

THE COLICKY HORSE: WHAT TO DO IN A FLASH AND MORE

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Introduction

Ultrasonography is invaluable in the diagnosis of the cause of colic in horses. The sonographic findings can aid the veterinarian in determining if the horse has a medical or surgical lesion. Diagnostic ultrasonography provides a window for noninvasive visualization of gastrointestinal viscera, which are otherwise difficult to examine. This sonographic information is used to decide if surgical intervention is indicated, to formulate a prognosis based upon the abnormalities detected and can be used to monitor response to treatment.

Patient Preparation and Scanning Technique

The ultrasonographic evaluation of the abdomen is well tolerated and sedation is rarely needed. Ideally, the hair should be clipped off the skin over the area under investigation with a number 40 surgical clipper blade, the skin cleaned and an ultrasonographic coupling gel applied. The entire abdomen should be clipped from ventral to the lung fields on both sides to the xiphoid and inguinal area.

However, in cases where this is not possible or a fast localized abdominal sonographic examination of the horse (FLASH) is being performed to decide if immediate surgical intervention is indicated, soaking the hair and skin with alcohol will usually suffice. The FLASH examination is a rapid examination (15 minutes or less) that includes 7 windows for rapid evaluation of specific GI viscera: ventral abdominal, gastric, nephrosplenic, left middle third of the abdomen, duodenal, right middle third of the abdomen and thorax. This examination is excellent for the detection of dilated turgid small intestinal loops where surgical intervention is indicated.

The horse should be scanned standing, if possible. The intraluminal bowel gas will rise to the more dorsal portions of the abdomen, enabling the clinician to examine a larger portion of the gastrointestinal tract. If the horse is recumbent, the scan should also be performed from the most ventral portion of the abdomen.

If performing a FLASH examination, a low frequency convex transducer and alcohol saturation of the skin and hair will enable the rapid screening examination in a horse presenting with acute colic. Transrectal ultrasonographic evaluation of abnormalities detected on rectal palpation can also be performed in adult horses to further clarify abnormal rectal findings. In a horse presenting with a history of chronic colic, high frequency transducers should be used to obtain superior images of the bowel wall with lower frequency transducers used as the deeper portions of the abdomen are investigated.

Normal Ultrasonographic Findings in the Equine Gastrointestinal Tract

Only large intestinal echoes are usually imaged in the intercostal spaces (ICS) and the flank in the adult horse. Occasionally small intestinal echoes are imaged between the stomach and spleen and dorsal to the left dorsal colon and in the ventral abdomen (usually caudally) of the adult horse. The large intestinal echoes are recognized by their large semi-curved, sacculated appearance, except for the right dorsal colon. The right dorsal colon has a smoother nonsacculated appearance and is usually imaged from the right 14th – 10th intercostal spaces. The large intestinal wall is hypoechoic to echogenic with a hyperechoic gas echo from the mucosal surface and normally measures 3.5 mm or less in thickness. The cecum is normally imaged in the right paralumbar fossa and right to mid ventral abdomen and has a sacculated appearance with a hyperechoic gas/ingesta and hypoechoic fluid contents with a wall thickness of 3.5 mm or less. Peristaltic activity is normally visualized. The small intestinal echoes are recognized by their small tubular and circular appearance. The wall of the jejunum is hypoechoic to echogenic with a hyperechoic echo from the mucosal surface and is usually 3 mm or less in thickness. Some anechoic fluid and hyperechoic gas is often imaged in the lumen of the jejunum. Peristaltic waves are also normally visualized. The duodenum is imaged around the caudal pole of the right kidney and medial to the right liver lobe to about the mid abdomen. It appears small and circular (when sliced in its short axis) with a hypoechoic to echogenic wall, also ≤ 3 mm in thickness, and has a fluid lumen. The duodenum usually appears partially collapsed and its peristaltic motion is easily visualized during real-time scanning. The gastric fundic echo is visualized in the left 9 - 12th ICS and is imaged as a large semi-circular structure medial to the spleen at the level of the splenic vein. The gastric wall is hypoechoic to echogenic with a hyperechoic gas echo from the mucosal surface and normally measures up to 7.5 mm in thickness. Gastric rugal folds can be often be imaged in adult horses. The feeding status of the horse (fasted versus fed) affects gastrointestinal motility. Alpha 2 adrenoreceptor agonists will decrease gastrointestinal motility and should be avoided if at all possible prior to the sonographic examination of the abdomen if GI motility is being assessed.

