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Iatrogenic Hemolytic Anemia and Endocarditis in New Zealand White Rabbits Secondary to *Achromobacter xylosoxidans* Infection

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During a 3-mo period, 9 of the 15 New Zealand White rabbits used in a heart failure study developed a hemolytic anemia. The heart failure model involved the creation of an aortic insufficiency (AI) followed 2 to 6 wk later by the creation of an aortic stenosis (AS). None of the 9 animals that developed hemolytic anemia responded to medical management, and 6 of the 9 were euthanized for humane concerns. Necropsies and blood cultures were performed on all anemic animals; 7 of these cultures yielded growth of *Achromobacter xylosoxidans*. In addition, cultures from the heart valves of 2 rabbits yielded growth of *Achromobacter xylosoxidans*. We presume that the endocarditis caused by *Achromobacter xylosoxidans* led to the mechanical damage of red blood cells (RBCs) and subsequent intravascular hemolysis or splenic destruction of damaged RBCs, resulting in a severe, regenerative hemolytic anemia. *Achromobacter xylosoxidans* is an aerobic, catalase-positive, oxidase-positive, gram-negative bacillus. This organism is an environmentally resistant and opportunistic bacterium that typically inhabits aqueous environments. Microbial samples from the investigator's laboratory and equipment were collected to identify the source of the bacteria. A pressure transducer and bag of intravenous fluid were identified as sources of contamination.

Abbreviations: AI, aortic insufficiency; AS, aortic stenosis; CBC, complete blood count; HCT, hematocrit; RBC, red blood cell

A colony of 50 New Zealand white rabbits (*Oryctolagus cuniculi*) was maintained for use in an approved protocol for conducting heart failure studies. These animals were acquired from a vendor and had tested negative for *Pasteurella multocida*, *Encephalitozoon cuniculi*, *Toxoplasma sp.*, *Bordetella bronchiseptica*, *Treponema cuniculi*, *Clostridium piliforme*, myxomatosis, rabbit hemorrhagic disease virus, and ecto- and endoparasites. Animals were housed in accordance with the *Guide for the Care and Use of Laboratory Animals*[17] and Animal Welfare Act regulations and were used in an animal care program accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International. The rabbits received 130 g of commercial Rabbit High Fiber Diet (Harlan Teklad, Madison, WI) daily. Water was available ad libitum.

The creation of the heart failure model involved a 2-step surgical process. All animals were premedicated with 35 mg/kg ketamine (Phoenix Pharmaceuticals, St Joseph, MO) intravenously, intubated with a size 3 cuffed, endotracheal tube, and maintained on 1.0% to 3.0% isoflurane gas anesthesia (Abbott Labs, North Chicago, IL) for the duration of the procedure. The first step was the creation of aortic insufficiency (AI), which involved placement of a 4-French angiographic catheter (Johnson and Johnson, Miami, FL) into the carotid artery. The catheter was forcefully passed back and forth across the aortic valve, from the aorta into the left ventricle. A perforative lesion occurred when there was 75% to 100% increase in the pulse pressure. This perforative lesion created a volume overload, thereby leading to aortic valve insufficiency. After 2 to 6 wk of rest, the rabbits underwent a second survival surgical procedure to create an aortic stenosis (AS). A 4-French angiographic catheter was placed into the femoral artery, which was connected via fluid-filled pressure tubing to a transducer whereby the femoral artery blood pressure was measured. A 4-French angiographic catheter also was placed into a patent carotid artery. Blood pressure was measured from the femoral artery and carotid artery catheters; a pressure gradient was calculated by subtracting the femoral artery systolic blood pressure from the carotid artery systolic blood pressure. Once that gradient had been determined, a silk ligature was placed around the abdominal aorta proximal to the renal arteries and was tightened slowly until a change in gradient of 10 to 15 mm Hg had been achieved. Throughout both procedures, the vital signs of rabbits were monitored closely, and intravenous fluids were administered.

