of the mass. Extensive small intestinal distention and intraoperative manipulation of the ileum may lead to postoperative ileus,[42] but recent studies indicate that this complication is less frequent as the duration of disease before admission decreases.[35] Recent studies indicate that the prognosis for survival is good.[35,36]

ILEAL HYPERTROPHY

Ileal hypertrophy is a disorder in which the muscular layers (circular and longitudinal) of the ileum hypertrophy for unknown reasons (idiopathic) or following an incomplete or functional obstruction. For idiopathic cases, proposed mechanisms include parasympathetic neural dysfunction resulting in chronically increased muscle tone and subsequent hypertrophy of the muscular layers of the ileal wall. Such neural dysfunction possibly could result from parasite migration. Alternative hypotheses include chronic increases in the muscular tone of the ileocecal valve, leading to muscular hypertrophy of the ileum as it contracts against a partially occluded ileocecal valve. The jejunum also may be hypertrophied, alone or with the ileum. Clinical signs include chronic intermittent colic as the ileum hypertrophies and gradually narrows the lumen diameter. In one study, partial anorexia and chronic weight loss (1 to 6 months) were documented in 45% of the horses, most likely because of intermittent colic and reduced appetite. Because hypertrophy does not affect the ileal mucosa, no reason exists to believe that these horses experience malabsorption of nutrients. One usually makes the diagnosis at surgery, although one may palpate the

hypertophied ileum per rectum in some cases. For treatment, one performs an ileocecal or jejunocecal anastomosis to bypass the hypertrophied ileum. Without surgical bypass, intermittent colic persists and the thickened ileum ultimately may rupture.[43] The prognosis is fair with surgical treatment.[44]

Secondary ileal hypertrophy is most commonly notable in horses that previously have had colic surgery and that may have a partial or functional obstruction at an anastomotic site. For example, in one case report, a horse developed ileal hypertrophy after surgical correction of an ileocecal intussusception.[45] Ileal hypertrophy also was noted in a horse with cecal impaction in which an ileocolic anastomosis was oriented incorrectly.[46] Horses are typically re-presented for recurrence of colic in these cases. Surgical therapy is directed at addressing the cause of small intestinal obstruction and resecting hypertrophied intestine.

MECKEL'S DIVERTICULUM

Meckel's diverticulum is an embryonic remnant of the vitelloumbilical duct, which fails to atrophy completely and becomes a blind pouch projecting from the antimesenteric border of the ileum.[47,48] However, similar diverticula also have been noted in the jejunum.[49] These diverticula may become impacted, resulting in partial luminal obstruction, or may wrap around an adjacent segment of intestine, causing strangulation.[47] Occasionally, an associated mesodiverticular band may course from the diverticulum to the umbilical remnant and serve as a point around which small intestine may become strangulated. Mesodiverticular bands also may originate from the embryonic ventral mesentery and attach to the antimesenteric surface of the bowel, thereby forming a potential space within which intestine may become entrapped. Clinical signs range from chronic colic for an impacted Meckel's diverticulum to acute severe colic for intestine strangulated by a mesodiverticular band. One makes the diagnosis at surgery, and treatment requires resection of the diverticulum and any associated bands. The prognosis is good for horses with simple impaction of a Meckel's diverticulum and is guarded for horses with an associated small intestinal strangulation.[50]

ADHESIONS

Adhesions of one segment of bowel to another or of a segment of intestine to other organs and the body wall most typically occur following abdominal surgery and may be clinically silent, cause chronic colic attributable to partial obstruction, or result in acute obstruction. These differing clinical syndromes are attributable to the type of adhesions that develop. For example, a fibrous adhesion that does not by itself obstruct the intestinal lumen might serve as the pivot point for a volvulus,

whereas an adhesion between adjacent segments of the intestinal tract may create a hairpin turn that causes chronic partial obstruction.[51] The number of adhesions that develop also may vary greatly from horse to horse. Some horses may develop a single adhesion adjacent to an anastomotic site or a discrete segment of injured intestine, whereas other horses may develop diffuse adhesions involving multiple segments of intestine, likely because of widespread inflammation of the peritoneum at the time of the original surgery.

The mechanism whereby adhesions develop is complex but likely involves initial injury to the serosa initiated by intestinal ischemia, reperfusion injury, and luminal distention.[52] Importantly, such injury involves infiltration of neutrophils into the serosa accompanied by loss of mesothelial cells. In one study assessing the margins of resected small intestine, extensive neutrophil infiltration was documented in the serosa, particularly in the proximal resection margin that had been distended before correction of a variety of strangulating lesions.[53] Regions of serosal injury and inflammation subsequently undergo reparative events similar to any wound, including local production of fibrin, de novo synthesis of collagen by infiltrating fibroblasts, and ultimately maturation and remodeling of fibrous tissue. Unfortunately, during this process, fibrin may result in injured intestinal surfaces adhering to adjacent injured bowel or an adjacent organ. Once a fibrinous adhesion has developed, new collagen synthesis may result in a permanent fibrous adhesion. Alternatively, proteases released by local phagocytes may lyse fibrinous exudate, thereby reversing the adhesive process. Thus one can view formation of adhesions as an imbalance of fibrin deposition and fibrinolysis.[54]

Prevention of adhesions depends on inhibition of the mechanisms involved in adhesion formation, including reduction of serosal injury with early intervention and good surgical technique, reduction of inflammation by administration of antiinflammatory medications, physical separation of inflamed serosal surfaces (e.g., carboxy-methylcellulose and hyaluronan),[55-57] and pharmacologic modulation of fibrinous adhesion formation (e.g., heparin).[58] In addition, early return of motility in the small intestine after surgery may reduce contact time between inflamed surfaces of intestine, thereby reducing the chances of adhesion formation.[54]

Horses at greatest risk of developing adhesions after colic surgery appear to be those that have small intestinal disease.[51,59] In one study of horses undergoing surgical correction of small intestinal obstruction, 22% developed a surgical lesion associated with adhesions. Foals appear to have an increased incidence of adhesions compared with mature horses regardless of the nature of the abdominal surgery.[51] One study indicated that 17% of foals developed lesions attributable to adhesions

regardless of the type of initial surgery.[60] Studies conflict as to whether the degree of surgical intervention influences adhesion formation,[51] but in one study, horses that require enterotomy or resection and anastomosis were at greatest risk of developing adhesions.[59] As an indication of the importance of postoperative adhesion formation, adhesions were among the most common reasons for repeat laparotomy in postoperative colic patients.[59,61]

Clinical signs of horses with adhesions vary greatly depending on whether the adhesion is causing partial obstruction or complete luminal obstruction or involves intestinal vasculature. Adhesions would be an important differential diagnosis for intermittent colic in the postoperative period, particularly if such colic was not relieved by nasogastric decompression of the stomach. Continued intermittent colic should prompt abdominocentesis to determine if septic peritonitis is present, which may contribute to adhesion formation. Placement of a large bore drain and peritoneal lavage (Figure 13.15-3) aids resolution of peritonitis and may reduce adhesion formation by reducing intraabdominal inflammation. If postoperative colic persists, one may
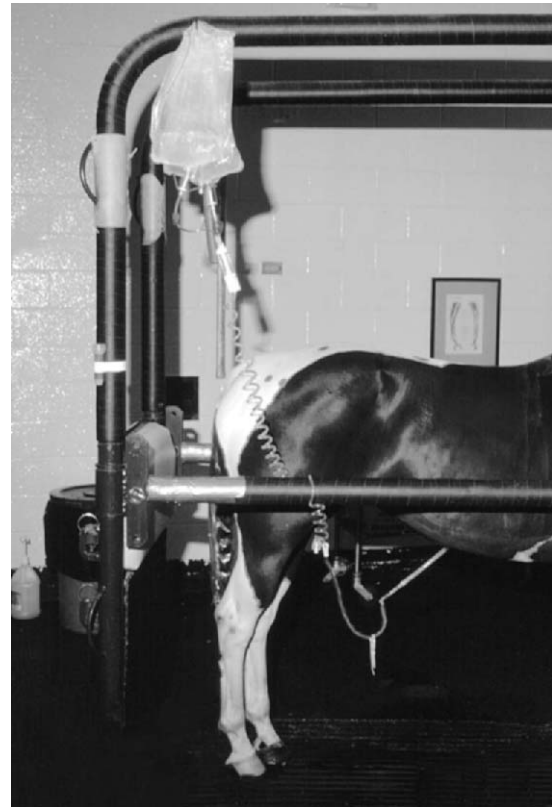
Figure 13.15-3 Peritoneal lavage in a horse. The use of an intravenous administration set and a large-bore catheter placed in the dependent portion of the abdomen adjacent to the ventral midline incision is notable.

elect repeat laparotomy or laparoscopy. In one study of adhesions, 70% of repeat laparotomies were performed within 60 days, suggesting that surgical colic attributable to adhesions typically occurs within 2 months of an initial surgical procedure. Unfortunately, the prognosis for horses with colic attributable to adhesions is low, with only 16% of horses in one study surviving from adhesion-induced colic.[51]

POSTOPERATIVE ILEUS

The definition of *ileus* is intestinal obstruction, including physical and functional obstructions. However, in veterinary medicine, the term typically is used to designate a lack of progressive aboral propulsion of ingesta resulting in functional obstruction.[62] One typically bases the diagnosis of postoperative ileus on the presence of excessive gastric fluid accumulation (reflected as excessive nasogastric reflux). Postoperative ileus may occur following any abdominal exploratory procedure. However, horses undergoing surgery for strangulating small intestinal lesions or small intestinal obstructive lesions such as an ileal impaction are at greatest risk.[42] Recently, the syndrome of postoperative ileus in horses has been broadened to include those horses that may have delayed transit of ingesta through the large intestine following surgery. This large intestinal ileus may follow any type of surgery, particularly horses that have had orthopedic surgery, and is characterized by reduced fecal output (fewer than three piles of manure per day) rather than excessive nasogastric reflux.[62] However, horses with excessive nasogastric reflux are unlikely to have normal fecal output, so the distinction between these two manifestations of ileus is not absolute.