Abnormal Findings in Horses with Colic

Herniation/Displacement

Abnormal positioning of the gastrointestinal viscera is difficult to diagnose ultrasonographically, unless the viscera are displaced into the scrotum, thoracic cavity or into an umbilical hernia.



Small intestine within scrotal sac

Displacement of the gastrointestinal viscera into the thoracic cavity through a diaphragmatic hernia can usually be diagnosed ultrasonographically by scanning the affected side of the thorax and cranial abdomen and looking for the rent in the diaphragm, as displacement of the overlying lung by the herniated viscera occurs. The approximate size of the diaphragmatic hernia can be estimated and the gastrointestinal viscera evaluated for the degree of bowel compromise. However, a diaphragmatic hernia could be missed ultrasonographically if it was located in the center of the diaphragm and the herniated viscera were not in contact with the thoracic wall.



Jejunum between lung and pericardium

Nephrosplenic ligament entrapment

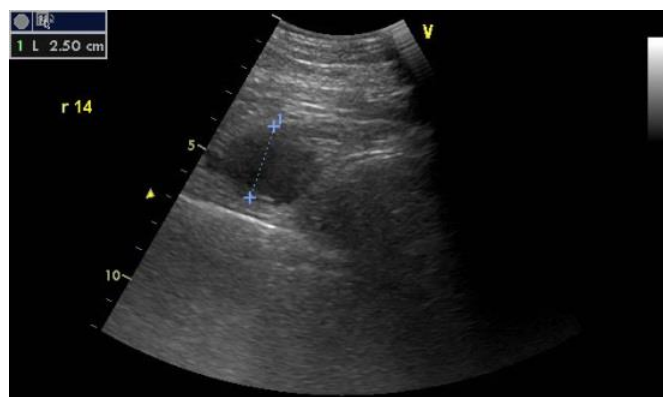
Diagnosis of a nephrosplenic ligament entrapment ultrasonographically is based upon the inability to visualize the left kidney transabdominally and the visualization of ingesta and/or gas filled large bowel instead in the dorsal aspect of the paralumbar fossa and the dorsal caudal left side of the abdomen. The spleen is ventrally displaced. The most dorsal portion of the spleen that can be imaged has a straight horizontal dorsal border extending from the paralumbar fossa to the 10-12th intercostal space, at which point the colon is no longer visible due to the intervening lung. Dorsal to the spleen a bright hyperechoic reflection is imaged from the displaced or entrapped large colon. The sonogram can be used to see if treatment with phenylephrine, followed by lunging, or rolling the horse has successfully corrected the nephrosplenic ligament entrapment.



Nephrosplenic ligament entrapment

Right dorsal displacement

The sonographic detection of enlarged colonic mesenteric blood vessels above the costochondral junction on the right side is indicative of a right dorsal displacement. This may also be imaged in some horses with an 180° large colon volvulus. Lack of visualization of the duodenum and liver is often noticed in horses with a right dorsal displacement. A right dorsal displacement, a 180° large colon volvulus or both were 32.5 times more likely to be found at surgery when a colonic mesenteric vessel was detected ultrasonographically on the right side of the abdomen above the costochondral junction. The detection of a colonic vessel on the right side of the abdomen is very specific for a problem involving the large colon. The detection of large colon dorsal to the right liver lobe is consistent with a large colon displacement or an epiploic foramen entrapment although usually small intestine is imaged in this location in horses with an epiploic foramen entrapment.