After the AI procedure, animals received an injection of 0.02 mg/kg buprenorphine (Phoenix Pharmaceuticals) intramuscularly prior to anesthetic recovery. During the 2-d postoperative period, rabbits received an oral dose of 0.2 mg/kg meloxicam (Phoenix Pharmaceuticals) once daily. After the AS procedure, rabbits received an intramuscular injection of 0.02 mg/kg buprenorphine in the immediate postoperative period and then received meloxicam (0.2 mg/kg orally) once daily for 3 d. The principal investigator had 19 y of experience in performing procedures with this heart failure model. During the past 6 y, approximately 250 AI procedures and 230 AS procedures were performed in this laboratory. Most rabbits recovered unevent-

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fully from the surgical procedures. Rarely did animals die as a result of heart failure, and development of hemolytic anemia was an unusual complication. Moreover, the presence of vegetative valvular lesions at necropsy was an uncommon finding in this model of heart failure.

Case Report

During a period of 3 mo, 9 of 15 animals in a heart failure study developed hemolytic anemia. Approximately 2 to 6 wk after undergoing the AI or AS procedure, 8 animals demonstrated signs of illness including anorexia, lethargy, and pallor; 2 of these 8 animals were febrile. The investigator's technician reported ill rabbits to the veterinarian, who performed appropriate diagnostic tests and instituted medical treatment. An additional rabbit, which did not demonstrate clinical signs of illness, was moribund immediately after the AS procedure and was euthanized for humane reasons.

Blood samples for determination of hematocrit (HCT) or complete blood count (CBC) were obtained from all 9 rabbits. The blood samples were evaluated in the facility's diagnostic laboratory; all of the 9 animals were anemic, with HCT values that ranged from 13% to 31% (normal, 34% to 43%). The CBCs of 5 animals revealed decreased red blood cell counts (1.77 to 3.77 $\times 10^6$/µl; normal, 5.3 to 6.8 $\times 10^6$/µl) and decreased hemoglobin concentrations (3.9 to 8.3 g/dl; normal, 9.8 to 14 g/dl). Two animals had slightly elevated white blood cell counts (9.42 to 10.63 $\times 10^3$/µl; normal, 5.1 to 9.7 $\times 10^3$/µl). Four animals had an increased percentage of reticulocytes (15.4% to 22.5%; normal, 1.9% to 3.8%) and an increased number of reticulocytes (422.4 to 725.9 $\times 10^9$/l; normal, are 82.6 to 335.2 $\times 10^9$/l). Serum chemistry panels performed in only 3 of the 9 rabbits. The chemistry panels of 2 rabbits revealed increased glucose (193 to 287 mg/dl; normal, 74 to 148 mg/dl), increased alanine aminotransferase (152 to 258 U/l; normal, 25 to 65 U/l), and decreased total protein (4.2 to 4.5 g/dl; normal, 5.0 to 7.5 g/dl). Urinalysis, performed on 1 rabbit, showed a mild to moderate proteinuria (30+) and hemoglobinuria (50+).

Clinically ill animals were treated with 5 mg/kg enrofloxacin (Baytril, Bayer Health Care, Kansas City, MO) intramuscularly twice daily for 7 to 10 d. Inappetant rabbits were given a nutritional caloric supplement (Critical Care, Oxbow Pet Products, Murdock, NE) and alfalfa hay ad libitum. In addition to nutritional support, rabbits received 60 to 100 ml lactated Ringer solution (Baxter Healthcare, Deerfield IL), subcutaneously twice daily.

Postmortem tests included bacterial culture of the blood or heart valves (or both) of all 9 affected animals and full or partial necropsy. Antimicrobial susceptibility testing (BBL Prompt Inoculation System, BioMerieaux, Hazlewood, MO) revealed 7 blood cultures positive for growth of *Achromobacter xylosoxidans*; 1 rabbit yielded growth of a gram-negative bacillus with a close identification to *A. xylosoxidans*. A positive blood culture from 1 rabbit showed resistance to ampicillin, penicillin-G, cefazolin, and clindamycin. In addition, the organism was sensitive to chloramphenicol and trimethoprim–sulfamethoxazole and moderately sensitive to gentamicin and ciprofloxacin (enrofloxacin). After the blood culture results were obtained, subsequent animals that became ill were treated with 5 mg/kg trimethoprim–sulfamethoxazole (Bactrim, McKesson Drug, Carol Stream, IL) orally for 7 to 10 d.

