Case Report

Successful management of bacterial cholangitis in a late pregnant dog

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Abstract

A previously healthy 5-year, female bull terrier, was presented for scheduled pregnancy radiographs; however, dog had acute vomiting, anorexia and marked mixed hepatopathy. Blood work, abdominal ultrasonography, bile cytology, and bile culture confirmed bacterial cholangitis. Initial medical treatment included intravenous fluids and fluoroquinolone antibiotics. After 72-hours of hospitalization, there were clinicopathologic and hepatic ultrasonographic evidences for clinical improvement, a positive response to treatment. Dog was discharged with antibiotics and outpatient medical therapy but returned after 72 hours for an elective cesarian surgery that was uneventful and 8 pups were delivered. One pup was stillborn and 1 died within 1 week (cause of death not determined). Dog recovered without postoperative complications. At week 8 reexamination the dog appeared healthy; however, congenital abnormalities were noted in 6 pups including linguoverted canine tooth, umbilical hernias, unilateral hearing loss, and focal renal cysts.

Keywords: Bacterial cholangitis, cesarian surgery, hepatopathy, sepsis, dog, fluoroquinolone

Background

In humans, cholangitis occurring during pregnancy has several well described manifestations and the most common is intrahepatic cholestasis of pregnancy (ICP),[1] a sterile cholestatic disease leading to bile acids buildup.[1] ICP and related disorders have been associated with an increased risk of adverse obstetrical outcomes, including fetal distress, preterm labor and sudden fetal death.[1] Although bacterial cholangitis in dogs is poorly characterized, it is suspected to occur due to ascending bacterial infections from the gastrointestinal tract.[2–4] A diagnosis is generally made through clinicopathologic and ultrasonographic findings, and hepatobiliary culture (common bacterial isolates include *Escherichia coli* [*E. coli*], *Enterococcus* spp., *Clostridium* spp.) and identifying multidrug resistance.[2–4] Prompt recognition and initiation of treatment are critical as bacterial cholangitis can result in serious adverse effects (septic bile peritonitis, systemic inflammatory response syndrome [SIRS] and death[2-4]). The mainstays of therapy described for the management of bacterial cholangitis in dogs are broad-spectrum antimicrobials and liver support medications (S-adenosylmethionine, ursodiol, vitamin E).[2–4] Although there is information available for the diagnosis and treatment of bacterial cholangitis, to authors' knowledge, there are no published reports describing the successful medical treatment of bacterial cholangitis in a late pregnant dog. Bacterial cholangitis with concurrent pregnancy presents additional management challenges, most of which are specific to achieving a balance of aggressive treatment of the dog and fetal safety. Successful diagnosis and management of this condition necessitate the use of pharmacological agents (e.g. fluoroquinolones) that may have harmful or teratogenic effects on the fetuses.[5] Additionally, a key factor in the management of cholangitis during pregnancy is the timing of surgical (cesarian surgery) intervention. Canine pregnancy is ~ 63 days; significant prematurity is a documented critical risk factor for perinatal mortality in pups due to interruptions in organ development (occurs during late pregnancy), low birth weights and other associated factors.[6–10] Although early surgical intervention may be indicated to prevent fetal exposure to

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the effects of maternal disease, the risk of significant prematurity can outweigh the risk of exposure to maternal disease.

Case presentation

A 5-year, female intact bull terrier, had a history of several failed breeding attempts with imported frozen semen, never becoming pregnant. Dog was ultimately bred via artificial insemination with frozen semen from dual sires. Dog was inseminated via transcervical insemination (TCI) using a TCI scope and a 5-French catheter that was passed ~ 5 cm past the cervical os. No backflow occurred and the cervical os was easily catheterized. No palpable stricture or septum was appreciated on digital examination at the vestibulovaginal junction. On day 56 of pregnancy, the dog was presented at the primary care veterinarian hospital for scheduled pregnancy radiographs; in addition, the dog had a 24-hour history of anorexia and vomiting, with acute cough after vomiting. Based on progesterone concentrations, the dog had a presumptive luteinizing hormone peak on day 58 before presentation to the teaching hospital; ovulation was on day 56 and breeding was on day 53 before presentation, respectively.

