Gastrointestinal Complications of Critical Illness in Small Animals

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After ingestion, the gastrointestinal (GI) tract stores, propels, mixes, and digests food; secretes enzymes and fluids; and selectively absorbs water, electrolytes, and nutrients. Enormous quantities of fluids and electrolytes are cycled through the intestine each day. Almost half of the total volume of extracellular fluid is secreted in the upper GI tract daily, an amount that greatly exceeds normal intake; yet loss of fecal water and electrolytes is less than 0.1% of the fluid cycled through the GI tract.[1,2] With abnormal secretion and/or impaired absorption, the potential for massive fluid and electrolyte imbalances exists.

The GI tract and liver are considered the shock organs of dogs.[1] GI dysfunction can accompany sepsis, and the systemic inflammatory response syndrome in patients with multiple organ dysfunction syndrome (MODS). The GI tract is subject to damage from a variety of systemic diseases and is commonly affected by MODS in veterinary patients.[3]

Symptoms of GI dysfunction, commonly seen in states of shock, cover a wide clinical spectrum from mild changes in appetite to serious loss of intestinal mucosal integrity, hemorrhagic diarrhea, enteric bacterial translocation, septicemia, and death. GI dysfunction can occur after any cause of tissue hypoxia, poor perfusion and impaired oxygen delivery, because organs supplied by the splanchnic circulation are particularly vulnerable to hypoxia.[4] This response is evident in the hemorrhagic models of shock in which splanchnic perfusion decreases rapidly and disproportionately to other major organ systems.[3]

Although the renal system has azotemia and oliguria to document dysfunction and the central nervous system has a more complex scoring system, the Glasgow Coma Score, to objectively define functional impairment,[5] the GI tract has many functions

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that are not subject to objective measurements, rendering dysfunction and failure of this system difficult to quantitate. The gut is not just for digestion and nutrient absorption but is a metabolically active, immunologically unique reservoir of potential pathogens.[4] However clinically difficult it may be to monitor splanchnic perfusion, the clinician must remain diligent and attempt to diminish the risk of complications associated with GI dysfunction. Treatment needs to be aggressive and focused on the underlying cause, generally supporting the patient by replacing lost fluids and proteins. Clinicians must also provide nutrition to the GI tract as it heals, all while attempting to prevent the translocation of pathogenic GI flora into the bloodstream.

GI DEFENSE MECHANISMS

Natural defenses against microbial invasion of the gut include the epithelial cell barrier, mucus, gastric acid, pancreatic enzymes, bile, and bowel motility. Structurally, the intestine is a single-layered columnar epithelium arranged in villi and crypts. Cell-to-cell junctional complexes offer selective permeability through tight junctions; maintain intercellular adhesion through intermediate junctions and desmosomes; and allow intercellular communication through gap junctions to control the movement of ions, fluids, and small hydrophilic uncharged compounds, including bacteria and lipopolysaccharides.[6] Mucins, secreted by epithelial goblet cells, hamper bacterial penetration and act as a lubricant to reduce mucosal abrasion and damage induced by acid and other luminal toxins.[7] Mucosal secretions are rich in IgA antibodies that effectively bind bacteria, preventing mucosal adherence and colonization.[8] Bile is another important barrier normally limiting enteric bacterial growth and translocation from the intestine.[9]

BACTERIAL TRANSLOCATION

Bacterial translocation was defined in 1979 as the passage of both viable and nonviable microbes and microbial products, such as endotoxin, from the intestinal lumen through the epithelial mucosa into the mesenteric lymph nodes and other organs.[10] Bacterial translocation can be caused by impaired host defenses, altered GI flora resulting in bacterial overgrowth, physical disruption of the gut mucosal barrier, direct injury to the enterocytes (eg, by irradiation or toxins), or reduced blood flow to the intestine.[11]

The oxygen tension at the tip of the intestinal villus is much lower than that in arterial blood, even under normal conditions; consequently, the susceptibility of the epithelium to hypoxic injury is increased.[11] Any reduction in blood flow aggravates these conditions, and epithelial cell injury may readily develop when the oxygenation of tissues is diminished. In animals with trauma and hemorrhagic, cardiogenic, and septic shock, there is diminished blood flow to the mucosa and submucosa of the jejunum, ileum, and colon, whereas flow to other organs is preserved. Ischemia-induced epithelial injury in the gut is a pathway common to shock and trauma, and this pathway may lead to dysfunction of the gut barrier and set the stage for bacterial translocation.[11] Increased intestinal permeability has been observed in patients with burns,[12] those who underwent elective or emergency surgery,[13] those with hemorrhagic shock,[14] and those with trauma and in intensive care.[15,16]

