Clinical, surgical, and pathological findings in client-owned rabbits with histologically confirmed appendicitis: 19 cases (2015–2019)

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OBJECTIVE
To report clinical, surgical, and pathological findings in client-owned rabbits with histologically confirmed appendicitis.

ANIMALS
19 rabbits.

PROCEDURES
Medical records for client-owned rabbits that had a histologic diagnosis of appendicitis were reviewed.

RESULTS
Median age of the rabbits at presentation was 24.0 months (range, 4 to 84 months). Seventeen cases occurred during the summer and fall seasons. Decreased appetite (17/19 rabbits), abnormal rectal temperature (hyperthermia, 9/16 rabbits; hypothermia, 4/16 rabbits), hypocalcemia (8/11 rabbits), and hypoglycemia (7/15 rabbits) were common signs. Abdominal ultrasonography and CT findings were suggestive of appendicitis in 6 of 8 rabbits and in 1 of 2 rabbits, respectively. Of the 6 rabbits that received medical treatment, 3 died at 48 hours, 1 died at 24 hours after hospitalization, and 1 died at 10 days after presentation; 1 rabbit was alive at 1,030 days after presentation. Of the 8 rabbits that underwent appendectomy, 3 died before discharge from the hospital and 1 died 113 days after surgery; 4 rabbits were alive at 315, 334, 1,433, and 1,473 days after presentation. The remaining 5 rabbits either died or were euthanized before treatment could be instituted. In each of the 19 rabbits, the appendix had evidence of severe inflammation with mucosal ulceration, heterophilic inflammation, and necrotic debris.

CLINICAL RELEVANCE
For rabbits with decreased appetite and an apparently painful abdomen, hyperthermia, hypocalcemia, or hypoglycemia, appendicitis should be considered as a differential diagnosis. Further comparisons of medical and surgical treatments are required to establish treatment recommendations for rabbits with appendicitis.

Rabbits are the third most common mammal in US and UK households based on current demographics,1,2 and many owners are extremely dedicated to their rabbits’ care.3 The most common reason for presentation of client-owned rabbits at veterinary clinics is anorexia and lack of defecation, sometimes referred as gastrointestinal stasis or gastrointestinal syndrome.4-6 Although in some cases a clear reason for this condition...
may become evident during the physical examination, a diagnosis of nonspecific system affected is generally made for > 30% of rabbits, whereas a similar diagnosis is made for approximately half as many dogs. The difficulty in making a diagnosis for many of these cases could be attributable to the intrinsic physiologic and anatomic characteristics of rabbits (eg, their ability to hide signs of pain and inability to vomit, prey animal behavior, and small size and the inherent difficulty in performing oral examinations in this species) and the numerous potential differential diagnoses. Also, the limited knowledge of certain disease processes that may affect this species could hinder the formulation of a diagnosis in specific cases.

One of the most notable anatomic characteristics of rabbits is the presence of a distinct vermiform appendix at the apex of the cecum. Few other mammals (including humans and some other primates, other lagomorphs, wombats, and selected rodents such as Cape dune mole-rats) have a well-developed appendix. On the basis of this characteristic, rabbits differ from other hindgut fermenter species that are commonly examined by veterinarians (eg, horses, guinea pigs, and mice). Anatomically, the appendix of rabbits has a readily discernable boundary with the cecum marked by a distinct decrease in diameter, change in tissue color, and lack of spiral muscular bands typical of the cecum (Figure 1). Physiologically, the appendix is part of the gut-associated lymphoid tissue, together with Peyer patches, ileocecal plaque, and sacculus rotundus. The appendix has predominant B-cell production as opposed to the other tissues that have predominant T-cell production. The appendix has been proven to be important for the development of an individual rabbit’s immune function. This contribution to immune function development occurs mostly early after birth, with a 99% reduction of B lymphopoiesis by 16 weeks of age and no evidence of progenitor B cells in the appendix of adult rabbits.

Considering the abundance of lymphoid tissue in the appendix of rabbits, it is not surprising that there have been reports of lymphoma affecting or originating from this structure. Reports of naturally occurring appendicitis in rabbits are less common. A search of the databases Medline, CABAbstracts, and ScienceDirect with the string “rabbit” AND “appendicitis” on July 15, 2020, and review of 3 recent textbooks yielded only 2 cases of appendicitis in client-owned rabbits. Two additional reports (1 published in German in 1977 and 1 published in Japanese in 1987) described naturally occurring mycotic and granulomatous appendicitis in non-client-owned rabbits. Experimental induction of appendicitis in laboratory rabbits has been performed. Because no other domestic animal has an appendix, it is possible that this disease process has been overlooked by veterinary educators and consequently by practicing veterinarians. Therefore, the purpose of the study reported here was to assess clinical, surgical, and pathological findings in client-owned rabbits with histologically confirmed appendicitis.

Figure 1—Illustrations of the anatomic features and location of the appendix (a) in healthy rabbits. A—The ileocecal fold (asterisks) connects the appendix to the ileum (i). The cecum (c) is identified. B—Histologically, the wall of the appendix contains follicles (f), domes (d), and crypts (cr). C—Photograph of the appendix (a) of a healthy 4-month-old farmed rabbit undergoing postmortem examination for reasons unrelated to the study. Notice the ileocecal fold (arrow) connecting the appendix to the ileum (i).
Materials and Methods

Case selection

All rabbits with a diagnosis of appendicitis made at 4 primary participating institutions (Clinic for Exotic Animals, Rome, Italy; Tai Wai Small Animals & Exotics Hospital, Hong Kong; Veterinary Hospital Frégis, Arcueil, France; and Ecole Nationale Vétérinaire d’Alfort, Maisons-Alfort, France) were eligible for inclusion in the study. To increase the generalizability of the case series, the pathologists (DB, DRR, A Nicolier, and ERG) that performed histologic analysis of the specimens submitted from these primary participating institutions were contacted and asked to search their databases for any additional cases of infection or inflammation of the vermiform appendix up to April 25, 2020, without restrictions based on the year of submission. The inclusion criteria for cases were notation of a histologic diagnosis of appendicitis in the medical record and agreement of the veterinarian who submitted the tissue sample to allow inclusion of the case in the study. Rabbits were included regardless of whether the diagnosis of appendicitis was obtained after death or euthanasia or following histologic examination of incisional or excisional biopsy (appendectomy) specimens.