Mechanisms involved in precipitating postoperative ileus characterized by small intestinal dysfunction likely involve local inflammation, reduced coordination of progressive motility, and increased sympathetic tone. A recent series of studies in the rat has shown that surgical manipulation of intestine results in delayed transit time associated with infiltration of neutrophils into intestinal longitudinal muscle[63-65] and upregulation of inducible nitric oxide synthase and COX-2. The mechanisms in the horse may be similar in that extensive manipulation of the intestine resulted in abnormal intestinal motility in ponies,[66] and prostanoids and nitric oxide alter or reduce intestinal motility in horses.[67-69]

Clinical signs of postoperative ileus following colic surgery include evidence of abdominal pain, increased heart rate, reduced gastrointestinal sounds, and reflux of gastric fluid via a nasogastric tube. Of these signs, heart rate is critical because it appears to be a more sensitive indicator of pain in the postoperative period than overt evidence of colic. Therefore a sudden increase in the heart rate of a postoperative patient following colic

surgery should prompt immediate nasogastric intubation to decompress the stomach. Treatment should include attempts at obtaining reflux from the horse at frequent intervals rather than relying on passive flow of reflux. In addition, administration of intravenous fluids should account for the maintenance requirement (50 ml/kg/day, about 1 L/hr in the average horse) and fluid losses via reflux. In practice, this requires frequent monitoring of packed cell volume and total protein to ensure that the horse remains well hydrated. Although concerns have arisen that overhydrating horses may contribute to increased nasogastric reflux,[42] keeping horses well-hydrated to avoid hypovolemic shock is critical. Additionally, one should monitor electrolytes frequently, particularly considering their potential role in smooth muscle contraction and nerve excitability. Because of the important role of inflammation in postoperative ileus, including elaboration of COX-2–produced prostanoids,[70] administration of NSAIDs is indicated. NSAID administration is particularly necessary if postoperative ileus is associated with endotoxemia, because lipopolysaccharide-induced prostanoid production disrupts propulsive motility in horses.[71,72] Interestingly, phenylbutazone is more effective than flunixin meglumine at reducing the deleterious actions of lipopolysaccharide on intestinal motility.[73] However, one should use caution when administering NSAIDs to patients with postoperative ileus in light of research suggesting that complete inhibition of prostanoid production can alter motility patterns in normal equine intestine.[68] The advent of selective COX-2 inhibitors may provide optimal antiinflammatory treatment in the future.[74]

Other treatments aimed at specifically modulating intestinal motility include lidocaine (bolus of 1.3 mg/kg followed by 0.05 mg/kg/min for 24 hours), erythromycin (0.5 to 1.0 mg/kg slow intravenous infusion in 1 L saline every 6 hours), and metoclopramide (0.04 mg/kg/hr).[66,75,76] The mechanism of lidocaine is presumed to be inhibition of sensory nerve activity within the wall of the intestine, thereby reducing reflex sympathetic inhibitory activity. In addition, intravenously administered lidocaine appears to be an effective analgesic. Thus an important feature of intravenous lidocaine therapy may be to control postoperative pain-induced reduction of gastrointestinal motility and mucosal secretory activity.[77] Metoclopramide may stimulate intestinal motility by several mechanisms, including dopamine receptor blockade, cholinergic stimulation, and adrenergic blockade.[66] Although metoclopramide has been shown to be beneficial for reversing postoperative ileus in clinical patients and research animals, it has central nervous system excitatory side effects in the horse that make its use difficult. Nonetheless, administration of metoclopramide to horses with postoperative ileus resulted in

a significantly reduced duration of reflux and shorter postoperative hospital stays compared with horses not receiving this drug.[76] In the same study, constant infusion of metoclopramide was superior to intermittent infusion. Recent in vitro studies indicate that metoclopramide effectively increases smooth muscle contractile activity throughout the small intestine. Similarly, the motilin agonist erythromycin had stimulatory effects on equine small intestine, although the results were not uniform throughout the small intestine. Erythromycin stimulates contractile activity in the longitudinal muscle of the pyloric antrum but inhibits contractile activity in circular smooth muscle in this segment of the gastrointestinal tract.[75] The latter may be attributable to activation of motilin receptors on inhibitory nerves and may result in enhanced gastric emptying. In vivo studies on erythromycin confirmed the stimulatory action of this drug on the distal small intestine and indicated this drug also stimulates contractile activity in the cecum and pelvic flexure. However, the stimulation depends on the temporal association with surgery. Erythromycin stimulated contractile activity in the postoperative period in the ileum and pelvic flexure but not the cecum,[78] suggesting this drug may be useful for treating select cases of postoperative ileus.

For horses with presumed ileus of the large colon, signs included reduced fecal output (fewer than three piles of manure per day), reduced gastrointestinal sounds, variable presence of colic, and on occasion a palpable impaction of the cecum or large colon. Risk factors for this syndrome include orthopedic surgery, length of the operative period, and most importantly inadequate treatment with phenylbutazone, presumably resulting from insufficient control of postoperative pain. Although treatment of large colon impaction in the postoperative period typically is uncomplicated, onset of cecal impaction is fatal in many cases because of the difficulty in recognizing horses that have cecal dysfunction. Therefore one should pay close attention to fecal production and optimal analgesic treatment in any horse following an orthopedic procedure.[62] Other painful procedures, including ophthalmologic procedures, also likely place horses at risk of developing ileus of the large intestine.

Large Intestinal Simple Obstruction

Simple obstructions of the large intestine such as impaction tend to have a more gradual onset than those of the small intestine, although horses may become acutely and severely painful with some forms of colon displacement. In fact, some of these cases mimic and may progress toward large colon volvulus. Medical therapy is frequently successful in correcting large colon impactions. However, cecal impactions present much more of a

dilemma because of the greater propensity of this organ to rupture, the relative difficulty of surgically manipulating the cecum, and the onset of cecal dysfunction that may prevent the cecum from emptying following surgical resolution of impaction.

CECAL IMPACTION

Cecal impaction may be divided into two syndromes: primary cecal impactions that result from excessive accumulation of ingesta in the cecum and secondary cecal impactions that develop while a horse is being treated for a separate problem.[79,80] Although primary impactions typically consist of impacted, relatively dry fecal material and secondary cecal impactions tend to have fluid contents, considerable overlap exists between the two syndromes, and one must approach each case carefully. In horses with primary cecal impactions, onset of abdominal pain occurs over a number of days, reminiscent of the development of a large colon impaction. One should differentiate cecal impactions from large colon impactions on the basis of rectal palpation findings. Cecal impactions have a propensity to rupture before the development of severe abdominal pain or systemic deterioration and therefore must be monitored closely.[79] Secondary cecal impactions typically develop following unrelated surgical procedures that result in postoperative pain (particularly orthopedic surgeries). Secondary cecal impactions may be even more difficult to detect because one may attribute postoperative depression and decreased fecal output to the operative procedure rather than to colic. By the time horses with secondary cecal impactions show noticeable signs of colic, the cecum may be close to rupture. In many cases, no signs of impending rupture are evident.[80] Therefore all horses that undergo surgeries in which considerable postoperative pain may develop should have feed intake and manure production closely monitored. A recent study indicated that horses that produce fewer than three piles of manure daily in the postoperative period are at risk of developing a large intestinal impaction. Furthermore, horses that underwent prolonged (>1 hour) orthopedic surgery that received inadequate treatment with phenylbutazone were at considerable risk of reduced postoperative fecal output.[62] These results are in contrast to statements indicating that NSAIDs may place horses at risk of impaction, statements that appear to be based largely on clinical impressions rather than on risk analysis.[80]

The diagnosis of primary cecal impaction is based on palpation of a firm, impacted cecum per rectum. In some cases, cecal impactions may be difficult to differentiate from large colon impactions. However, careful palpation reveals the inability to move the hand completely dorsal to the impacted viscus because of the attachment of the cecum to the dorsal body wall. Treatment for horses

with primary cecal impactions may include initial medical therapy, including aggressive administration of intravenous fluids and judicious use of analgesics.[80] However, if the cecum is distended grossly or if medical therapy hasno effect within a reasonable period of time, surgical evacuation of the cecum via a typhlotomy is indicated.[79] In addition, performing an ileocolostomy to bypass the cecum is advisable, because postoperative cecal motility dysfunction with recurrence of the impaction is common.[46,81]

In horses that develop secondary cecal impactions, diagnosis is based on palpation of a greatly distended cecum filled with semifluid intestinal contents. The nature of the contents likely is related to the more rapid progression of this disease compared with primary cecal impaction. One should not delay surgery because of the risk of cecal rupture.[82] However, if the cecum appears healthy following typhlotomy and evacuation, bypass of the cecum is not as critical as it is for primary impactions as long as one can control the inciting cause of the impaction (such as orthopedic pain).

The prognosis is guarded for surgical treatment of all cecal impactions because of the potential for the cecum to rupture during prolonged medical treatment or during surgical manipulation, the possibility of abdominal contamination during surgery, and the extensive surgical procedures required. In a recent report, seven of nine horses for which cecal impaction was treated by typhlotomy and ileocolostomy or jejunocolostomy lived long term.[46] However, a separate report indicated that all horses with cecal impaction following another disease process had cecal rupture without any signs of impending rupture.[80]

LARGE COLON IMPACTION

Ingesta impactions of the large colon occur at sites of anatomic reductions in luminal diameter, particularly the pelvic flexure and the right dorsal colon.[83] Although a number of risk factors have been reported, most have not been proved. However, a sudden restriction in exercise associated with musculoskeletal injury appears frequently to be associated with onset of impaction.[84] Another consideration is equine feeding regimens, which usually entail twice daily feeding of concentrate. Such regimens are associated with large fluxes of fluid into and out of the colon, associated with readily fermentable carbohydrate in the colon and subsequent increases in serum aldosterone, respectively. One may prevent these fluid fluxes, which may cause dehydration of ingesta during aldosterone-stimulated net fluid flux out of the colon, with frequent small feedings.[32]

Amitraz, an acaricide associated with clinical cases of colon impaction, can induce impaction of the ascending colon.[85,86] This effect may provide some clues as to the pathogenesis of large colon impaction. In particular, amitraz appears to alter pelvic flexure pacemaker activity, resulting in uncoordinated motility patterns between the left ventral and left dorsal colon and excessive retention of ingesta. Absorption of water from the ingesta increases with retention time, dehydrates the contents of the colon, and results in impaction. Conceivably, parasite migration in the region of a pacemaker may have a similar action.[87] Other factors implicated in large colon impaction include limited exercise, poor dentition, coarse roughage, or dehydration.