HEMORRHAGIC DIARRHEA

Acute hemorrhagic diarrhea is one of the most serious clinical manifestations of GI failure faced by small animal practitioners.[17] Diarrhea can cause massive loss of fluids, electrolytes, and proteins. Hemorrhagic diarrhea, regardless of the cause,

is the clinical sign of a loss of mucosal integrity. With the loss of this barrier, enteric flora can enter the bloodstream, leading to septicemia. The combination of dehydration, anemia, hypoproteinemia, and septicemia reduces systemic perfusion and oxygen delivery, putting the patient at risk for MODS.[4] Diarrhea results from accumulation of osmotically active particles in the intestinal tract, excess solute secretion, impaired absorption, or alterations in intestinal motility. All these mechanisms should be reviewed because 1 or all may occur together in the individual patient with diarrhea.[1,17]

Osmotic diarrhea results when unabsorbable solutes increase the fecal water content. Osmotic diarrhea can result from overeating, sudden dietary changes, maldigestion, or malabsorption. Some bacterial enterotoxins pathologically enhance secretion. Bacterial pathogens that are known to cause secretory diarrhea include *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Yersinia enterocolitica*, *Salmonella typhimurium*, *Campylobacter* spp, and *Clostridium perfringens*.[17,18] Enteric hormones, fatty acids, and bile acids also stimulate intestinal secretion. Malabsorption can be caused by anything affecting the mucosal or submucosal layers of the intestine. With damage to the mucosa, normal sodium reabsorption is impaired, fecal water increases, and diarrhea results. Motility changes that speed intestinal transit cause diarrhea. By decreasing transit time, normal water resorption cannot take place and diarrhea results. The most common mechanism of severe hemorrhagic diarrhea is an increase in intestinal permeability.[17]

DIAGNOSTIC EVALUATION

Obtunded dehydrated febrile animals with anorexia, vomiting, and/or diarrhea should be evaluated for concurrent systemic disease and dysfunction of other organ systems. A complete physical examination should identify life-threatening complications associated with loss of blood and fluids. Priority is given to the cardiopulmonary systems. Therapy includes intravenous fluids, supplemental oxygen, electrolyte replacement, and broad-spectrum parenteral antimicrobials. Treatment should commence immediately although a definitive diagnosis is pursued. Severe increases in intestinal permeability are characterized by hypoproteinemia, melena, and hematochezia.[1,4] A complete blood count should always be evaluated. Animals with idiopathic hemorrhagic gastroenteritis may have packed cell volumes as high as 75%. Severe intestinal blood loss can also lead to anemia and panhypoproteinemia. Infection with either *Salmonella* spp or canine parvovirus is associated with neutropenia. Leukocytosis with immature bands is a common finding with systemic infection. Leukocytosis with lymphopenia and eosinopenia (stress leukogram) is a common finding in any debilitated animal with gastroenteritis. A normal leukogram in a sick animal with GI disease should prompt a corticotropin stimulation test to evaluate possible adrenocortical insufficiency.

A complete serum biochemical profile is necessary to evaluate other organ systems. Glucose level should be checked on admission and at least once a day thereafter to detect hypoglycemia associated with sepsis. Concentrations of electrolytes including sodium, chloride, potassium, and magnesium can drop precipitously in anorectic animals with diarrhea. Hyperkalemia with hyponatremia is another indication of adrenocortical insufficiency; however, these changes can also been seen with whipworm (*Trichuris vulpis*) infections. Hypocholesterolemia is another finding with hypoadrenocorticism. Samples to assess baseline renal function, including serum urea nitrogen (BUN), creatinine, phosphorous, calcium, and urine specific gravity, should be collected before intravenous fluid therapy begins.

A fecal examination is indicated in any diarrheic state. In a study, infectious agents were identified in more than 25% of dogs with diarrhea presented to a veterinary teaching hospital.[19] Direct fecal examination should be performed, as should zinc sulfate flotation. Some parasites, *Giardia* spp and *Trichuris*, may be difficult to identify; so multiple examinations or alternative testing modalities should be performed. Acid-fast staining is useful to confirm *Campylobacter jejuni*. Enzyme-linked immunosorbent assays are available to detect canine parvovirus, *Giardia* spp, and *Cryptosporidium parvum* antigens.

