Pathology of the Small and Large Intestine (16-Dec-2003)

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Abstract
The pathophysiologic events that take place during an acute abdominal crisis include bowel distension, bowel ischemia, and alterations in tissue perfusion. The classic pathological degeneration is initiated early in the disease by changes in the microvascular permeability, endothelial cell changes, neuron response, and neutrophil activation. Reperfusion injury occurs as part of the disease process during resuscitation during shock or re-establishing tissue perfusion at surgery. An understanding of these physiologic and morphologic alterations helps the clinician determine the type of disease, the severity and the treatment.

Obstruction
In the small intestine, obstruction of the intestinal lumen usually is due to intraluminal blockage from a dehydrated food mass or extraluminal pressure from adhesions, thickening of the intestinal wall or infection. Adynamic ileus may cause functional obstruction due to lack of intestinal movement. Adynamic ileus is associated with peritonitis, ischemic intestinal insults, anesthesia, endoparasitism and electrolyte imbalances. In the large colon or small colon, impaction by dry ingesta, concretions or sand most often causes obstruction. The immediate response to obstruction is increased motility of the segment of bowel oral (proximal) to the blockage and relaxation of the intestine aboral (distal) to the blockage. The muscular activity of the intestine is increased around the obstruction, increasing intraluminal pressure in this segment of intestine. Distension of the intestine stretches the wall of the intestine and combines with the reflex muscular spasm to initiate colic. When the small intestine is obstructed, the enterosystemic circulation of fluid is blocked so that fluid from saliva, stomach fluid, bile, pancreatic fluid and small intestinal secretion is prevented from passing to the large intestine where it is reabsorbed. Because normal secretion of fluid continues, the small intestine becomes distended oral (proximal) to the blockage. Once the luminal pressure is elevated, the tissue pressure compresses the capillaries and reduces venous drainage. Subsequently blood flow to the intestine is decreased as the capacitance of the vascular system is decreased. Due to the increased capillary hydrostatic pressure, water moves into the lymphatic system or the intestinal lumen, or through the serosa. The increased intraluminal hydrostatic pressure created by the enhanced secretion of fluid then initiates cyclic increases in secretion by continuing to elevate the intraluminal pressure. Because the fluid secreted is isotonic, there is minimal acute change in serum electrolyte values. The consequences of intestinal distension are dehydration from third-space sequestration of the secreted fluid, mucosal injury, serosal injury, abdominal pain, and increased movement of protein across the serosa into the abdominal cavity. The distension eventually reaches a level that inhibits motility in the affected segment of intestine as well as other portions of the intestinal tract. The clinical signs that result are colic, increased heart rate due to pain and decreased circulatory fluid volume, reduced borborygmi, gastric and intestinal fluid sequestration (gastric reflux), and increased protein concentration in peritoneal fluid. An example of this type of disease process is ileal impaction (Fig. 1).

Figure 1. An ileal impaction with distension of the ileum and proximal small intestine (1A). The serosa (1B) looses the mesothelial cell layer and becomes edematous with fluid and cell infiltration. - To view this image in full size go to the IVIS website at www.ivis.org . -

If the intraluminal pressure is acutely decreased such as occurs at surgery, intestinal hyperemia and reperfusion injury occur. The layer of the small intestine most affected is the serosa. The edema already present from increased vascular leakage is increased. The endothelial cells are damaged initiating cytokine production and chemotaxis of inflammatory cells.
Neutrophils migrate into the serosa and cause further inflammation within the serosa. Blood flow in serosal vasculature is decreased during reperfusion. This "no reflow phenomena" is caused by swollen endothelial cells, neutrophils, and platelets plugging capillaries and by collapse of capillaries from increased tissue pressure. The inflammatory response continues for several days causing fibrin deposition within and on the surface of the serosa. The long term result is scarring and adhesion formation of the intestine.

