*Case Report*

# Pulmonary embolism as a complication after abdominal surgery and colitis in a foal

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## Summary

This report describes a fatal pulmonary embolism in a foal, as a sequela of septic thrombophlebitis of the right jugular vein and/or a generalised hypercoagulable state. The foal underwent abdominal surgery and suffered from severe and prolonged colitis. Despite intense supportive care, the colt developed venous thrombophlebitis and subsequently died suddenly 12 days after discharge from the hospital, following an initial improvement. On post-mortem examination, a large pulmonary embolism was discovered. Pulmonary thromboembolism is a potentially fatal sequelae of thrombus formation. It is difficult to detect and therefore likely to be underdiagnosed.

## Introduction

Pulmonary embolism (PE) accounts for 5–15% of deaths in human hospitalised patients in the USA. However, a survey of the recent equine literature revealed only a single case series in detailing pulmonary thromboembolism in six horses (fatal in three) (Norman *et al.* 2008) and a separate case report which described pulmonary thrombosis in a single foal (Barton *et al.* 1998). Our report details a case of sudden death due to PE, which was related to thrombophlebitis of the right jugular vein (RJV) and altered coagulation state due to colitis and therefore a proinflammatory state. Hypercoagulable states occur due to changes in the clotting cascade and endothelial function, and can be linked to gastrointestinal disease, sepsis and endotoxaemia (Lankveld *et al.* 2001; Dias and De Lacerda Neto 2013). Altered coagulation status can increase the likelihood of formation of thrombi both as a direct complication of i.v. catheterisation and at other sites around the body (Cotovio *et al.* 2008).

Thrombophlebitis can occur as a complication of intravenous catheterisation, typical clinical signs of which include an indurated jugular vein, decreased blood flow, variable heat, swelling and pain (Dias and De Lacerda Neto 2013; Geraghty *et al.* 2009). Other than pulmonary thromboembolism traditional concerns about thrombophlebitis have been associated with lack of a patent intravenous catheter, possible sepsis, lack of drainage from the head (therefore laryngeal and pharyngeal oedema and consequent dysphagia and dyspnoea), endocarditis, pain and long-term aesthetic/performance issues (Moreau and Lavoie 2009).

## Case history

A 3-month-old colt presented to Massey University Equine Hospital with a 4-day history of diarrhoea and discomfort. He had been treated with trimethoprim–sulfadiazine and biosponge orally for 4 days on the farm. On the day of referral he became acutely painful and was unresponsive to management in the field.

On presentation to the hospital the foal was dull and exhibited severe signs of abdominal pain. He was found to be hypovolaemic at admission with dry mucous membranes, tachycardia, delayed capillary refill time (>3 s), delayed skin tenting and a packed cell volume of 55% (relevant other blood results in **Table 1**). He had a severely distended abdomen, dyspnoea and gastric reflux, but no joint swelling or petechiation. Abdominal ultrasonography revealed a distended fluid filled large colon and an excessive quantity of free abdominal fluid. Abdominocentesis yielded a sample of slightly cloudy fluid, and analysis with a refractometer revealed low protein content (0.2 g/L). A 16 gauge over the wire Mila catheter was inserted into the RJV and isotonic crystalloid fluids (bolus of 30 mL/kg bwt) were given. Due to his severe abdominal distention and unrelenting pain he was taken for exploratory laparotomy. Ceftiofur (Calefur[1] 2 mg/kg bwt i.v. b.i.d.) was administered prior to surgery for broad based antimicrobial cover as the foal was considered to be in a high risk group for post-operative complications and aminoglycosides were contraindicated due to dehydration (Corley and Hollis 2009; Mair and Smith 2005), it was continued until 9 days post-operatively (Day 9).

The primary finding at laparotomy was a small colon impaction. The entire gastrointestinal tract proximal to this point was severely distended. Enterotomy was performed at the pelvic flexure. The recovery from anaesthesia was uneventful.

