

## Standard Article

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## Cholangiohepatitis in Dairy Cattle: 13 Cases

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**Background:** The signalment, clinicopathologic, bacteriological, histopathological, ultrasonographic characteristics, and the treatment and outcomes of adult cattle with cholangiohepatitis are poorly defined.

**Animals:** Thirteen Holstein cows with cholangiohepatitis.

**Methods:** Retrospective study of medical records of cattle admitted to the CHUV and the AVC between 1992 and 2012 and 2000 and 2012, respectively, for cattle older than 3 months of age with a histopathological diagnosis of cholangiohepatitis. Cholangiohepatitis was defined as the presence of portal inflammation surrounding or infiltrating bile ducts, with or without epithelial damage, and extending into the adjacent lobules.

**Results:** At the time of diagnosis of cholangiohepatitis, cows had decreased appetite ( $n = 7$ ) or were anorectic ( $n = 6$ ), had fever ( $n = 5$ ), and had tachycardia ( $n = 8$ ). Icterus was detected in 5 cows. Yellow discoloration was identified on the skin of the udder ( $n = 3$ ), conjunctiva ( $n = 2$ ), and vulva ( $n = 1$ ). There was leukocytosis ( $n = 6$ ), neutrophilia ( $n = 9$ ), and hyperfibrinogenemia ( $n = 8$ ). Alteration in the serum biochemistry profile included hyperglobulinemia ( $n = 8$ ), hypoalbuminemia ( $n = 10$ ), increased activity of GGT ( $n = 12$ ), AST ( $n = 8$ ), and ALP ( $n = 10$ ), and hyperbilirubinemia ( $n = 10$ ). Histopathological diagnosis included mild, subacute, nonsuppurative cholangiohepatitis ( $n = 4$ ), mild suppurative cholangiohepatitis ( $n = 4$ ), mild mixed (neutrophilic and lymphocytic) cholangiohepatitis ( $n = 3$ ), and moderate, chronic, nonsuppurative cholangiohepatitis ( $n = 1$ ). Six cows were discharged from the hospital, and 7 were euthanized.

**Conclusions and Clinical Importance:** Cholangiohepatitis is a rare condition in adult cattle. Antemortem diagnosis can be challenging because clinical signs are unspecific.

**Key words:** Cholangitis; Cholestasis; Hepatic; Icterus.

Diseases of the biliary tract such as cholecystitis, cholangitis, and cholangiohepatitis in cattle are rare and result from both intrahepatic and extrahepatic causes.<sup>1</sup> By definition, cholecystitis describes the inflammation of the gallbladder and cholangitis describes the inflammation of the bile ducts. Almost inevitably, inflammation from the ducts spreads to the periportal hepatic parenchyma, creating lesions that can accurately be regarded as cholangiohepatitis.<sup>2</sup> Anecdotal reports have associated cholangiohepatitis with abdominal fat necrosis, choleliths, fascioliasis, foreign bodies, liver abscesses, neoplasia, and suppurative cholecystitis.<sup>3</sup> Cattle grazing on turnips or other brassica forage crops occasionally develop cholangiohepatitis.<sup>4</sup> Suppurative inflammation and ascending biliary tract infection by a wide variety of bacteria (both Gram-negative and Gram-positive enteric bacteria) have also been

**Abbreviations:**

ALP	alkaline phosphatase
AST	aspartate aminotransferase
AVC	Atlantic Veterinary College, University of Prince Edward Island, Canada
CBC	complete blood cell
CHUV	Centre Hospitalier Universitaire Vétérinaire de l'Université de Montréal
GGT	gamma-glutamyl transférerase
SBP	serum biochemistry profile
SDH	sorbitol dehydrogenase

associated with cholangiohepatitis in cattle.<sup>3</sup> However, there are a limited number of reports in the literature describing cholangiohepatitis in cattle.<sup>5,6</sup> Therefore, the objective of this retrospective study was to describe the signalment, history, clinicopathologic, bacteriological, and postmortem findings as well as treatments and outcomes of adult cattle diagnosed with cholangiohepatitis at the Centre hospitalier universitaire vétérinaire (CHUV) de l'Université de Montréal and the Atlantic Veterinary College (AVC), University of Prince Edward Island, Canada.