Obstruction of the cecum or large colon often blocks passage of ingesta, but allows gas to escape. Exceptions to this include extremely dehydrated ingesta, sand impactions, enteroliths or entrapment displacements of the colon. Reflex muscular contractions increase in frequency, the intraluminal pressure increases and the intestine relaxes aborally. Pain is intermittent and is associated with peristalsis, which increases intraluminal pressure oral to the obstruction. Fluid entering from the small intestine continues to be absorbed in the cecum and segments of colon oral to the obstruction. The process slowly produces dehydration due to lack of water intake and also results in intermittent pain with reduction of borborygmi. Clinical signs seen with this type of obstruction include intermittent colic (usually mild to moderate), a slight increase in heart rate, mild dehydration, reduced borborygmi, and peritoneal fluid total protein levels ranging from normal to increased, depending on the duration of the obstruction. The cecum and colon appear to be more compliant that the small intestine with higher intraluminal pressure required to cause necrosis and reperfusion injury. Examples of this type of obstruction are large colon impaction, entrapment of the large colon in the renosplenic space and right dorsal colon displacement.

If obstruction is complete, gas no longer escapes resulting in rapid distension of the proximal segments of the bowel. In many instances, this may include the entire colon and cecum. The massive distension creates other systemic effects including severe stretching of the intestinal wall produces severe pain and cessation of intestinal motility. Intraabdominal pressure also reduces diaphragmatic movement, which decreases tidal volume, and initiates hypoxemia eventually occurs. Prolonged distension of the cecum or colon can cause mural ischemia and degeneration of the bowel. Though the specific cause of impaction is unknown, it is possible that segmental ileus sets up the conditions for accumulation of ingesta. The cecum can distend rapidly with fluid and ingesta causing increased intraluminal pressure, which leads to mural edema. Congestion of the vasculature is followed by cecal mucosa degeneration and damage to the musculature (Fig. 2a and Fig. 2b).

![Figure 2a](http://www.ivis.org)
Figure 2a. Cecal impaction causes marked distension of the cecum with eventual cecal wall ischemia, which causes wall thickening and hemorrhage. - To view this image in full size go to the IVIS website at www.ivis.org.

![Figure 2b](http://www.ivis.org)
Figure 2b. Microscopically the cecal wall becomes edematous with hemorrhage into the serosa, submucosa and muscular layers. - To view this image in full size go to the IVIS website at www.ivis.org.

Obstruction of the colon does not usually cause the marked distension seen in the small intestine or cecum. Therefore the colon has less chance of mural ischemia and reperfusion damage. Focal distension around a lesion is not usually cause necrosis. However, persistent pain and tight distension felt via rectal examination are indicators of wall ischemia. Persistent or chronic large colon distension has been associated with thickening of the muscular wall and decreased numbers of neurons and glial cell proliferation in the myenteric plexuses (Fig. 3).

![Figure 3](http://www.ivis.org)
Figure 3. The normal myenteric plexus (3A) has large neurons surround by fascia and a few glial cells, whereas the myenteric plexus from a colon obstructed for greater than 24 hours has decreased neuron numbers and marked glial cell infiltration (3B). - To view this image in full size go to the IVIS website at www.ivis.org.
**Strangulation Obstruction**

Strangulation obstruction of intestine is a combination of luminal obstruction and mural ischemia. Strangulation obstructs the blood supply by vascular constriction and usually is due to intestinal torsion-volvulus or incarceration of the small intestine in a variety of intraabdominal sites, including the epiploic foramen, inguinal ring or rents in the mesentery. Depending upon the degree of constriction, venous return may be impeded without a loss of arterial flow. This causes red blood cell accumulation into the extracellular space of the intestine, with most of the blood accumulating in the submucosa and lamina propria (Fig. 4).

![Figure 4. During venous strangulation obstruction the interstitial tissues (lamina propria) are filled with red blood cells, which add to the ischemic damage.](image)

Arteriovenous constriction can occur acutely or may follow venous constriction. Both types of circulatory interruption result in development of lesions in the intestine. This may be "low-flow ischemia" or total ischemia. In both cases necrosis will eventually occur or reperfusion will cause a progression of the degeneration and can lead to necrosis.

Ischemia causes similar lesions in the large and small intestine. The lack of perfusion reduces oxygen delivery, which affects the mucosal cells first due to their high metabolic activity. The cells start to separate from the basement membrane because of formation of extracellular edema at their attachment to the capillary tuft of the lamina propria. Thus, the cells slough before development of severe intracellular damage. Sloughing of the epithelial cells of the villi occurs in the small intestine and from the surface and into the crypts of the cecum and colon. The slough is graded from 0 (normal) to 5 (total slough) with necrosis of the crypt cells (Fig. 5).