Medical records review

Data collected from each medical record included (age, sex, and sexual status), anamnesis (diet, husbandry, and previous medical history), date and season (summer, fall, winter, or spring) of occurrence and patient presentation, reason for presentation, physical examination findings, clinicopathologic findings, diagnostic imaging findings, whether diagnosis was made after death or euthanasia of the rabbit or there was ante mortem indication of appendicitis, clinical management (medical treatment, surgical treatment, or euthanasia), details of medical treatment, details of surgical treatment, outcome, histologic findings, and tissue culture results (aerobic or anaerobic bacterial growth) and results of antimicrobial susceptibility testing. The primary veterinarians of all cases contributed by the laboratories were contacted and given the option to provide additional clinical information on a standardized electronic spreadsheet.

Reasons for presentation and physical examination findings—The reasons for presentation of each rabbit were defined as the motivation of the owners for having the rabbit examined at the admission event that generated the histologic diagnosis. For each rabbit, the following reasons for presentation were extracted from the medical record: presentation of anorexia or hyporexia, lack of defecation, and presence of lethargy, dullness, or decreased activity. Each of these 3 findings was classified as yes, no, or not reported. The duration of clinical signs related to anorexia or hyporexia, lack of defecation, and lethargy, dullness, or decreased activity was recorded. Other reasons for presentation of rabbits were noted if reported by the primary veterinarians.

Physical examination findings were defined as the findings recorded at the time of hospital admission of the rabbit or, in instances of internal hospital transfers, during the first physical examination that the primary veterinarian performed. For each rabbit included in the study, the following data were extracted when available: body weight (kg), rectal temperature (°C), mentation (normal, lethargic, hyperactive, or not reported), mucous membrane color (normal, pale, or not reported), respiratory rate (or respiratory characteristics if respiratory rate was not available or not reported), presence of signs of abdominal pain (yes, no, or not reported), and presence of a palpable abdominal mass (yes, no, or not reported). Other findings observed during physical examination were noted if reported by the primary veterinarians. A rectal temperature ≥ 38.0 and ≤ 39.9 °C was considered normal.

Clinicopathologic and diagnostic imaging findings—Results of hematologic, serum biochemical, and blood gas analyses were extracted from the medical records and tabulated. For each analyte, each rabbit was characterized as normal or abnormal on the basis of recently published reference intervals for client-owned rabbits.

With regard to whole-body or abdominal radiography, information extracted from the records included presence of gas in the cecum, presence of gas in the stomach, and presence of a distended stomach. Each of these findings was classified as yes, no, or not reported. Other radiographic findings were noted if reported by the primary veterinarians. With regard to abdominal ultrasonography, information extracted from the records included presence of reactive peritoneum, presence of free fluid, lymphadenomegaly, appendix appearance and measurements (mm), and presumed ultrasonographic diagnosis. Each of these findings was classified as yes, no, or not reported. Other ultrasonographic findings were noted if reported by the primary veterinarians. For each CT assessment, information was extracted as reported by the radiologist because only 2 data sets were available.

Results of diagnostic tests performed > 14 days before the histologic diagnosis was made were not included. When multiple assessments with the same diagnostic tool were performed on the same rabbit, the data obtained closest to the time of the histologic diagnosis were used, and the earlier data were mentioned only for purposes of comparison.

Medical management, surgical procedures, and outcome—Medical treatments administered to rabbits were extracted from the medical records and categorized as antimicrobials, opioids, NSAIDs, gastrointestinal medications (including prokinetics, gastrectomies, and anti-foaming agents), fluid therapy, and miscellaneous. The names of the specific active agents administered were extracted from the records. For each surgical procedure performed, information collected included surgical approach (ventral midline abdominal approach, other approaches, or...
not reported), use of retractors (yes, no, or not reported), method used to excise the ileocecal fold (radiosurgery, sutures, or not reported), method used to ligate and excise the appendix (ligation of the appendix after placement of circumferential sutures or excision of the appendix and placement of sutures at a later stage), suture material and suture technique used for ligation of the intestinal tract (type and size of suture material), abdominal lavage (yes, no, or not reported), and abdominal closure technique (routine closure, others closures, or not reported).

For each rabbit, it was determined whether the rabbit survived the surgical procedures, survived to hospital discharge, was alive at the first recheck examination, or was alive at the time of data analysis. The first recheck examination was performed at a variable point depending on the directions of the primary veterinarian. For all rabbits that were considered alive by the primary veterinarians, their owners were contacted approximately 13 weeks after the close of data collection to confirm each rabbit’s status.

**Pathological and bacteriologic findings**—Histologic examination of submitted specimens was performed routinely at each participating laboratory. Tissue specimens were fixed in neutral-buffered 10% formalin, processed routinely, embedded in paraffin wax, and sectioned for histologic examination. Sections were stained with H&E stain in all except 1 case; for that rabbit, sections were also stained with hematoxylin-eosin-saffron stain. Information collected from each pathology report included presence of mucosal ulceration, follicular hyperplasia, lymphoid follicle necrosis and abscess formation, heterophilic inflammation, necrotic debris, brown pigment-laden macrophages, edema, hemorrhage, transmural inflammation, serosal involvement, vasculitis, and presence of bacteria. Each of these findings was classified as present or absent.