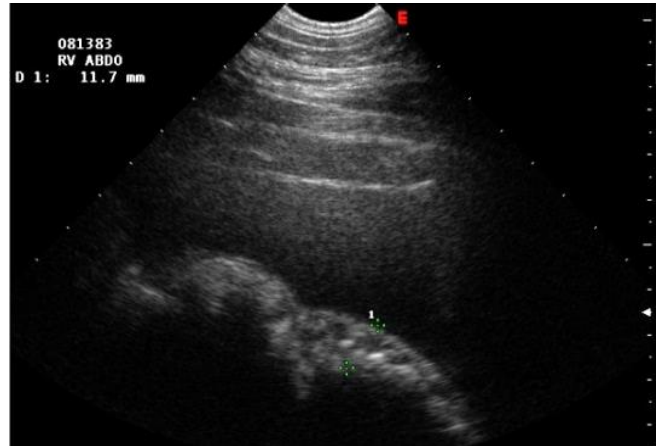


Distended mesenteric blood vessel above the costochondral junction

Large colon torsion

Marked thickening of the wall of the large colon is consistent with a diagnosis of large colon torsion. A colonic wall thickness ≥ 9 mm is an accurate predictor of a large colon torsion in horses with surgical colic localized to the large colon (sensitivity – 67%) and correctly determined that large colon torsion was absent with a specificity of 100%. However, other causes

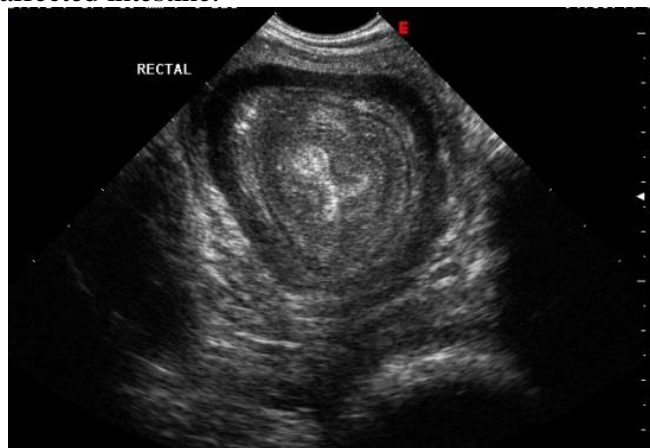
of large intestinal wall thickening do occur and the entire clinical picture is important to consider. The detection of nonsacculated large colon in the left ventral abdomen in horses with abdominal pain is indicative of large colon volvulus. The rate of decrease in the bowel wall thickness post-surgical correction of a large colon volvulus correlates with outcome.



Large colon torsion

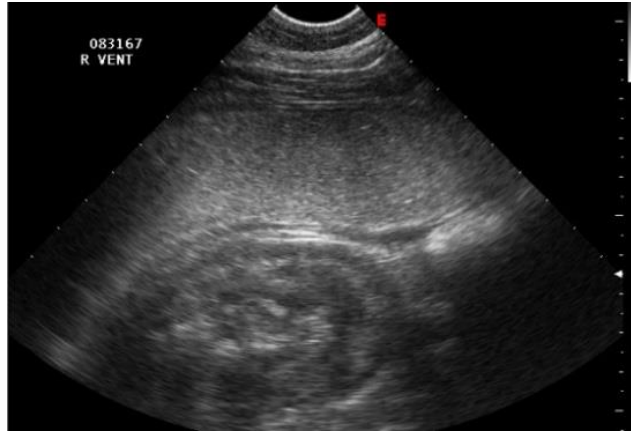
Intussusceptions

Intussusceptions have a characteristic target or bull's eye sign in the affected portion of intestine. There are many different possible sonographic appearances for the intussusception, depending upon which portion of the intussusception is being imaged. Often fibrin is imaged between the 2 loops of affected intestine.



Ileal-ileal intussusception

In yearlings and young horses, ileal intussusceptions are more common and may be imaged rectally or transcutaneously. Intussusceptions in adult horses usually involve the ileum and/ or large bowel. The majority of intussusceptions imaged in adult horses are imaged from the right side of the abdomen because the cecum or right ventral colon is involved.