Necropsies of the heart were performed on all animals. Grossly, the aortic and mitral valves of all 9 animals were markedly thickened with loose, fibrous, connective tissue (Figure 1 A through C) and attached thrombi. The thrombi typically contained large numbers of gram-negative coccobaccilli free or within macrophages. The diagnosis based on gross and histologic findings was fibrinous and heterophilic vegetative valvular endocarditis and was presumed caused by the gram-

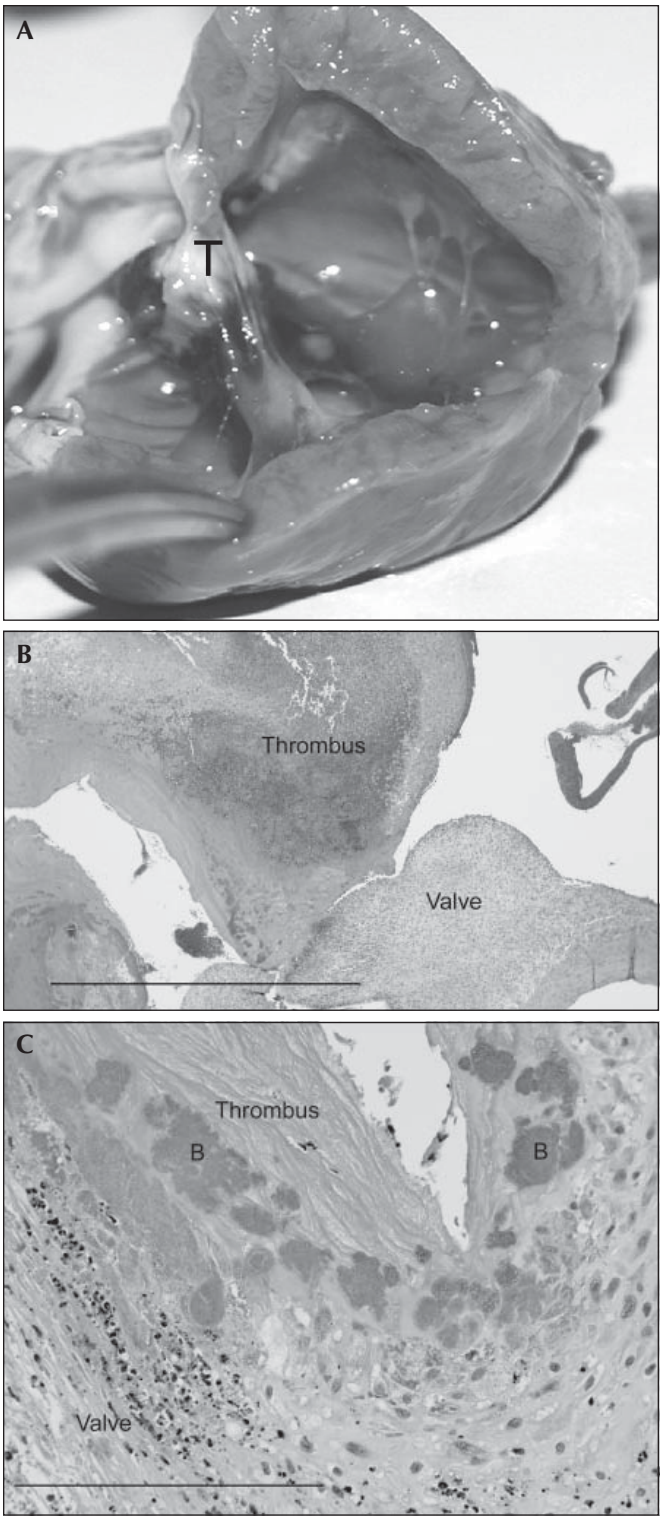

Figure 1. Heart obtained from an affected rabbit. (A) Heart with marked thickening (T) of the mitral valve. (B) A large thrombus is attached to the markedly thickened valve in the heart shown in panel A. (C) Higher magnification of the thrombus in panel B. Degenerating inflammatory cells border the valve which is undergoing degeneration, and the thrombus which consists of fibrin with scattered bacterial colonies (B). Hematoxylin and eosin stain; bar, 2 mm (B) 200 µm (C).