Results of bacteriologic culture were reported if swabs of the appendix were submitted by the primary veterinarian. Culture and antimicrobial susceptibility testing were routinely performed at each participating laboratory. Swab samples were inoculated on 7% sheep blood agar and incubated under aerobic or anaerobic conditions for 24 to 48 hours at 37 °C. Colonies from each swab sample were biochemically identified. Every aerobic isolate was tested for antimicrobial susceptibility by the Kirby-Bauer method and according to the Clinical and Laboratory Standards Institute protocol. For each bacteriologic culture report, information extracted included bacterial growth, isolate identification, and antimicrobial susceptibility.

**Data reporting**

Categorical data were reported as count data, with the number of animals for which the data were available reported. Continuous data were reported as medians and interquartile (25th to 75th percentile) ranges. Survival times (days) were quantified from the time of histologic diagnosis to the time of death or euthanasia and reported for each individual rabbit because of the small sample size.

**Results**

**Patient inclusion**

A total of 21 cases were identified by the 4 diagnostic laboratories for possible inclusion in the study. The laboratories contributed 15, 3, 2, or 1 case. Two cases were not included in the study because the primary veterinarians did not explicitly allow inclusion of the rabbit in the case series. Thus, 19 rabbits that originated from Italy (n = 14), Hong Kong (2), France (2), and the US (1) were included in the study. Twelve primary veterinarians provided care to the 19 rabbits. One veterinarian (ND) provided care to 4 rabbits, 1 veterinarian (DP) provided care to 3 rabbits, and 2 veterinarians (GN, SR) each provided care to 2 rabbits; the remaining 8 veterinarians each provided care to 1 rabbit. Cases were identified with a progressive number from 1 to 19 based on the date of histologic diagnosis (Supplementary Table S1).

**Signalment and anamnesis**

Information regarding sex, sexual status, age, breed, and month of occurrence and presentation was available for all 19 rabbits. Among the 19 rabbits, there were 8 spayed females, 2 sexually intact females, 6 neutered males, and 3 sexually intact males. The median age for the 19 rabbits was 24.0 months (range, 4 to 84 months). Seven rabbits were < 1 year old, 6 rabbits were 1 to 3 years old, and 6 rabbits were > 3 years old. Rabbits were described as dwarf (n = 8), Lion (4), Mini Rex (1), Harlequin mix (1), and California giant (1). Nine cases occurred during summer, 8 cases occurred during fall, 1 case occurred during spring, and 1 case occurred during winter. Dietary information was available for all 19 rabbits, all of which were fed a diet composed of hay, greens, and commercial pellet. Husbandry information was available for 15 rabbits, all of which lived indoors. Previous medical history varied (Supplementary Table S1).

**Reasons for presentation**

Reasons for presentation at the 4 primary participating institutions were available for all 19 rabbits. For many rabbits, the reasons were multiple and included anorexia or hyporexia (n = 17), decreased activity (11), and a decrease in or absence of fecal production (10). The duration of these clinical signs ranged from 0 to 89 days; 2 rabbits had no clinical signs, 2 rabbits had intermittent signs for 29 and 89 days, and 14 rabbits had clinical signs for < 48 hours. Two owners also reported that their rabbit had abnormal micturition; 1 rabbit had dark urine and 1 rabbit urinated in an abnormal location. Four rabbits were presented because of restlessness during the night before presentation, diarrhea, abnormal breathing, or fur loss.

**Physical examination findings**

Information regarding physical examination findings was available for all 19 rabbits. During the initial
physical examination, the mention of 9 rabbits was quiet to dull, whereas 1 rabbit was hyperactive. The remaining 9 rabbits did not have specific behavior changes noted in the medical record. Median body weight of 18 rabbits was 1.76 kg (range, 1.1 to 4.8 kg); 13 rabbits weighed between 1.0 and 1.9 kg (median weight, 1.60 kg), 4 rabbits weighed between 2.0 and 2.5 kg (median weight, 2.15 kg), and 1 rabbit weighed 4.8 kg. The body weight of 1 rabbit was unknown. Information about respiratory rate was available for 7 rabbits. Five rabbits had a high respiratory rate (3 rabbits had polypnea, and the medical records for 2 rabbits stated respiratory rates of 80 and 100 breaths/min). The respiratory rate of 2 rabbits was considered normal. The mucous membrane color was noted for 6 rabbits, 3 of which had pale mucous membranes.

Abdominal physical examination findings were reported for 16 rabbits. Eight rabbits had signs of discomfort during palpation of the abdomen. Four rabbits had a palpable mass. All 4 medical records identified the mass as tubular. For 2 rabbits, the mass was localized in the midabdomen, and for 1 rabbit, the mass was localized in the dorsocaudal portion of the abdomen; for the remaining rabbit, the location of the mass was not specified. Other findings included a distended stomach (n = 2), a tense stomach (1), gas in the stomach (1), gas in the cecum (1), and no auscultated borborygium (1).

Rectal temperature was reported for 16 rabbits and ranged from 36.4 to 41.2 °C (reference range, 38.0 to 39.5 °C). Three rabbits were normothermic (median rectal temperature, 38.4 °C; range, 38.0 to 38.5 °C). Two rabbits were hyperthermic (median rectal temperature, 40.1 °C; range, 39.7 to 41.2 °C), and 4 rabbits were hypothermic (median rectal temperature, 37.2 °C; range, 36.4 to 37.6 °C).