Clinical signs of large colon impaction include slow onset of mild to moderate colic. Fecal production decreases, and the feces are often hard, dry, and mucus-covered because of delayed transit time. The heart rate may be elevated mildly during episodes of pain but is often normal. Signs of abdominal pain are typically well controlled with administration of analgesics but become increasingly more severe and refractory if the impaction does not resolve. The diagnosis is based on palpation of a firm mass in the large colon per rectum. However, one may underestimate the extent of the impaction by rectal palpation alone because much of the colon is out of reach. Adjacent colon may be distended if the impaction has resulted in complete obstruction. One should attempt initial medical treatment. Administration of analgesics (e.g., flunixin meglumine at 0.5 to 1.1 mg/kg intravenously every 8 to 12 hours; butorphanol at 0.04 to 0.1 mg/kg intramuscularly every 4 to 6 hours; or xylazine at 0.3 to 0.5 mg/kg intravenously as needed) controls intermittent abdominal pain. Administration of oral laxatives such as mineral oil (2 to 4 L by nasogastric tube every 12 to 24 hours) and the anionic surfactant dioctyl sodium sulfosuccinate (6 to 12 g/500 kg diluted in 2 to 4 L of water by nasogastric tube every 12 to 24 hours) are used commonly to soften the impaction. Saline cathartics such as magnesium sulfate (0.1 mg/kg in 2 to 4 L by nasogastric tube) also may be useful. One should not permit access to feed. For impactions that persist, one should institute aggressive oral and intravenous fluid therapy (2 to 4 times the maintenance fluid requirement). If the impaction remains unresolved, the horse becomes uncontrollably painful, or extensive gas distention of the colon occurs, surgery is indicated. In addition, one can monitor abdominal fluid serially to determine the onset of intestinal compromise.[83] At surgery, one evacuates the contents of the colon via a pelvic flexure enterotomy. The prognosis is good for those horses in which impactions resolve medically (95% long-term survival in one study) and fair in horses that require surgical intervention (58% long-term survival in the same study).[84]

ENTEROLITHS

Enteroliths are mineralized masses typically composed of magnesium ammonium phosphate (struvite).[88] However, magnesium vivianite also has been identified in

enteroliths, along with variable quantities of sodium, sulfur, potassium, and calcium. The formation of magnesium-based minerals is puzzling because of the relative abundance of calcium in colonic fluids, which would favor the formation of calcium phosphates (apatite) rather than struvite.[89] However, elevated dietary intake of magnesium and protein may play a role. Many horses that develop enteroliths are located in California and are fed a diet consisting mainly of alfalfa hay. Analysis of this hay has revealed a concentration of magnesium approximately 6 times the daily requirements of the horse.[90] Furthermore, the high protein concentration in alfalfa hay may contribute to calculi formation by increasing the ammonia nitrogen load in the large intestine. Enteroliths most commonly form around a nucleus of silicon dioxide (a flintlike stone), but nidi have included ingested nails, rope, and hair.[88] Enteroliths usually are found in the right dorsal and transverse colons.[90] Although enterolithiasis has a wide geographic distribution, horses in California have the highest incidence. In one California study, horses with enterolithiasis represented 28% of the surgical colic population, and Arabians, Morgans, American Saddlebreds, and donkeys were at greatest risk of this disease.[91] In a study of enterolithiasis in Texas, risk factors also included feeding of alfalfa hay and Arabian breed. However, in that study, miniature horses were also at risk.[92] Horses with enteroliths are rarely under 4 years old,[90] although an enterolith in an 11-month-old miniature horse has been reported recently.[93]

Enterolithiasis is characterized by episodic, mild to moderate, intermittent abdominal pain.[90] Progressive anorexia and depression may develop. The amount of pain depends on the degree of obstruction and amount of distention. Partial luminal obstruction allows the passage of scant, pasty feces. Heart rate varies and depends on the degree of pain. In some cases, an enterolith is forced into the small colon, where it causes acute small colon obstruction. One may diagnose enteroliths by abdominal radiography or at surgery. On rare occasions, one may palpate an enterolith per rectum, particularly if it is present in the distal small colon.

In general, these cases require surgery, although enteroliths being retrieved per rectum have been reported. In fact in one study, 14% of horses presented for treatment of enterolithiasis had a history of passing an enterolith in the feces. However, enteroliths typically are located in the right dorsal colon, transverse colon, or small colon. At surgery, one gently pushes the enterolith toward a pelvic flexure enterotomy, but removal frequently requires a separate right dorsal colon enterotomy to prevent rupture of the colon. Following removal of an enterolith, one must conduct further exploration to determine if other enteroliths are present. Solitary enteroliths are usually round, whereas

multiple enteroliths have flat sides. The prognosis is good (92% 1-year survival in one study of 900 cases), unless the colon ruptures during removal of an enterolith. In one recent study, rupture occurred in 15% of cases.[91]

SAND IMPACTIONS OF THE LARGE COLON

Sand impactions are common in horses with access to sandy soils, particularly horses eating feed placed on the ground. Some horses, especially foals, deliberately eat sand. Fine sand tends to accumulate in the ventral colon, whereas coarse sand may accumulate in the dorsal colon.[94,95] However, individual differences in colonic function may contribute to accumulation of sand, because some horses can clear consumed sand, whereas others cannot. Distention from the impaction itself, or gas proximal to the impaction, causes abdominal pain. In addition, sand may trigger diarrhea, presumably because of irritation of the colonic mucosa.[96] In horses with sand impactions, clinical signs are similar to those of horses with large colon impactions.[94] One may find sand in the feces, and auscultation of the ventral abdomen may reveal sounds of sand moving within the large colon.[97] However, unlike sand-induced diarrhea, one may not hear sand impactions easily because of the lack of colonic motility. To determine the presence of fecal sand, one places several fecal balls in a rectal palpation sleeve or other container, which subsequently is filled with water. If sand is present, it accumulates at the bottom of the container. In addition, one may detect mineral opacity within the colon on abdominal radiographs, particularly in foals, ponies, and small horses. Abdominal paracentesis typically yields normal fluid and poses some risk because large quantities of sand in the ventral colon make inadvertent perforation of the colon more likely.[95] Peritoneal fluid is often normal but may have an elevated protein concentration.

Initially, medical therapy is warranted. Administration of psyllium hydrophilic mucilloid (0.25 to 0.5 kg/500 kg in 4 to 8 L of water by stomach tube) may facilitate passage of sand. One should administer the solution rapidly because it will form a viscous gel. An alternative method of administration is to mix psyllium with 2 L of mineral oil, which will not form a gel and can be pumped through a nasogastric tube easily. One then pumps 2 to 4 L of water through the tube. The psyllium separates from the oil phase and mixes with the water, forming a gel within the gastrointestinal tract. Psyllium is thought to act by stimulating motility or by agglutinating the sand. However, a recent experimental study failed to show a benefit of this treatment for clearing sand from the colons of otherwise normal horses.[98] If a severe impaction is present, one should not give the psyllium until softening the impaction by administrating intravenous or

oral fluids and other laxatives. Perforation is a potential complication in horses with sand impactions because the sand stretches and irritates the intestinal wall and causes inflammation. Therefore if colic becomes intractable, one should perform surgical evacuation of the large colon. The prognosis is generally good.[94,95]

LARGE COLON DISPLACEMENT

Displacement of the ascending colon is a common cause of large intestinal obstruction. The ascending colon is freely movable except for the right dorsal and ventral colons. Contact with adjacent viscera and the abdominal wall tends to inhibit movement of the ascending colon from a normal position; however, accumulation of gas and fluid or ingesta may cause the colon to migrate.[99] Feeding practices, including feeding of large concentrate meals, likely plays a role in initiating displacement of the large colon. Large concentrate meals increase the rate of passage of ingesta, allowing a greater percentage of soluble carbohydrates to reach the large intestine,[31] which in turn increases the rate of fermentation and the amount of gas and volatile fatty acids produced. The production of large amounts of volatile fatty acids stimulates the secretion of large volumes of fluid into the colon.[100] The association between feeding concentrate and development of displacements of the large colon is illustrated by studies indicating that ascending colon displacement is more prevalent in horses fed a high-concentrate, low-roughage diet.[101] Abnormal motility patterns of the ascending colon also have been suggested to contribute to the development of colonic displacement. Feeding stimulates colonic motility via the gastrocolic reflex, but large meals may alter normal motility patterns and concurrently allow rapid accumulation of gas and fluid from fermentation.[31,102] Migration of parasite larvae (strongyles) through the intestinal wall also has been shown to alter colonic motility patterns. Other experimental studies also have shown that *Strongylus vulgaris* infection results in reduced blood flow to segments of the large intestine without necessarily causing infarction. Electric activity of the colon and cecocolic junction increases after infection with *S. vulgaris* and cyathostome larvae, probably reflecting a direct effect of migration through the intestine and an early response to reduced blood flow.[103]

Displacements of the ascending colon generally are divided into three types: left dorsal displacement, right dorsal displacement, and retroflexion. Left dorsal displacement is characterized by entrapment of the ascending colon in the renosplenic space. The colon often is twisted 180 degrees such that the left ventral colon is situated in a dorsal position relative to the left dorsal colon. The entrapped portion may be only the pelvic flexure or may involve a large portion of the ascending colon, with the pelvic flexure situated near the diaphragm. The colon may become entrapped by migrating dorsally between the left abdominal wall and the spleen or may migrate in a caudodorsal direction over the nephrosplenic ligament. Occasionally, one can palpate the ascending colon between the spleen and abdominal wall, lending support to the first mechanism of displacement. Gastric distention is thought to predispose horses to left dorsal displacement of the ascending colon by displacing the spleen medially, allowing the colon room to migrate along the abdominal wall. Right dorsal displacement begins by movement of the colon cranially, medial (medial flexion) or lateral (lateral flexion) to the cecum. According to one author, the proportion of right dorsal displacements with medial versus lateral flexion is approximately 1:15.[104] In either case the pelvic flexure ends up adjacent to the diaphragm. Retroflexion of the ascending colon occurs by movement of the pelvic flexure cranially without movement of the sternal or diaphragmatic flexures.