![Figure 5. A normal small intestinal villus with normal mucosal cells (3A). As ischemia progresses the mucosal cells separate at the tip of the villous and eventually break away to expose the capillary to the intestinal contents.](image)

The loss of cells is sequential starting at the villus tip and progressing to the crypts. At the same time, the mesothelium of the serosa also sloughs and the fibrous tissue layer and muscle becomes edematous. Ischemic changes continue as progressive necrosis unless blood flow resumes. Vascular damage initiates leakage of protein and erythrocytes out of the vascular space into the interstitium, bowel lumen and peritoneal fluid. Loss of the mucosal barrier allows bacteria and endotoxin to escape into the peritoneal cavity causing increased neutrophil numbers in peritoneal fluid. With severe necrosis, bacteria are seen in the fluid or within the neutrophils, and the fluid itself may become serosanguineous.

Initially strangulation obstruction causes clinical signs similar to those of simple obstruction. Clinical signs that separate strangulating lesions from simple obstruction relate to the rapid bowel distension, disruption of the mucosal barrier, and absorption of bacteria and endotoxin from the intestine into the circulation. Strangulating lesions often have severe abdominal pain from stretching of the mesentery, necrosis of the intestine, and endotoxin release with subsequent cytokine and prostaglandin production, seen with many of these diseases. These events initiate shock by movement of fluid from the extracellular and intracellular compartments into the intestinal lumen, and by the response to endotoxemia. Ischemia initiates production of hypoxanthine via breakdown of ATP to AMP during the period of hypoxia. When oxygen is brought back to the tissue by reperfusion, xanthine oxidase, activated from xanthine dehydrogenase in the presence of calcium and protease present in high concentration in the small intestine, reacts with the hypoxanthine to make superoxide and hydrogen peroxide radicals, and subsequently hydroxyl radicals (Fig. 6).

![Figure 6. Schematic diagram of superoxide and hydroxyl radical production.](image)

In endothelial cells this intracellular response causes cell membrane alterations with subsequent release of cytokines and increases incapillary permeability. Neutrophils migrate into the damaged tissue causing more damage by releasing proteinases, oxygen radicals, and hypochlorous acid. Tissue damage is progressive including progressive mucosal epithelial cell slough, collagen disruption, edema and neutrophil infiltration of the submucosa and muscular layers and serosa (Fig. 7a,
When intestinal strangulation or distension is released during surgery, reperfusion produces a hyperemic reflex with increased blood flow through out the ischemic intestinal segments. Though the bowel appears to have improved color and motility, the hyperemic response may prevent the surgeon from recognizing bowel undergoing reperfusion injury. Progressive degeneration of intestine due to reperfusion injury usually occurs 24 - 48 hours after surgery and causes colic or depression, ileus, increased heart rate, discolored mucous membranes and alterations in the peritoneal fluid. These effects are dependent on the amount of intestine involved. Large colon torsion or small intestinal volvulus that involves a large portion of bowel induces more rapid systemic changes than conditions involving only small segments of intestine. Conditions such as intussusceptions or inguinal hernias in which the strangulated bowel is isolated from the abdomen do not produce the same acute signs of shock. There is evidence that reperfusion injury can be decreased by administration of DMSO, NSAID and rinse solutions applied topically or intra-arterially. All are effective at a particular part of the reperfusion cascade and must be administered at the time of reperfusion to be effective. Because reperfusion can occur as a cyclic event, repeated treatment may be of benefit.

**Nonstrangulating Infarction**

Nonstrangulating infarction is a reduction of blood flow to the intestine due to an intravascular obstruction. This can be caused by blockage of a large artery of low flow through the capillaries. In horses, this is most often due to Strongylus vulgaris larval migration in the cranial mesenteric artery and its branches. The incidence of this problem has decreased markedly with the use of larvacidal drugs such as ivermectin. The migrating larvae cause an endothelial lesion and initiate thrombus formation. This appears to be a chronic process, with active coagulation taking place during the entire time the larvae are in the artery. This process includes platelet aggregation and thrombus formation, and hypothetically could lead to thromboxane production in the arterial system and thromboembolism. The degree of ischemia varies and usually does not cause clinical signs. Blood flow to the intestine can be decreased more than 50% before the intestine is affected. This is due to the ability of the intestine to increase oxygen uptake at lower blood flows and its ability to shunt blood to the mucosa, the area with the highest metabolic rate. Often the intestinal lesions appear to have developed slowly due to chronic ischemia. The ischemic change is similar to that seen with strangulation except that with arterial obstruction there often is minimal leakage of RBC’s into the extracellular space and the intestine does not become thickened. The affected intestine first turns purple, then green brown, with subsequent necrosis (Fig. 8).
The mucosal epithelium is lost and there may be simultaneous mural necrosis. Bacteria from the lumen leak through the degenerated tissue and seed the peritoneal cavity. The peritoneal lining responds with a massive accumulation of neutrophils and protein. The peritoneal fluid becomes serosanguineous. Bacterial often can be found in the fluid or within neutrophils. The horse responds with pain due to ischemia and endotoxemia. Depending on the size of the lesion, the horse develops peritonitis before severe signs of shock become apparent. Once endotoxin leakage occurs, the sequence of events is similar to that of strangulation; however, the rate of bacterial and endotoxin diffusion seems to be dependent on the stage of intestinal degeneration.