Mild dental abnormalities were reported for 2 rabbits, of which 1 had lingual points and 1 had an irregular occlusal plane, and 1 rabbit had severe dental abnormalities. One rabbit had head tilt and exophthalmos, and 1 rabbit had loss of fur and poor body condition.

Clinicopathologic analyses
Complete or partial results of hematologic analyses were available for 12 rabbits. The most common hematologic alteration was anemia (7/12 rabbits). Of the 12 rabbits, 5 had a low RBC count, low hemoglobin concentration, and low Hct; 1 had low hemoglobin concentration and low Hct; and 1 had low PCV. Complete or partial results of blood biochemical analyses were available for 15 rabbits. The most common alterations were hypocalcemia and hypoglycemia. Serum total calcium concentration was measured in 11 rabbits. Of those 11 rabbits, 8 were hypocalcemic (median calcium concentration, 11.5 mg/dL; range, 8.9 to 12.0 mg/dL; reference interval, 12.1 to 17.2 mg/dL) and 3 were normocalcemic (median calcium concentration, 14.3 mg/dL; range, 12.5 to 14.9 mg/dL). Blood glucose concentration was measured in 15 rabbits. Of those 15 rabbits, 7 were hypoglycemic (median glucose concentration, 94 mg/dL; range, 75 to 108 mg/dL; reference interval, 112 to 231 mg/dL) and 8 were normoglycemic (median glucose concentration, 150 mg/dL; range, 120 to 209 mg/dL). Other abnormalities included high BUN concentration (5/12 rabbits), high creatinine concentration (4/12 rabbits), high alanine transaminase activity (2/13 rabbits), high alkaline phosphatase activity (1/12 rabbits), low alkaline phosphatase activity (1/12 rabbits), low amylase activity (1/12 rabbits), low phosphorus concentration (1/11 rabbits), and low sodium concentration (1/11 rabbits).

Two rabbits underwent blood sample collection before and after appendectomy. One rabbit initially had heterophilic leukocytosis (WBC count, 17.0 X 10⁹ WBCs/L; [reference interval, 2.7 X 10⁹ to 12.2 X 10⁹ WBCs/L]); heterophil count, 15.2 X 10⁹ heterophils/L [reference interval, 0.9 X 10⁹ to 7.8 X 10⁹ heterophils/L]) and hypoglycemia (83 mg/dL) that resolved the day after surgery (WBC count, 5.1 X 10⁹ WBCs/L; heterophil count, 1.1 X 10⁹ heterophils/L; and blood glucose concentration, 147 mg/dL) and had not recurred at 2 weeks after surgery (WBC count, 9.5 X 10⁹ WBCs/L; heterophil count, 5.6 X 10⁹ heterophils/L; and blood glucose concentration, 126 mg/dL). The other rabbit had azotemia (BUN concentration, 50 mg/dL; reference interval, 7.4 to 28.8 mg/dL) and high creatinine activity (2.1 mg/dL; reference interval, 0.6 to 1.7 mg/dL) that both resolved 7 days after surgery (BUN concentration, 29 mg/dL; creatinine concentration, 1.1 mg/dL).

Diagnostic imaging findings
Fourteen rabbits underwent whole-body or abdominal radiography < 14 days before histologic diagnosis of appendicitis was made. Radiography revealed evidence of gas in the cecum (n = 6), gas in the stomach (5), subjective distension of the stomach (4), presence of a soft tissue structure in the midcaudal portion of the abdomen (1), and mild urinary bladder sludge (1). For 3 rabbits, multiple radiographic views were obtained prior to diagnosis of appendicitis that indicated a progressive increase in the amount of gas in the gastrointestinal tract (n = 2) or minimal radiographic changes over time (1).

Eight rabbits underwent abdominal ultrasonography performed < 2 days before histologic diagnosis of appendicitis was made. Ultrasonography revealed an abnormal appearance of the appendix (n = 6), lymphadenomegaly (3), focal hyperchoic peritoneum (2), free fluid in the abdomen (2), thickening of the wall of the sacculus rotundus (1), presumed intestinal mass (1), hepatomegaly (1), and hyperchoic particulate material in the urinary bladder that was interpreted as urine sludge (1). During ultrasonographic examination of 4 rabbits, the overall diameter of the appendix or the thickness of the appendix wall was measured. For 2 of the 4 rabbits, the appendix diameter was 0.9 mm, wall thickness was 0.2 mm, and the appendix diameter was 0.45 cm and wall thickness was 0.25 cm; for the other 2 rabbits, appendix wall thickness was 0.35 cm and 0.48 cm. The ultrasonographer reported
an abnormal appearance of the appendix because of the presence of fluid or mucoid content rather than alimentary content in the appendix in 5 rabbits, abnormally thick appendix wall in 4 rabbits (reference interval, 0.11 to 0.21 cm), loss of the typical multilayered structure of the wall of the appendix in 2 rabbits, abnormally large diameter of the appendix in 2 rabbits (reference interval, 0.39 to 0.88 cm), or a combination of these factors (Figure 2).

Two rabbits underwent CT. For 1 rabbit, CT revealed peribronchial thickening of the right caudal lung lobe with inhomogeneous contrast enhancement, mesenteric lymphadenomegaly, and no other abnormalities. For the other rabbit, CT revealed severe segmental intestinal dilation, which was thought to represent the appendix given the location, and orientation of the blind-ended tubular structure, with suspected focal necrosis of the caudal wall of that structure, potential concurrent sacculitis (as evidenced by the thickness of the wall of the sacculus rotundus), a small volume of peritoneal effusion, and no other abnormalities (Figure 3).