**Materials and Methods**

We searched medical records of cattle admitted to the CHUV and the AVC between 1992 and 2012 and 2000 and 2012, respectively, for cattle older than 3 months of age with a histopathological diagnosis of cholangiohepatitis. Cholangiohepatitis was defined as the presence of portal inflammation surrounding or infiltrating bile ducts, with or without epithelial damage, and extending into the adjacent lobules.<sup>2</sup> Records from cows with suspected cholangiohepatitis but missing liver biopsy or postmortem examination results were excluded.

We systematically reviewed medical records and extracted information about: age, sex, breed, month and year of hospitalization,

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presenting complaint, clinical signs before hospital admittance, and lactation stage. Data from clinical signs, complete blood count (CBC), serum biochemistry profile (SBP), and ultrasonographic findings from the date immediately before liver biopsy were performed or when cholangiohepatitis was included as a differential diagnosis was recorded. Information on liver biopsy, bacteriological culture, treatments, duration of hospitalization, and outcome was collected. Postmortem findings were reviewed.

## Results

### Signalment and History

At CHUV, 12 of 5,519 cases met inclusion criteria, whereas at AVC, 1 of 245 patients was included. The diagnosis of cholangiohepatitis was confirmed antemortem from a liver biopsy in 12 cases and during postmortem examination in 1 case. Cases included 12 Holstein cows and 1 Holstein heifer. The median age was 4 years (range: 0.4–7 years). Information regarding the lactation status was available for eleven of the twelve cows. Six cows were in the first 150 days of lactation, 1 cow was over 150 days of lactation, and 4 cows were dry. Reasons for veterinary consult included the following: fever ( $n = 5$ ), decreased appetite ( $n = 4$ ), colic ( $n = 2$ ), stranguria ( $n = 1$ ), sunburns ( $n = 1$ ), right displacement of the abomasum ( $n = 1$ ), and decreased milk and fecal output after omentopexy ( $n = 1$ ).

### Physical Examination

At the time of diagnosis of cholangiohepatitis, 6 cows were anorectic and 7 had decreased appetite. The median rectal temperature was 39°C (range: 37.7–40°C) and 5 cows were febrile (temperature >39.2°C). Median heart rate was 92 beats per minute (bpm) (range: 60–110 bpm), and 8 cows were tachycardic (HR >80 bpm). Icterus was detected in 5 cows. Yellow discoloration was identified on the skin of the udder ( $n = 3$ ), conjunctiva ( $n = 2$ ), and vulva ( $n = 1$ ). Hydration status was recorded for eleven cows: 7 cows were mildly (5–7%), 3 moderately (8–10%), and 1 severely (>10%) dehydrated. Characteristics of the feces were recorded in twelve cows; 6 cows had absent or scant feces, 3 had diarrhea, 1 had diarrhea with hematochezia, 1 had feces with partially digested fibers, and 1 had normal feces. Five cows had abdominal distension, and 4 had mild colic.

### Clinicopathological Findings

Hematologic findings included leucocytosis ( $>12 \times 10^9$  cells/L) in 6 cases (median:  $11 \times 10^9$  cells/L, range:  $6\text{--}26 \times 10^9$  cells/L), neutrophilia ( $>4 \times 10^9$  cells/L) in 9 cases (median:  $8 \times 10^9$  cells/L, range:  $2.3\text{--}19 \times 10^9$  cells/L), toxic changes identified in the neutrophil morphology in 4 cases, and hyperfibrinogenemia ( $>5$  g/L) in 8 cases (median: 7 g/L, range: 3–11 g/L). Alteration in the SBP included hyperglobulinemia ( $>4.5$  g/L) in 8 cases (median: 48 g/L, range: 20–65 g/L), hypoalbuminemia ( $<30$  g/dL) in 10 cases (median: 28 g/L, range: 19–35 g/L), increased GGT activity ( $>39$  IU/L) in twelve cases (median: 156 IU/L, range: 30–2,137 IU/L),