Cecocecal intussusception

Strangulating small intestinal lesions

Distended, fluid-filled small intestine is usually imaged proximal to a strangulated portion of small intestine. The strangulated small intestine usually has thickened, edematous, hypoechoic walls with little or no peristaltic activity. Two populations of small intestine, one collapsed with some motility and normal wall thickness and the other with a thickened wall, turgid appearance and little or no motility is consistent with a strangulating lesion. In older horses, a strangulating lipoma is likely although the lipoma itself is rarely imaged. Complete volvulus of the small intestine may also occur, similarly affecting the entire small intestine. Distended small intestine with thickened walls is most frequently detected in the ventral portion of the abdomen, as the increased weight of these loops brings them in contact with the ventral portion of the abdomen. Amotile edematous loops of small intestine have been imaged in the right side of the abdomen in horses with epiploic foramen entrapment of the small intestine. Mucosal thickening of the wall of the strangulated loops of small intestine is usually less echogenic than wall thickening associated with a cellular infiltration, fibrosis or hypertrophy of the intestinal wall, usually seen in nonstrangulating lesions. Surgical intervention was indicated in one study of horses with colic when edematous small intestine was imaged in conjunction with decreased small intestinal motility.



Small intestinal distention & ileus with epiploic foramen entrapment

Strangulating lesions of the small colon

Increased wall thickness of the small colon and intestinal distention have been reported in several horses with strangulating lesions in the small colon caused by a pedunculated lipoma using transrectal ultrasonography. Transabdominal ultrasonography has been useful in diagnosing strangulating lesions in the small colon in miniature horses.

Impaction

An impaction can often be imaged from the flank or side of the abdomen in horses with cecal or right dorsal colon impactions. Small colon impactions may be imaged transrectally, when scanning the caudal abdomen, as echogenic intraluminal masses. Distension of the more proximal portion of intestine, proximal to an impaction, is usually present, making ultrasonographic visualization of the impaction easier. Small colon impactions have also been imaged from the flank in miniature horses. Impactions can only be imaged sonographically when the impacted portion of the large colon or cecum is adjacent to the body wall or fluid is interposed between the affected portion of the intestine and the body wall. The impaction appears as a round to oval amotile distended viscus, often measuring 20 - 30 cm or more, lacking any visible sacculations. The bowel wall may be normal thickness or may be thicker than normal and there is a large acoustic shadow cast from the impacted ingesta adjacent to the colonic mucosa. In larger horses, small or large colon impactions can be imaged transrectally if palpable.



Right dorsal colon impaction

Enteritis/Duodenitis

Fluid distension of the intestinal tract with increased peristalsis indicates developing enteritis. The wall of the affected portion of the intestine may be thickened, edematous and more hypoechoic than normal, particularly with severe inflammatory bowel disease. Shreds of intestinal mucosa may be imaged in the lumen of the intestinal tract. Marked fluid distension of the stomach should prompt gastric decompression. Fluid distension of the duodenum can also be imaged with anterior enteritis and other more distal obstructions. The lack of motility in these intestinal segments is consistent with an ileus and the thickness and echogenicity of the bowel wall are an indication of the degree of involvement of the bowel wall.

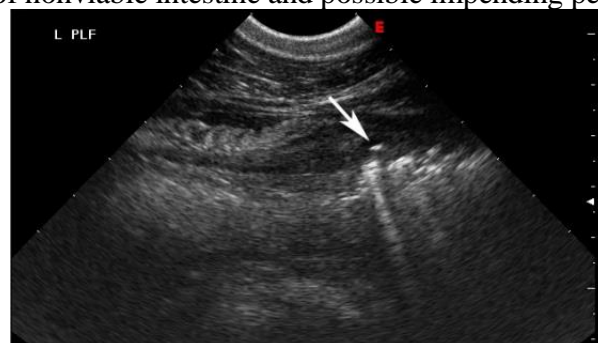


Duodenal distention with anterior enteritis

Adults with proximal duodenitis/ anterior enteritis may have an associated cholangiohepatitis with elevated biliary enzymes.