Diagnosis

In 7 of the 19 rabbits, appendicitis was a postmortem diagnosis and had not been suspected prior to death or euthanasia. Of the remaining 12 rabbits, 7 had initial diagnostic imaging findings suggestive of appendicitis, and 5 had gross evidence of appendicitis detected during exploratory laparotomy. Among the 5 rabbits for which the diagnosis was made during surgery, 3 underwent appendectomy, 1 underwent incisional biopsy, and 1 was euthanized. For the 7 rabbits with suspected appendicitis based on the diagnostic imaging findings, the diagnosis was confirmed by histologic examination of tissue specimens after appendectomy (n = 5) or after death or euthanasia (2).

Clinical management, treatment, and outcomes

Fourteen rabbits received medical or surgical treatments (or both). Five rabbits did not receive medical treatment; 2 rabbits died shortly after hospital admission, 1 rabbit died during abdominal ultrasonography, 1 rabbit was euthanized at the time of presentation, and 1 rabbit was euthanized during exploratory laparotomy. The rabbit euthanized during exploratory laparotomy received drugs the day before the surgery (Supplementary Table S2) but was not classified as having medical treatment owing to the short duration of the treatment.

Rabbits receiving medical treatment—Of the 6 rabbits that underwent medical treatment, 1 died at 24 hours and 3 died at 48 hours after hospitalization, 1 died at 10 days after presentation, and 1 was alive at 1,030 days after presentation. The rabbit that was alive at 1,030 days after presentation had been treated with enrofloxacin, tramadol, and fluid therapy. The 5 rabbits that died received antimicrobials (n = 4), fluid therapy (4), opioids (3), an NSAID (3), and gastrointestinal medications (2). Antimicrobials administered to the rabbits that died were metronidazole (2), marbofloxacin (2), and enrofloxacin (2). Opioid treatments included buprenorphine (n = 1), fentanyl administered as constant rate infusion together with lidocaine (1), and tramadol (1). All rabbits received meloxicam as an NSAID. Gastrointestinal medications administered were ranitidine (n = 2), clebopride (1), and trimebutine (1).
Rabbits that underwent appendectomy—Of the 8 rabbits that underwent appendectomy, 5 survived until discharge from the hospital and were alive at recheck examinations; 2 died in the postoperative period and 1 died 3 days after the surgery (median survival time, 113 days; range, 0 to 1,473 days). Of the 5 rabbits that survived to hospital discharge, 4 were alive at 315, 334, 1,433, and 1,473 days, and 1 died 113 days after surgery. The rabbits that underwent appendectomy received antimicrobials (n = 8), opioids (8), fluid therapy (8), NSAIDs (7), gastrointestinal medications (4), and an enema (1). Antimicrobials administered to the rabbits included enrofloxacin (n = 7), metronidazole (5), trimethoprim-sulfamethoxazole (1), penicillin G procaine (1), and fenbendazole (1). Opioids administered to the rabbits included buprenorphine (n = 4), tramadol (3), and fentanyl administered as a constant rate infusion together with lidocaine and ketamine (1). Gastrointestinal medications administered to the rabbits included ranitidine (n = 2), simethicone (2), metoclopramide (1), and cisapride (1). All rabbits received meloxicam as an NSAID.

Figure 3—Pre- and postcontrast CT images obtained from a rabbit with appendicitis. A—Dorsal pre- (left image) and postcontrast (right image) views illustrating severe segmental dilation of a section of the intestinal tract consistent with the appendix (arrows). The structure is 9.3 cm in length and 2.1 cm in diameter. B—Sagittal pre- (upper image) and postcontrast (lower image) views of the appendix (arrows). C—Enlarged sagittal postcontrast image. Notice the 3-mm-long area of focal discontinuous wall enhancement of the structure (arrow), with adjacent peritoneal fluid (asterisk). Ca = Caudal. Cr = Cranial. R = Right.

Figure 4—Photographs obtained during appendectomy in a rabbit with chronic appendicitis. A—Externalization of the appendix following celiotomy. Notice that the appendix (a) is abnormally distended and filled with compacted ingesta and that the appendix wall has disseminated, somewhat circular whitish spots on its surface and an area of necrosis (asterisk). The intact ileocecal fold (arrow) connects the appendix to the ileum (i). B—Transection of the ileocecal fold by use of a bipolar radiosurgical device. The dissected ligament is indicated by the arrow. C—Placement of a circumferential suture at the base of the appendix, at its point of origin in the cecum. D—View of the appendix after excision. Notice the markedly large diameter of the appendix, the area of necrosis of the appendix wall (asterisk), and the remainder of the ileocecal fold (arrow).