Complete blood count ([CBC]; LaserCyte Dx Hematology Analyzer, IDEXX Laboratories, Westbrook, ME, USA) and serum biochemistry (Catalyst Dx Chemistry Analyzer, IDEXX Laboratories) at the primary care veterinarian revealed leukocytosis (white blood count [WBC] 26.72 k/µl (RR: 5.5-16.9 k/µl), neutrophilia 22.57 k/µl (reference range [RR]: 2.00-12.00 k/µl), eosinophilia 2.42 k/µl (RR: 0.10-1.49 k/µl), a marked mixed hepatopathy (increases in alanine transaminase [ALT], 533 u/l (RR: 10-125 u/l), alkaline phosphatase [ALP], 1,533 u/l (RR: 23-212 u/l), GGT 40 u/l (RR: 0-11 u/l), total bilirubin [TBIL], 6.2 mg/dl (RR: 0-0.9 mg/dl), cholesterol 335 mg/dl (RR:110-320 mg/dl), amylase 357 u/l (RR: 500-1,500 u/l)); potassium 3.2 mmol/l (RR: 3.5-5.8 mmol/l), chloride 108 mmol/l (RR: 109-122 mmol/l) were within normal RR. Dog was referred the same day to a tertiary veterinary teaching hospital for further examination. On initial evaluation, the dog appeared quiet, alert and responsive, had a body condition score of 7 out of 9, heart rate was 120 beats per minute ([bpm], RR: 60-100), respiratory rate was 36 breaths per minute [brpm], RR: 10-30), and rectal temperature was 100°F (RR: 100.5-102.5).[11] Aside from icteric mucous membranes, rest of the general physical examination was unremarkable. Serum biochemistry (Cobas c501, Roche Diagnostics, Indianapolis, IN, USA), CBC (Advia 2120i Hematology Analyzer, Siemens Healthineers, Tarrytown, NY, USA), coagulation panel (Compact MAX Coagulation Analyzer, Stago Diagnostica, Mount Olive, NJ, USA), WITNESS Leptospirosis Rapid Tet, and urinalysis [UA], Cobas U411 Dipstick reader, Roche Diagnostics) from a mid-stream voided urine sample were performed. Results are summarized (Tables 1-4). The WITNESS Leptospirosis Rapid Test was negative. Blood chemistry revealed hypercholesterolemia (431 mg/dl; RR: 130-300 mg/dl), hyperbilirubinemia (6.1 mg/dl; RR: 0.0-0.2 mg/dl), increases in ALP (1,556 u/l: RR:15-140 u/l), ALT (848 u/l; RR: 10-90 u/l), AST (352 u/l; RR: 15-45 u/l), gamma-glutamyl transferase [GGT] 70 IU/l; RR: 0-9 u/l), hypoferremia (35 µg/dl; RR: 80-270 µg/dl), hyponatremia (139 meq/l; RR: 142-152 meq/l), hypokalemia (3.22 meq/l; RR: 3.9-5.4 meq/l) and hypochloremia (104.4 meq/l; RR: 108-118 meq/l) (Table 1). The pertinent findings on CBC were mild reticulocytosis (135.4 x 10^3/µl; RR: 0-100 x 10^3/µl), monocytosis (2.0 x 10^3/µl; RR: 0.2-1.0 x 10^3/µl) and neutrophilia (25 x 10^3/µl; RR: 2.6-11 x 10^3/µl; Table 2). Initial venous blood gas (ABL800 Flex Blood Gas Analyzer, Radiometer America, Brea, California) revealed hypokalemia (3.1 meq/l; RR: 4.1-5.6 meq/l) and hyponatremia (141 meq/l; RR: 145-156 meq/l). UA revealed a specific gravity that was isosthenuric to minimally concentrated (1.013), had marked bilirubinuria (3+), protein (1+), few rods, 0-3 white blood cells, and no red blood cells (Table 3). A stained preparation of urine sediment was examined that had rod bacteria appearing in chains. Some disrupted cells were also present that could not be definitively identified; however, a small number had a vaguely lobular nucleus (possibly neutrophils). Bacteria were often associated with disrupted nuclei and could definitively be identified as intracellular. Bacterial presence in urine may have been consistent with either a urinary tract infection or incidental contamination of a voided sample; however, UA and urine culture were not repeated. The coagulation panel represented a hypercoagulable state compatible with early disseminated intravascular coagulation or sepsis-associated coagulopathy (Table 4). Additionally, the dog met multiple SIRS criteria (WBC < 6,000 or > 16,000; heart rate > 120 bpm; respiratory rate > 20 brpm; rectal temperature < 100.6°F or > 102.6°F; band cells > 3%) with neutrophilia of 28.2 x 10^3/µl, heart rate of 120 bpm, respiratory rate of 36 brpm and rectal temperature of 100°F.[12] Since the dog met SIRS criteria (≥ 2/4) and had a high suspicion for infection it also met Sepsis-2 criteria.[13] No further viscoelastic testing was performed, anticoagulant therapy was not initiated due to lack of clinical thrombosis, and suspicion of sepsis as an underlying cause for hypercoagulability. Clinical signs and bloodwork results were suggestive of hepatobiliary disease and a possible underlying septic process; therefore, a focused hepatobiliary ultrasonographic examination and thoracic radiographs were performed (the latter indicated a radiographically normal thorax).