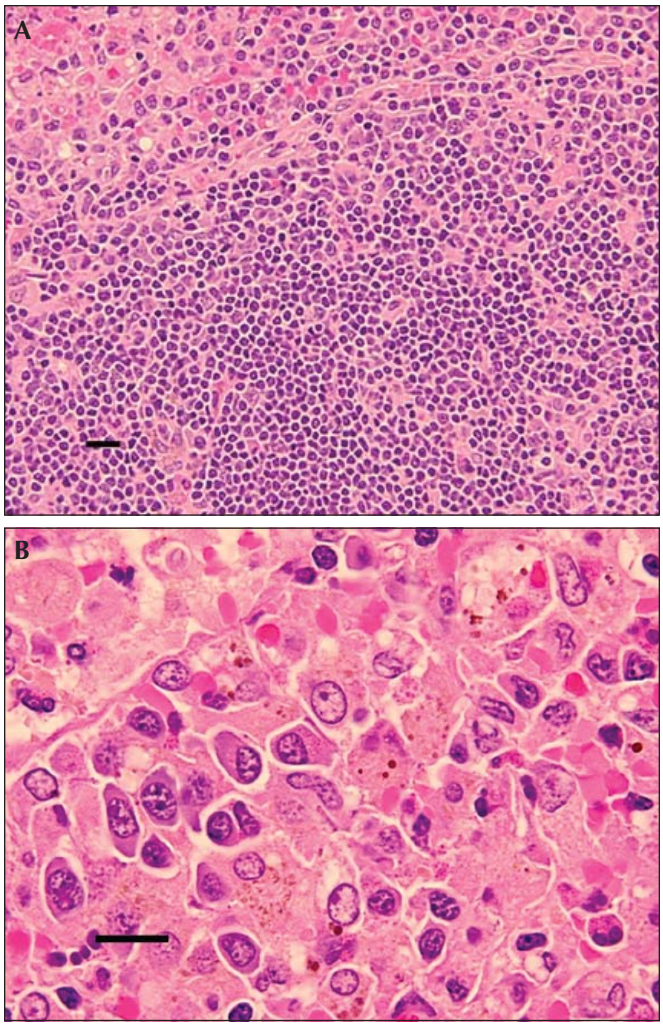

Figure 2. Histologic examination of spleen demonstrating (A) markedly expanded cords and (B) large numbers of hemosiderin-containing reticuloendothelial cells, which are present due to hemolysis. Hematoxylin and eosin stain; bar, 20 µm.

negative bacteria. Further, 5 of the necropsied animals had histiocytic pneumonia, which may have been due to bacterial infection and may have been the source of or a sequel to bacterial endocarditis.

In 3 rabbits, the liver had centrilobular to midzonal hepatocellular degeneration and necrosis. These lesions most likely were caused by hypoxia, which was produced by the severe anemia. Splenomegaly was present in 3 animals. These spleens had markedly expanded cords in the white pulp with evidence of extramedullary hematopoeisis as well as marked splenic histiocytosis with erythrophagocytosis and hemosiderosis (Figure 2 A, B). In addition, the bone marrow demonstrated a severe erythroid hyperplasia with a myeloid to erythroid ratio of 0.2 to 1.0 and a paucity of myeloid precursors (Figure 3). The marrow finding in addition to an anemia with marked polychromasia and many schistocytes (Figure 4) implied a regenerative, hemolytic process. Moreover, 1 rabbit had mild nephrosis, which may have developed from hemoglobinuria.[11]

As part of the protocol, all rabbits in the heart failure study underwent cardiac ultrasonography. Ultrasound tapes were viewed and evaluated after necropsy assessment. Retrospectively, it was noted that 4 of the 9 rabbits had vegetative lesions on the aortic valves. These vegetative lesions were consistent with the necropsy findings.