Figure 5—Photographs obtained during appendectomy in a rabbit with acute appendicitis. A—Externalization of the appendix following celiotomy. Notice the abnormal gross external appearance of the appendix wall, characterized by disseminated, somewhat circular whitish spots. The intact ileocecal fold (arrow) connects the appendix (a) to the ileum (i). B—Transection of the ileocecal fold by use of a bipolar radiosurgical device. The dissected ligament is indicated by the arrow. C—View of the appendix after excision of the ileocecal fold (arrow). D—The appendix is excised (dotted line) after placement of double circumferential ligatures at its base (asterisks).
Appendectomy—A ventral midline approach was used for all 8 celiotomies. A self-retaining retractor with elastic stays (Lone Star self-retaining retractor; CooperSurgical Inc) was placed in 2 rabbits as a standard procedure to improve exposure of the intestinal tract (Figures 4 and 5). The ileocecal fold was cauterized and excised with bipolar radiosurgical forceps (5/8 rabbits) or simple interrupted sutures (2/8 rabbits). In 1 rabbit, the ileocecal fold was incorrectly identified as serosal adhesions and was bluntly dissected with a cotton top applicator, which resulted in a 2-mm-long laceration on the small intestinal side. Four rabbits underwent simple or double circumferential ligation of the appendix at its point of origin in the cecum, followed by placement of an intestinal clamp distal to the sutures and subsequent excision of the appendix. The other 4 rabbits underwent excision of the appendix after placement of intestinal clamps or application of digital pressure by an assistant at the base of the appendix, followed by closure of the cecum with simple interrupted sutures. Monofilament, absorbable suture materials (3-0 or 4-0 polydioxanone [PDS; Ethicon Inc] or poliglecaprone [Monocryl; Ethicon Inc]) were used in 7 of the 8 rabbits. In 1 rabbit, braided, absorbable suture material (2-0 synthetic polyester [glycolide and lactide; Polysorb; Covidien]) was used for ligation of the appendix and a monofilament, absorbable suture material (a 3-0 glycolide, ε-caprolactone, trimethylene carbonate [Monosyn; B. Braun Medical Inc] copolymer) was used to oversew the cecal stump. In all rabbits, abdominal lavage was performed following appendectomy and closure was routine.

Pathological and bacteriologic findings
Twelve rabbits had only specimens of the appendix submitted for histologic examination (8 excisional biopsy

Table 1—Antimicrobial susceptibilities of aerobic bacterial isolates obtained from 6 rabbits with appendicitis.

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Antimicrobial susceptibility was classified according to Clinical and Laboratory Standards Institute standards (susceptible [S], resistant [R], and intermediate [I]).

* = Intrinsically resistant.
— = Not determined.
Pure cultures of E coli were obtained from 3 rabbits, a mixed culture of E coli and Y pseudotuberculosis was obtained from 1 rabbit, and a pure culture of P aeruginosa was obtained from 1 rabbit. No bacterial growth was obtained from samples from the remaining rabbit.
specimens obtained during appendectomy, 3 specimens harvested during necropsy, and 1 incisional biopsy specimen). For 7 rabbits, the appendix and other organs were submitted as part of the postmortem examination (Supplementary Table S3). Histopathologic findings for the other organs were summarized (Supplementary Table S4). Except for 1 rabbit from which a full-thickness biopsy specimen of the appendix was submitted, all the other submissions included the entire appendix.

For all 19 appendices, histologic examination revealed mucosal ulceration, heterophilic inflammation, and necrotic debris (Figure 6). Among the appendices, 17 had lymphoid follicle necrosis and abscesses, 17 had edema, 15 had transmural inflammation and brown pigment-laden macrophages, and 11 had hemorrhages. Eight appendices had serosal involvement and presence of bacteria, and 4 appendices had follicular hyperplasia and vasculitis.

Results of aerobic and anaerobic bacteriologic cultures were available for 6 and 5 rabbits, respectively. Under aerobic conditions, pure cultures of Escherichia coli were obtained from 3 rabbits, a mixed culture of E coli and Yersinia pseudotuberculosis was obtained from 1 rabbit, and a pure culture of Pseudomonas aeruginosa was obtained from 1 rabbit. No bacterial growth was obtained from 1 rabbit. The 6 aerobic isolates each had resistance to ≥ 1 antimicrobial. All 6 isolates underwent susceptibility testing against marbofloxacin, doxycycline, and enrofloxacin. Only 1 aerobic isolate was resistant to marbofloxacin, whereas 5 aerobic isolates were resistant to both doxycycline and enrofloxacin (Table 1). Under anaerobic conditions, pure cultures of Bac teroides fragilis were obtained from 3 rabbits, and no bacterial growth was obtained from 2 rabbits.

Discussion

Rabbits are the only animal species that is commonly kept as a pet and has a well-developed appendix. In humans, appendicitis has an incidence of 1.1 cases/1,000 people and is the most common cause of acute abdominal pain requiring surgical intervention. Until recently, there have been only 2 reports5,6 of appendicitis in client-owned rabbits, to our knowledge. The intent of the present study was to assess clinical, surgical, and pathological findings in a comparatively large number of client-owned rabbits with histologically confirmed appendicitis.

The inconsistent use of nomenclature for the appendix in rabbits in the veterinary medical literature could be one of the reasons that appendicitis in rabbits has been rarely diagnosed. In some reports,11,12 this structure has been considered to be the cecum itself despite the fact that the anatomic features and function of these 2 contiguous tissues are completely different. Considering the abundance of lymphoid tissue in the appendix of rabbits, it is not surprising that there have been reports11,12 of lymphoma originating from or affecting this structure. Interestingly, one of these reports11 failed to acknowledge the origin of the structure, defining the tumor as arising from the cecum. On the basis of the image in the report, it is evident that the tumor involved only the vermiform appendix. In the other report,12 the main text mentioned that the appendix caecii (ie, the vermiform appendix) was affected, whereas the abstract indicated that the cecum was affected.12 Those 2 examples are indications of the current problem in identifying and describing disorders of the vermiform appendix in rabbits. We suggest that authors should carefully specify which structure is affected, whether it is the cecum (using terminology such as typhlitis or cecal lymphoma) or the appendix (using terminology such as appendicitis or appendiceal lymphoma).

In the present study, a most interesting factor related to appendicitis in rabbits was the season of occurrence. With the exception of 2 rabbits, all cases occurred in summer and fall. Although this pattern could merely reflect the presentation of a higher number of rabbits in that period of the year, a previous epidemiological study involving rabbits revealed no seasonal variations in the number of animals that were presented for evaluation of gastrointestinal hypomotility. In humans, appendicitis is more common in summer months,26 even if the reason for this is still unclear.27,28 Interestingly, in some colder countries (eg, Wales), there is no seasonal variation in the incidence of appendicitis among humans. In European countries, where most reported cases in rabbits have originated, there is less widespread use of air conditioning, compared with that in the US; it is possible that the higher environmental temperature to which domestic rabbits are exposed during warmer months, especially in European countries, is a factor in the development of acute appendicitis.