Post-operatively the colt exhibited signs of pain, tachycardia and started to pass copious amounts of diarrhoea. Supportive treatment included fluid therapy (Hartmann's[2] 3–5 mL/kg bwt/h i.v.; colloids (Volvulen[3], plasma[4]) 20 mL/kg bwt i.v. on Days 1 and 2), pain relief (flunixin meglumine[5] 1.1 mg/kg bwt i.v. b.i.d.; butorgesic[6] 0.01 mg/kg bwt as required), gastroprotectants (carafate[7] 20 mg/kg bwt *per os* q.i.d.) and biosponge[8] (500 mg *per os* t.i.d. for 2 days, then b.i.d. for 3 days). Approximately 72 h after surgery his condition started to improve and his faeces became gradually more formed. In addition to the blood tests (**Table 1**), faecal culture was performed three times and

**TABLE 1: Relevant blood work tabulated by days of hospitalisation**

|  | Day 0 | Day 4 | Day 7 | Day 14 | Day 18 | Day 22 | Day 24 | Reference range |
|---|---|---|---|---|---|---|---|---|
| White blood cells ($\times 10^9$/L) | 8.7 | 7.6 | 37.3 | 34.7 | 16.6 |  |  | 5.9–15.0 |
| Band neutrophils ($\times 10^9$/L) | 2.2 | 1.1 | 0.75 | 31.2 | 0 |  |  | 0.0–0.2 |
| Segmented neutrophils ($\times 10^9$/L) | 3.5 | 4.2 | 33.2 | 2.1 | 12.5 |  |  | 3.2–10.3 |
| Lymphocytes ($\times 10^9$/L) | 3 | 1.9 | 3.4 | 1 | 3.7 |  |  | 1.8–5.6 |
| Albumin (g/L) | 30 | 18 | 13 | 16 | 16 |  |  | 28–38 |
| Globulin (g/L) | 35 | 19 | 16 | 27 | 29 |  |  | 21–39 |
| SAA (mg/L) |  |  |  |  |  | 406 | 36 | 0–8 |
| Fibrinogen (g/L) | 6.4 | 6.9 | 8.3 | 9.3 | 9 |  |  | 0–4.0 |

no *Salmonella* or other clearly causative organism was isolated (Mallicote *et al.* 2012). No signs of laminitis, joint swelling, petechiation of mucous membranes or anterior uveitis were observed at any time.

## Clinical findings

On Day 6, palpable heat and thickening were evident at the catheter site in the RJV. The catheter was immediately removed and another one was placed in the left cephalic vein to allow continuation of fluid therapy. Unfortunately, the catheter tip was not cultured at this point, which would have allowed more targeted and more effective antimicrobial therapy. An ultrasound examination of the site showed mild thickening of the jugular vein (JV) wall and intraluminal heterogeneous hyperechoic material with irregular borders (thrombus). The intraluminal material was focused at the catheter site and occupied approximately 75% of the lumen of the vein. Some blood flow within the vein around the material was confirmed with colour Doppler. Immediately, gentamicin (Gentavet[9] 6.6 mg/kg bwt i.v. s.i.d.), aspirin (Aspro clear[9] 10 mg/kg bwt per os every 2 days) and low molecular weight heparin[10] (50 iu/kg bwt subcut. s.i.d.) were added to the colt's treatment regime along with topical application of flamazine cream[11] and hot packing.

Over the next 24–48 h, the RJV became increasingly hot and hard. The thrombus became more extensive and occupied the entire palpable RJV from the thoracic inlet to the mandible. The colt became hyperthermic and developed septic thrombophlebitis with abscessation which was confirmed on ultrasound (**Fig 1**).

Nine days post-operatively, the colt's colitis had resolved. The catheter was removed from the cephalic vein. He was switched to oral rifampicin (Rifadin[12] 5 mg/kg bwt b.i.d.) and doxycycline (Doxine[13] 10 mg/kg bwt b.i.d.); this decision was made for practical reasons of continuing oral medication after discharge and reported penetrative properties of rifampicin (Giguère and Prescott 1997). Fourteen days post-operatively, the foal appeared bright, but still had a consistently raised temperature (up to 39.4°C) and heart rate (80–92 beats/min), and ongoing presence of systemic oedema, particularly in the distal limbs causing a shifting hindlimb lameness. Efforts made to control the oedema included colloid therapy (Volvulen[3]) during acute colitis and a further 1 L bolus given on Day 8, limb bandaging and hand walking. Blood work performed at the time revealed hyperfibrinogenaemia, stable hypoalbuminaemia and leucocytosis (**Table 1**). Lack of response to therapy of the septic thrombophlebitis prompted the decision to switch