Clinical signs of nonstrangulating infarction are variable and may resemble those of simple obstruction or severe strangulation obstruction. Colic varies from mild to severe, as does the degree of dehydration. Absorption of endotoxin apparently can be slow, creating sublethal shock. The peritoneal fluid also can vary greatly but often has a large increase in neutrophils and protein when clinical signs are first noticed, rather than a progressive increase as occurs with prolonged obstruction or strangulation. Red blood cell numbers in the peritoneal fluid often are not as high as occurs with strangulating lesions.

**Intestinal Healing and Adhesions**

Mucosal and serosal regeneration is a rapid and can be a totally reparative process that follows any of the intestinal injuries discussed. The mucosa can heal as long as viable enterocytes are present to migrate up the crypt or villus lamina propria. Though the villus is shorted by contraction and loss of the capillary tuft, it is covered by epithelium within 12 - 24 hours. Lack of healing leaves the lamina propria open to bacteria and endotoxin migration into the peritoneum. Within 10 days, the villus can regenerate to normal length and the intestine can return to its normal absorptive capacity.

Serosal responses to ischemia and bacterial invasion include edema, deposition of fibrin, and infiltration of neutrophils and macrophages. Endothelial damage is severe and progresses during reperfusion. The serosa thickens with deposition of fibrin within the inflamed layer and on its surface. The injured serosal surface adheres to other peritoneal surfaces in the abdomen because there often is lack of normal movement in the abdomen and because a layer of fibrin and cellular debris covers the injured mesothelial surface. The response of the entire peritoneal cavity to leakage of bacterial depends upon the rate of healing and level of contamination. With severe contamination due to bowel leakage, there is a massive influx of white blood cells and protein into the peritoneal cavity. Diffuse fibrin clots form and the omentum often is adhered to the site of leakage. The response after surgery includes cytokine production, which regulates fibrinolysis.

Work in laboratory animals and horses suggests interleukin 1 and tumor necrosis factor are both produced in peritoneum and regulate macrophages to produce both plasminogen activator and plasminogen inhibitor. The cyclic response of these cytokines helps to breakdown fibrin and reduces adhesion formation unless the inflammatory process causes excess fibrin production and inhibition of fibrin breakdown. The end result with excessive inflammation is scarring of the serosal surface and mesentery. Adhesions, restrictive mesenteric shortening, and scar contracture, cause intestinal lumen narrowing and stricture of the mesenteric vasculature. Several weeks after an apparent successful surgery these horses have recurrent obstruction, which causes colic and in some horses distended small intestine with gastric reflux. The adhesions will often require surgery to by-pass or remove the affected bowel (Fig. 9).

Experimental ischemia in foal jejunum caused bowel and bowel and bowel to mesenteric adhesions. Gross adhesions were prevented with intravenous DMSO at 20 mg/kg every 12 hours for 72 hours and by flunixin meglumine, combined with gentamicin and penicillin for 72 hours (Fig. 10). Film made of hyaluronic acid and carboxymethylcellulose, or intra-abdominal hyaluronic have also been used in foal and adults with evidence of preventing adhesions. Controlling inflammation appears to be the best treatment for decreasing adhesions and scarring after ischemia.
Figure 10. After one hour of ischemia foal jejunum had constricting adhesions and scarring (10A), which was prevented by systemic administration of DMSO or flunixin meglumine, gentamicin and penicillin (10B). - To view this image in full size go to the IVIS website at www.ivis.org.

References


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