The median age of the rabbits in the present study was 2 years, indicating that appendicitis could be more common in young rabbits. This finding should be interpreted cautiously because it could also only reflect a higher number of young rabbits presented for consultation in veterinary practices. However, the median age of rabbits presented for primary veterinary care in England is 3.2 years,31 and the mean age of rabbits presented for evaluation of gastrointestinal hypomotility is 3.1 years; thus, the median age of rabbits in the present report was approximately two-thirds of those values. It has been observed that appendix size decreases with age both in laboratory rabbits32 and in client-owned rabbits.23 Therefore, it is possible that acute appendicitis affects rabbits that are undergoing involution of the organ. In humans, appendicitis affects all age groups, although the incidence is increased between the ages of 10 and 20 years.24

Although presenting clinical signs were unspecific in most of the rabbits of the present report, almost all 19 rabbits were anorectic (n = 17), and over half of the rabbits (11) had decreased activity or responsiveness. Also, there were some physical examination findings that could be suggestive of appendicitis in clinical patients. These findings include high rectal temperature, palpation of a tubular abdominal mass, and signs of discomfort during abdominal palpation. In the present case series, rectal temperature was high in 9 of 16 rabbits, with the remaining rabbits being hypothermic (n = 4) or normothermic (3). This may not be surprising because hyperthermia develops in humans with transmural appendicitis.24 The role of fever
has been a matter of debate in clinical rabbit medicine because hyperthermia is rare in hospitalized rabbits, with an estimated prevalence of 1.7% (7/316 rabbits) to 2.2% (2/117 rabbits). However, results of laboratory research indicate that hyperthermia increases the survival rate of rabbits experimentally infected with bacteria. Given the fact that hyperthermia is uncommon in rabbits, it would be worthwhile to rule out appendicitis with additional diagnostic imaging in rabbits with unexplained hyperthermia. It is also worth noting that, although most rabbits in the present study had clinical signs for < 48 hours or no clinical signs at all, 2 rabbits had intermittent clinical signs for 29 and 89 days. Those data have suggested that there may be an acute and a chronic form of this disorder in rabbits.

In the present study, the most characteristic clinical-pathologic findings were hypocalcemia (8/11 rabbits) and hypoglycemia (7/15 rabbits). In rabbits, hypoglycemia is an uncommon finding that has been described in just 1.7% (16/907) of rabbits presented for veterinary consultation and in 4% (2/50) of rabbits with signs of gastrointestinal tract dysfunction. In cases for which a diagnosis was achieved, hypoglycemia was caused by pancreatic disorders (n = 2), dental problems (2), and enteritis (2). In the rabbits of the present report, hypoglycemia could have been a consequence of ineffective colonic fermentation or decreased intestinal absorption or could have been associated with the development of sepsis. In 1 rabbit with hypoglycemia at hospital admission, analysis of a blood sample collected the day after appendectomy revealed normalization of glucose concentration. Anemia was the most common hematologic abnormality, affecting 7 (58.3%) of 12 rabbits. The most likely cause of anemia in association with appendicitis was systemic inflammation because rabbits with inflammatory disorders have increased RBC fragmentation with consequent mild regenerative anemia.

Ultrasonography and CT were the only nonsurgical techniques that resulted in an antemortem diagnosis of an appendicular disorder in some of the rabbits included in the present case series. The use of these techniques was previously described for a rabbit with appendicitis and sacculitis. In rabbits, the appendix has characteristic ultrasonographic features, compared with features of the rest of the gastrointestinal tract. Recently, our research group investigated the ultrasonographic morphology of the appendix in 42 clinically normal rabbits and determined overall appendix diameter and appendix wall thickness for 40 and 39 rabbits, respectively. The appendix was observed in median or left paramedian views in 95.2% (40/42) of the rabbits. The appendix appeared as a tubular structure with a multilayered wall, a luminal content with alimentary pattern, and a rounded, closed end. In healthy rabbits, the appendix had no evidence of fluid content; in only 1 of 40 healthy rabbits, the luminal pattern generated a posterior acoustic shadow that limited visualization of the distal wall of the appendix. In the present case series, an appendiceal disorder was suggested by the increased thickness of the wall of the appendix, loss of the typical multilayered structure of the appendix wall, increased overall diameter of the appendix, presence of fluid or mucoid content rather than alimentary content in the appendix, or a combination of these factors. Contrast-enhanced CT after IV contrast medium administration, Doppler ultrasonography, and ultrasonography after contrast medium administration are effective techniques for detection of liver lobe torsion, another common disorder of rabbits with clinical signs similar to those of appendicitis (ie, anorexia, lack of defecation, lethargy, and an apparently painful abdomen). Therefore, use of one of those diagnostic imaging methods in rabbits with such clinical signs is recommended to diagnose or rule out these diseases.