Necrotizing enterocolitis

Sonography can characterize the peritoneal fluid; identify intramural gas (pneumatosis intestinalis), portal venous gas, intraperitoneal gas, bowel wall thickening, and bowel wall perfusion in horses with necrotizing enterocolitis. Thinning of the bowel wall and lack of bowel wall perfusion and indicative of nonviable intestine and possible impending perforation.



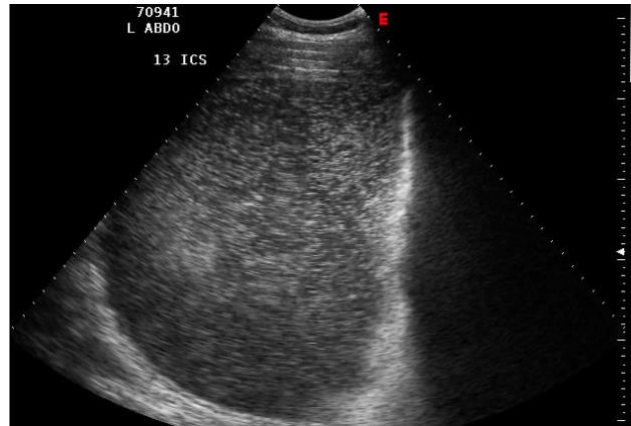
Pneumatosis intestinalis

Gastritis/gastric ulceration

Irregular thickening of the gastric wall with prominent rugal folds may be detected in some horses with gastritis. Gastric ulcers cannot usually be imaged ultrasonographically, but have been seen by the author in one yearling with a severe gastric impaction.

Gastric distention

Fluid, gas and ingesta can all be imaged sonographically in the horse with colic and gastric distention.



Gastric fluid distention with dorsal gas cap

Gastric impaction

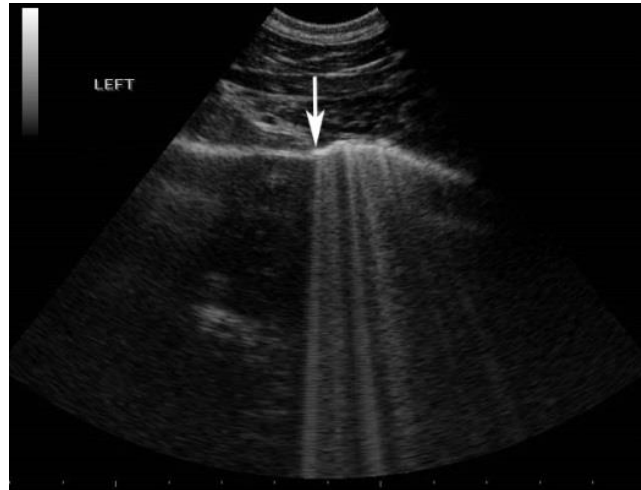
Gastric emptying problems may be identified sonographically if large amounts of ingesta persist unchanged in the stomach in a fasted, anorexic or refluxing horse on repeat examinations. The distended stomach is less circular than normal, with hyperechoic ingesta or anechoic to hypoechoic fluid in the lumen of the stomach. The sonographic appearance of a gastric impaction is a markedly enlarged gastric echo extending over 7 or more intercostal spaces on the left side of the abdomen. Gastric impactions appear as a markedly enlarged stomach that is imageable over many intercostal spaces with ventral and caudal displacement of the spleen.



Gastric impaction

Gastric rupture

Gastric rupture can be imaged if the rupture involves the greater curvature of the stomach. Gas in the mesentery adjacent to the stomach or stuck in the fibrin present within the peritoneal fluid is suggestive of a gastric rupture. Fibrin and particulate matter are imaged floating within the large amount of free peritoneal fluid. A pneumoperitoneum is often present in horses with gastric rupture.