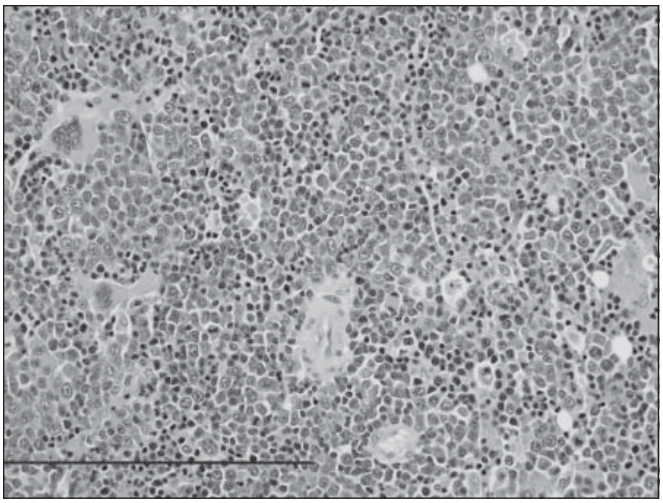

Figure 3. Histologic examination of bone marrow demonstrating marked hematopoiesis and myelopoiesis. Hematoxylin and eosin stain; bar, 200 µm.

Discussion

Endocarditis is an inflammation of the endothelial lining of the heart; it is usually confined to the covering of a valve and sometimes the lining membrane of the chambers.[13] Infectious endocarditis is a microbial infection of the endothelial surface of the heart.[13] In humans, an increased incidence of endocarditis has been associated with intravenous drug abuse, native valve endocarditis, and prosthetic valves.[5,16,25] In animals, endocarditis has been associated with infectious organisms, congenital heart defect, and trauma (for example, catheterization).[2,18] Most cases of endocarditis occur as a result of turbulence or trauma to the endothelial surface of the heart.[5,16] Bacteria can seed the disrupted surfaces of the heart valves, leading to an infectious endocarditis. The bacteria continue to grow on the disrupted surfaces producing vegetative lesions, which break off and travel to the lungs, brain, kidneys, or skin.[16,25] We hypothesize that in the presented rabbits, the damaged endothelium of the aortic valve from the perforative lesions created as part of the AI procedure provided an ideal location and environment for the bacterial contaminants to seed and spread. In humans, the inciting bacteria typically are found in the mouth, intestinal tract, or urinary tract.[4,25] Infection can lead to tissue destruction, emboli, vasculitis, and immune complex glomerulonephritis.[4,13,25] Anorexia, weight loss, headaches, myalgias, dyspnea, cough, and chest pain are frequently reported symptoms.[16,25] Animals may present with similar clinical signs, including lethargy, fever, lameness, dyspnea, cough, anorexia, and weight loss.[2,18]

Achromobacter xylosoxidans is an aerobic, motile, oxidase-positive, catalase-positive, gram-negative rod first described in 1971 in patients with chronic, purulent, otitis media.[24] Although *Achromobacter* species have been isolated occasionally from the human gastrointestinal tract and ear canal, it is unclear whether the organisms are an usual component of human endogenous flora.[3] *Achromobacter* species inhabit aquatic environments, including well water, intravenous fluids, and water in humidifiers.[20] Other environmental sources of *Achromobacter* include swimming pools, dialysis fluids, distilled water, deionized water, tap water, nonbacteriostatic saline, and chlorhexidene disinfectant solutions.[4,20] There have been reports of *Achromobacter xylosoxidans* contamination of intravenous saline solutions[7,8] and atomizers used in hospitals for respiratory therapy.[21,23]

In the present case report, the sources of *Achromobacter* contamination were the transducer and the bag of lactated Ringer

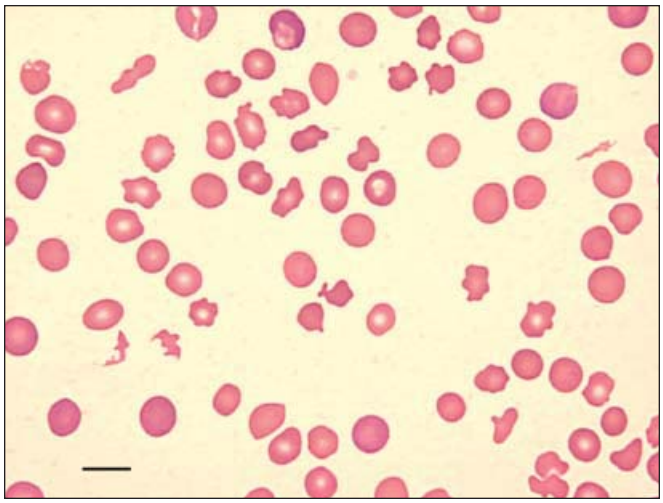

Figure 4. Blood smear demonstrating polychromasia and schistocytosis. Giemsa stain; bar, 10 µm.