In humans, appendectomy is one of the most common surgical procedures and has been the standard treatment for acute appendicitis for over a century. Currently, appendicitis in humans can be distinguished as uncomplicated and complicated, depending on the presence of appendicoliths, perforation, abscesses, or neoplasia. Recently, results of randomized trials have indicated that cases of uncomplicated acute appendicitis can be treated safely and effectively with antimicrobials. A comparison of medical and surgical treatments for resolution of appendicitis in rabbits is not within the scope of the present study. The present case series included only rabbits that had a histologic diagnosis of appendicitis; therefore, any calculation of the risk of death of rabbits with appendicitis undergoing medical versus surgical treatment would have an inherent bias toward surgery. In the present study, 3 rabbits underwent medical treatment because of a clinical suspicion of appendicitis, but only 1 of the 3 animals survived. To date, in the only other reported case of medical treatment of a client-owned rabbit with appendicitis, the rabbit survived. Also, 7 of the 19 rabbits in the present study died shortly after presentation without an antemortem diagnosis of appendicitis. Finally, the 2 rabbits with chronic appendicitis that underwent surgical treatment had grossly evident tears of the appendix, along with signs of peritonitis.

The ileocecal fold is a short mesenteric ligament that connects the ileum to the appendix in rabbits. The ileocecal fold is infiltrated by a number of small, short vessels. To isolate the appendix from the remainder of the intestinal tract in a rabbit, the ileocecal fold has to be excised. Considering the large number and small size of the vessels and the length of the ileocecal fold, radiosurgery is well suited for excision of this ligament. In the present study, ligation of the appendix in 8 rabbits was performed with 1 of 2 distinct approaches. Half of the rabbits underwent circumferential ligation of the appendix at its point of origin in the cecum, followed by placement of an intestinal clamp distal to the sutures and subsequent excision of the appendix. The other half of the rabbits underwent excision of the appendix after placement of intestinal clamps or application of digital pressure by an assistant at the base of the appendix, followed by closure of the cecum with simple interrupted sutures. All the rabbits treated with the first approach survived, whereas 3 of the 4 rabbits treated with the second approach died before hospi-
tal discharge. There are a variety of confounders that could be responsible of this potential difference in survival rates; however, it is worth noting that the first approach is that currently used for open appendectomy in human medicine because results of a randomized trial indicated that simple ligation was as effective as invagination. Therefore, until more evidence is accrued, it is safer to ligate the appendix with a simple or double ligation before its excision, leaving a residual appendiceal stump no longer than 3 mm.

The appendix of rabbits is characterized by large lymphoid follicles that protrude toward the lumen, forming the dome villi. Each follicle is composed of 4 sections, namely, the dome, corona, germinal center, and interfollicular area; the dome region is lined by follicle-associated epithelium, a specialized type of epithelium. Infiltration with organisms from the lumen, presence of bacteria and debris in the macrophages, and presence of multinucleated giant cells are all typical features of the appendix of clinically normal rabbits. In the present report, the rabbits with appendicitis had some characteristics in common, such as mucosal ulceration, heterophilic inflammation, and lymphoid follicle necrosis and abscess formation. These findings were likely representative of an acute or hyperacute process and associated with a severe inflammatory process. A less common characteristic was follicular hyperplasia, which was detected in 4 rabbits and considered chronic in 2 of those rabbits.

With regard to humans, there is controversy over the exact pathophysiology of appendicitis and whether the bacterial flora within the appendix differ between patients with and without appendicitis. Findings of a recent study suggest that an increased risk of acute appendicitis in humans is associated with a comparatively greater diversity of anaerobic bacteria and the specific types of anaerobic bacteria in appendices of humans, rather than an association with aerobic bacteria. In the present study, unfortunately only 5 anaerobic cultures were performed, with growth of B. fragilis observed in 3 cultures. Of the 6 aerobic isolates, 4 were identified as E. coli. Both Bacteroides spp and E. coli are common inhabitants of the cecum of rabbits.

In 1 study, epizootic rabbit enteropathy was induced in rabbits by administration of a diet with low fiber content. In the rabbits with epizootic rabbit enteropathy, the abundance of certain bacteria, including those of the genera Escherichia and Bacteroides, increased. None of the rabbits included in this report were fed a diet with low fiber content or had pathological findings consistent with epizootic rabbit enteropathy. Whether the bacteria isolated from the rabbits of the present study were responsible for the development of appendicitis or proliferated as a consequence of the intestinal dysbiosis attributable to the disrupted activity of the intestinal tract is currently unclear. Many organisms have been isolated from the appendices of presumed healthy farm rabbits, including Mycobacterium avium avium, and therefore the isolation of microorganisms does not prove causation of disease.

The present case series had several limitations, including the fact that culture swabs were obtained from a limited number of appendices and that the manner in which the swab specimens were collected was not consistent among all veterinarians. As in most case series, there was no common standardized recheck time-frame for all rabbits that underwent appendectomy. Gross and microscopic findings related to tissues other than the appendix were not consistently available for all rabbits in this study. This was unfortunate, especially with regard to the sacculus rotundus, because sacculitis has been associated with appendicitis in a rabbit. Further studies that examine the appendix and sacculus rotundus of rabbits with appendicitis would help determine the prevalence of sacculitis in rabbits with appendicitis. Also, for certain clinical findings (such as the results of abdominal auscultation), it was impossible to ascertain the actual prevalence among the study rabbits because of the lack of a standardized physical examination sheet. Finally, it is not possible to prove the effectiveness of an intervention without a control group; however, it was possible, although unlikely, especially in the cases with peritonitis, that the medical treatment received by appendectomized rabbits was responsible for their recovery.

Results of the present study indicated that appendicitis in client-owned rabbits is often associated with unspecific presenting clinical signs but has some clinico-pathologic and diagnostic imaging features that could direct veterinarians toward an appropriate diagnosis. It should be remembered that appendicitis in rabbits may be an acute or chronic clinical condition, which may develop more frequently during warmer months. Appendectomy may be a viable treatment in selected cases. Further studies are required to compare the safety and effectiveness of medical and surgical treatments for appendicitis in pet rabbits.

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References

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