Displacement of the ascending colon partially obstructs the lumen, resulting in accumulation of gas or ingesta and causing distention. Secretion of fluid in response may exacerbate the distention.[105] Tension and stretch of the visceral wall is an important source of the pain associated with colonic displacement. Tension on mesenteric attachments and the root of the mesentery by the enlarged colon also may cause pain.[99] Ischemia rarely is associated with nonstrangulating displacement of the colon. However, vascular congestion and edema often occur in the displaced segments of colon, resulting from increased hydrostatic pressure from reduced venous outflow. Morphologic damage to the tissues is usually minor.

Clinically, displacement of the ascending colon is characterized by intermittent signs of mild to moderate abdominal pain of acute onset. However, one also may note an insidious onset of colic.[104] One may note dehydration if the duration of the displacement is prolonged. The heart rate may be elevated during periods of abdominal pain but is often normal. Abdominal distention may be present if the colon is enlarged by gas, fluid, or ingesta. Fecal production is reduced because progressive motility of the large intestine is absent. One often diagnoses left dorsal displacements by palpation per rectum. One can feel the left ventral colon in a dorsal position; it often is filled with gas. One can trace the ascending colon to the nephrosplenic space, and the spleen may be displaced medially. Alternatively, one can reach a tentative diagnosis using abdominal ultrasonography. The spleen is visible on the left side of the abdomen, but the gas-distended bowel obscures the left kidney. Evaluation of this technique indicates that false positives occur in few instances, although false negatives occasionally may occur.[106] A definitive diagnosis therefore may require

surgery. Right dorsal displacements are characterized by the presence of the distended ventral colon running across the pelvic inlet and may be felt between the cecum and the body wall if a lateral flexion is present. The pelvic flexure is usually not palpable. Retroflexion of the ascending colon may produce a palpable kink in the colon. If the displaced colons are not distended by gas in the instance of right dorsal displacement and retroflexion, the ascending colon may not be palpable and is conspicuous by its absence from a normal position. Peritoneal fluid may increase in amount, but the color, protein concentration, and white blood cell count are usually normal. However, as the displaced segment becomes edematous, fluid leaking through the serosa into the peritoneal fluid increases the protein concentration.

Surgical correction of colon displacement is the most effective means of resolving this disorder. However, nonsurgical intervention has been successful in select cases of nephrosplenic entrapment of the large colon.[106-108] Before attempting such manipulations, the clinician must be certain of a diagnosis. One anesthetizes the horse and places it in right lateral recumbency, rotates the horse up to dorsal recumbency, rocking it back and forth for 5 to 10 minutes, and then rolls the horse down into left lateral recumbency.[109] One should palpate the nephrosplenic space per rectum to determine whether the entrapment has been relieved before recovering the horse from anesthesia. One may administer phenylephrine (3-6 µg/kg/min over 15 minutes) to decrease the size of the spleen.[110] More recently, phenylephrine has been used successfully with 30 to 45 minutes of exercise to reduce nephrosplenic entrapments in four of six horses.[26] The authors suggested that the technique be used on horses with mild to moderate colonic distention, particularly when financial constraints are severe. A number of cases occur in which nonsurgical interventions do not correct the problem and others in which nonsurgical manipulations correct the entrapment but result in large colon volvulus or displacement.[111] One should take horses in such condition to surgery promptly. The prognosis for horses with large colon displacement is good. In one study on horses with nephrosplenic entrapment of the large colon, survival exceeded 90%.[108]

FOREIGN BODY AND FECALITH OBSTRUCTION
The horse, particularly young horses, may ingest foreign material that can cause obstruction, such as bedding, rope, plastic, fence material, and feedbags. These foreign bodies may result in impaction with ingesta and distention of the intestine, typically in the transverse or descending colon. Young horses usually are affected. In one study the obstructing mass could be palpated per rectum in three of six horses.[112]

Figure 13.15-4 Intramural hematoma of unknown origin in the small colon of a horse taken to surgery for persistent signs of colic. The lack of a complete physical obstruction suggested a functional obstruction at the site of the hematoma.

Fecaliths are common in ponies, miniature horses, and foals.[113] Older horses with poor dentition also may be predisposed to fecaliths because of the inability to masticate fibrous feed material fully. Fecaliths commonly cause obstruction in the descending colon and may cause tenesmus.[112] Other clinical signs are similar to those of enterolithiasis. Abdominal radiography may be useful in smaller patients to identify the obstruction, especially if gas distention around the foreign body or fecalith provides contrast. The horse usually requires surgical treatment.

MURAL MASSES AND STRICTURES
Mural masses such as abscesses, tumors (adenocarcinoma, lymphosarcoma), granulomata, and hematomas (Figure 13.15-4) can cause luminal obstruction and impaction, typically in older horses. Impaction may result from obstruction of the lumen or impaired motility in the segment of intestine with the mass. Abscesses may originate from the lumen of the intestine or may extend from the mesentery or mesenteric lymph nodes. Intramural hematomas form most commonly in the descending colon and cause acute abdominal pain.[114] Once the acute pain from the hematoma subsides, impaction proximal to the hematoma develops because of impaired motility through the affected portion of the colon. Trauma, ulceration of the mucosa, and parasitic damage are speculated causes of intramural hematomas.[114,115] Stricture of the large intestine occurs when fibrous tissue forms in a circular pattern around or within the intestine, reducing the luminal diameter and the ability of the wall to stretch. Strictures may be

congenital or may follow peritonitis, previous abdominal surgery, or inflammatory bowel disease. In a report of 11 horses with inflammatory bowel disease, 6 horses had strictures, four of which were in the small intestine and two of which were in the large colon.[116]

Clinical signs vary according to the degree of luminal obstruction. Partial obstruction and impaction tend to produce mild to moderate abdominal pain of insidious onset. Mural hematomas tend to produce signs of acute abdominal pain.[114,115] Per rectal palpation of the abdomen may reveal the presence of a mass or simply the impacted segment but not the mass itself. One may note fever, weight loss, and anorexia if an abscess or tumor is the cause. An elevated white blood cell count; hyperfibrinogenemia; hyperglobulinemia; or normocytic, normochromic anemia may occur with abscesses or tumors. Peritoneal fluid may reflect the cause of the mass. Tumor cells may occur infrequently. One may note evidence of inflammation with bacteria if the cause of colic is an abscess or granuloma, in which case one should culture the fluid. Hematomas may cause hemorrhage into the peritoneal fluid. Treatment usually requires surgical resection of the mass. One may treat abscesses with appropriate antibiotics if the impaction can be resolved medically with oral or intravenous analgesics and laxatives. *Streptococcus* spp, *Actinomyces pyogenes, Corynebacterium pseudotuberculosis, Rhodococcus equi,* anaerobic bacteria, and gram-negative enteric organisms commonly are involved in abscesses.

ATRESIA COLI

Atresia of a segment of the colon is a rare congenital abnormality in horses. The heritability and causes of the condition are unknown. One potential mechanism for development of the lesion is intestinal ischemia during fetal life, which results in necrosis of a segment of intestine. Clinical signs include a failure to pass meconium and colic within the first 12 to 24 hours of life. Secondary abdominal distention results from complete intestinal obstruction, and abdominal radiographs may reveal gas-distended colon. One makes the diagnosis at surgery. Any portion of the colon may be absent, but the distal segment of the large colon or the proximal small colon usually is affected most severely. If sufficient tissue is present, one may attempt anastomosis to the proximal blind end of the colon.[117] The prognosis depends on which segment of the colon is absent but is usually poor because of an absence of distal colon.

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13.16—Neoplasia of the Alimentary Tract

Dana N. Zimmel

Neoplasia in the alimentary tract of the horse is uncommon.[1] Primary and metastatic neoplasia can affect multiple locations within the oral cavity and gastrointestinal tract (Boxes 13.16-1 and 13.16-2). Neoplasia is not limited to older horses. The average age of horses with squamous cell carcinoma is 8.6 to 14.6 years.[2,3] The alimentary form of lymphoma occurs most commonly in horses less than 5 years of age.[4] Identification of benign versus malignant tumors is imperative to justify treatment and predict survival.

Clinical Signs

Clinical signs associated with alimentary neoplasia are related to the tumor location. Clinical signs of oral neoplasia can include enlargement or ulceration of the mandible or maxilla.[48] Neoplasia of the tongue results in weight loss, quidding, prepharyngeal dysphagia, halitosis, and nasal discharge containing feed material if the oropharynx is involved.[6-8] Tumors of the esophagus cause signs typical of esophageal dysphagia, ptyalism, choke, intermittent colic, fever, weight loss, and halitosis.[10,49,50] Gastric neoplasia can be associated with abnormal chewing and swallowing behavior, anorexia, weight loss, chronic intermittent colic, abdominal distention, and intermittent fever.[16] Abdominal neoplasia has been implicated in 4% of horses with intermittent or chronic colic.[51,52] Altered stool character, weight loss, ventral edema, and recurrent fever have been associated with intestinal neoplasia.[4] Acute signs of abdominal discomfort can occur in intestinal obstructions from malignant and benign neoplastic disease.

Paraneoplastic syndromes may occur in the horse. The most common syndromes are cancer cachexia, ectopic hormone production, anemia, leukocytosis, thrombocytopenia, hypergammaglobulinemia, fever, and neurologic abnormalities.[53] Horses with cancer cachexia have profound weight loss despite adequate consumption of calories.

Diagnostic Evaluation

Diagnosis of alimentary neoplasia can be challenging. Data collected from a complete blood count, biochemistry panel, and urinalysis may support the diagnosis of neoplasia but rarely confirms it. Normocytic normochromic anemia indicates chronic disease and is the most likely cause of anemia associated with neoplasia. Blood loss anemia (via gastrointestinal tract) and immune-mediated hemolytic anemia (lymphoma)[54] are less frequent causes of anemia associated with abdominal neoplasia. Peripheral eosinophilia has been reported in association with multisystemic eosinophilic, epitheliotropic disease with lymphoma.[14] Leukocytosis and hyperfibrinogenemia are common findings.

