The first case of Tyzzer's disease in a young foal in Italy: a case report

Nicola Ellero*, Aliai Lanci, Giancarlo Avallone, Jole Mariella, Carolina Castagnetti, Luisa Vera Muscatello, Chiara Di Maio and Francesca Freccero

Department of Veterinary Medical Sciences (DIMEVET), University of Bologna, Via Tolara di Sopra 50, Ozzano dell'Emilia, 40064 Bologna, Italy

*Corresponding author at: Department of Veterinary Medical Sciences (DIMEVET), University of Bologna, Via Tolara di Sopra 50, Ozzano dell'Emilia, 40064 Bologna, Italy.
E-mail: nicola.ellero3@unibo.it.

Veterinaria Italiana 2021, **57** (3), 239-246. doi: 10.12834/VetIt.1983.12227.1
Accepted: 27.05.2020 | Available on line: 31.12.2021

Keywords
Clostridium piliforme,
Foals,
Infectious necrotic hepatitis,
Tyzzer's disease.

Summary
Seizures, coma and death rapidly appeared after admission in a one-month-old foal with a history of lethargy, fever and anorexia. Severe icterus and necrotizing hepatitis were observed at necropsy. Clinical signs, laboratory and postmortem findings were compatible with a suspect of clostridial hepatitis. Tyzzer's disease was confirmed by the presence of organisms morphologically consistent with *Clostridium piliforme* in the hepatocytes at the margins of multiple areas of hepatic necrosis. To the authors' knowledge, this is the first reported case of clostridial hepatitis caused by *Clostridium piliforme* in a horse in Italy.

Introduction

Clostridium piliforme is the causative agent of Tyzzer's disease, an acute and fatal necrotizing hepatitis (Duncan *et al.* 1993). The number of species in which the disease has been reported, has rapidly increased in the last few years (Sellon and Long 2013a). It includes horse, cow, dog, cat, rat, mouse, hamster, gerbil, guinea pig, rabbit, muskrat, wombat, red panda, coyote, snow leopard, grey fox, raccoon and serval. This form of clostridial hepatitis is rarely observed in equids although some cases have been reported in foals (Pulley and Shively 1974, Harrington 1975, Harrington 1976, Whitwell 1976, Thomson *et al.* 1977, Dickinson 1980, Turk *et al.* 1981, Brown *et al.* 1983, Carrigan *et al.* 1984, Copland *et al.* 1984, Nold *et al.* 1984, Scarrat *et al.* 1985, Van Der Lugt 1985, Humber *et al.* 1988, Shirakawa *et al.* 1989, Peek *et al.* 1994, Appel and Burdinski 1995, St Denis *et al.* 2000, Borchers *et al.* 2006). United States, United Kingdom, Canada, Australia and New Zealand are the most affected countries (Pulley and Shively 1974, Harrington 1975, Harrington 1976, Turk *et al.* 1981, Whitwell 1976, Thomson *et al.* 1977, Carrigan *et al.* 1984, Dickinson 1980). In this report, we describe the clinicopathological and histological features of a case of equine clostridial hepatitis caused by *Clostridium piliforme* that, to the best of the authors' knowledge, is the first case of Tyzzer's disease reported in a horse in Italy. Possible environmental and management risk factors are also considered.

Case description

A thirty one-day-old Quarter Horse male foal, 96 kg in bodyweight, was referred to the Perinatology and Reproduction Unit (Equine Clinical Service, Department of Veterinary Medical Sciences) of the University of Bologna, following the acute onset of depression and anorexia. The foal was born from a 10-year-old Quarter Horse mare, with attended foaling, and had assumed colostrum from the udder. The placenta was macroscopically normal. The breeding farm was located in a mountain area in the Emilia-Romagna Apennines. The property, extended for 3.9 hectares, is bordered by a medium-sized torrent and thick forest. Moreover, a little calf stable was present in the farm. The breeding farm included forty-five horses: 2 stallions, 14 show horses, 7 mares with their respective suckling foals and 15 yearlings. A group of six foals, with their dams, was housed in a paddock with free access to a three-sided outdoor stall. Mares were fed with *ad libitum* hay and concentrate (13.0% protein, twice daily) diet during lactation and foals were also supplemented with 100 grams of concentrate (19.0% protein) for suckling