The focused hepatobiliary ultrasonography revealed a mildly hypoechoic liver, although a complete evaluation was limited due to both the conformation of the patient and cranial displacement of the liver and diaphragm. Gallbladder had mild hyperechoic sediment lining the gravity-dependent wall, with the remainder filled with anechoic fluid. The region of the cystic and common bile ducts was evaluated, and no large tortuous tubular structure was identified. One moderately sized tubular structure (~ 6-7 mm diameter) with a straight course was identified near the region that was suspected to represent a blood vessel (e.g. portal vein branch). Doppler evaluation was not possible due to both depth and patient respiratory motion. The duodenum was evaluated and appeared normal, with no distended tubular structures identified near the expected level of the major duodenal papilla; hepatic lymph nodes were not identified. Multiple viable pups were identified throughout the abdomen. One fetal heart rate was ~ 250 bpm. Given the marked inflammatory response that was identified in CBC and findings on the coagulation panel, infectious cholangitis or cholangiohepatitis was prioritized over other hepatobiliary differentials. As a result, ultrasonography-guided fine needle aspirates (FNA) were performed on the liver and gall bladder (for cytology and culture). Cytology of the liver revealed large amount of peripheral blood with nucleated cell content predominated by peripheral blood leukocytes and mesothelial cells. A small number of hepatocellular aggregates were observed. The cells were relatively normal in appearance with amphophilic cytoplasm and green pigment granules interpreted to be bile, iron, copper, or lipofuscin. Bile cytology had no nucleated cells; rather, there was gray material interpreted to be mucus and abundant bacteria present, including large rods of various

Table 1. Serun biochemistry ~ 72 hours after presentation

Test	Day 56 of pregnancy	Day 59 of pregnancy	Reference range	Unit
Blood urea nitrogen	12	14	7-30	mg/dl
Creatinine	0.68	0.87	0.6-1.6	mg/dl
Phosphorus	3.4	5	2.5-6	mg/dl
Calcium	9.6	9.4	9.0-11.5	mg/dl
Magnesium	1.9	1.8	1.8-2.4	mg/dl
Total protein	6.4	5.3	5.0-7	g/dl
Albumin	3.3	**2.8 (low)**	3.0-4.3	g/dl
Globulin	3.1	2.5	1.5-3.2	g/dl
Albumin/globulin	1.06	1.12	0.9-2.4	ratio
Cholesterol	**431 (high)**	**361 (high)**	130-300	mg/dl
Creatine kinase	199	181	50-275	u/l
T-bilirubin	**6.1 (high)**	**0.5 (high)**	0.0-0.2	mg/dl
ALP	**1556 (high)**	**1051 (high)**	15-140	u/l
ALT	**848 (high)**	**315 (high)**	10-90	u/l
AST	**352 (high)**	**66 (high)**	15-45	u/l
GGT	**70 (high)**	**47 (high)**	0-9	u/l
Iron	**35 (low)**	106	80-270	ug/dl
Sodium	**139 (low)**	149	142-152	meq/l
Potassium	**3.22 (low)**	**3.6 (low)**	3.9-5.4	meq/l
Chloride	**104.4 (low)**	113	108-118	meq/l
Bicarbonate concentration	17.4	21.1	15-25	meq/l
Anion-gap	20	19	12-23	mmol/l
Calcium osmolality	274	295		mosm/kg
Lipemia	11	26	0-80	mg/dl
Hemolysis	4	12	0-100	mg/dl
Icterus	**7 (high)**	1	0-1	mg/dl