Serum chemistry can confirm hypoalbuminemia caused by inflammation of the bowel wall. Hyperglobulinemia can be characterized with serum electrophoresis, which is nonspecific and can reveal chronic inflammation. A few cases of lymphoma have been identified with monoclonal hypergammaglobulinemia.[55] Ectopic hormone production may result in hypercalcemia (calcium >14 mg/dl), which is associated with alimentary neoplasia such as lymphoma, multiple myeloma, carcinomata, and ameloblastoma.[2,56] Hypoglycemia (blood glucose <70 mg/dl) can occur with neoplasia of the pancreas or liver.[2]

Rectal examination may detect an abdominal mass, thickening of the intestinal wall, lymph node enlargement, or a gritty texture in horses with carcinomatosis.[2] Rectal biopsy can reveal lymphoma in some cases.[42] Fecal occult blood test is nonspecific for neoplastic disease but can reveal blood loss through the gastrointestinal tract. Occasionally, abdominocentesis can identify neoplasia if the tumor exfoliates cells into the abdomen. One can diagnose squamous cell carcinoma, adenocarcinoma, and mesothelioma from peritoneal fluid.[10,45,46,57] Characterization of peritoneal fluid as an inflammatory exudate or modified transudate without any neoplastic cells present is common. Cytologic analysis of peritoneal fluid samples collected by abdominocentesis accurately predicted the presence of neoplasia in 11 of 25 cases in one study.[58] Cytologic examination of two or more peritoneal fluid samples increases the sensitivity of this test for detecting abdominal neoplasia. Measurement of peritoneal fluid glucose concentration and pH is valuable to differentiate inflammation in the peritoneum caused by neoplasia from bacterial peritonitis. Abdominal neoplasia typically is associated with peritoneal glucose concentrations similar to blood and pH higher than 7.3. D-xylose absorption tests can reveal malabsorptive diseases that include lymphoma.[42,59]

Immunoglobulin M deficiency is associated with lymphoma in some young adult horses, but the prevalence of immunoglobulin M deficiency in horses with lymphoma and the value of measuring serum immunoglobulin M concentrations for the diagnosis of lymphoma have not been evaluated.[60] DNA cell cycle analysis of suspect neoplastic cells has been used to detect lymphoma in equine patients confirmed with the disease. This method

BOX 13.16-1

NEOPLASIA OF THE ORAL CAVITY

**Odontogenic Tumors
(Originate From Dental Tissue)[5]**

Ameloblastic odontoma
Ameloblastoma
Cementoma
Complex odontoma
Compound odontoma
Fibromyxoma
Odontoblastoma

Osteogenic Tumors (Originate >From Bone)[5]

Myxoma
Osteoma
Osteosarcoma

Soft Tissue Tumors[5]

Epulis
Fibrous dysplasia
Juvenile ossifying fibroma
Melanoma
Papilloma
Salivary adenocarcinoma
Sarcoid
Squamous cell carcinoma

Tongue

Lymphosarcoma[6]
Multiple myeloma[7]
Rhabdomyosarcoma[8]
Paraneoplastic bullous stomatitis[9]

BOX 13.16-2

NEOPLASIA OF THE GASTROINTESTINAL TRACT

Esophagus

Squamous cell carcinoma[10,11]

Stomach

Gastric polyp[12]
Leiomyosarcoma[13]
Lymphoma (lymphosarcoma)[14,15]
Squamous cell carcinoma[10,16,17]

Small Intestine

Adenocarcinoma[18]
Adenomatous polyposis[19]
Ganglioneuroma[20]
Intestinal carcinoid[21]
Leiomyoma[22-24]
Leiomyosarcoma[25]
Lipoma[26]
Lymphoma (lymphosarcoma)[27]
Neurofibroma[28]

Cecum

Adenocarcinoma[29]
Intestinal myxosarcoma[30]
Stromal tumor[31]

Large Colon

Adenocarcinoma[32,33]
Lipomatosis[34]
Lymphoma (lymphosarcoma)[35]
Neurofibroma[36]

Small Colon

Leiomyoma[37,38]
Lipoma[26,39]
Lipomatosis[34]

Rectum

Leiomyosarcoma[40]
Lipoma[41]
Lymphoma (lymphosarcoma)[42]
Polyps[43]

Peritoneum

Disseminated leiomyomatosis[44]
Mesothelioma[45,46]
Omental fibrosarcoma[47]

of evaluating fluid or tissues aspirates may increase the accuracy for diagnosing neoplasia in the future.[61]

A complete evaluation of the oral cavity may include using a full-mouth speculum, radiographs, and endoscopy of the pharynx. Evaluation of the esophagus and stomach with a 3-m endoscope can reveal intralumenal masses.[11] Pleuroscopy has been used to obtain biopsy samples of extralumenal masses surrounding the esophagus.[49] Contrast radiography can assist in the diagnosis of neoplasia within the wall or outside of the esophagus.[49,62] Ultrasonography of the stomach, small intestine, cecum, and large colon is useful in detecting intestinal wall thickness, abdominal masses, and excessive peritoneal fluid.[63] Identification of neoplasia in the liver, kidney or spleen may support metastasis to other parts of the gastrointestinal tract or lymph nodes. Laparoscopy and exploratory laparotomy often are required to obtain a final diagnosis.[64]

Specific Neoplasia

LYMPHOMA (LYMPHOSARCOMA)

Lymphoma is the most common neoplasia in the horse and has been divided into four categories. This section covers only the intestinal/alimentary form. In the past, lymphoma has been called lymphosarcoma, but the preferred term by oncologists is *lymphoma* because no benign form of this disease exists.[2] Lymphoma originates from lymphoid tissue and predominantly affects the small intestine and intestinal lymph nodes. Chronic weight loss from malabsorption, intermittent colic, and fever are the most common clinical findings.[27,65] Chronic diarrhea has been reported in some cases.[66] Paraneoplastic pruritus and alopecia have been identified in one case of diffuse lymphoma.[67] One generally does not note peripheral lymphadenopathy, but one may palpate enlargement of the intestinal lymph nodes on rectal examination.[4] Large colon resection for treatment of lymphoma in horses has increased short-term survival in two horses.[35] Chemotherapy in two mares that were pregnant extended their lives long enough to foal normally.[68] Long-term prognosis for intestinal lymphoma is poor.

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma (SCC) is a malignant tumor of the gastrointestinal epithelium. SCC is the second most common neoplasia in the horse and is the most common oral neoplasia. However, the incidence of SCC is rare.[10,16,50] In the oral cavity SCC may affect the lips, tongue, hard palate, pharynx, and mucosa.[69,70] Treatment for SCC in the oral cavity may involve surgical resection, iridium-192 brachytherapy, 5-fluorouracil, or intralesional cisplatin.[5,71-73] The prognosis for survival is good if complete removal of the tumor is possible. Metastasis beyond the regional lymph nodes is rare for oral SCC.

Squamous cell carcinoma is the most common tumor of the stomach and esophagus[11,16] and can invade these areas and metastasize to the lymph nodes and lungs. Abnormal masses were palpated on rectal examination in four of five cases of gastric SCC.[16] Treatment by surgical resection is not possible in most cases and the horses die or are euthanized.[2]

ADENOCARCINOMA

Adenocarcinoma is a malignant tumor that can occur in the small intestine, cecum, and large colon.[18] The tumor arises from the glandular crypts of the gastrointestinal tract and has been reported in middle-aged and older horses. Metastasis to the lymph nodes, liver, and lungs can occur. Intestinal adenocarcinoma has been reported to metastasize to the bone and was diagnosed using nuclear scintigraphy following injection of technetium-99m hydroxymethylene diphosphate.[29,32] No reports of successful surgical resection have been published.

LEIOMYOSARCOMA

Leiomyosarcoma is a malignant tumor of the smooth muscle lining the gastrointestinal tract and has been reported in the stomach, small intestine, and rectum.[13,22,23,40,58] In one case report, gastroscopy could not identify the mural mass in the stomach that was found during exploratory surgery. Another report describes a favorable outcome for surgical resection of a leiomyosarcoma that was protruding from the anal sphincter in a 4-year-old Quarter Horse.[40] Prognosis for survival is favorable if surgical resection is possible.

LEIOMYOMA

Leiomyoma is a benign tumor of the smooth muscle of the gastrointestinal tract that can occur in the stomach, small intestine, and small colon.[37,38] Clinical signs are consistent with intestinal obstruction. Surgical resection and anastomosis of the affected portion of the intestine have been performed without complications.

LIPOMA

Lipoma is a benign tumor that occurs in older horses (10 to 26 years) and arises from mesenteric adipocytes. The tumor grows on a stalk that wraps around the intestine, causing a strangulating lesion manifested clinically by acute obstructive colic. Intestinal injury caused by pedunculated lipomata may occur in the small intestine, small colon, and rectum. Long-term survival with surgical resection and anastomosis of the affected segment has been reported to be 40% to 50%.[26,74]

ORAL NEOPLASIA

Oral cavity neoplasia may involve the dental tissue (odontogenic tumors), bone (osteogenic tumors), or soft tissues (see Box 13.16-1). Ameloblastoma occurs in horses greater than 10 years old and mainly affects the mandible. Ameloblastic odontoma affects younger horses and usually involves the maxilla. Both are benign but locally invasive. Radiographs may distinguish the difference between an ameloblastoma (radiolucent lesion) and ameloblastic odontoma (radiolucent lesion with partially mineralized density). The best treatment option is surgical resection and radiation therapy regardless of the type.[48]

Juvenile mandibular ossifying fibroma occurs in the rostral mandible of young horses between the ages of 2 months and 2 years. The fibroma may cause significant distortion of the bone. With early diagnosis and surgical excision of the mass, the horse has a good prognosis.[75]

Melanomas, sarcoids, and oral papilloma occur on the mouth and lips. Melanomas rarely metastasize, but they commonly are found in the parotid salivary glands and lymph nodes. Sarcoids are the most common skin tumor that can involve the mouth. Ulcerations of the buccal mucosa are difficult to treat. Intralesional cisplatin, cryosurgery, radiation, and laser excision have been tried with limited success.[5] Equine papilloma virus is responsible for the common skin wart found on the lips and muzzle of young horses. These lesions are usually self-limiting but may be removed successfully by cryosurgery or excision.