Fecal culture is indicated in animals with inflammatory changes on the fecal smear. Pathogenic and zoonotic bacteria causing enterocolitis include *Salmonella* spp, *C jejuni*, *Shigella* spp, and *Y enterocolitica*. The presence of these species of bacteria is of particular concern in hospitalized patients, multi-animal households, kennels, and homes of immunocompromised individuals.[19]

SYMPTOMATIC TREATMENT

The treatment of any medical problem should be based on the primary cause; however, there are numerous serious and predictable systemic complications of acute GI dysfunction that require immediate supportive care. Mild complications may simply require antiemetic therapy and starvation for 12 to 48 hours with a gradual reintroduction of small amounts of an easily digestible diet for several more days.[1] The absence of nutrients in the GI tract reduces secretions and decreases the concentration of osmotically active particles. For this reason, starvation seems a logical step for secretory and osmotic diarrhea. When animals with acute GI disease are starved, the GI tract receives most of its nourishment from the food passing through the bowel. Early feeding of patients with diarrhea may make more sense in those with increased mucosal permeability. Enteral feeding maintains an increase in mucosal barrier integrity and helps minimize malnutrition.[20–22] Human and animal studies have shown that antibacterial host defenses, including lymphocytes, neutrophils, and gut-associated immune functions, are better preserved in enterally fed humans and animals.[11,21] Enteral nutrition has been linked with the maintenance of intestinal mucosal integrity. In an animal model, starvation and total parenteral nutrition were found to promote bacterial overgrowth, reduce intestinal mucin production, decrease the level of intestinal IgA, cause mucosal atrophy, and accelerate oxidative stress.[21] In critically ill patients, early enteral nutrition reduces septic complications.[11]

FLUID THERAPY

Intravenous fluid therapy is aimed at restoring lost fluids, resolving dehydration, providing normal maintenance requirements, and keeping up with ongoing losses. Oral fluid therapy may be adequate for simple diarrhea in a hydrated animal. Animals with signs of dehydration, hemorrhagic diarrhea, or MODS should have an intravenous catheter placed to receive parenteral fluids and antibiotics. Fluid therapy must be individualized for each patient based on acid-base status, electrolyte concentrations, plasma protein concentrations, and packed cell volume, because these can be highly variable in patients with diarrhea. Choices of which crystalloid fluid to use and the use of whole blood, packed red blood cells, plasma, albumin, or synthetic colloids as required should be based on serial physical examination and monitoring of packed cell volume, serum total solids, and electrolyte concentrations.

ANTIBIOTICS

Normal resident microbial flora of the intestinal tract includes anaerobic bacteria, which outnumber the aerobic gram-negative organisms 100 to 1000 times.[4] The presence of anaerobic flora, which occupies the mucous layer adjacent to the epithelial cells, can prevent the adherence of other potential pathogens. Antibiotic therapy should not simply target the anaerobes. Instead, the clinician should use a balanced approach toward both gram-negative and anaerobic pathogens. The use of antibiotics is controversial with simple diarrhea. However, with severe hemorrhagic diarrhea, the clinician must assume that the patient has a serious loss of intestinal mucosal barrier integrity, and parenteral bactericidal antibiotic therapy is indicated. The goal of antibiotic therapy is to eliminate enteric bacteria that have passed through the mucosa, entered the bloodstream, and occupied the portal and pulmonary circulations. Animals with fecal cultures positive for bacterial pathogens may be treated according to the sensitivity pattern of the culture. Animals with positive blood cultures should have their antibiotic regimen refined based on the organisms identified.