AST ( $>127$  IU/L) in 8 cases (median: 156 IU/L, range: 40–1411 IU/L), and ALP ( $>100$  IU/L) in 10 cases (median: 165 IU/L, range 34–385 IU/L). SDH activity values were available for 7 cases with 5 cases having increased SDH activity ( $>12$  IU/L, median: 24, range 4–2,309 IU/L). Hyperbilirubinemia ( $>14$   $\mu\text{mol/L}$ ) was detected in 10 cases (median 53  $\mu\text{mol/L}$ , range 7–188  $\mu\text{mol/L}$ ). In this study, 4 of 5 cases with icterus had a bilirubin concentration  $>77$   $\mu\text{mol/L}$  (range: 77–188  $\mu\text{mol/L}$ ), whereas 1 of 5 icteric cases had a bilirubin concentration of 9  $\mu\text{mol/L}$ . On the other hand, 1 of 8 without icterus had a bilirubin concentration of 124  $\mu\text{mol/L}$ , whereas 7 of 8 cases without icterus had a bilirubin concentration  $<56$   $\mu\text{mol/L}$  (range: 7–56  $\mu\text{mol/L}$ ). Icteric serum was noted in 5 cases. Serum bilirubin concentrations of all cases with icteric serum were  $>77$   $\mu\text{mol/L}$  (range: 77–188  $\mu\text{mol/L}$ ). Serial serum liver enzyme activity and bilirubin concentration from the time that cholangiohepatitis was suspected to the day of discharge or euthanasia were available in 6 cases (4 survivors and 2 nonsurvivors). Despite the clinical improvement of surviving cases, a marked improvement in the serum activity of hepatobiliary enzymes or hyperbilirubinemia was not noted during hospitalization.

### Ultrasonographic Findings

Transabdominal ultrasonographic examination results were available in 7 cases. Subjective abnormal findings included distension of the gallbladder ( $n = 4$ ), increased thickness of the wall of the gallbladder ( $n = 3$ ), presence of sediment in the gallbladder occupying two-thirds of the volume of the gallbladder ( $n = 2$ ), and increased diameter of the bile duct ( $n = 3$ ).

### Liver Biopsy Findings

Liver biopsy and bacteriological culture were performed in twelve of thirteen cases. Final histopathological diagnosis, using the description suggested previously,<sup>2</sup> included mild, subacute, nonsuppurative cholangiohepatitis ( $n = 2$ ), mild, chronic, nonsuppurative cholangiohepatitis ( $n = 2$ ), mild or severe, subacute, suppurative cholangiohepatitis ( $n = 4$ ), mild mixed (neutrophilic and lymphocytic) cholangiohepatitis ( $n = 3$ ), and moderate, chronic, suppurative cholangiohepatitis ( $n = 1$ ).

### Bacteriological Culture Findings

Bacteriological culture from liver biopsy tissue yielded growth in 3 of twelve cases in which it was performed. Bacterial isolation included *Bacteroides* spp. ( $n = 1$ ), *E. coli* ( $n = 1$ ), *E. coli*, and *Trueperella pyogenes* ( $n = 1$ ). In 1 animal, culture of the liver tissue obtained on necropsy yielded growth of a multidrug resistant *E. coli*. In 2 animals in which bacteriological cultures from liver biopsy were negative, however, *Salmonella* spp. was cultured from a fecal sample submitted during their hospitalization. Antimicrobial therapy was administered before biopsy procedure in 8 of twelve cows.

### **Comorbidities**

In addition to cholangiohepatitis, other diseases diagnosed included peritonitis (n = 3), photosensitization (n = 2), salmonellosis (n = 2), abomasal dilatation/displacement (n = 2), glomerulonephritis (n = 1), pyelonephritis (n = 1), enteritis of unknown origin (n = 1), and bronchopneumonia (n = 1).

### **Treatment and Hospitalization Time**

Treatment consisted of administration of broad-spectrum antibiotic treatment and supportive treatment with intravenous or oral fluids (12/13). Antimicrobial therapy included procaine benzyl penicillin (22,000 U/kg, IM q12h) (n = 10), trimethoprim-sulfadoxine (TMS, 16 mg/kg IV q12h) (n = 4), oxytetracycline (11 mg/kg IV or IM q12h) (n = 3), ampicillin (10 mg/kg IV q8h) (n = 2), ceftiofur (1 mg/kg IM q24h) (n = 2), and lincomycin (dose was not recorded) (n = 1). The number of days (median) of treatment with antimicrobials was 10 (range: 1–35 days). For surviving cases, the number of days of antimicrobial therapy ranged from 4 to 35 days. Two cows underwent a laparotomy—1 was to correct a right abomasal displacement, and the second was an exploratory laparotomy. In the exploratory laparotomy, a large distended gallbladder was palpated and no other abnormal findings were detected. After surgery, the cow developed suppurative peritonitis and bilirubin and biliary acids were detected on abdominocentesis.