sizes and chains of diploid cocci. Bile culture was submitted for culture and sensitivity and grew *E. coli, Klebsiella pneumoniae* (*K. pneumoniae*), and *Clostridium perfringens. E. coli and K. pneumoniae* were resistant to amoxicillin/clavulanic acid, and ampicillin. *Clostridium perfringens* did not have full susceptibility data available.

Medical management

Given the severity of clinical signs, suspicion for bacterial cholangitis, and clinicopathologic findings suggestive of severe systemic inflammation, hospitalization in the critical care unit was elected. A 7-French 15-cm triple lumen catheter (Mila International, Florence, KY, USA) was placed in dog's right jugular vein, and a 10-French nasogastric tube (Mila International) placed and confirmed with a single lateral radiograph. Treatment was initiated, including intravenous PlasmaLyte (50 ml/hour; Dechra Veterinary Products, Overland Park, KS, USA), ondansetron (1 mg/kg, once 8 hours a day; West-Ward, Eatontown, NJ, USA), intravenous methadone (0.2 mg/kg, PRN; Methadone, Akorn, Lake Forest, IL, USA), intravenous N-acetylcysteine (140 mg/kg, once then 70 mg/kg, every 6 hours; Somerset Therapeutics, Somerset, NJ, USA), intravenous enrofloxacin (10 mg/kg, once a day; Enroflox, Norbrook, Lenexa, KS, USA), Royal Canin Recovery (50% resting energy requirement via nasogastric tube; Royal Canin Recovery, Royal Canin SAS, St. Louis, MO, USA), intravenous metoclopramide (2 mg/kg, once a day; Teva Pharmaceuticals, Parsippany, NJ, USA), and intravenous potassium chloride (0.4 meq/kg, every hour, Fresenius Kabi, Lake Zurich, IL, USA). Enrofloxacin was discussed as the recommended antimicrobial therapy, given the previously established susceptibility spectrum for common pathogenic bacterial cholangitis microorganisms and presence of criteria consistent with sepsis. However, this was considered off-label given the concurrent pregnancy and risk for fetal arthropathy. The total duration of enrofloxacin prior to cesarian surgery was for 6 days and treatment discontinued.

Throughout the first night of hospitalization, the dog was bright and alert with an improved appetite; therefore, nasogastric tube was removed and potassium treatment was discontinued the following morning. Throughout the first full day of hospitalization, dog clinically appeared more energetic, continued to eat well and passed soft formed feces. Dog's feeding frequency was increased to every 4 hours with smaller volumes per feeding, due to ongoing regurgitation. On the second day of hospitalization, dog continued to clinically improve, maintained a strong appetite with decreasing regurgitation, and the N-acetylcysteine was discontinued. On the third day of hospitalization, metoclopramide was discontinued as there was no more regurgitation.