solution that was connected to the transducer. The veterinary literature includes other reports of gram-negative sepsis due to administration of contaminated intravenous fluids.[15,19] One report described the contamination of intravenous fluids that were used in a nonsurvival surgical procedure.[19] Dogs in that report developed decreased total protein, packed cell volume, and RBCs,[19] as did the rabbits in the present report. But unlike the rabbits, the dogs developed acidosis, diarrhea, and became hypotensive.[19] Other possible sources of contamination that were culture-negative in the present case included the rabbit restrainer, sink counter, ventilator, heparin flush, tap water from the laboratory, a bottle of injectable enrofloxacin, Betadine solution, Betadine scrub, a 4-French catheter, and 2 bottles of heparin flush.

To eliminate *Achromobacter* from the laboratory microenvironment, procedures related to aseptic technique were reviewed, and all surfaces in the investigator's laboratory were disinfected with a 3% hydrogen peroxide solution. Prior to the outbreak, the investigator used the transducers multiple times, flushing them with sterile saline between uses. Since the outbreak, sterile transducers have become a single-use item. Moreover, punctured fluid bags, which previously did not have a shelf-life, now have a 30-d shelf life and are checked on a regular basis for contaminants as part of the institution's quality assurance program. Since instituting these measures, no additional cases of anemia or endocarditis have occurred in rabbits used in this study.

Contaminated solutions or contaminated hospital equipment are also sources for human cases of *A. xylosoxidans* infection. [4] *Achromobacter* species can survive in aqueous environments with minimal nutrients and are likely to cause nosocomial infection when there is a breakdown of infection-control techniques.[4,20] The most common clinical syndromes associated with *A. xylosoxidans* infection are primary bacteremia, in which no source of contamination is identified, and bacteremia related to the use of intravenous catheters.[4,20] Both immunocompetent and immunocompromised humans infected with *A. xylosoxidans* may present with bacteremia, meningitis, urinary tract infections, abscesses, osteomyelitis, corneal ulcers, prosthetic valve endocarditis, pericarditis, peritonitis, and pneumonia.[1,4,9,13,16,20] Naturally acquired infection with *A. xylosoxidans* in animals has not been reported; however, catheter-associated infections in baboons[15] and in a dog with a total hip prosthesis[6] have been reported.

Treatment of *A. xylosoxidans* infection is difficult, and an optimal antimicrobial regimen has not been determined. In the presented rabbits, treatment was initiated with enrofloxacin, which was changed to trimethoprim–sulfamethoxazole when we realized that the bacteria were more susceptible to this antibiotic. Rabbits initially responded to antimicrobial therapy, yet the infection could not be eradicated. Most *Achromobacter* isolates are resistant to first- and second-generation cephalosporins, aminoglycosides, and narrow-spectrum penicillins.[1,4,20] *Achromobacter* species are susceptible to sulfonamides, carbapenems, broad-spectrum penicillins, and third-generation cephalosporins and have variable susceptibility to fluoroquinolones.[4,13,20] The results of sensitivity testing performed on the *A. xylosoxidans* colony isolated from the blood culture of 1 rabbit were similar to those just described: the bacteria were resistant to cefazolin and ampicillin, susceptible to trimethoprim–sulfamethoxazole, and moderately sensitive to enrofloxacin.

Two key objectives must be achieved to treat endocarditis effectively: 1) eradicating the infecting microorganism in the vegetative lesion and 2) resolving the complications of infection.[13] Invasive cardiac lesions are very difficult to treat, and surgical intervention is required.[13] The majority of human patients infected with *A. xylosoxidans* infections often have substantial underlying illnesses, including malignancies and cardiovascular diseases.[4,5,13,16,20] As far as we can determine, the rabbits in the present report were of good health and did not have any underlying malignancies or nonexperimental conditions that would have contributed to their susceptibility to *Achromobacter* infection.