### **Outcome**

Six cows were discharged from the hospital, whereas 7 were euthanized most likely due to poor prognosis or poor response to the instituted therapy. Three of 7 euthanized cows had chronic changes on the histopathology examination, and 1 had severe suppurative cholangiohepatitis. The median time of hospitalization for the surviving cows was 9.5 days (range: 8–12 days). The median time of hospitalization for non-surviving cows was 24 hours (range 1–10 days). Long-term follow-up was not studied for the surviving cattle.

### **Postmortem Examination Findings**

Postmortem examination was performed for 7 cows. The most common macroscopic lesion was a mild-to-severe increase in thickness of the gallbladder wall (n = 6). The presence of blood clots in the gallbladder was observed in 3 cows. The mucosal surface of the gallbladder showed different grades of multifocal ulceration and coalesced areas of ulceration with or without hemorrhage. Fibrin plaques admixed with necrotic material were commonly identified in the gallbladder (n = 4). In 2 cases, peritonitis and adhesions from the duodenum to the liver leading to obstruction of the bile flow were confirmed. Adhesions producing obstruction of the bile flow after omentopexy was confirmed in 1 case. Peritonitis of unknown origin was identified in 2 cases, but in both cases, peritonitis was suspected to

have occurred after bile flow obstruction. One cow was diagnosed with pyelonephritis, and 1 cow had glomerulonephritis.

### **Discussion**

The proportion of cattle diagnosed with cholangiohepatitis in this study confirmed that the disease appears to be rare. It is possible that the low prevalence of cholangiohepatitis found in this retrospective study could have been biased by the chosen case definition.<sup>7</sup> The diagnosis of cholangiohepatitis was established based on the histopathological findings on a liver biopsy or postmortem examination. Some cases of suspected cholangiohepatitis based on history, clinicopathologic examination, ancillary test, and ultrasonographic examination could have been treated symptomatically without a liver biopsy being performed, and therefore, some potential cases were likely missed. Also, postmortem examination archives at the teaching hospitals compile only the 2 or 3 most important diagnoses in each case. Those cases in which cholangiohepatitis was an incidental finding could also have been missed. Doing a search directly in the pathology records could have minimized this bias.

Cholangiohepatitis can be a primary or secondary disease.<sup>3</sup> In healthy cattle, a relatively sterile biliary duct system is preserved by the continuous flow of bile from the gallbladder and biliary tree through the sphincter of Oddi into the duodenum.<sup>8</sup> Primary cholangiohepatitis results from alteration of the normal bile flow, which leads to the ascending bacterial colonization of the biliary and hepatic tissue and results in cholangitis and cholangiohepatitis.<sup>1</sup> Secondary cholangiohepatitis results from obstruction of normal bile flow due to external mechanical pressure exerted on the common bile duct by liver abscesses, by extensive adhesions in the area of the cystic and common bile ducts, or by severe inflammatory lesions of the common duct near the hilus or the duodenal papilla.<sup>1</sup>

Due to the retrospective nature of this study, it was not possible to accurately determine in which cases primary or secondary cholangiohepatitis occurred. However, primary cholangiohepatitis was suspected in 4 cows in which comorbidities were not identified on physical or postmortem examination. Two of those cows had photosensitization as the primary complaint and was considered to be secondary to cholangiohepatitis and liver insult. The other 2 cows had acute septic peritonitis as the principal diagnosis, suspected to have resulted from a primary biliary obstruction. Secondary cholangiohepatitis was suspected in 9 cases where comorbidities were identified on physical examination, postmortem examination, or both. Comorbidities that could have resulted in secondary cholangiohepatitis included enteritis, adhesions of the small intestine blocking the biliary duct, renal infections, and abomasal displacement.<sup>1</sup>