Table 2. Complete blood count ~ 72 hours after presentation

Test	Day 56 of pregnancy	Day 59 of pregnancy	Reference range	Unit
Plasma protein	7.7	6.2	6.0-7.5	g/dl
Hemoglobulin	15.4	13.1	13-20	g/dl
Hemoglobulin (cell)	15.3	**12.9 (low)**	13-20	g/dl
Hematocrit	42	**38 (low)**	40-55	%
Red blood cell count	6.43	5.57	5.5-8.5	10^6/ul
Mean corpuscular volume	66	68	62-74	fl
Red cell distribution width	13.2	13.2	12-15	%
Mean corpuscular hemoglobin concentration	36	34	33-36	g/dl
Mean cell hemoglobin concentration	36	34	33-36	g/dl
Reticulocyte	2.1	1.3	–	%
Reticulocytes	**135.4 (high)**	70.6	0-100	10^3/ul
Reticulocyte hemoglobin content	24.6	25.8	22.3-27.9	pg
Mean corpuscular volume reticulocytes	85	91	78-100	fl
Platelets	496	324	200-500	10^3/ul
Mean platelet volume	13.5	14.2	7.5-14.6	fl
Nucleated cells	**28.2 (high)**	**22 (high)**	4.5-15.0	10^3/ul
Neutrophils	**25.1 (high)**	**17.8 (high)**	2.6-11	10^3/ul
Lymphocytes	1.1	2	1-4.8	10^3/ul
Monocytes	**2.0 (high)**	**2.0 (high)**	0.2-1	10^3/ul
Eosinophils	0.0	0.2	0.1-1.2	10^3/ul
Neutrophils	**25 (high)**	**16.9 (high)**	2.6-11	10^3/ul
Clumped platelets	Absent	Exist	–	
Neutrophil	89	81	–	%
Lymphocyte	4	9	–	%
Monocyte	7	9	–	%
Eosinophil	0	1	–	%

Table 3. Urinalysis (voided sample) ~ 72 hours after presentation

Test	Day 56 of pregnancy	Unit
Specific gravity	1.013	
Squamous cells	None	per hpf
Transitional/renal epithelial cell	1-3	per hpf
White blood cell	0-3	per hpf
Red blood cell	None	per hpf
Casts	None	per hpf
Crystals	None	per hpf
Bacteria	Yes	per hpf
Sperm	No	
Fat	Few	
Protein	1+	
Glucose	Negative	
Ketone	Negative	
Blood	Trace	
Bilirubin	3+	
pH	8	

A follow up hepatobiliary ultrasonography was performed that revealed similar mild echogenic gallbladder sediment without evidence of extrahepatic biliary obstruction or mucocele, mildly decreased conspicuity of the portal walls, and the hepatic parenchyma appeared more normal in echogenicity. Additionally, progesterone (IMMULITE, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA) concentrations were 4.7 ng/ml, adequate (~ 2 ng/ml) to maintain pregnancy.[14] Follow up CBC and serum biochemistry were performed prior to discharge (72 hours after initial presentation). Serum biochemistry revealed marked improvement in the hepatopathy ALP (1,556 to 1,051 u/l; RR: 15-140 u/l), ALT (848 to 315 u/l; RR: 10-90 u/l), AST (352 to 66 u/l; RR: 15-45 u/l), and GGT (70 to 47 u/l; RR: 0-9 u/l) and improvement in the previous electrolyte derangements (Table 1). The CBC no longer had a reticulocytosis and the neutrophilia had improved (25 to 17.8 x 10^3/µl; RR: 2.6-11 x 10^3/µl; Table 2). Given the resolution of clinical signs, improving clinicopathologic and ultrasonographic findings, dog was discharged with oral enrofloxacin (9.3 mg/kg once a day), with instructions to return in 3 days for potential cesarian surgery.

Surgical management

Due to concerns for recovery after surgery in the face of acute bacterial cholangitis and to allow for improved fetal

Table 4. Results of coagulation panel

Test	Day 56 of pregnancy	Unit	Reference range
Prothrombin time	8.3	sec	7.4-9.4
Activated partial thromboplastin time	**15 (high)**	sec	9.8-13.3
Antithrombin III	**89 (low)**	%	104-162
D-dimer	**1.21 (high)**	ug/ml	0.03-0.4
Quantitative fibrinogen	**478 (high)**	mg/dl	123-210
Fibrin degradation Product	Negative < 5	u/l	0-4