GLUTAMINE, ARGININE, AND OMEGA-3 FATTY ACID SUPPLEMENTATION

Glutamine, arginine, and omega-3 fatty acids have the potential to modulate the activity of the immune system in clinical situations in which altered supply of nutrients exists.[23,24] Enteral diets enhanced with these nutrients have been shown to have significant benefits, including reducing morbidity, mortality, days hospitalized, and septic complications, compared with normal diets.[23,25]

Glutamine is the main metabolic substrate exerting trophic effects on enterocytes, supporting their normal function. Primarily extracted via luminal absorption, adequate glutamine is also synthesized in the normal gut to be considered a nonessential amino acid. However, during states of illness, this synthetic ability is inadequate to meet these metabolic needs of the enterocytes. In these instances, glutamine supplementation may be necessary to form and repair intracellular tight junctions and maintain mucosal integrity. Glutamine is also important in the synthesis of the protective mucous gel layer and is an essential nutrient for proper cellular immune functions.[26] Glutamine metabolism increases in animals with critical illness. Glutamine levels decrease rapidly after injury, and the magnitude of decrease is predictive of mortality in the intensive care unit.[27] Animals can store this important substrate only for 24 to 48 hours. Because glutamine induces stress tolerance and protects against cellular injury, supplementation may prove beneficial in critically ill patients. Dosages for glutamine supplementation have been extrapolated from the human literature. The recommended dosage for dogs with hemorrhagic diarrhea secondary to parvovirus enteritis is 0.5 g/kg/d divided twice a day in drinking water.[28] Several commercial veterinary critical care diets contain added glutamine and arginine.

Arginine level is reduced in patients with trauma and postoperative patients compared with patients with sepsis and controls. This condition is likely because of the increased levels of arginase from activated myeloid cells in these patients.[29] Meta-analysis of human studies evaluating arginine supplementation in nonseptic critically ill patients has shown improved outcomes.[30] Myeloid cells express another enzyme, inducible nitric oxide synthase (iNOS). Unlike in patients with trauma and postoperative patients, patients with sepsis do not have reduced arginine levels. This is probably because, as opposed to arginase, iNOS is predominantly expressed by activated myeloid cells in patients with sepsis.[29] This has potential clinical implications because excess nitric oxide in sepsis may potentiate hypotension and organ dysfunction. In a canine sepsis model, arginine administration was associated with

increased plasma arginine; increased nitric oxide products; and worsening shock, organ injury, and mortality rates.[31] The authors concluded that arginine supplementation is not recommended for patients with sepsis.

Omega-3 fatty acid supplementation has been shown to downregulate arginase expression after injury, and like arginine supplementation, omega-3 fatty acid supplementation has been shown to have beneficial outcomes.[32] Fish oil–enriched diets have also been shown to preserve intestinal blood flow and to enhance the host's ability to kill translocated bacteria in various experimental models of bacterial translocation.[33] This effect was attributed to the increased synthesis of vasodilatory prostaglandins, reversing endotoxin-induced intestinal vasoconstriction, enhanced mucous secretion, and downregulated the synthesis of inflammatory cytokines.[34]

ANALGESIC AND ANTIEMETIC THERAPY

Analgesia should be considered in patients showing signs of abdominal pain. Objective serial monitoring of critically ill patients is necessary when pain is appropriately treated. Nonsteroidal and steroidal antiinflammatory drugs may complicate GI hemorrhage by inhibiting the production of normal protective prostaglandins. Narcotic analgesics can be used as long as respiratory and pulmonary functions are monitored and their effects on GI motility considered. Animals with acute inflammation of the GI tract may be extremely nauseous. Nausea may manifest clinically as anorexia, hypersalivation, or emesis. Antiemetic drugs can provide a degree of relief not offered by fluids or analgesics. Maropitant, metoclopramide, ondansetron, dolasetron, and chlorpromazine are all antiemetic drugs available and appropriate for use in veterinary patients.

PROGNOSIS

The prognosis for patients with acute GI dysfunction depends on the etiology and presence of concurrent organ dysfunction. Young dogs with hemorrhagic gastroenteritis syndrome and patient's with hypoadrenocorticism generally respond quickly to volume replacement, and corticosteroid replacement in the case of hypoadrenocorticism, and have an excellent prognosis despite profound bloody diarrhea.[10] Parvoviral enteritis can produce severe dehydration, shock, and multiple organ failure. With aggressive supportive care, mortality rates of 5% to 20% have been reported.[35] Morbidity and mortality for other causes of acute GI hemorrhage depend on the primary cause, presence of bacterial translocation and sepsis, and concurrent organ failure. The challenge to the veterinary clinician is to replace the lost fluids, electrolytes, and proteins while preventing septic complications. It is vital to monitor the major organ function and treat the primary disease and secondary organ dysfunction in a timely manner.

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