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13.17—Peritonitis

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Structure and Function

A number of detailed and informative reviews are available describing the anatomy, physiology, and pathophysiology of the equine peritoneum.[1-5] The peritoneum consists of a single layer of mesothelial cells lining the peritoneal cavity and serosal surfaces of the intraabdominal viscera. The mesothelial lining of the diaphragm, abdominal walls, and pelvic cavity is termed *parietal peritoneum.* The visceral peritoneum includes the serosal surfaces of the intraabdominal organs. The parietal and visceral portions of the peritoneum are contiguous with each other through the omentum, mesenteries, and ligaments. Caudally, the peritoneum reflects over the surfaces of the pelvic organs (portions of the urogenital tract and rectum), excluding them from the peritoneal space, and thus much of the pelvic cavity and contents are described as retroperitoneal. The peritoneal space communicates with the lumen of the uterus (and thus the external environment) via the fallopian tubes in females. In males the peritoneum forms a true blind sac. The vascular supply and nervous innervation of the visceral peritoneum are supplied by the splanchnic vessels and visceral autonomic nerves, respectively. Branches of the intercostal, lumbar, and iliac arteries supply the parietal peritoneum, and

the phrenic and intercostal nerves provide nervous innervation. The clinical relevance is that inflammation of the parietal peritoneum is perceived as somatic pain, resulting in a splinted abdominal wall, pain on external palpation, and reluctance to move. Visceral pain is mediated by small type C sensory fibers, which are believed to be stimulated by bowel distention, smooth muscle spasms, tension on the mesentery, and ischemia.

The peritoneal lining functions as a semipermeable barrier to the diffusion of water and low-molecular weight solutes between the blood and the abdominal cavity.[1] The peritoneum secretes a serous fluid that lubricates the abdominal cavity, inhibits adhesion formation, and has minor antibacterial properties.[1,2] Macrophages, mast cells, mesothelial cells, and lymphocytes provide immune function within the peritoneum.[2,3] Peritoneal macrophages impart antibacterial activity via complement receptors, phagocytic activity, interaction with T lymphocytes, neutrophil chemotaxis, and fibroblast activation. The peritoneal surface maintains a high level of fibrinolytic activity through the production of plasminogen activators by mesothelial cells. This function, together with the lubricant properties of the peritoneal fluid, helps to maintain gliding surfaces within the peritoneum and prevent adhesion formation. In quadrupeds, peritoneal fluid produced by the mesothelium tends to move ventrally and cranially, aided largely by diaphragmatic movement. Peritoneal fluid, waste products, and foreign material (including bacteria) exit the peritoneal cavity to enter the lymphatic system through diffusely distributed subendothelial pores or via the large diaphragmatic stomata, depending on particle size. Large molecules and particles greater than approximately 40,000 MW (such as bacteria) exit through the diaphragmatic stomata and ultimately enter the thoracic duct.

Peritonitis is inflammation of the mesothelial lining of the peritoneal cavity and is characterized by desquamation and transformation of mesothelial cells; chemotaxis of neutrophils; release of several soluble mediators of inflammation; exudation of serum, fibrin, and protein into the peritoneal cavity; and depression of fibrinolytic activity.

Etiopathogenisis

Peritonitis occurs in association with a variety of disorders that result in mechanical, chemical, or infectious insult to the peritoneal lining.[1-4] Any process resulting in disruption or irritation of the peritoneal lining, inflammation or infection of abdominal organs, or compromise of the intestinal wall can result in peritonitis (Box 13.17-1). Common mechanical injuries include blunt or perforating trauma to the abdominal wall, breeding and foaling accidents, and abdominal surgery. A variety of traumatic insults of iatrogenic origin can cause peritonitis, such as

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BOX 13.17-1

CAUSES OF PERITONITIS IN FOALS AND HORSES

Foals

Meconium impaction
Ruptured bladder
Urachal infection
Gastric/duodenal ulcer perforation
Septicemia
Enteritis
Intestinal vascular accident
Ascarid impaction
Intussusception
Streptococcus abscess
Rhodococcus equi abscess
Neoplasia

Adults

Iatrogenic
Rectal tear
Enterotomy
Trocharization
Enterocentesis
Castration
Vaginal perforation
Trauma
Foreign body penetration
Gunshot
Capture dart
Fence post
Uterine/vaginal perforation during foaling
Vaginal perforation during breeding
Splenic tear
Vascular accident
Verminous arteritis
Intestinal strangulation
Nonstrangulating infarction
Thromboembolism
Ruptured uterine artery
Bowel contamination
Rupture of stomach, cecum, or colon
Strangulating intestinal obstruction
Nonstrangulating intestinal obstruction
Foreign body perforation
Anastomosis leakage/dehiscence
Intestinal mural abscess/neoplasia
Perforating colitis
Other
Mesenteric abscess
Pyometra
Cholelithiasis
Pancreatitis
Retroperitoneal abscess
Neoplasia

abdominocentesis, enterocentesis, splenic puncture, bowel trocharization, liver biopsy, uterine biopsy, castration, and rectal tear. Chemical insults of endogenous origin include blood, urine, pancreatic enzymes, bile, gastric juice, chyme, and chyle. Talc, contrast agents, antibiotics, and lavage solutions are additional examples of chemical insults. Traumatic events often involve bacterial contamination at the time of injury and mechanical and chemical injuries can become infected secondarily. The most common manifestation of peritonitis is acute, diffuse, septic peritonitis following inflammation, vascular insult, perforation, or surgical manipulation (enterotomy, resection, anastomosis) of the gastrointestinal tract. The septic process in such cases involves mixed bacteria of gastrointestinal origin. Penetrating abdominal wounds also result in mixed infections. Less commonly, singular bacterial forms gain access to the peritoneum though hematogenous spread, extension from a contiguous organ, or through the female genital tract. Primary, monomicrobial infections involving *Streptococcus equi, S. zooepidemicus, Actinobacillus equuli*,[6] *Rhodococcus equi*, and *Corynebacterium pseudotuberculosis* are examples. Septicemia, septic omphalophlebitis, ascending urinary tract infections, and uterine infections are additional examples. Parasites also play a role in peritonitis. Verminous arteritis caused by strongylosis can lead to vascular damage (thromboembolism, infarction) to the intestine. The activities of strongyles, ascarids, and tapeworms can result in perforation of the bowel and damage to other abdominal organs. Peritonitis has been associated with viral infections, including influenza, viral arteritis, and African horse sickness virus. Neoplastic diseases also can result in peritoneal inflammation. Although a number of potential causes of peritonitis exist, sepsis is a common and serious complication, and the identification and control of bacterial sepsis is critical for a successful outcome.

Bowel leakage (as well as external trauma) results in contamination of the peritoneum with large numbers of many types of bacteria. The intestinal tract contains a mixed population of bacteria, and the quantity of bacteria and prevalence of anaerobic species increase in the distal segments.[1-7] There are approximately 1×10^9 anaerobic and 1×10^5 aerobic bacteria per milliliter of cecal and colonic fluid, thus the potential for bacterial contamination of the peritoneum is great. High mortality is associated with contamination from the lower bowel because of the large numbers of bacteria present.[8] Hirsch and Jang[9] reported isolation of an infective agent from equine peritoneal fluid in approximately 25% of attempts. Obligate anaerobic bacteria were cultured most frequently, followed by members of the Enterobacteriaceae family *(Escherichia coli)*. Penicillin-resistant *Bacteroides fragilis* was isolated from 10% to 20% of cases. In another study in which bacteria were identified in equine abdominal fluid by cytologic examination or culture, *E. coli* was the organism most commonly isolated.[10] In human beings and laboratory animals the well-established fact is that despite the variety of organisms initially introduced subsequent to these events, established infections are characterized by only a few types of bacteria, which are often gram-negative aerobes and anaerobic bacteria.[2] This selectivity occurs through the processes of selective reduction of bacterial populations and bacterial synergism. A well-known example of synergism in human beings and laboratory animals is peritonitis involving *E. coli* and *B. fragilus*. The presence of each organism is beneficial to the survival of the other, and each is important in the overall pathogenesis of the disease. *E. coli* is associated with septicemia and early mortality, whereas *B. fragilis* infection tends to result in chronic abscessation with delayed morbidity and mortality. Some evidence suggests that in horses, in addition to coliforms and anaerobes, streptococci and perhaps *C. psuedotuberculosis* may survive selective reduction and participate in synergistic infection following polymicrobial contamination.

Biologic events resulting from contamination of the abdomen or injury to the mesothelial cells have been described[1-4] and include release of catecholamines, histamine, and serotonin from peritoneal mast cells; vasodilation and hyperemia; increase in peritoneal vascular permeability; secretion of protein-rich fluid into the peritoneum; transformation of mesothelial cells into macrophages; and influx of polymorphonuclear cells, humoral opsonins, natural antibodies, and serum complement into the peritoneal cavity. Additionally, depression of the peritoneal fibrinolytic activity, fibrin deposits on the peritoneal surface, and sympathetic-mediated ileus of the gastrointestinal tract can occur.

These processes benefit the animal by confining contamination and infection, and indeed, with clean, minimally invasive procedures such as enterocentesis or trocharization, this is effective. However, with greater severity of peritoneal contamination or irritation, these processes are magnified and become deleterious, resulting in problems such as hypovolemia, hypoproteinemia, ileus with resultant bowel distention, ischemia of the bowel wall with subsequent absorption of bacteria and toxins, and ultimately adhesion and abscess formation. Additionally, systemic responses to bacterial toxins, particularly lipopolysaccharide,[11,12] can compromise the metabolic condition of the patient further. Equine peritoneal macrophages release several mediators when exposed to bacterial lipopolysaccharide,[13] undoubtedly an important component of septic peritonitis.

Pathologic description of peritonitis includes origin (primary or secondary), onset (peracute, acute, chronic), distribution (localized versus diffuse), and presence of bacteria (septic versus nonseptic).[3,4] Clinically, viewing

the pathogenesis of peritonitis as a series of stages, as reviewed and described by Trent, is useful.[2] The contamination stage, lasting 3 to 6 hours, involves introduction of bacteria into the peritoneum and initiation of the acute inflammatory response previously described. If the organisms are not eliminated and infection is established, the process evolves to the stage of acute diffuse peritonitis. Although the overall movement of contaminants is toward the diaphragmatic stomata and into the thoracic duct, the nature of the peritoneal circulation is such that regardless of the location of the initial contamination, bacteria spread throughout the peritoneum within several hours. The stage of acute diffuse peritonitis lasts up to 5 days. The inflammatory response persists and escalates with continued exudation of proteinaceous fluid and influx of inflammatory cells. Offending organisms are delivered to the lymphatic system and may be eliminated by the immune system. Organisms, however, may gain access to the systemic circulation in sufficient numbers to result in clinically relevant septicemia. In human beings and laboratory animals having undergone polymicrobial contamination of the peritoneum, the organisms causing septicemia at this stage are usually coliforms, *E. coli* in particular. This stage of the disease process has the highest mortality because of the effects of severe peritoneal inflammation, endotoxemia, and septicemia. If the animal survives this stage but fails to eliminate the infection in the peritoneal cavity, the disease enters a transitional phase referred to as the acute adhesive (or localizing) stage. This stage occupies a time frame of perhaps 4 to 10 days after the initial insult. Neutrophils are still active, macrophages are increasing in numbers, and fibrin aggregates are being organized or lysed. In human beings and laboratory animals, selective reduction and synergism continue such that anaerobes and gram-negative aerobes predominate. If infection persists beyond this point, organization of fibrin proceeds and organisms become isolated from host defenses. At this point, the disease process enters the stage of chronic abscessation. This stage can begin as early as 8 days after inoculation and persists indefinitely.

