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Clostridium sordellii–associated gas gangrene in 8 horses, 1998–2019

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Abstract. Gas gangrene occurs in several animal species and is caused by one or more clostridial species. In horses, the disease is most often caused by *Clostridium perfringens* type A. Although *Clostridium sordellii* has been associated with gas gangrene in ruminants and humans, cases of the disease associated with this microorganism have not been described in horses, to our knowledge. We report herein 8 cases of gas gangrene caused by *C. sordellii* in horses. These cases were characterized by myonecrosis and cellulitis, associated with systemic changes suggestive of toxic shock. The diagnosis was confirmed by gross and microscopic changes combined with anaerobic culture, fluorescent antibody test, immunohistochemistry, and/or PCR. The predisposing factor in these cases was an injection or a traumatic skin injury. *C. sordellii* should be considered as a possible etiologic agent in cases of gas gangrene in horses.

Key words: *Clostridium sordellii*; gas gangrene; horses; muscle; subcutaneous tissue.

Introduction

Gas gangrene (formerly known as malignant edema) is a rapidly progressing infection of muscle and subcutaneous tissue produced by one or more clostridial species, characterized by severe myonecrosis and/or cellulitis in humans and several animal species.[28,32] The pathogenesis of gas gangrene involves skin or mucosal wounds through which vegetative forms or spores of the clostridial species involved gain entry to the animal. At the port of entry, the organism multiplies rapidly and produces toxins that act locally and enter the bloodstream, producing toxic shock syndrome and multi-organ failure.[22,29] Septicemia is also a common complication of the disease.[8,28]

Gas gangrene in horses is most often caused by *Clostridium perfringens* type A,[23] although sporadic cases have been described in association with other clostridial species, including *C. septicum, C. chauvoei, C. novyi, C. ramosum, C. sporogenes*, and *C. fallax*.[2,5,7,14,23,24,28,37] The majority of cases of equine gas gangrene described in the literature have been produced by a single clostridial species, although mixed infections with 2 or more clostridial species have been reported occasionally.[15,23,27,37]

Clostridium sordellii is one of the members of the gas gangrene complex and has been described as a cause of gas gangrene in humans,[3,10,16,30] cattle,[38] and sheep,[20,35] and also in a series of cases of omphalitis in foals.[22] However, to our knowledge, cases of gas gangrene associated with *C. sordellii* have not been described in horses.

C. sordellii is a gram-positive, anaerobic bacillus, which is a common inhabitant of soil[29] and, rarely, the intestinal content of healthy animals. Most cases of clostridial gas gangrene, including those produced by *C. sordellii*, occur via contamination of wounds, including those associated with parturition and injections. Trauma-associated tissue necrosis generates local hypoxia, alkaline pH, and protein breakdown products required for clostridial proliferation.[26] In humans, clostridial toxic shock is a rare syndrome occurring postpartum and post-abortion, characterized by tachycardia, hypotension, and lack of fever.[39] The patients frequently progress to fatal toxic shock syndrome.[12]

Most strains of *C. sordellii* characterized to date encode sordellilysin (*sdl*), phospholipase C, and neuraminidase.[9] In addition, some *C. sordellii* isolates may produce lethal toxin (TcsL) and/or hemorrhagic toxin (TcsH), both of which are considered the main virulence factors for toxic shock syndrome in humans.[29,31] Although the role of these toxins in animal gas gangrene has not been determined, it is likely that the toxins play a role similar to that in human disease. We describe herein 8 equine cases of gas gangrene produced by *C. sordellii*.

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Table 1. Signalment, clinical history, main clinical signs, and affected region of 8 horses with gas gangrene caused by *Clostridium sordellii*.