foals twice daily. The paddock was characterized by an earthy soil, without grass. The evening before hospitalization, the foal had shown less interest in following the mare and, in the next morning, it was found recumbent and too weak to stand up. The veterinarian referred that the foal was depressed and showed a low rectal temperature (34 °C). The foal was treated with dexamethasone (0.1 mg/kg iv), sodium hemisuccinate hydrocortisone (0.5 mg/kg iv), equine plasma (one liter iv), dimethyl sulfoxide (1 g/kg, 5% solution) and Lactated Ringer's solution (two liters iv). Due to the worsening of the clinical condition, the foal was then admitted to the clinic. At admission, the foal was recumbent, severely depressed and presented bilateral horizontal nystagmus. The rectal temperature was 39.9 °C. The respiratory rate was 56 breaths/minute, with increased abdominal effort. The heart rate was 120 beats per minute (bpm), with weak peripheral pulse, cool limbs and prolonged capillary refill time (3 seconds). The oral mucous membranes were dark red and sticky. Petechiae were present on ears and the upper lip. The right eye showed a severe hyphema and the sclerae were hyperaemic.

Venous blood was collected from jugular vein for bacteriology, haematology, biochemistry, serum immunoglobulin G (IgG) determination and blood gas analysis. Blood culture was performed using 10 mL of jugular blood withdrawn after clipping and aseptic preparation of the skin. The sampling needle was then discarded, and a new needle was used to inoculate the blood into the commercially available culture bottle (OXOID signal blood culture system, Oxoid Limited, Basingstoke, Hampshire, EN, UK). Hypoglycaemia (37 mg/dL, reference range 130 to 216 mg/dL; Corley and Stephen 2008) and hyperlactatemia (19.9 mmol/L, reference range 0.2 to 0.7 mmol/L; Corley and Sthepen 2008) were detected through rapid methods (Medisense Optium, Abbott Laboratories Medisense Products, Bedford, MA, US and Lactate SCOUT+, Gesellschaft zur Entwicklung und Herstellung, bioelektrochemischer Sensoren mbH, Leipzig, GE, EU, respectively). The adequate serum IgG level was confirmed by immunoturbidimetric method (DVM Rapid Test II, MAI Animal Health, Elmwood, WI, US): 1,618 mg/dL (reference range 930 to 1,930 mg/dL; Perkins and Wagner 2015). Total leucocyte count appeared normal (7,770 cells/mm^3, reference range 5,300 to 12,200 cells/mm^3; Corley and Stephen 2008), but the differential cell count showed lymphocytosis (5,370 cells/mm^3, reference range 1,730 to 4,850 cells/mm^3; Corley and Stephen 2008), monocytosis (1,620 cells/mm^3, reference range 50 to 630 cells/mm^3; Corley and Stephen 2008) and neutropenia (480 cells/mm^3, reference range 2,760 to 9,270 cells/mm^3; Corley and Stephen 2008). Serum amyloid A (SAA) concentration was 282 µg/dL and fibrinogen concentration was normal (3.27 g/L, reference range 2.0 to 7.0 g/L; Corley and Stephen 2008). The biochemistry profile showed increased total bilirubin (7.52 mg/dL, reference range 0.5 to 1.7 mg/dL; Corley and Stephen 2008), triglycerides (594 mg/dL, reference range 45 to 155 mg/dL; Corley and Stephen 2008), aspartate aminotransferase (2,053 U/L, reference range 252 to 440 U/L; Corley and Stephen 2008), bile acids (42.6 µmol/L, reference range 7.4 to 19.4 µmol/L; Barton and LeRoy 2007), creatine kinase (12,023 U/L, reference range 81 to 585 U/L; Corley and Stephen 2008), creatinine (2.25 mg/dL, reference range 1.1 to 1.8 mg/dL; Corley and Stephen 2008) and urea (46.71 mg/dL, reference range 6 to 21 mg/dL; Corley and Stephen 2008). Blood gas analysis revealed metabolic acidosis (pH 7.051, reference range 7.33 to 7.41; Corley and Stephen 2008) with hypocapnia ($PaCO_2$ 34.7 mmHg, reference range 46 to 64 mmHg; Corley and Stephen 2008) and decrease in bicarbonates (HCO_3 9.6 mmol/L, reference range 31.6 to 37.7 mmol/L; Corley and Stephen 2008). Electrolyte imbalances included hyponatremia (133 mmol/L, reference range 136 to 154 mmol/L; Corley and Stephen 2008) and hypocalcemia (total calcium 0.9 mmol/L, reference range 2.7 to 3.3 mmol/L; Corley and Stephen 2008). Blood culture was negative.