The clinical signs of the cows with cholangiohepatitis reported in this study included anorexia, obtundation, fever, and colic. Although these signs are nonspecific,

they are observed consistently with cholangiohepatitis in different species.<sup>9–11</sup> Icterus is also commonly reported in cases of cholangiohepatitis.<sup>9,10</sup> It has been suggested that clinical icterus in cattle develops when serum bilirubin is greater than 51  $\mu\text{mol/L}$ .<sup>8</sup> In this study, icterus was present in 5 of 13 cows and serum bilirubin concentrations were greater than 77  $\mu\text{mol/L}$  in 4 of these 5 cows. Further, icteric serum was identified in 5 cows in which serum bilirubin was  $>77 \mu\text{mol/L}$ . These results support the current understanding that a marked increase in serum bilirubin occurs before jaundice becomes easily recognized.<sup>8</sup>

In this study, the majority of cows had increased activity of at least 5 variables (bilirubin, GGT, AST, ALP, and SDH). GGT, ALP, and bilirubin were consistently increased, demonstrating insult of the biliary tree. Neutrophilia, hyperfibrinogenemia, and hyperglobulinemia were also common findings consistent with an active inflammatory process. These findings were expected as it was likely that those changes prompted the clinicians to proceed with a liver biopsy to confirm the diagnosis of cholangiohepatitis. Increased serum activity of hepatobiliary enzymes or hyperbilirubinemia or both conditions are commonly reported in cases of cholangiohepatitis. Similar results have been reported in both horses and cattle with cholangiohepatitis.<sup>3,11–13</sup> It is possible that comorbidities such as peritonitis, pyelonephritis, or glomerulonephritis can also contribute to the increase in inflammatory markers. Importantly, cows suffering with hepatic lipidosis in combination with an inflammatory process (e.g. acute metritis or mastitis) can have similar laboratory results to the cattle with cholangiohepatitis found in this study. Therefore, the changes in CBC and SBP are not specific to cholangiohepatitis.

During ultrasonographic examination, distension of the gallbladder alone is not an indication of cholestasis as the volume of the gallbladder increases without any impairment of bile flow in anorexic cattle.<sup>14</sup> Abnormal gallbladder content, such as sediment or concretion, without thickening of the wall of the gallbladder can also be observed in anorexic cows with various diseases not specific to the liver.<sup>15</sup> However, distension of the gall bladder in combination with thickening of the wall and sediment due to inflammation suggests disease such as cholangiohepatitis.<sup>14,16,17</sup> Ultrasonographic findings compatible with cholangiohepatitis in cattle included distension and increased thickness of the wall of the gallbladder with the presence of sediment and increased diameter of the bile canaliculi.

In cattle with suspected cholestasis, the diagnostic approach should also include the histologic and bacteriological examination of a liver biopsy specimen. All the liver biopsy samples in this study were processed for aerobic and anaerobic culture, but only 3 samples yielded a positive result. These results are similar to those reported in horses. For instance, a previous study in horses with cholangiohepatitis revealed that only 2 of 9 liver biopsy samples submitted for both aerobic and anaerobic culture yielded a positive result. Negative bacteriological cultures were obtained in horses with or

without receiving prebiopsy antimicrobials.<sup>13</sup> It is possible that antimicrobial therapy administered before the biopsy procedure prevents positive results. However, culture can be negative in horses with cholangiohepatitis even in the absence of prior antimicrobial therapy.

In the present study, liver samples and gallbladder content yielded growth of *E. coli*, *Trueperella pyogenes* and *Bacteroides* spp. These findings were not unexpected. Several studies in humans, horses, dogs, and cattle have reported that enteric Gram-negative bacteria are frequently encountered in patients with cholangiohepatitis, cholelithiasis or both. Bile cultures are positive in 80–100% of humans who have cholangitis.<sup>18</sup> Enteric Gram-negative organisms including *E. coli*, *Klebsiella* spp., and *Enterococcus* spp. are commonly isolated from bile, and anaerobic bacteria such as *Clostridium* spp. and *Bacteroides* spp. are isolated more commonly in polymicrobial infections in humans who have severe disease.<sup>13,19–21</sup> Gram-negative enteric bacteria, such as *E. coli*, *Salmonella* spp., *Aeromonas* spp., *Bacteroides* spp., and *Citrobacter* spp., are associated with cases of cholangiohepatitis and cholelithiasis in horses.<sup>11,13</sup> Consistently, bacteria involved in previous reports of cholangiohepatitis in dogs were *E. coli*, *Klebsiella* spp., and *Clostridium* spp., which are all normal constituents of the intestinal flora.<sup>22</sup> In this study, *Salmonella* spp. was isolated from the feces, but not from liver tissue, of 2 cows suffering from enteritis, however, whether salmonella was the cause of cholangiohepatitis remains unclear.