Table 5. Venous blood gas prior to cesarian surgery ~ 6 days after initial presentation and diagnosis

Test	Day 62 of pregnancy	Reference range	Unit
Hemoglobin	14.5	0-0	g/dl
Barometric pressure	632	0-0	mm Hg
pH	**7.46 (high)**	7.33-7.45	
Partial pressure of carbon dioxide	30.3	24-39	mm Hg
Partial pressure of oxygen	**54.4 (low)**	67-92	mm Hg
Bicarbonate concentration	21.6	17-27	mmol/l
Absolute base excess	-1.2	0-0	mmol/l
Oxygen saturation	91.8	0-0	%
Sodium	153	145-156	meq/l
Potassium	4.1	4.1-5.6	meq/l
Chloride	**115 (high)**	104-113	meq/l
Anion-gap	20	13-24	meq/l
Calcium	1.32	1.12-1.4	mmol/l
Glucose	113	67-114	mg/dl
Lactate	**3.5 (high)**	0.2-1.44	mmol/l
Fraction of carboxyhemoglobin	5.4	0-0	%
Fraction of methemoglobin.	1.7	0-0	%

maturation, an elective cesarian surgery was performed 6 days following initial presentation and on day 62 of pregnancy (from ovulation), calculated based on progesterone concentrations. No preanesthetic medications were given and propofol was titrated to have an effect for induction. A venous blood gas (ABL90 Flex PLUS Blood Gas Analyzer; Radiometer America, Brea, CA, USA) was performed preoperatively that had a mildly elevated lactate (3.5 mmol/l; RR: 0.2-1.44 mmol/l) but was otherwise clinically unremarkable (Table 5). The dog was placed on dorsal recumbency, the ventral abdomen clipped, aseptically prepped and draped in a standard fashion. Intravenous cefazolin (22 mg/kg, Cefazolin, Hikma, Berkeley Heights, NJ, USA) was given every 90 minutes intraoperatively. A ventral midline approach from the umbilicus to the pubis was made using electrosurgery through the skin, subcutaneous tissues and linea alba. Uterine horns were exteriorized, with moistened lap sponges and towels used to pack off the uterus and isolate it from the rest of the abdomen. A ventral midline incision was made into the body of the uterus with a number 15 scalpel blade; the incision was extended with Metzenbaum scissors. Total of 8 pups were identified in uterine horns. Steady traction was applied until fetal membranes were released from attachment zone. Each fetus was handed off to a surgical assistant in a sterile fashion. A total of 7 pups (3 female, 4 male) were resuscitated successfully; none exhibited gross congenital abnormalities. One stillborn pup (no palpable or auscultable heartbeat) had green discoloration of the mucous membranes; it was reported to have been detached in-utero at cesarian surgery. It is unclear if the cause of the in-utero death of this pup was due to fetal membranes detachment or if fetal membranes detachment occurred secondary to in-utero death. No gross placental abnormalities were observed at surgery. The uterine incision was closed with 4-0 glycomer 631 (Biosyn, Medtronic, Plainfield, IN, USA) in a simple, continuous, full-thickness appositional pattern. This was followed by a Lembert pattern with 4-0 glycomer 631 (Biosyn, Medtronic). The abdomen was then lavaged with warm sterile saline. 0 polyglyconate (Maxon, Medtronic) was used to close the linea alba in a simple continuous pattern. A liposomal bupivacaine block was infiltrated into the subcutaneous tissue along the length of the incision, and 4-0 glycomer 631 (Biosyn, Medtronic) was used to close the subcutaneous tissues using a horizontal continuous pattern. An intradermal suture pattern was used to oppose the skin using a 4-0 glycomer 631 (Biosyn, Medtronic) on a taper needle.