To provide respiratory support, intranasal oxygen therapy was started at 8 litres per minute (LPM). Intravenous (iv) therapies were administered through a jugular vein catheter. Broad-spectrum antimicrobial therapy was initiated with sodium ampicillin (50 mg/kg iv QID) and amikacin sulfate (30 mg/kg iv SID). Initial fluid therapy included 5% dextrose at 5.0 mL/kg/h and Lactated Ringer's solution at 5.2 mL/kg/h. Within thirty minutes of hospitalization, seizures started and diazepam (0.4 mg/kg iv) was administered. Despite treatments, the clinical condition rapidly progressed to high fever (40.7 °C), severe dyspnea and further seizures. Flunixin meglumine (1.1 mg/kg iv) and butorphanol (0.04 mg/kg iv) were administered and the foal was then intubated through the mouth with a sterile endotracheal silicone tube (14.3 mm in diameter, 55 cm in length). The tube was attached to a self-inflating resuscitation bag (Ambu bag), connected to an oxygen supply (8 LPM), and supported ventilation was started at 10 breaths per minute. The condition deteriorated to refractory pyrexia (42.5 °C), cyanotic mucous membranes, shock and death within two hours of hospitalization.

Due to the onset of central nervous system (CNS) signs, immediately after death a cerebrospinal fluid (CSF) sample was collected through cisternal puncture method. The biochemistry profile showed increase in lactate dehydrogenase (90 U/L, reference range 0 to 8 U/L; Corley and Stephen 2008) and

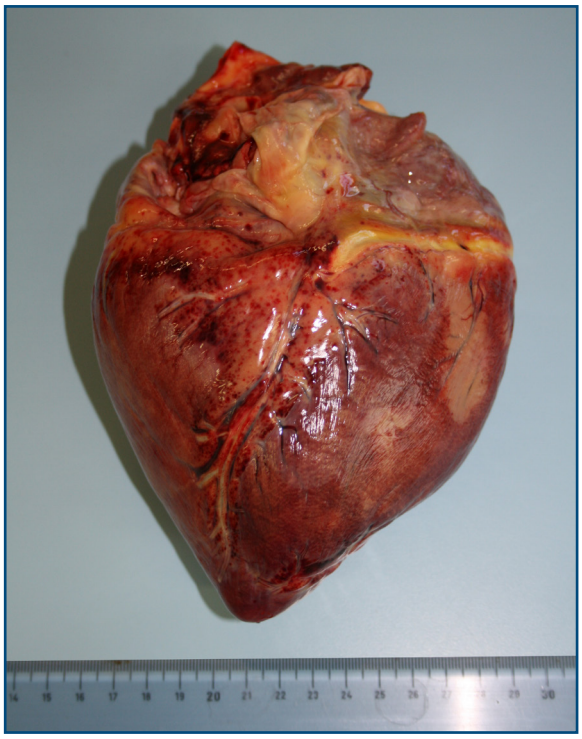

Figure 1. *Foal, heart.* Epicardial surface is affected by multifocal petechial hemorrhages.

decrease in glucose (26 mg/dL, reference range 30 to 70 mg/dL; Corley and Stephen 2008), while total proteins were normal (112.41 mg/dL, reference range 10 to 120 mg/dL; Corley and Stephen 2008).

At necropsy, a severe yellow discoloration was evident on mucosal surfaces, and multiple, disseminates petechiae were present on all serosal surfaces, being more evident on the epicardium (Figure 1), and in the CNS. Hepatic parenchyma was characterized, on cut surface, by multifocal, few

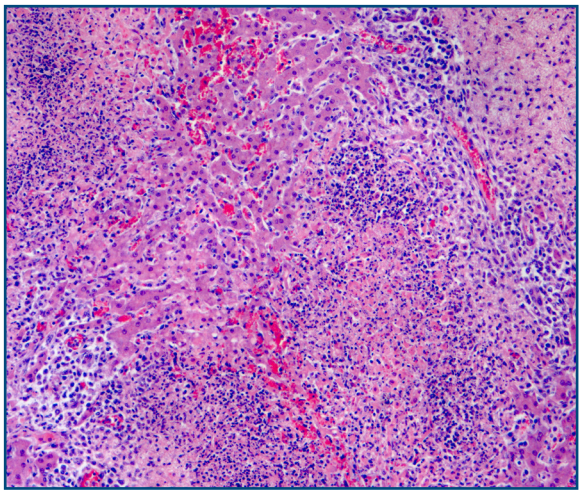

Figure 3. *Foal, liver.* Histological section of liver characterized by multifocal areas of necrosis bordered by degenerated neutrophils. Hematoxylin and eosins stain.