Clinical Signs

Clinical signs of peritonitis depend on the primary disease process, the duration of the problem, and the extent of peritoneal inflammation. Localized peritonitis may have few or no systemic manifestations, whereas severe localized or generalized peritonitis often is accompanied by severe toxemia or septicemia or both. Septic peritonitis usually causes more severe clinical signs because of the inflammatory mediators released in response to bacterial toxins and because of the presence of endotoxin when gram-negative organisms are involved.

Most clinical signs are nonspecific and include fever, depression, inappetance, decreased borborygmi, and dehydration. Additional signs, reported in 30 horses (ages 2 months to 16 years) with peritonitis, were colic, ileus, weight loss, and diarrhea.[14]

Horses with peracute peritonitis, as occurs with rupture of the bowel or rectal tear, have severe toxemia, weakness, depression or severe colic, tachycardia, tachypnea, and circulatory failure. Fever may not be present depending on the degree of shock. Typical clinical findings include sweating, pawing, muscle fasciculations, weak peripheral pulses, red to purple mucous membranes, prolonged capillary refill time, and decreased skin elasticity. Parietal pain, characterized by reluctance to move, splinting of the abdominal wall, and sensitivity to external abdominal pressure occur in some acute cases. Urination or defecation may be painful for the horse, and urine and fecal retention may be evident on rectal examination. Palpation of the abdomen externally may elicit flinching, aversion movements, or groaning. With extensive abdominal fecal contamination, rectal examination may reveal a gritty feeling of the serosal and parietal surface of the peritoneum because of fibrin deposition and a dry texture of the peritoneum. In horses with more chronic peritonitis, rectal examination findings can include pain on palpation of fibrinous or fibrous adhesions, intestinal impaction or distention following ileus and dehydration, an abdominal mass (abscess or neoplasia), or an impression of bowel floating in fluid. In many cases, one can detect no abnormalities on rectal examination.

Horses with localized, subacute, or chronic peritonitis may have signs of chronic or intermittent colic, depression, anorexia, weight loss, intermittent fever, ventral edema, exercise intolerance, decreased or absent intestinal sounds, and mild dehydration. Heart rate and respiratory rate may be normal. Fecal output may be normal; however, horses with chronic diarrhea and weight loss have been reported.[14]

Foals with peritonitis usually exhibit signs of colic (acute or chronic) and are febrile, depressed, and inappetant. In some foals with primary peritonitis, pleural effusion occurs. In young foals, peritonitis can cause rapid metabolic deterioration, and determination and correction of the primary problem requires immediate attention. In older foals, peritonitis may occur insidiously, as occurs following *S. equi* or *R. equi* infections.

Clinicopathologic Findings

HEMATOLOGY AND SERUM CHEMISTRY
Clinicopathologic abnormalities vary depending on the time of onset and severity of peritonitis. Horses with acute, septic peritonitis can have leukopenia,

hemoconcentration, metabolic acidemia, azotemia, and electrolyte imbalances reflective of systemic inflammation from endotoxemia and hypovolemia. Horses with peritonitis of a few days' duration may have leukocytosis and hyperfibrinogenemia. Plasma protein levels vary depending on the hydration status, degree of exudation into the peritoneum, and type of underlying problem. In chronic peritonitis, hyperproteinemia with hyperglobulinemia may be present.

Neonates with uroperitoneum caused by urinary bladder rupture or urachal disease tend to develop azotemia, hyponatremia, hypochloremia, hyperkalemia, and acidosis. Foals with peritonitis following septicemia, severe enterocolitis, severe meconium impaction, intussusception, small intestinal volvulus, gastric or duodenal rupture, or ascarid impactions usually have clinicopathologic findings reflective of systemic inflammation, such as inflammatory leukogram or leukopenia, hemoconcentration, and acidosis. Chronic abscessation, as occurs in foals with *R. equi* and streptococcal infections, results in clinicopathologic findings reflecting chronic inflammation (anemia, hyperfibrinogenemia, hyperglobulinemia).

PERITONEAL FLUID

Abnormalities in the composition of peritoneal fluid occur with peritoneal inflammation, and peritoneal fluid analysis is principal to the diagnosis of peritonitis. One collects peritoneal fluid through puncture of the abdomen on the ventral midline. One should clip and prepare an area aseptically. Usually, the lowest point of the abdomen, 5 to 10 cm caudal to the xiphoid cartilage, is prepared for puncture; although in some cases one may perform paracentesis more caudally, particularly when one suspects a specific area of sequestered fluid or abscessation. In addition, one may choose a site to the right of midline in an attempt to avoid the spleen. One can perform peritoneal puncture using a 1½-inch, 18-gauge needle or, following local anesthesia and a stab incision with a No. 15 scalpel blade, using a sterile cannula. One collects fluid by gravity flow and should collect fluid in a tube containing anticoagulant, preferably EDTA for cytologic examination, and in a sterile tube without anticoagulant for visual inspection and, if desired, for culture. One should fill the EDTA tube to half its volume, because the EDTA will alter the refractive index of the fluid, resulting in a falsely elevated value for total solids when one collects only a small volume and tests it with a refractometer.

One should evaluate peritoneal fluid routinely as to color, turbidity, total protein, white blood cell (WBC) count and differential, and the presence of bacteria as determined by Gram stain. Normal peritoneal fluid is clear and straw-colored and does not coagulate spontaneously. Peritoneal fluid becomes turbid when increased numbers of white blood cells and concentration of protein are present. Pink or red fluid indicates free hemoglobin or hemorrhage. Blood introduced into the peritoneal fluid iatrogenically in some cases may be differentiated from blood from internal hemorrhage based on the presence of platelets and hematocrit. Fluid with iatrogenic blood contamination contains platelets, whereas fluid with blood following internal hemorrhage or diapedesis often does not have platelets. Blood contamination resulting from splenic puncture often results in the packed cell volume of the sample being greater than that of the blood. Large volumes of dark brown or green fluid with a fetid odor obtained from several sites strongly suggest bowel rupture, but one should perform cytologic examination for confirmation.

The distribution of polymorphonuclear and mononuclear cells varies widely, and one should interpret the results of cell counts and differentials as supporting a number of disorders rather than a specific diagnosis. Normal equine peritoneal fluid contains fewer than 5000 nucleated cells per microliter.[2,15]

WBC counts in acute peritonitis (>100,000/μL) are reported to be higher than those in chronic peritonitis (20,000 to 60,000/μL)[14-16]; however, this is not always the case, and the WBC count depends most on the cause of the peritonitis. The WBC level does not always correlate with severity of peritonitis or the prognosis. The peritoneal fluid WBC count can be greater than 100,000/μL following enterocentesis, with no clinical signs or problem.[17] Conversely, peritoneal WBC counts of fewer than 100,000/μL may be found in foals or horses with intraabdominal abscesses.[18] The peritoneal WBC count can increase to greater than 150,000/μL following celiotomy[19] and can be higher if an enterotomy is done. Postoperatively, the WBC count normally continues to decline and returns to near normal by 5 to 7 days. Failure of the WBC count to decrease suggests peritonitis resulting from a postoperative complication. Finally, peritoneal fluid WBC counts greater than 500,000/μL indicate severe focal or generalized peritoneal sepsis.

The distribution of polymorphonuclear and mononuclear cells varies in normal peritoneal fluid,[2,15] but polymorphonuclear cells usually predominate. With acute peritonitis, polymorphonuclear cells typically increase to a greater degree than mononuclear cells, but this depends on the cause. In horses that have bowel disease accompanied by endotoxemia, the number of peritoneal mononuclear cells increases, as does transformation of mesothelial cells to macrophages. In chronic cases, one easily may mistake transforming mesothelial cells for neoplastic cells, which can make diagnosis difficult, particularly when the presenting problem is compatible with a neoplastic process. In such cases, consultation with a clinical pathologist regarding cytologic findings is prudent.

Normal peritoneal fluid protein concentration is less than 1.5 g/dl.[15] Protein levels between 1.5 g/dl and 2.5 g/dl can be difficult to interpret, but one should consider levels greater than 2.5 g/dl to be elevated abnormally. Fibrinogen concentration increases with inflammation, and levels greater than 10 mg/dl in the peritoneal fluid suggest that an acute inflammatory process is present.[20] Fibrinogen content will also increase from blood contamination.

The presence of free and phagocytosed bacteria in peritoneal fluid indicates generalized suppuration, abscessation, or compromised bowel. If one observes numerous microorganisms of mixed types free in the peritoneal fluid or if one observes plant material, massive bacterial contamination of the abdomen following bowel rupture likely has occurred. The presence of toxic or degenerate neutrophils and bacteria within polymorphonuclear cells helps to distinguish peritoneal fluid from intestinal contents in such cases. Enterocentesis yields discolored fluid containing mixed microorganisms and plant material and that is largely devoid of white blood cells. Bacterial contamination of a sample can occur during collection of the sample, and iatrogenic contamination of a sample can result in free and intracellular bacteria in peritoneal fluid, particularly if processing is delayed. In such cases the bacterial numbers are few and the neutrophils appear healthy. In some cases of gastrointestinal perforation the luminal material, inflammatory cells, and protein may be sequestered by the omentum and further contained by fibrinous adhesions. Abdominal fluid obtained via standard ventral paracentesis may have low cellularity and protein content but large numbers of mixed bacteria indicating bowel rupture.[5] Examples include gastric rupture along the greater curvature of the stomach between the omental layers (omental bursa) and perforated gastric or duodenal ulcers in foals. Correlating all cytologic findings with clinical and clinicopathologic findings is important for interpreting the results of peritoneal fluid cytologic examination.