Case	Age (y)	Sex	Breed	Clinical history	Main clinical signs	Anatomic region affected
1	NR	NR	NR	Vaccination (EHV-1, influenza, tetanus) 3 d before onset	Local edema and pain	Left side neck and chest
2	14	F	Quarter Horse	Vaccination (rabies) 3 d before onset	Anorexia and seizures	Left gluteal region
3	3	F	Arabian	Injection (selenium-tocopherol, DMSO) 2 d before onset	Local pain, colic, and shock	Lumbar region and both thighs
4	5	F	Quarter Horse	NR	Sudden death	Both thighs
5	20	F	NR	Traumatic skin wound before onset (interval NR)	NR	Left thigh
6	2	M	Appaloosa	Traumatic skin wound 5 d before onset	NR	Left thigh
7	19	F	Quarter Horse	Chronic cellulitis of unknown origin and duration	Anorexia	Both thighs
8	7	F	Quarter Horse	Traumatic skin wound 7 d before onset	Local edema and pain	Right shoulder

F = female; M = male; NR = not reported.

Materials and methods

We searched the records of the California Animal Health and Food Safety Laboratory System (CAHFS) at the University of California in Davis for cases of horses submitted for autopsy between 1998 and 2019 that had a diagnosis of gas gangrene that was attributed to *C. sordellii*. This included 8 cases in which: 1) the horses had severe necrotizing cellulitis and/or myositis, 2) *C. sordellii* had been isolated from the affected muscle and/or detected intralesionally by immunohistochemistry, fluorescent antibody test, and/or PCR, and 3) the horses had died spontaneously or been euthanized because of severe clinical disease associated with this infection (Table 1). An autopsy was performed in all cases. Three horses died (cases 2, 4, and 5), and 2 were euthanized (cases 3 and 8). Information on the manner of death was not available in cases 1, 6, and 7.

Samples of lung, liver, kidney, heart, skeletal muscle, stomach, small and large intestine, spleen, thymus, lymph node, uterus, ovary, adrenal gland, pituitary gland, thyroid gland, salivary gland, peripheral nerve, trachea, spinal cord, sciatic nerve, trigeminal ganglia, tongue, pancreas, urinary bladder, subcutaneous tissue, and/or the whole brain were collected in most cases and fixed in 10% neutral-buffered formalin (pH 7.2) for several days. The brains were then cut into ~0.5-cm thick slices, and fixed in fresh formalin for an additional 7–10 d; next, samples of parietal cortex, corpus striatum, thalamus, mid-brain at the level of rostral colliculi, pons, cerebellar peduncles, cerebellum, and medulla at the level of the obex were collected. All tissues were routinely processed to obtain 4-µm thick, hematoxylin and eosin–stained sections. In all cases, selected sections of subcutaneous tissue and muscle were also stained with Gram stain.

Samples of muscle and subcutaneous tissue from grossly affected areas, and multiple organs including one or more of liver, spleen, lung, skin, peripheral lymph nodes, peritoneal fluid, aqueous humor, and small intestinal and cecal content from most horses were collected aseptically, inoculated onto 5% sheep blood agar, and incubated aerobically and/or anaerobically at 37°C for 48 h (Table 2). Subsamples of most of these specimens were also inoculated into cooked meat medium and incubated anaerobically at 37°C for 48 h. All isolates were identified by conventional biochemical techniques.

Muscle smears of cases 1, 2, 7, and 8 were also subjected to direct fluorescent antibody test (FAT) for *C. sordellii, C. chauvoei, C. novyi*, and *C. septicum* as described previously[22] (Table 2). Reference strains of the clostridial species mentioned above were used as controls for each FAT preparation.

Immunohistochemistry (IHC) was performed on formalin-fixed, paraffin-embedded (FFPE) sections of skeletal muscle and subcutaneous tissue of cases 3, 4, 6, and 8 as described previously.[22] Briefly, a streptavidin–biotin kit was used according to the manufacturer's instructions (LSAB-peroxidase K675; Dako, Carpinteria, CA). Primary rabbit polyclonal antibodies against *C. sordellii* (VMRD, Seattle, WA) were used. Positive controls consisted of muscle sections of a horse from which *C. sordellii* had been isolated. Negative controls consisted of sections incubated with normal rabbit serum instead of the primary antibody, and of muscle sections of a healthy horse from which no anaerobes had been isolated.