Pneumoperitoneum secondary to gastric rupture

Peritoneal fluid

Normally only a small amount of anechoic peritoneal fluid is imaged during an abdominal ultrasonographic examination. The detection of a large amount of anechoic fluid is consistent with ascites (rare in horses), peritonitis or neoplasia. The detection of hypoechoic or echogenic, flocculent, composite fluid, fibrin and/or adhesions between the serosal surfaces of the intestine and the abdominal wall is compatible with peritonitis.



Fibrin tag with peritonitis

Free gas echoes, pneumoperitoneum and/or particulate echogenic debris are consistent with a ruptured viscus. Homogeneous, hypoechoic to echogenic cellular fluid is imaged in horses with hemoperitoneum, which is usually distinguished from septic fluid by the detection of swirling fluid, associated with movement of the gastrointestinal viscera and respiration and the settling and stirring of blood components. The ribs, diaphragm, kidneys, liver, spleen, uterus and ovaries should be carefully examined in horses with hemoperitoneum to determine if these structures are the cause of the hemorrhage.

Selected References

1. Abutarbush SM. Use of ultrasonography to diagnose large colon volvulus in horses. *J Am Vet Med Assoc* 2006;228:409-413.
2. Beckman KE, del Piero F, Donaldson MT, et al. Imaging diagnosis – Intramural hematoma, jejunal diverticulum and colic in a horse. *Vet Radiol & Ultrasound* 2008;49:81-84.
3. Beccati F, Pepe M, Gialletti R, et al. Is there a statistical correlation between ultrasonographic findings and definitive diagnosis in horses with acute abdominal pain? *Equine Vet J Suppl* 2011;39:98-105. doi: 10.1111/j.2042-3306.2011.00428.x.
4. Bell RJ, Textor JA. Caecal intussusceptions in horses: a New Zealand perspective. *Aust Vet J*. 2010;88:272-6. doi: 10.1111/j.1751-0813.2010.00591.x.
5. Brianceau P, Chevalier H, Karas A, et al. Intravenous lidocaine and small-intestinal size, abdominal fluid and outcome after colic surgery in horses. *J Vet Intern Med* 2002;16:736-741.
6. Biscoe EW, Whitcomb MB, Vaughan B, et al. Clinical features and outcome in horses with severe large intestinal wall thickening diagnosed with transabdominal ultrasonography: 25 cases (2003-2010). *J Am Vet Med Assoc* 2018;253:108-116.
7. Busoni V, De Busscher V, Lopez D, et al. Evaluation of a protocol for fast localised abdominal sonography of horses (FLASH) admitted for colic. *Vet J*. 2011;188:77-82.
8. Dechant JE, Whitcomb MB, Magdesian KG. Ultrasonographic diagnosis – idiopathic muscular hypertrophy of the small intestine in a miniature horse. *Vet Radiol & Ultrasound* 2008;49:300-302.
9. Epstein K, Short D, Parente E et al. Serial gastrointestinal ultrasonography following exploratory celiotomy in normal adult ponies. *Vet Radiol & Ultrasound* 2008;49:584-588.
10. Epstein K, Short D, Parente E, et al. Gastrointestinal ultrasonography in normal adult ponies. *Vet Radiol & Ultrasound* 2008, 49:282-286.
11. Fontaine GL, Rodgerson DH, Hanson RR, Steiger R. Ultrasound evaluation of equine gastrointestinal disorders. *Compend Contin Educ Pract Vet* 1999;21:253-262.
12. Freeman SL. Diagnostic ultrasonography of the mature equine abdomen. *Equine Vet Educ* 2003;407-422.
13. Freeman SL, Boswell JC, Smith R KW. Use of transrectal ultrasonography to aid diagnosis of small colon strangulation in two horses. *Vet Rec* 2001;14:812-813.
14. Freeman SL, England GC. Effect of romifidine on gastrointestinal motility, assessed by transrectal ultrasonography. *Equine Vet J* 2001;33:570-576.