*Fig 1: Ultrasonographic transverse section of the external jugular vein distal to the location of catheterisation. Heterogeneous echogenicity of the luminal contents, with diffuse gas hyperechogenicity and thickened venous wall.*

antibiotic therapy to marbofloxacin (Marbocyl[14] 3 mg/kg *per os* s.i.d.), although available culture results could have enabled more targeted therapy. All medications were ceased at 21 days post-surgery when the foal's temperature had dropped consistently to <39°C and leucocyte count had fallen (**Table 1**), although fibrinogen remained high. The colt was discharged from hospital 2 days later. At this stage, he appeared well. The RJV was still hard and thrombosed but no longer discharging any purulent material. Discharge instructions included continued nursing care, hot packing the JV and close monitoring including daily temperature checks. Two weeks later at follow-up the colt was doing well and had gained weight. Twelve hours later he was found dead in the pasture.

## Post-mortem findings

A firm thrombus (10 × 2 cm) was adhered to and occluding the lumen of the right pulmonary artery (**Fig 2**). The RJV

*Fig 2: A post-mortem image of the pulmonary embolism lodged in the right pulmonary artery.*



*Fig 3: A post-mortem image of the right jugular vein containing the large thrombus.*

contained a single large thrombus extending from the origin at the connection of the linguofacial and maxillary veins to the thoracic inlet (**Fig 3**). There was some thickening of the left cephalic vein but no thrombus. Histological examination of the lungs revealed multifocal, partial occlusion of capillaries with fibrin thrombi admixed with Gram-negative cocci (suspected but not confirmed contamination), and diffuse congestion of capillaries and interstitium with inflammatory cells. Severe chronic thrombophlebitis of the RJV and severe acute multifocal septic pulmonary thromboemboli (PTE) were confirmed. The cause of death was attributed to the large thromboembolus occluding the right pulmonary artery. No abnormalities of the gastrointestinal tract were noted.

## Discussion

Although PTE is an important cause of human death (5–15% of hospital deaths in the USA), it is only reported in a single case series in six mature horses (Norman *et al.* 2008), and, in a second publication, post-mortem PTE is described in a single foal but antemortem signs are not specifically reported (Barton *et al.* 1998). Antemortem clinical signs, including tachypnoea, cough, haemoptysis and cardiac murmur, were observed in the mature horses. None of these were observed in this colt. PTE occurs in massive or classical forms, the former being an event that occludes >50% of the pulmonary vasculature and the latter only peripheral pulmonary vessels. Therefore, many cases of classic PTE may cause minor clinical signs and go unnoticed or be misdiagnosed (Ryu *et al.* 2004; Norman *et al.* 2008).

Premortem diagnosis of PTE is difficult; even in human medicine, only one-third of affected patients are diagnosed, with the gold standard diagnostic being angiography. Radiography or pulmonary nuclear perfusion scans can be attempted but are reportedly not sensitive (Norman *et al.* 2008), and were not performed in this case due to prioritisation of costs and availability. As diagnosis of embolism is difficult, the clinical emphasis should be focused on preventing thrombus formation. According to recent literature and Virchow's triad (local trauma, venous stasis and altered coagulation status all predispose to thrombus formation), this case falls into the highest risk category, being

in a hypercoagulable state and having two catheters inserted after multiple venepunctures (Lankveld *et al.* 2001; Dias and De Lacerda Neto 2013; Mair and Smith 2005; Dolente *et al.* 2005). Prevention thrombus formation therefore falls into two categories, systemic measures to reduce a hypercoagulable state and local measures.