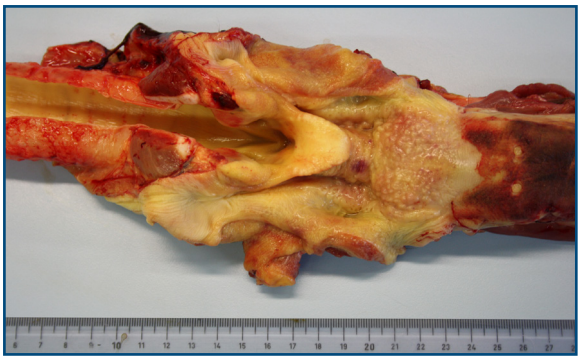

Figure 2. *Foal, pharynx. Pharyngeal mucosa is diffusely and moderately thickened by follicular inflammatory infiltrate.*

millimeters in diameter, yellowish foci. Additional gross lesions included a mild follicular pharyngitis (Figure 2) and moderate meningeal hyperemia. Histologically, the liver was characterized by multifocal to coalescing, randomly distributed, foci of coagulative necrosis infiltrated by small number of degenerated neutrophils (Figure 3). Within the cytoplasm of hepatocytes adjacent to necrotic foci, a moderate number of intracytoplasmic filamentous bacteria, evidenced with Giemsa and Warthin Starry stains, were clear and were morphologically consistent with *Clostridium piliforme* (Figure 4). Brain sections revealed multiple bilateral and asymmetrical perivascular microhemorrhages consistent with diffuse endothelial damage secondary to septicemia.

Discussion

Tyzzer's disease is characterized by an acute necrotizing hepatitis caused by *Clostridium piliforme*, a spore-forming, gram-negative, motile, obligate intracellular bacillus (Duncan *et al.* 1993).

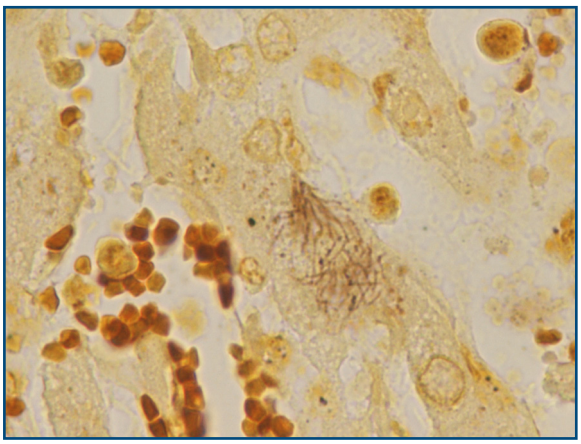

Figure 4. *Foal, liver.* Numerous intracellular filiform bacteria are evidenced within the cytoplasm of hepatocytes adjected to necrotic areas. Warthin Starry stain.

Although the organism has often been reported to be gram-negative in tissue sections, it can also appear as gram-variable or gram-positive if fixation and staining are done under anaerobic conditions (Duncan *et al.* 1993). The organism can be found in form of spores in the environment and its spreading may be due to the movement of the soil. In equine species, adults are rarely affected but they may be sources and carriers of infection to susceptible foals. The most likely route of infection in foals is through ingestion of spores shed in the feces of adult carrier horses (Swerczek *et al.* 1973, Humber *et al.* 1988). Foals normally consume freshly feces from their dams during the second to fifth week of age (Francis-Smith and Wood-Gush 1977). Interestingly, foals are affected at 1 to 5 weeks of age (Swerczek *et al.* 1973, Chanter 1995, Fosgate *et al.* 2002). Others species susceptible to infection, such as rodents and rabbits, are possible source of environmental contamination, since the infection is confined to the gastrointestinal tract (Ganaway *et al.* 1971). The breeding farm, in the presented case, is bordered by a torrent, on one side, and thick forest on three sides. In association with the presence of a little calf stable, it is not possible to exclude contacts between horses and wild animals, such as rodents.