15. Gaughan EM, Hackett RP. Cecocolic intussusception in horses: 11 cases (1979-1989). *J Am Vet Med Assoc* 1990;197:1371-1375.
16. Gift LJ, Gaughan EM, DeBowes RM, Pintchuk PA, Nickels FA, Foreman JH. Jejunal intussusception in adult horses: 11 cases (1981-1991). *J Am Vet Med Assoc* 1993;202:110-112.
17. Gomaa N, Uhlig A, Schusser GF. Effect of Buscopan compositum on the motility of the duodenum, cecum and left ventral colon in healthy conscious horses. *Berl Munch Tierarztl Wochenschr.* 2011;124:168-74.
18. Hendrickson EH, Malone ED, Sage AM. Identification of normal parameters for ultrasonographic examination of the equine large colon and cecum. *Can Vet J* 2007;48:289-291.
19. James AE, Osterman FO, Bush RM, et al. The use of compound B-mode ultrasound in abdominal disease of animals. *J Am Vet Radiol Soc* 1976;17:106-112.
20. Jenei TM, Garcia-Lopez JM, Provost PJ, Kirker-Head CA. Surgical management of small intestinal incarceration through the gastrosplenic ligament: 14 cases (1994-2006). *J Am Vet Med Assoc* 2007, 231:1221-1224.
21. Johnson PJ, Wilson DA, Keegan KG, et al. Retrospective study of cecocolic intussusception (cecal inversion) in nine horses. (1982-1998).
22. Jones SL, Davis J, Rowlingson K. Ultrasonographic findings in horses with right dorsal colitis: five cases (200-2001). *J Am Vet Med Assoc* 2003;222:1248-1251.
23. Kirkenberger RM, van den Berg JS, Gottschalk RD, Guthrie AJ. Duodenal ultrasonography in the normal adult horse. *Vet Radiol and Ultrasound* 1995;36:50-56.
24. Kilcoyne I, Dechant JE, Spier SJ, et al. Clinical findings and management of 153 horses with large colon sand accumulations. *Vet Surg* 2017;46:860-867. doi: 10.1111/vsu.12679. Epub 2017 Jun 19.
25. Klohnen A, Vachon AM, Fischer AT. Use of diagnostic ultrasonography in horses with signs of acute abdominal pain. *J Am Vet Med Assoc* 1996;209:1597-1601.
26. Lores M, Stryhn H, McDuffee, et al. Transcutaneous ultrasonographic evaluation of gastric distention with fluid in horses. *Am J Vet Res* 2007;68:153-157.
27. Martin BB Jr, Freeman DE, Ross MW, et al. Cecocolic and cecocecal intussusception in horses: 30 cases (1976-1996). *J Am Vet Med Assoc.* 1999;214:80-4.
28. Matthews S, Dart AJ, Dowling BA, et al. Peritonitis associated with *Actinobacillus equuli* in horses: 51 cases. *Aust Vet J.* 2001 Aug;79(8):536-9.
29. McGladdery A. Ultrasonography as an aid to the diagnosis of equine colic. *Equine Vet Educ* 1992;4:248-251.
30. Mitchell CF, Malone ED, Sage AM, et al. Evaluation of gastrointestinal activity patterns in healthy horses using B mode and Doppler ultrasonography. *Can Vet J* 2005;46:134-140.
31. Moll HD, Schumacher J, Dabareiner RM, et al. Left dorsal displacement of the colon with splenic adhesions in three horses. *J Am Vet Med Assoc* 1993;203:425-427.
32. Ness SL, Bain FT, Zantingh AJ, et al. Ultrasonographic visualization of colonic mesenteric vasculature as an indicator of large colon right dorsal displacement or 180° volvulus (or both) in horses. *Can Vet J.* 2012;53:378-82.
33. N6grádi N, T6th B, Macgillivray KC. Peritonitis in horses: 55 cases (2004-2007). *Acta Vet Hung.* 2011;59:181-93. doi: 10.1556/AVet.2011.011.