PCR for 3 genes specific to *C. sordellii* [i.e., sordellilysin (*sdl*), lethal toxin of *C. sordellii* (*tcsL*), and hemorrhagic toxin of *C. sordellii* (*tcsH*)] was performed on muscle from cases 4, 6, and 8. For this, three 5-µm thick scrolls of FFPE skeletal muscle were placed into 1.5-mL microcentrifuge tubes for dewaxing by adding 1 mL of xylene, followed by centrifugation for 2 min at 13,000 × *g*. The xylene was then removed, and the pellet was washed with 1 mL of 100% ethanol and

Table 2. Microbiologic and molecular findings in skeletal muscle of 8 horses with gas gangrene caused by *Clostridium sordellii*.

Case	*C. sordellii* isolation	Gram stain	FAT		*C. sordellii* PCR			*C. sordellii* IHC	Other bacteria isolated
			C. sordellii	*C. chauvoei; C. septicum; C. novyi*	*sdl*	*tcsL*	*tcsH*		
1	+	+	–	–	NP	NP	NP	NP	–
2	+	+	+	–	NP	NP	NP	NP	–
3	+	–	NP	NP	NP	NP	NP	–	*C. perfringens*
4	+	+	NP	NP	+	+	–	+	*C. perfringens; Enterococcus* spp.
5	+	+	NP	NP	NP	NP	NP	NP	Mixed flora; *Streptococcus* sp. gamma-hemolytic*
6	+	+	NP	NP	+	+	–	+	*E. coli*
7	+	+	+	–	NP	NP	NP	NP	–
8	+	NP	+	–	+	+	–	+	Mixed flora; *Enterococcus* spp.

FAT = fluorescent antibody test; IHC = immunohistochemistry; + = positive; – = negative; NP = not performed.
* Bacteria isolated from a muscle different from which *C. sordellii* was isolated.