The predisposing factors for Tyzzer's disease include age of foals (9 to 30 days), time of the year of their birth (April to May), rainfall in the spring and high protein and nitrogenous diets fed to nursing mares (Swerczek 2013). Passive transfer of *Clostridium piliforme*-specific antibodies through colostrum may play a role in foals' protection (Hook *et al.* 1995). Foals born to non-resident mares or less than 6 year-old mares, having a lower quality of colostrum (LeBlanc *et al.* 1992), were more likely to develop Tyzzer's disease (Fosgate *et al.* 2002), suggesting that variability in colostral quality may be a potential risk factor. In the presented case, the colt was born in April and had been admitted to the clinic in May, at one-month of age. The authors do not have information about the level of serum IgG after the ingestion of colostrum but at admission it was appropriate, considering the admin-istration of equine plasma by the referring veterinarian shortly before hospitalization. There is also no information about antibody status towards *Clostridium piliforme* of the mare and the other members of the group. Both the mare and the foal were supplemented with high protein concentrate but no information is available regarding the quality of the forage and the pasture composition. During the month before admission, the paddock was characterized by an earthy soil, without grass, and the weather was characterized by a mean temperature of 5.5 °C and a high level of humidity (91.1%), precipitation (25 rainy days out of 31) and wind (21.7 km/h). Following the case described here, the owner reported that the five other suckling foals have shown fever, which responded to ceftiofur (5 mg/kg im twice a day) for five days, with no further deterioration in their clinical condition.

In some of the previously reported cases, foals were found dead on pasture without previous clinical signs but often infected foals showed weakness, pyrexia, tachypnea and icterus (Carrigan *et al.* 1984, Scarratt *et al.* 1985). Some foals showed a yellowish liquid diarrhea. After ingestion, spores replicated in the gastrointestinal tract and reached the liver through hepatic portal system, where they caused necrotizing hepatitis. The subsequent septicemia was responsible for the myocarditis, colitis and pulmonary hemorrhage. Hepatic encephalopathy finally ensued and death occurred after appearance of CNS signs: seizures and coma rapidly appeared within 2 to 48 hours (Swerczek *et al.* 1973, Whitwell 1976, Turk *et al.* 1981). In the present case, the foal had shown depression and loss of suckle reflex the evening before hospitalization and has developed signs of sepsis (fever, tachycardia, tachypnea, hypoperfusion, petechiae) in the next twelve hours. CNS signs, such as horizontal nystagmus, were present at admission, seizures appeared after thirty minutes and death occurred within two hours. In this case, histological findings consistent with hepatic encephalopathy were not evident, and neurological signs were more likely secondary to the microhemorrhages caused by the septicemic status.

Previously reported hematological and biochemical findings included leukopenia, elevated serum fibrinogen, hypoglycemia, metabolic acidosis, elevated bilirubin and increase in hepatic enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) (Brown *et al.* 1983, Humber *et al.* 1988, Swerczek 2013). In this case, severe neutropenia was present, reflecting the hyperacute course of the disease. Hypoglycemia, hyperlactatemia likely due in part to hypoperfusion, metabolic acidosis and electrolyte imbalances were also present, which can all be attributed either to compromised liver function or septicemia. In the biochemistry profile, increased AST activity was associated with liver disease, such as acute liver failure or cholangiohepatitis, in association with increased bile acids, sign of decreased liver function (Barton and LeRoy 2007), and increased total bilirubin, sign of intra- or extrahepatic obstruction. No alterations were detected in ALT, ALP and γ-glutamyl transferase activities. CSF analysis showed increase in LDH and decrease in glucose, while total protein was normal. In human medicine, elevated LDH level was observed in the CSF of patients with bacterial meningitis, because this enzyme may be secreted by granulocytes (Lampl *et al.* 1990). CSF glucose concentration was probably

due to hypoglycaemia, as it was more than 50% of the serum glucose concentration (Hussein and Shafran 2000). Normal level of CSF total protein was probably due to the preserved permeability of the blood-brain barrier. Neutrophilic pleocytosis and increased total protein are the most commonly reported findings in the CSF of horses with infectious meningitis (Corley and Stephen 2008, Furr 2008), although cases with normal CSF cell counts have been described (Pellegrini-Masini and Livesey 2006). In this case, total nucleated cell count and intracellular bacteria in the CSF sample were not evaluated but it is not possible to exclude certainly a diagnosis of bacterial meningoencephalitis due to the histopathological evidence of multiple perivascular microhemorrhages in the CNS.