Follow up

Dog recovered uneventfully after surgery and pups were successfully nursed for their first feeding. Dog was discharged with oral tramadol (75 mg, once every 8-12 hours; Tramadol hydrochloride, Amneal Pharmaceuticals LLC, Glasgow, KY, USA). Based on culture and susceptibility results, the patient was treated with oral cefpodoxime (200 mg, once a day; Simplicef, Zoetis, Parsippany, NJ, USA) for 14 days to target *E. coli* and *K. pneumoniae* that were resistant to amoxicillin-clavulanate, ampicillin, and first-generation cephalosporins. Amoxicillin and oral clavulanate potassium were prescribed (500 mg, twice a day for 14 days (Clavacillin, Dechra Veterinary Products) to target *Clostridium* isolated from the culture. This strategy enabled pathogen-specific coverage while minimizing exposure to potentially nephrotoxic alternatives. On day 14 follow up, the owner did not report any postoperative complications in the dog, although 1 pup died within 1 week (cause unknown). At 8 weeks, the 6 remaining pups were evaluated for brainstem auditory evoked response (BAER) and renal dysplasia in order to assess general health and breed-specific disease screening; 2 pups had no abnormalities; 1 pup had bilateral linguoverted canine tooth, bilateral inguinal testes, and its right ear failed BAER testing; 1 pup had a left linguoverted canine tooth with no other abnormalities; and 1 pup had slight linguoverted canine tooth and a small reducible umbilical hernia. Lastly, another pup had linguoverted canine tooth and a 1.5-cm diameter umbilical hernia. The renal dysplasia ultrasonography screening revealed few small renal cortical and medullary cysts in 3 pups and normal kidneys in all 6 patients. These renal cysts were of unknown clinical significance and presumed to be congenital and incidental.

Discussion

Bacterial cholangitis is relatively uncommon in dogs; however, it is suspected in cases with compatible clinical signs, clinicopathologic findings, and ultrasonographic findings, and is confirmed with bile culture.[2–4] Previous studies identified that gallbladder ultrasonography alone had a positive predictive value of 20% for infectious hepatobiliary disease in dogs, and have established that bile culture is the gold standard for diagnosis of bacterial cholangitis.[15] In cases where bacterial cholangitis is confirmed with culture, common isolates include *E. coli*, *Enterococcus* spp., and *Clostridium* spp., with multidrug-resistant organisms (MDRO) frequently reported.[2,3] In this case, *E. coli* and *K. pneumoniae* were both resistant to amoxicillin/clavulanic acid, ampicillin, and cephalexin. Although the level of resistance was significant, it was not consistent with MDRO that is often present with bacterial cholangitis.

Because 3 organisms were recovered from culture, contamination was initially considered. However, in previous studies, polymicrobial growth was a common finding in these cases.[2,3] Further, the bacterial isolates recovered in this case were consistent with previously reported bacterial isolates for bacterial cholangitis in dogs, including *E. coli*, *Enterococcus* spp., *Klebsiella* spp., and *Clostridium* spp.[2,3,16] Lack of cytologic inflammation in this case might also increase the index of suspicion for contamination. However, in prior studies of bacterial cholangitis, bactibilia commonly exists without detectable concurrent cytologic inflammation.[16] Additionally, when antibiotics were not given within 24 hours prior to bile aspiration, agreement between cytologic identification of bacteria and positive culture results is high, supporting the clinical relevance of polymicrobial cultures.[17] Given that antibiotics was not given in this case prior to bile aspiration, the cytologic presence of bacteria was supportive of true infection. Lastly, when considering the severity of the mixed hepatopathy, the systemic inflammatory response, and coagulation abnormalities with the lack of an alternative infectious focus, a true biliary infection was prioritized in this case.

With the severity of liver injury, assessment of Sepsis-2 criteria, and expected bacterial isolates, enrofloxacin was the recommended antimicrobial therapy. Clear owner communication was a key factor in this case, as enrofloxacin was used off-label and is generally contraindicated in pregnant animals due to its well documented risk for arthropathy in young growing dogs.[5]

Because reports describing cholangitis in late pregnant dogs are lacking, comparison to human medicine provides useful context. In humans, the most common form of pregnancy associated cholangitis is ICP.[1] Unlike bacterial cholangitis, ICP is a noninfectious cholestatic disorder and is thought to be multifactorial, with genetic, hormonal and environmental factors having key roles.[1] Given that ICP can cause adverse obstetrical outcomes including fetal demise, the recommended treatment is typically aggressive medical management with ursodeoxycholic acid to improve bile flow and reduce the concentration of harmful bile acids.[1] Although the underlying pathophysiology and treatment for ICP is different than bacterial cholangitis, the management principles overlap in prioritizing maternal stability and minimizing fetal risk. In both conditions, the critical nature of timing of parturition induction or surgical (cesarian surgery) is a key consideration in balancing fetal maturity against progression of maternal disease.