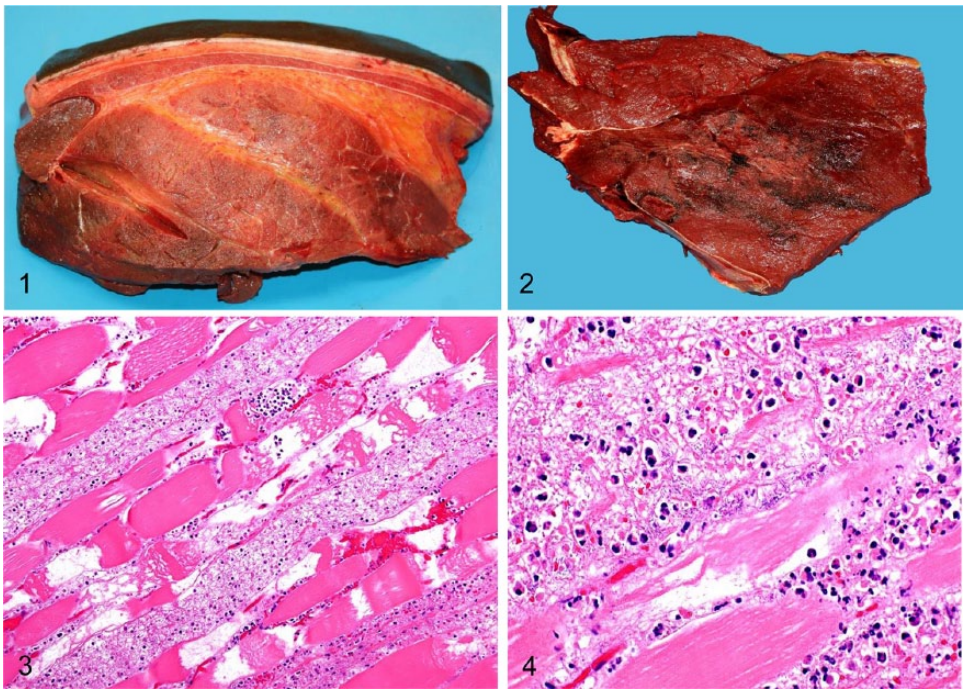
centrifuged for 2 min at 13,000 × *g*. The ethanol was discarded, and the samples were air-dried at room temperature for 45 min. Then, DNA was extracted from dewaxed tissues (QIAamp DNA FFPE tissue kit; QIAGEN, Hilden, Germany) following the manufacturer's instructions. The extracted DNA was used as template for conventional PCR detection of *sdl, tcsL*, and *tcsH* genes using the following sets of primers, respectively: 5'-CCATAAGTGGTGGTGCTTCG-3' (sdlF) and 5'-TGATTGCAGCGTATAAGCAAAT-3' (sdlR; 138 bp); 5'-GACCCAACGAAGAGTGGAGC-3' (TcsLF) and 5'-TCAAGTGTACCAGCAGGAGC-3' (TcsLR; 146 bp); 5'-GGGACACCTTCTGTAAGTGTAGG-3' (TcsHF) and 5'-AGGTTCAACTGTATGCCCAACT-3' (TcsHR; 133 bp). PCR was performed in a total volume of 25 µL containing 5 µL of extracted DNA, 0.25 µL of each primer (10 µM), 7 µL of nuclease-free water, and 12.5 µL of DreamTaq green PCR master mix 2× (Thermo Scientific, Waltham, MA), which contains DreamTaq DNA polymerase, 2× DreamTaq green buffer, dNTPs (0.4 mM each), and $MgCl_2$ (4 mM). The following thermocycler profiles were used: 95°C for 4 min, 35 cycles at 95°C for 30 s, 54°C for 30 s, and 72°C for 1 min followed by a final extension step at 72°C for 5 min, and a final hold at 4°C. DNA extracted from the *C. sordellii* JGS6382 strain was used as positive control. This strain is positive for *sdl, tcsL*, and *tcsH*. Scrolls from the *C. sordellii*–negative skeletal muscle used for IHC (see above) and reactions in which nuclease-free water was used instead of DNA were used as negative controls. PCR amplicons were visualized in ethidium bromide–stained 1.5% agarose gels (Agarose SFR; Amresco, Solon, OH).

Results

In cases 1–3 and 5–8, there was a history of skin injury that was thought to be the portal of entry for *C. sordellii.* No information about a possible portal of entry was available in case 4. The skin injuries were injections (cases 1–3), trauma (5, 6, and 8), and chronic cellulitis (7). The clinical signs were observed 2–7 d before death and included local edema (cases 1 and 8), pain (1, 3, and 8), anorexia (2 and 7), seizures (2), and colic and shock (3). No information about clinical signs was available for cases 5 and 6. Case 4 was found dead without clinical signs being observed.

Grossly, the lesions involved muscle and/or subcutaneous tissue underneath areas of skin injuries except for one case (case 4), in which no skin lesions were seen. In all cases, the affected subcutaneous tissue had extensive, moderate-to-severe, foul-smelling, yellow, gelatinous edema, and hemorrhage, which frequently extended into the underlying musculature, separating muscle bundles (Fig. 1). The muscle of these areas was multifocally dark red with irregular pale areas, and was friable, soft, and dry, often with gas bubbles (Fig. 2). The lungs were diffusely congested and edematous, and had petechiae throughout the parenchyma and on the pleura. The heart had epicardial, myocardial, and subendocardial petechiae and ecchymoses that were most marked in the left and right ventricle, but were also observed in both atria. In addition, ascites, hydrothorax, and hydropericardium were observed in cases 1, 4, 6, and 8. Diffuse mucosal edema and subserosal petechiae were observed in the colon of cases 1, 2, 4, 5, and 8.