In the majority of cases, foals responded temporarily to fluid therapy, antimicrobial and anti-inflammatory drugs and parenteral nutrition, but then rapidly deteriorated and succumbed to the disease (Scarratt *et al.* 1985, Humber *et al.* 1988, St Denis *et al.* 2000). In the reported case, oxygen, antimicrobial and fluid therapies did not improve the clinical condition of the foal. Pyrexia and seizures were refractory to nonsteroidal anti-inflammatory drugs and benzodiazepines, respectively. Successful treatment has been reported only in one presumptive case (Peek *et al.* 1994) and in one confirmed case (Borchers *et al.* 2006) of Tyzzer's disease, reflecting the poor prognosis. Interestingly, the foal was treated with corticosteroids by the referring veterinarian before hospitalization. The effects of corticosteroids are numerous and include alteration of cytokine production, decreased adhesion molecule and immunoglobulin receptor expression, and decreased phagocytosis and cell migration (Sellon and Long 2013b). In horses, corticosteroids induce an increase in peripheral blood neutrophil and a decrease in lymphocyte concentrations (Burguez *et al.* 1983). From studies conducted in laboratory animals, the severity of Tyzzer's disease varies with the host immune status. The disease is more severe in young mice with immature immune systems than in adults, and iatrogenic immunosuppression increases susceptibility of all mice to *Clostridium piliforme* infection (Riley *et al.* 1990). For these reasons, immune suppressive therapies seem to increase the severity of the disease even in infected foals.

Classical gross findings of Tyzzer's disease have been detected in the presented case, including hepatomegaly with multifocal areas of necrosis in the hepatic parenchyma (Harrington 1975, Harrington 1976, Whitwell 1976, Thomson *et al.* 1977, Carrigan *et al.* 1984, Nold *et al.* 1984, Scarratt *et al.* 1985). The hepatic and mesenteric lymph nodes often appeared hyperplastic and edematous (Pulley and Shively 1974, Harrington 1975, Whitwell 1976, Carrigan *et al.* 1984, Nold *et al.* 1984, Copland *et al.* 1984, Scarratt *et al.* 1985, Humber *et al.* 1988). Petechiae and ecchymosis featured the serosal surface of the diaphragm, heart, small and large intestine (Whitwell 1976, Turk *et al.* 1981, Scarratt *et al.* 1985, Van Der Lugt 1985, Humber *et al.* 1988, St Denis *et al.* 2000). The gastrointestinal tract showed a semi-solid or liquid contents, often yellowish, and subcutaneous or visceral icterus was present (Harrington 1975, Harrington 1976, Copland *et al.* 1984, Humber *et al.* 1988, St Denis *et al.* 2000).

Clinical signs, laboratory and postmortem findings suggested a presumptive diagnosis, which was confirmed by pathognomonic histopathologic findings of multifocal areas of liver necrosis and hepatitis (Carrigan *et al.* 1984, Copland *et al.* 1984, Nold *et al.* 1984, Scarratt *et al.* 1985, Van Der Lugt 1985, Humber *et al.* 1988, Paar *et al.* 1993, St Denis *et al.* 2000). In the center of the necrotic areas, hepatocytes were destroyed and replaced by red blood cells, neutrophils and mononuclear cells. At the periphery of the necrotic areas, hepatocytes contained intracellular filamentous bacilli, highlighted with Warthin-Starry silver stains (Ganaway *et al.* 1971). Histologic hepatic lesions in the presented case were consistent with this description. Bacilli and microscopic inflammatory changes might be present in the hepatic lymph nodes, in the intestinal mucosal cells and in myocardial cells (Whitwell 1976, Carrigan *et al.* 1984, Humber *et al.* 1988), but were not detected in the present case.

Clostridium piliforme is very difficult to culture from clinical or postmortem samples (Ganaway *et al.* 1971, Franklin *et al.* 1994). In fact, in the presented case, blood culture was negative, in face of the evidence of hematogenous spread. The bacterium can be isolated in the yolk sac of developing chicken embryos (Ganaway *et al.* 1971). A recently developed real-time polymerase chain reaction (qPCR) assay represents a valid diagnostic test (Borchers *et al.* 2006). The PCR, targeting 16S ribosomal ribonucleic acid (rRNA) genomic sequences, can detect the organism in both antemortem and postmortem liver samples of foals with clinical signs and provides early diagnosis and opportune treatment. In this case, differential diagnosis were based on clinical signs, laboratory and postmortem findings and included acute hepatitis, bacterial septicemia and toxic hepatitis. Tyzzer's disease was confirmed by the presence of organisms morphologically compatible with *Clostridium piliforme* in the hepatocytes, in association with anamnesis, clinical signs and age of the foal.

This is the first reported case of Tyzzer's disease in a horse in Italy but in the authors' opinionmany other cases might have been misdiagnosed. Foals found dead on pastures should undergo postmortem

examination with the aim of detecting the causative agent specific qPCR or histopathological techniques.