A key learning opportunity in this case was the diagnosis of congenital abnormalities in pups at 8 week follow up appointment. Although enrofloxacin is well documented to cause arthropathy in immature, young growing animals, its contraindication in pregnancy is generally based on potential damage to immature chondrocytes and not based on true teratogenicity (in vivo data).[5] It is documented that bull terriers are predisposed to certain genetic conditions including, base narrow canine teeth due to the selective breeding of their skull shape (klinorhynchy), deafness and polycystic kidney disease.[18,19] The documented congenital abnormalities in this case included linguoverted canine tooth, inguinal testes, failed BAER testing, umbilical hernia, and focal renal cysts. Of these findings, inguinal testes and umbilical hernias were plausibly incidental and observed in many breeds whereas the renal cysts, failed BAER testing, and linguoverted canine tooth are all conditions for which bull terriers are historically predisposed. Given that exposure to enrofloxacin occurred in late pregnancy, teratogenic causation cannot be reliably established nor ruled out.

This case demonstrated the successful medical management of bacterial cholangitis during late pregnancy, followed by surgical (cesarian surgery) intervention that enabled dog and most pups to survive. However, there are several limitations to this case. The first is that no causal link can be established for the congenital abnormalities in the pups, making it challenging to determine whether the potential benefit of enrofloxacin treatment outweighed the potential risk to the fetuses. Additionally, several diagnostics were either not performed or were not successful, such as the nondiagnostic cytologic sample from the liver FNA, lack of urine culture and lack of necropsy on 2 pups. These diagnostics could have provided a more comprehensive clinical picture.

Bacterial cholangitis should remain on the list of differentials for an acute mixed hepatopathy in any dog. Diagnosis can be made with a combination of clinicopathologic, imaging, and bile culture; furthermore, prompt initiation of broad-spectrum antimicrobial therapy is key, given the high incidence of multidrug-resistant organisms. In pregnant animals, management of bacterial cholangitis requires balancing maternal stability, fetal safety and timing of surgical (cesarian surgery) intervention to optimize the chance of dam and offspring survival.

Conclusion

Although uncommon, bacterial cholangitis in dogs carries a risk of severe adverse consequences. Medical management of this disease with concurrent pregnancy presents unique clinical challenges, with early identification and initiation of treatment preventing adverse consequences associated with this disease. This case illustrated that aggressive medical management, judicious antimicrobial usage, and appropriate surgical timing successfully protected the dog and pups. Future research is needed to better characterize this disease and describe the most appropriate management strategies.

Learning points

- Aggressive medical management, including antimicrobial therapy and supportive care, may allow stabilization of severe hepatobiliary disease in late pregnant dogs while maintaining pregnancy until fetal maturity
- Antimicrobial selection in pregnant dogs requires balancing effective treatment of maternal infection with potential fetal risks, particularly when drugs with theoretical developmental toxicity are considered
- Careful timing of cesarian delivery following stabilization of maternal disease may improve neonatal outcomes when serious maternal illness occurs during late pregnancy

Authors' contribution statement and agreement

BG: literature review, writing original draft, editing; **JC:** diagnosis, case management, case supervision, interpretation of results, treatment plan, editing; **DD:** diagnosis, case management, case supervision, interpretation of results, treatment plan, editing; **KG:** writing original draft, editing; **GB:** TCI procedure, writing original draft, editing: **EM:** cesarian surgery, editing; and **CT:** writing original draft, editing. Authors have read and approved final submission.

Conflict of interest

The authors report no conflict of interests.

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