Microscopically, the lesions in skeletal muscle were similar in all animals. There was multifocal-to-coalescing necrosis of muscle fibers, characterized by a diffuse, dense, eosinophilic, and glassy appearance of the cytoplasm, with loss of cross-striations, fragmentation, vacuolation, hypercontraction bands, mineralization, karyorrhexis, and karyolysis (Figs. 2, 3). Multifocally, within the cytoplasm of the necrotic myofibers, there were moderate numbers of degenerate and viable neutrophils, and fewer macrophages (Fig. 4). The interstitium and fascia were expanded by moderate-to-severe hemorrhage, edema, fibrin, neutrophils, and fewer



Figures 1–4. Skeletal muscle from horses with gas gangrene produced by *Clostridium sordellii*. **Figure 1.** Severe subcutaneous and interstitial edema. **Figure 2.** Focally extensive necrosis and hemorrhage. **Figure 3.** Coagulative necrosis, hemorrhage, edema, and neutrophil infiltration. H&E. **Figure 4.** Neutrophil infiltration within necrotic fibers, and large numbers of intralesional rods. H&E.

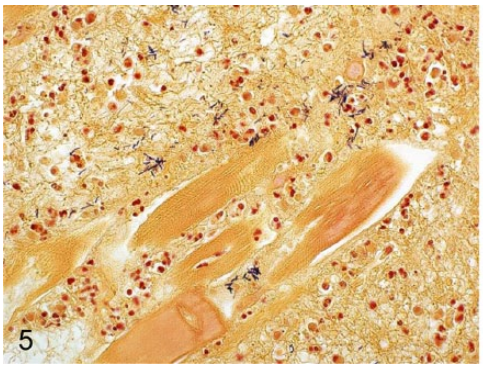
lymphocytes, plasma cells, and macrophages. The interstitium also had multifocal, large empty clear vacuoles with well-defined borders in cases 1–3 and 5–8, and large numbers of gram-positive rods, singly or in clusters (Fig. 5). These bacteria were ~5–7 µm × 0.8–1 µm, with parallel borders and round ends, and many of them had central or subterminal spores (Fig. 5). Fibrinoid, necrosuppurative vasculitis was observed in areas of muscle necrosis in cases 1 and 6. The subcutaneous tissue overlying the areas of myonecrosis in all cases showed pronounced expansion with edema, hemorrhage, fibrin, neutrophils, lymphocytes, plasma cells, and macrophages. The deep dermis was distended by fibrin, edema, and hemorrhage; blood vessels had multifocal and perivascular neutrophil infiltrates. In addition, cases 3, 5, and 7 had mild, multifocal myocardial necrosis, characterized by swollen myofibers with hypercontraction bands, which were surrounded by a mild neutrophilic and lymphoplasmacytic infiltrate. Multifocal, mild-to-severe interstitial hemorrhage was seen in endocardium, myocardium, and epicardium. The kidneys of cases 1–6 were congested, with homogeneous eosinophilic protein casts in the lumen of renal tubules. Acute proximal tubular necrosis was observed in cases 1 and 3.

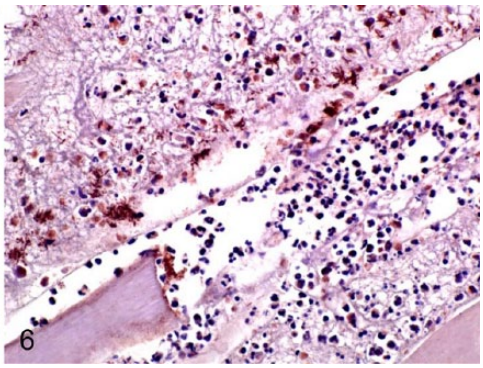
C. sordellii was isolated from muscle in all horses (Table 2). In addition, *C. perfringens* type A, *Streptococcus* spp., *Enterococcus* spp., *Escherichia coli*, and mixed aerobic and anaerobic flora were also isolated from affected muscle in cases 3–6 and 8. All 3 FFPE samples analyzed by PCR were positive for *C. sordellii sdl* and *tcsL* genes, but negative for the *tcsH* gene.