Biochemical analysis of peritoneal fluid may be useful in detecting sepsis when cytologic examination and culture are negative or otherwise unavailable. In a prospective study by Van Hoogmoed, Rodger, Spier, et al., peritoneal fluid pH and glucose concentrations from horses with septic peritonitis were significantly lower than horses with nonseptic peritonitis and healthy horses.[21] Peritoneal fluid pH less than 7.3, glucose less than 30 mg/dl, and fibrinogen concentration greater than 200 mg/dl were considered highly predictive of septic peritonitis. Serum to peritoneal glucose concentration differences of greater than 50 mg/dl was considered the most diagnostically useful test for septic peritonitis in the study. Increased activities of alkaline phosphatase, lactic dehydrogenase, creatine kinase, aspartate aminotransferase, tumor necrosis factor, and interleukin-6 have been measured in the peritoneal fluid of horses with abdominal disorders, but the diagnostic and prognostic implications of the presence or absence of these enzymes and analytes is limited.[20-22]

One should submit peritoneal fluid samples in appropriate media (Port-A-Cul Vial, BBL Microbiology System) for aerobic and anaerobic cultures in an attempt to identify the pathogenic organism(s). Obligate anaerobic bacteria such as *Bacteroides* are difficult to culture, because one must collect, transport, and culture the sample under strict anaerobic conditions. Frequently, bacterial cultures are negative when bacteria are present in peritoneal fluid. To enhance recovery of bacteria, one can inoculate peritoneal fluid into blood culture medium (Septi-Chek Columbia, Hoffmann-LaRoche Inc., Nutley, New Jersey), and if the horse has received antimicrobial treatment, one first should pass fluid through an antimicrobial removal device (A.R.D., Becton Dickinson & Co., Cockeysville, Maryland).

Treatment

Early and aggressive therapy is required if treatment of peritonitis is to be successful. The goals of treatment are to resolve the primary problem, minimize the inflammatory response, and prevent long-term complications. In the acute phase, one gives primary consideration to the arrest of endotoxic, septic, or hypovolemic shock; correction of metabolic and electrolyte abnormalities and dehydration; and management of pain. In the absence of blood gas and electrolyte determinations, adequate volumes of a balanced electrolyte solution are required to correct dehydration and support the cardiovascular system. If the plasma protein concentration of the horse is less than 4.0 g/dl, one should consider administration of plasma or synthetic colloids.

One should administer flunixin meglumine (Banamine) for its local and systemic antiinflammatory effects. Dosages vary depending on the severity of peritonitis, degree of toxemia, severity of pain, and hydration status of the horse and range from 0.25 mg/kg intramuscularly or intravenously every 6 to 10 hours to 1.0 mg/kg intramuscularly or intravenously every 12 hours. The higher dosage provides greater visceral analgesia, whereas the lower dosage is effective in modifying the effects of experimental endotoxemia.[23] In addition to analgesic and general antiinflammatory effect, flunixin meglumine may be effective in retarding adhesion formation when administered early in the acute, diffuse stage of septic peritonitis.[2]

Heparin therapy has been recommended to prevent adhesion formation and to render bacteria more susceptible to cellular and noncellular clearing mechanisms. In experimental models using laboratory animals,

heparin therapy was associated with decreased adhesions in septic peritonitis.[24] Heparin has not yet been demonstrated clearly to have similar efficacy in horses, although it may. Suggested dosages range from 20 to 40 IU subcutaneously every 12 hours for 48 hours[4] to 40 to 80 IU/kg subcutaneously every 8 hours.[5] One should note that heparin induces red blood cell aggregation in horses,[25] which may adversely affect capillary blood flow.

One should initiate antimicrobial therapy after making a diagnosis of peritonitis and before the results of peritoneal culture are available, because isolating an organism may take several days and often culture fails to isolate the organism(s). Intravenous administration of antimicrobials is preferred over oral or intramuscular routes in acute, diffuse, septic peritonitis because more reliable levels of drug are achieved in the tissues and peritoneal fluid than otherwise would be obtained in horses with hypovolemia or decreased intestinal motility.[26] The combination of a β-lactam antibiotic with an aminoglycoside is appropriate in most circumstances and certainly in the acute diffuse stage of septic peritonitis. These drugs act synergistically to provide a broad spectrum of activity against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria.[27] Potassium penicillin (22,000 to 44,000 IU/kg intravenously every 6 hours) combined with gentamicin (6.6 mg/kg every 24 hours) is an appropriate regimen. In most cases, peritonitis will have resulted from bowel contamination, and thus one should presume a mixed infection with gram-negative aerobic bacteria and gram-positive and gram-negative anaerobic bacteria.[2] One also should presume the same in many cases of traumatic peritonitis, as occurs with foreign body puncture, breeding trauma, or foaling trauma. Therefore a strong possibility exists of infection involving penicillin resistant *Bacteroides fragilis,* so that adding metronidazole (15 mg/kg orally every 6 to 8 hours) to the regimen is prudent. Combination therapy with β-lactam and aminoglycoside antibiotics (and metronidazole when indicated) is a standard and generally effective protocol. One can modify this antimicrobial regimen when culture and antimicrobial sensitivity results become available.

Aminoglycosides and nonsteroidal antiinflammatory drugs have the potential to induce acute renal tubular damage, particularly when dehydration and decreased renal perfusion are present. Therefore adequately rehydrating the patient and ensuring that renal function is intact before initiating treatment with these drugs are important. Furthermore, maintaining hydration and monitoring renal function during the course of treatment are important. Monitoring serum creatinine concentration; performing serial urinalysis observing for pigment, red blood cells; and casts; determining the ratio of γ-glutamyl-transferase to creatinine in the urine; and therapeutic drug monitoring[26] of aminoglycoside levels are useful in this regard.

Sodium ampicillin and ceftiofur sodium are β-lactam antibiotics that may be useful in combination therapy. These drugs have an extended gram-negative spectrum compared with penicillin. However, as a third-generation cephalosporin, ceftiofur is less effective against anaerobes than penicillin. One also may consider ceftiofur, trimethoprim-potentiated sulfonamides, amikacin, and enrofloxacin for treatment of gram-negative infection based on culture and sensitivity results. Enrofloxacin is a quinolone drug with excellent activity against gram-negative pathogens, including *Pseudomonas,*[27] and also can be effective against resistant staphylococci (personal observation). Such staphylococci may be involved in infections caused by traumatic puncture of the abdominal wall. Enrofloxacin has a variety of potential toxic effects, including cartilage damage in young growing animals.[29] However, a recent study concluded the drug was safe when administered to adult horses intravenously at 5 mg/kg every 24 hours for 3 weeks.[30] One probably should avoid using the drug in young, growing animals until the issue of cartilage damage is resolved. Administration of enrofloxacin to horses constitutes off-label usage.

One should treat horses with acute, diffuse, septic peritonitis with antibiotics until the white blood cell count, plasma fibrinogen, and abdominal fluid analysis are normal. In horses that respond to therapy, this process takes a variable amount of time depending on the offending organisms and stage of disease at the time treatment is initiated. Horses with abdominal abscessation resulting from polymicrobial infection may require many months of antibiotic treatment. Abdominal abscesses caused by streptococci and *Corynebacterium pseudotuberculosis* also may require long-term treatment (weeks to months). Long-term antibiotic treatment generally necessitates the use of oral antibiotics, and the options are limited. Trimethoprim-potentiated sulfonamides are administered orally and are effective against a variety of gram-positive and gram-negative organisms, although some streptococci are resistant. Metronidazole is an orally administered drug effective against anaerobic bacteria, as previously discussed. Other orally administered antimicrobials one may consider for long-term use include doxycycline (broad spectrum), erythromycin (gram-positive spectrum), and enrofloxacin (mostly gram-negative spectrum). Importantly, rifampin, when used with other drugs, can be effective in penetrating and resolving abscesses. Combination therapy with erythromycin and rifampin is the standard treatment for *Rhodococcus equi* infection in foals.

Peritonitis caused by *Actinobacillus equuli* usually is manifested as a diffuse, suppurative peritoneal exudate.[6] The same is true for some cases involving streptococci

(personal observation). These infections generally respond well to combination therapy with penicillin and gentamicin. If streptococci are involved as the sole pathogen, then penicillin alone should be effective. Streptococci potentially can be involved in mixed, synergistic peritoneal infections in horses.[2]

Drainage or lavage of the peritoneal cavity may be of benefit in removing toxic bacterial by-products and products of inflammatory cells.[31] High numbers of inflammatory cells and release of their mediators can persist even after the primary stimulus of the inflammatory response has resolved. Infusing large volumes of isotonic, warmed fluid into the peritoneal cavity also dilutes the inflammatory mediators, possibly reducing their deleterious effects. When successful, peritoneal lavage decreases the peritoneal fluid WBC count and total protein, potentially reflecting a decrease in diffuse inflammation. The benefits of peritoneal lavage are controversial, and a positive effect may be more likely during the acute, diffuse stage of disease.[2,4] Some studies suggest peritoneal lavage, along with heparin therapy, may reduce the incidence of adhesions.[2]

One should perform peritoneal drainage and lavage using a drain of no less than 24F diameter. Foley-type catheters can be used, but "mushroom" drains provide a larger area for fluid to enter the drain. Two approaches to peritoneal lavage are (1) retrograde irrigation through a ventrally placed ingress-egress drain and (2) placement of ingress catheter(s) in the paralumbar fossa(e) for infusion of fluids, with a drain placed ventrally for removal of infused fluid. One must recognize that thorough peritoneal lavage can be achieved only via ventral midline laparotomy.

Complications associated with the use of abdominal drains or repeated peritoneal penetration to drain fluid include retrograde infection, local irritation, pneumoperitoneum, and subcutaneous seepage around the drain and resultant cellulitis. If the patient is hypovolemic or hypoproteinemic, one should consider volume replacement and administration of plasma before removing large quantities of fluid from the abdomen.

In horses with suspected parasite involvement, such as verminous arteritis, one should give larvicidal doses of an anthelmintic once the condition of the horse is stabilized. Ivermectin, fenbendazole, and thiabendazole have been recommended as larvacidal therapies.

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