34. Pease AP, Scrivani PV, Erb HN, et al. Accuracy of increased large-intestine wall thickness during ultrasonography for diagnosing large-colon torsion in 42 horses. *Vet Radiol Ultrasound* 2004;45:220-224.
35. Pihl TH, Nielsen MK, Olsen SN, et al. Nonstrangulating intestinal infarctions associated with *Strongylus vulgaris*: Clinical presentation and treatment outcomes of 30 horses (2008-2016). *Equine Vet J* 2017 Nov 7. doi: 10.1111/evj.12779. [Epub ahead of print]
36. Prades M, Peyton L, Pattio N, et al. Surgical treatment of an abdominal abscess by marsupialisation in the horse: A report of 2 cases. *Equine Vet J* 1989;21:459-461.
37. Rantanen NW. Diseases of the abdomen. *Vet Clin North Am [Equine Pract]* 1986;2:67-88.
38. Reef VB. Abdominal ultrasonography. In Reef VB, Ed. *Equine Diagnostic Ultrasound* Philadelphia, WB Saunders Co., 1998; 273-363.
39. Reef VB. Sonographic evaluation of the adult abdomen. *Clin Tech Equine Pract* 2004;3:294-307.
40. Reimer JM. The gastrointestinal tract. In Reimer JM (Ed). *Atlas of Equine Ultrasonography*, St. Louis: Mosby 1998:200-211.
41. Rhoads WS, Barton MH, Parks AH. Comparison of medical and surgical treatment for impaction of the small colon in horses: 84 cases (1986-1996). *J Am Vet Med Assoc* 1999;214:1042-1047.
42. Santschi EM, Slone DE, Frank WM. Use of ultrasound in horses for diagnosis of left dorsal displacement of the large colon and monitoring its nonsurgical correction. *Vet Surg* 1993;22:281-284.
43. Schumacher J, Mair TS. Small colon obstructions in the mature horse. *Equine Vet Educ* 2002;14:27-36.
44. Sheats MK, Cook VL, Jones SL, et al. Use of ultrasound to evaluate outcome following colic surgery for equine large colon volvulus. *Equine Vet J*. 2010 Jan;42(1):47-52.
45. Tennent-Brown BS, Mudge MC, Hardy J, et al. Liver lobe torsion in six horses. *J Am Vet Med Assoc* 2012;241:615-20. doi: 10.2460/javma.241.5.615.
46. Torske K, Lofstedt J, Miller L, Horney B. Dysuria and stranguria associated with colonic ulceration and abdominal abscess in a horse. *Can Vet J* 1992;33:809-811.
47. Traub-Dargatz JL, Schultheiss PC, Kiper ML, Stashak TS, Wrigley R, Schlipf J, Applehaus FM. Intestinal fibrosis with partial obstruction in five horses and two ponies. *J Am Vet Med Assoc* 1992;201:603-607.
48. Vachon AM, Fischer AT. Small intestinal herniation through the epiploic foramen: 53 cases (1987-1993). *Equine Vet J* 1995;27:373-380.
49. Wallace KC, Selcer BA, Becht J. Techniques for transrectal ultrasonography of the cranial mesenteric artery of the horse. *Am J Vet Res* 1989;50:1695-1698.
50. Wallace KC, Selcer BA, Tyler DE, et al. Transrectal ultrasonography of the cranial mesenteric artery of the horse. *Am J Vet Res* 1989;50:1699-1703.
51. Wallace KC, Selcer BA, Tyler DE, et al. In vitro ultrasonographic appearance of the normal and verminous equine aorta, cranial mesenteric artery, and its branches. *Am J Vet Res* 1989;50:1774-1778.
52. Williams S, Horner J, Orton E, et al. Water intake, faecal output and intestinal motility in horses moved from pasture to a stabled management regime with controlled exercise. *Equine Vet J* 2015;47:96-100. doi: 10.1111/evj.12238. Epub 2014 Mar 21.
53. Yamout SZ, Nieto JE, Anderson J, et al. Pathological evidence of pancreatitis in 43 horses (1986-2011). *Equine Vet J Suppl.*2012 Dec;43:45-50.