Among the preventive strategies, paddock management is essential in horse farms with a history of Tyzzer's disease: young foals should graze in healthy environment characterized by well-grassed paddocks, free from potentially contaminated soil. Excessive number of horses entering and leaving the farm and temporary holding fences used by a large number of horses should be avoided, because they can increase the incidence of infection. Although there are no information about the survival of the endospores on open pastures, they are sensitive to exposure to 0.4% peracetic acid, 0.015% sodium hypochlorite, 1% idophol and 5% phenol (Ganaway 1980, Itoh *et al.* 1987). In the present case, the foal shared the paddock with other foals and mares. For these reasons, the authors have advised the owner to isolate each foal from adult horses excepting their dams, to remove horse manure daily and to clean farm areas with one of the appropriate chemical disinfectants.

Environmental hygiene and high-quality colostrum remain the only ways of prevention Tyzzer's disease in foals. Although the mortality rate of the disease is high, successful outcome seems possible if intensive care and antimicrobial therapy are initiated promptly (Borchers *et al.* 2006).

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors wish to thank the referring veterinarian Doctor Andrea Banchio.

References

Appel G. & Burdinski K. 1995. Tyzzer's disease in a pony foal from Schleswig-Holstein. *Dtsch Tierarztl Wochenschr*, **102** (5), 204-205.

Barton M.H. & LeRoy B.E. 2007. Serum bile acids concentrations in healthy and clinically Ill neonatal foals. *J Vet Int Med*, **21** (3), 508-513.

Borchers A., Magdesian K.G., Halland S., Pusterla N. & Wilson W.D. 2006. Successful treatment and polymerase chain reaction (PCR) confirmation of Tyzzer's disease in a foal and clinical and pathologic characteristics of 6 additional foals (1986-2005). *J Vet Int Med*, **20** (5), 1212-1218.

Brown C.M., Ainsworth D.M., Personett L.A. & Derksen F.J. 1983. Serum biochemical and haematological findings in two foals with focal bacterial hepatitis (Tyzzer's disease). *Equine Vet J*, **15** (4), 375-376.

Carrigan M.J., Pedrana R.G. & McKibbin A.W. 1984. Tyzzer's disease in foals. *Aust Vet J*, **61** (6), 199-200.

Chanter N. 1995. Infection of horses by Tyzzer's bacillus. *Equine Vet J*, **27** (1), 1-3.

Copland M.D., Robartson C.W., Fry J. & Wilson G. 1984. Tyzzer's disease in a foal. *Aust Vet J*, **61** (9), 302-304.

Corley K.T.T. & Stephen J. 2008. The equine hospital manual. Appendix (K.T.T. Corley & J. Stephen, eds). Blackwell, Oxford, 654-689.

Dickinson L.G. 1980. Tyzzers disease in foals. *New Zealand Vet J*, **28** (4), 60.

Duncan A.J., Carman R.J., Olsen G.J. & Wilson K.H. 1993. The agent of Tyzzer's disease is a *Clostridium* species. *Clin Infect Dis*, **16** (Suppl. 4), S422.

Fosgate G.T., Hird D.W., Read D.H. & Walker R.L. 2002. Risk factors for *Clostridium piliforme* infection in foals. *JAVMA*, **220** (6), 785-790.

Francis-Smith K. & Wood-Gush D.G.M. 1977. Coprophagia as seen in thoroughbred foals. *Equine Vet J*, **9** (3), 155-157.

Franklin C.L., Motzel S.L., Besch-Williford C.L., Hook Jr R.R. & Riley L.K. 1994. Tyzzer's infection: host specificity of *Clostridium piliforme* isolates. *Lab Anim Sci*, **44** (6), 568-572.

Furr M.O. 2008. Bacterial infections of the central nervous system. *In* Equine neurology (M.O. Furr & S. Reed, eds). Wiley-Blackwell, Oxford, 187-194.

Ganaway J.R. 1980. Effect of heat and selected chemical disinfectants upon infectivity of spores of *Bacillus piliformis* (Tyzzer's disease). *Lab Anim Sci*, **30** (2 Pt 1), 192-196.

Ganaway J.R., Allen A.M. & Moore T.D. 1971. Tyzzer's disease. *Am J Pathol*, **64** (3), 717-730.

Harrington D.D. 1975. Naturally-occurring Tyzzer's disease (*Bacillus piliformis* infection) in horse foals. *Vet Rec*, **96** (3), 59-63.

Harrington D.D. 1976. *Bacillus piliformis* infection (Tyzzer's disease) in two foals. *JAVMA*, **168** (1), 58-60.