In humans, nonregenerative anemia is a common manifestation of infectious endocarditis; regenerative, hemolytic anemia, as in the described rabbits, is uncommon.[9] Regenerative anemia can occur by blood loss or by hemolysis.[14] The rabbits did not have noteworthy blood loss during the surgical procedures nor did they manifest other signs of blood loss. As a result, the anemia associated with the rabbits in this case report is most likely associated with hemolysis, which is supported by the degree of reticulocytosis noted.[14] Moreover, the rabbits demonstrated other signs typical of regenerative anemia, including anisocytosis with polychromasia of the RBCs and a marked RBC hyperplasia in the bone marrow, which would be expected in a regenerative anemia. Other signs of hemolytic anemia, such as hemoglobinemia, were not present in the affected animals; however, the 1 animal for which a urinalysis was performed had hemoglobinuria. The necropsy of another affected rabbit, which did not undergo urinalysis, revealed nephrosis, which may have been due to hemoglobinuria.[11] Only 3 chemistry panels and 1 urinalysis were performed; additional animals may have had hemoglobinemia and hemoglobinuria that were not detected.

Hemolytic anemia can be caused by intravascular or extravascular events. In these cases intravascular hemolysis was considered to be the primary mechanism of hemolytic anemia. In this mechanism, RBCs lyse in the circulation, releasing hemoglobin into the plasma. The free hemoglobin is immediately bound by haptoglobin, a process leading to a decrease in serum haptoglobin levels. After haptoglobin is saturated, excess hemoblobin is filtered in the kidney. Therefore, low serum haptoglobin and hemoglobinuria would be 2 additional laboratory test results providing support for intravascular hemolysis in these rabbits. Causes of intravascular hemolysis include mechanical trauma, complement fixation, and toxic damage to RBCs. [3]

Fragmentary, hemolytic anemia has been reported to occur in patients with vegetative endocarditis of prosthetic and native heart valves.[9,22] In these patients, several mechanisms are

postulated to contribute to the hemolysis of RBCs, including blood flow disturbances, regurgitant jets, and high shear stress on RBCs.[1,9,22] The progression of the vegetative lesions is likely to have resulted in a powerful turbulent flow that caused intravascular hemolysis.[4,9,10,20] The hallmark of valve failure has been suggested to be the presence of regenerative anemia with schistocytes on a blood smear,[9,10,22] which is a distinguishing feature in the cases reported herein.

The presence of splenomegaly in these rabbits provides evidence that an extravascular mechanism also contributed to the hemolytic anemia. Extravascular hemolytic destruction by splenic macrophages could have resulted from sequestration of schistocytes caused by the mechanical damage to the RBCs associated with the vegetative lesions or antibody-coated erythrocytes associated with *Achromobacter* infection. This hypothesis is supported in part by a *Streptococcus viridans* model of infective endocarditis, in which rabbits demonstrated reticulocytosis and splenomegaly due to RBC sequestration linked to the production of antierythrocytic antibodies.[12] Evidence of extravascular hemolysis in the presented cases was also supported by marked splenic histiocytosis with erythrophagocytosis and hemosiderosis. Coombs testing was not pursued, because species-specific reagents were not available.

As far we are aware, these rabbits represent only the third reported outbreak of *Achromobacter xylosoxidans* in the veterinary literature and demonstrates how ubiquitous environmental bacteria can cause substantial illness when contamination of surgical equipment or intravenous fluids occurs. Of interest in these cases is how *A. xylosoxidans* was able to seed the traumatized aortic valve associated with the heart failure model and cause infectious vegetative endocarditis. This case report is the first in the veterinary literature in which *A. xylosoxidans* has been implicated in causing infectious vegetative endocarditis. Of special interest in these cases is the manner in which the animals presented clinically: 8 of the 9 animals presented with anorexia, lethargy, and anemia. The primary cause of the anemia is presumed to be the result of intravascular processes associated with the vegetative lesions on the aortic valve, which resulted in fragmentary hemolytic anemia. Depending on use history, signalment, and diagnostic findings, hemolytic anemia, as indicated in this case report, may warrant thorough assessment of the heart to rule in or out infectious valvular endocarditis as a potential cause.

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