Treatment in all cases was similar and consisted of antimicrobial therapy and supportive medical care. All 6 surviving cases were treated medically. In human medicine, medical treatment without surgery is effective in approximately 80% of patients.<sup>21</sup> There are 6 cases in the literature regarding cholangitis and cholangiohepatitis in dogs in which 4 of 6 responded to medical treatment alone.<sup>9,22,23</sup> In human medicine, antibiotics are given early when acute cholangitis is suspected. In this study, in surviving cases, the number of days on antimicrobial therapy ranged from 4 to 35 days. In humans, broad-spectrum antibiotics with adequate biliary excretion such as ampicillin, potentiated sulphas, and third- or fourth-generation cephalosporins and quinolones are widely used in empirical antimicrobial therapy of biliary tract infection.<sup>24–26</sup> Antimicrobial therapy for cattle suffering from cholangiohepatitis should be selected based on culture and sensitivity results from liver biopsy. However, in clinical practice, empirical antimicrobial therapy often needs to be instituted before culture results are available and must respect the judicious use of antibiotics. Initial treatment options for cattle with cholangiohepatitis include aminopenicillins (ampicillin), potentiated sulphas (trimethoprim-sulfadoxine, where allowed), third-generation cephalosporins (ceftiofur) as biliary excretion is one of the major routes of elimination for these antimicrobials.<sup>27</sup> Tetracycline can also be used for treatment of cholangiohepatitis. Tetracyclines are excreted in bile, they are reabsorbed from the intestine and returned to the liver (enterohepatic cycle) for reentry into systemic circulation.<sup>27</sup> Once

the microorganisms have been identified and their susceptibility has been determined, the antimicrobials should be adjusted to cover the identified microorganism.<sup>28</sup> The duration of antimicrobial therapy for surviving cows ranged from 4 to 35 days. In humans, the duration of antimicrobial therapy is based on the clinical response and the presence of bacteremia. For mild disease, antibiotics are generally continued for 5–7 days and for patients who have a positive blood culture, a 10–14 days course of antibiotics is recommended.<sup>21,24</sup> Long-term parenteral antimicrobials were associated with survival in horses<sup>13</sup> and dogs.<sup>9,22</sup> In this study, clinical improvement in surviving cattle during hospitalization was noted despite of a persistent increased in hepatobiliary enzyme activity and hyperbilirubinemia. Therefore, extended antimicrobial could be beneficial for cattle with cholangiohepatitis; however, the optimal duration of antimicrobial therapy in cattle cannot be withdrawn from the present study and remains to be established.

The pathological grading system failed to demonstrate any association between the severity and chronicity of the lesion and prognosis. Similar observations have been reported in horses.<sup>13</sup> It appeared that the diagnosis of cholangiohepatitis carried a guarded prognosis, at least in the small group of hospitalized cattle included in this study. It is possible that this study had a bias toward sicker patients, but such cattle seem to be representative of the population presented to referral teaching hospitals. The prognosis for cholangiohepatitis in dogs<sup>9,22</sup> and horses<sup>13</sup> appeared to be good, with most of the cases making a full recovery. Based on the information registered in the medical records used in this study, it was not possible to determine whether the reason for euthanasia was primarily cholangiohepatitis or comorbidities or both, and further deductions could not be drawn.

In conclusion, the results of this study revealed that cholangiohepatitis is a rare condition in adult cattle. Antemortem diagnosis may be challenging because clinical signs and laboratory results are unspecific. Diagnostic processes should include clinical history collection, physical examination, hematologic and serum biochemistry profile, ultrasonography imaging, and liver biopsy with bacteriological culture and histopathology examination. Initial treatment should include antimicrobials and supportive intravenous fluid therapy.

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*Conflict of Interest Declaration.* Authors declare no conflict of interest.

*Off-label Antimicrobial Declaration.* Authors declare no off-label use of antimicrobials.

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