Hook R.R., Riley L.K., Franklin C.L. & Besch-Williford C.L. 1995. Seroanalysis of Tyzzer's disease in horses: implications that multiple strains can infect *Equidae*. *Equine Vet J*, **27** (1), 8-12.

Humber K.A., Sweeney R.W., Saik J.E., Hansen T.O. & Morris C.F. 1988. Clinical and clinicopathologic findings in two foals infected with *Bacillus piliformis. JAVMA*, **193** (11), 1425-1428.

Hussein A.S. & Shafran S.D. 2000. Acute bacterial meningitis in adults. A 12-year review. *Medicine*, **79** (6), 360-368.

Itoh T., Ebukuro M. & Kagiyama N. 1987. Inactivation of *Bacillus piliformis* spores by heat and certain chemical disinfectants. *Exp Anims*, **36** (3), 239-244.

Lampl Y., Paniri Y., Eshel Y. & Sarova-Pinhas I. 1990. LDH isoenzymes in cerebrospinal flu-id in various brain tumours. *J Neurol Neurosurg Psychiatry*, **53** (8), 697-699.

LeBlanc M.M., Tran T., Baldwin J.L. & Pritchard E.L. 1992. Factors that influence passive transfer of immunoglobulins in foals. *JAVMA*, **200** (2), 179-183.

Nold J.B., Swanson T. & Spraker T.R. 1984. *Bacillus piliformis* infection (Tyzzer's disease) in a Colorado foal. *JAVMA*, **185** (3), 306-307.

Paar M., Stockhofe-Zurwieden N., Pohlmeyer G., Gerhards H. & Pohlenz J. 1993. Infection with *Bacillus piliformis* (Tyzzer's disease) in foals. *Schweiz Arch Tierheilkd*, **135** (3), 79-88.

Peek S.F., Byars T.D. & Rueve E. 1994. Neonatal hepatic failure in a Thoroughbred foal: successful treatment of a case of presumptive Tyzzer's disease. *Equine Vet Edu*, **6** (6), 307-309.

Pellegrini-Masini A. & Livesey L.C. 2006. Meningitis and encephalomyelitis in horses. *Vet Clin: Equine Pract*, **22** (2), 553-589.

Perkins G.A. & Wagner B. 2015. The development of equine immunity: current knowledge on immunology in the young horse. Equine Vet J, **47** (3), 267-274.

Pulley L.T. & Shively J.N. 1974. Tyzzer's disease in a foal. Light-and electron-microscopic observations. *Vet Pathol*, **11** (3), 203-211.

Scarratt W.K., Saunders G.K., Welker F.H., Halpern N.E., Cordes D.O. & Camp G.M. 1985. *Bacillus piliformis* infection (Tyzzer's disease) in two Virginia foals. *J Equine Vet Sci*, **5** (3), 135-138.

Sellon D.C. & Long M. 2013. Equine infectious diseases. Elsevier Health Sciences, 370.

Shirakawa T., Maruyama K., Nakamura N., Awakura T., Ohishi H., Senba H. & Matsui T. 1989. Tyzzer's disease in a foal. *Nippon Juigaku Zasshi*, **51**, 444-446.

St Denis K.A., Waddell-Parks N. & Belanger M. 2000. Tyzzer's disease in an 11-day-old foal. *Canadian Vet J*, **41** (6), 491-492.

Swerczek T.W. 2013. Tyzzer's disease in foals: retrospective studies from 1969 to 2010. *Canadian Vet J*, **54** (9), 876-880.

Swerczek T.W., Crowe M.W., Prickett M.E. & Bryans J.T. 1973. Focal bacterial hepatitis in foals: preliminary report. *Modern Vet Pract*, **54** (11), 66-67.

Thomson G.W., Wilson R.W., Hall E.A. & Physick-Sheard P.

1977. Tyzzer's disease in the foal: case reports and review. *Canadian Vet J*, **18** (2), 41-43.

Turk M.A., Gallina A.M. & Perryman L.E. 1981. *Bacillus piliformis* infection (Tyzzer's disease) in foals in northwestern United States: a retrospective study of 21 cases. *JAVMA*, **178** (3), 279-281.

Van Der Lugt C.H.B. 1985. Suspected Tyzzer's disease in two foals. *J S Afr Vet Assoc*, **56** (2), 107-108.

Whitwell K.E. 1976. Four cases of Tyzzer's disease in foals in England. *Equine Vet J*, **8** (3), 118-122.