FAT for *C. sordellii* was positive in 3 of the 4 cases tested; FAT was negative for *C. chauvoei, C. novyi*, and *C. septicum* in the 4 cases. Sections of skeletal muscle and subcutaneous tissue from 3 of the 4 cases tested by *C. sordellii* IHC were positive (Fig. 6). The positive-stained bacteria were in the same location and had similar morphology to those described for the Gram-stained sections. Positive control tissues stained positively with FAT, and no staining was observed in any of the negative controls.

Discussion

We established a diagnosis of gas gangrene by *C. sordellii* on the basis of clinical history, gross and microscopic findings, and detection of the microorganism by bacterial culture, IHC, FAT, and/or PCR. Although Gram stain and IHC were negative in 1 case, *C. sordellii* was isolated from that animal, which, coupled with the gross and microscopic lesions, confirmed the diagnosis. It is likely that the sections used for IHC and Gram stain in that case were prepared from an area with low or no bacterial load, which resulted in negative IHC and Gram stain. The isolation of *C. sordellii* in pure culture from muscle of 3 horses and the supportive gross and microscopic lesions suggest that this microorganism can act as a primary pathogen to produce gas gangrene in horses.





Figures 5, 6. Muscle from horses with gas gangrene produced by *Clostridium sordellii*. **Figure 5.** Clusters of gram-positive rods. Gram stain. **Figure 6.** *C. sordellii* stained by immunohistochemistry.

Although *C. perfringens* type A was isolated in only small numbers in 2 cases, it is possible that it acted synergistically with *C. sordellii* to produce gas gangrene. Other microorganisms that can produce similar lesions in horses (e.g., *C. septicum, C. novyi*, and *C. chauvoei*) were ruled out by culture and/or FAT.

Clostridial gas gangrene has been reported in horses previously.[4,18,23,25,27,33,34] However, *C. sordellii* has not been reported associated with gas gangrene in horses to our knowledge. In a previous report of 37 cases of gas gangrene,[23] *C. perfringens* type A was isolated in purity in 25 cases, and in combination with other clostridia in 4 cases. Based on those results, the authors concluded that *C. perfringens* type A is the most common cause of gas gangrene in horses; *C. sordellii* was not isolated from any case.[23]

In a 2003 study, lesions consisted of severe necrotizing fasciitis and myositis in the region of the inciting wound, coupled with splenic, hepatic, renal, and/or myocardial necrosis.[23] In our cases, similar local and systemic lesions were observed, the latter suggesting that toxic shock syndrome also occurred. These lesions are similar to those described in cases of gas gangrene in several animal species.[20,28]

C. sordellii has been associated with multiple histotoxic infections in a variety of animals, including omphalitis in foals,[22] gas gangrene in ruminants,[20,35] emphysematous abomasitis in lambs,[36] and metritis in sheep.[6] This microorganism has also been blamed for sudden death syndrome in cattle[38] and lions.[11] Solid evidence for the role in the latter is, however, lacking. *C. sordellii* and its TcsL have also been suggested to be associated with equine atypical myopathy,[31] a condition also affecting skeletal muscle.

In humans, *C. sordellii* has been associated with fulminant necrotizing omphalitis in babies,[1,17,19] and endometritis and toxic shock syndrome in women.[21] The cause of death of humans with *C. sordellii* infection is thought to be septic shock, including disseminated intravascular coagulation. The toxins generated by the microorganism at the site of infection are thought to spread systemically, leading to septic shock.[13] The gross and microscopic findings described in the 8 horses of our study suggest that a similar mechanism of death occurred in these horses. In our study, a skin injury, either iatrogenic (injection) or accidental, was considered the portal of entry of the agent. This is consistent with most cases of gas gangrene reported previously in horses and other animal species.[24,25,27,33,34]

In humans, it is believed that 1 or 2 of the 2 main virulence factors of *C. sordellii* (TcsL and TcsH) are responsible for the main lesions and clinical signs observed in cases of gas gangrene.[10] TcsL triggers apoptosis of endothelial cells, leading to vascular compromise, edema, and shock.[12] The gene encoding TcsL was identified in the 3 cases available for PCR in our study, suggesting that this toxin might have been the main virulence factor responsible for these infections.

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Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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