A hypercoagulable state is haemostatic dysfunction due to impairment of factors involved in coagulation (Hopper and Bateman 2005). This can occur with acute inflammation, sepsis or endotoxaemia; and conditions related or predisposing to the aforementioned conditions such as colic, endotoxaemia, salmonellosis, hypoproteinaemia, pyrexia and haemoconcentration, which are all in turn risk factors for thrombophlebitis (Lankveld *et al.* 2001; Mair and Smith 2005; Dolente *et al.* 2005). Septic processes cause a hypercoagulable state by elevating procoagulants (tissue factor) and reducing anticoagulants (antithrombin, protein C and thrombomodulin) (Hopper and Bateman 2005). Tissue factor is particularly important in thrombophlebitis as circulating levels rise as a result of septic processes. In addition, tissue factor is released from the endothelium in response to endothelial damage (catheterisation) (Hopper and Bateman 2005). A hypercoagulable state is controlled by systemic management of inflammation and effective antimicrobial use to treat underlying conditions. In this case, antimicrobials were chosen without culture results, which may have limited the capacity to control infection. Systemic anti-inflammatories (flunixin) were used from an early stage in this case. However, during treatment of the colt, we faced persistent hyperfibrinogenaemia and hyperthermia, indicating ongoing infection and inflammation. The high fibrinogen was of particular relevance to the case as fibrinogen deposits in the various tissues including the lungs of foals are reported following a hypercoagulable state (Cotovio *et al.* 2008).

A key limitation of the case was removal of the catheter without culture of the tip which precluded a targeted antimicrobial choice and might have helped us to avoid the undesirable use of multiple antimicrobials over a short period of time (Bowen 2013). The switch from ceftiofur and gentamicin to doxycycline and rifampicin was undertaken due to outpatient practicality of oral medication. Additionally, rifampicin was used to attempt to increase penetration into the thrombus, which appeared on ultrasound as a walled off, almost abscess like structure (Giguère and Prescott 1997). However, we encountered persistent signs of infection. It became evident that doxycycline did not provide sufficient coverage for Gram-negative micro-organisms. Furthermore, we were limited in

the availability of an adequate and safe antimicrobial for oral use in the horse (Corley and Hollis 2009). After careful consideration, we decided that marbofloxacin at an appropriate dose was our best option for a positive outcome in this colt; nevertheless, this required off-label use of this drug. Initially, we avoided the use of fluoroquinolones as strict antimicrobial stewardship primarily reserves these antimicrobials for human use and due to their potential detrimental effects on articular cartilage in young animals (Vivrette et al. 2001; Bowen 2013).

In addition to addressing the patient's systemic condition, local precautions against thrombophlebitis included: aseptic technique during catheterisation (Ryu et al. 2004; Dias and De Lacerda Neto 2013), catheter hygiene, minimal venepuncture and the use of polyurethane catheters (Lankveld et al. 2001; Russell et al. 2010). The foal had both jugular veins used, the risk of thrombus formation increases both with number of venepunctures and with prolonged placement of indwelling catheters (Dias and De Lacerda Neto 2013). Certain medications including glycerol guaiacolate, thiopental, calcium gluconate and oxytetracycline are irritant and increase the risk of phlebitis (Dias and De Lacerda Neto 2013). None of these were used in the foal. Nonsteroidal anti-inflammatory drugs require strict i.v. injection. Their administration via catheter reportedly reduces rate of thrombus formation; however, perivenous administration via needle injection greatly increases risk of phlebitis (Geraghty et al. 2009).

To act appropriately, early identification of a thrombus formation is essential (Dallap Schaer and Epstein 2009). In the reported case, regular clinical examinations monitoring for localised firmness, pain and heat, a cord-like JV, or difficulty 'raising' the vein (Dias and De Lacerda Neto 2013) were performed every 4–6 h with catheter flushing with sterile heparinised saline. Ultrasound was used to assess the extent of the thrombophlebitis, but can also be used for early detection of vascular changes with increased sensitivity compared to manual palpation (Geraghty et al. 2009; Dias and De Lacerda Neto 2013). Ultrasonographic monitoring of every catheter could be seen as excessive; however, application in high risk patients such as this foal could be appropriate, as early removal and application of therapy are the most important factors for successful treatment and outcome. Echocardiography could have been considered in this case for detection of systemic thrombus formation but is more indicated if there is a clinical suspicion of endocarditis (Banse et al. 2012).

Once detected treatment of thrombophlebitis (in addition to already discussed medication) includes basic care such as hot packing and topical application of dimethyl sulfoxide (Russell et al. 2010), which were done for this foal. Anticoagulants (aspirin and low molecular weight heparin) were used in this case. They are particularly indicated in cases of generalised coagulopathy, and should only be used with care and daily monitoring of prothrombin time (Feige et al. 2003; Dias and De Lacerda Neto 2013). Additionally thrombolytic therapy (streptokinase) is applied in human medicine but not in the veterinary field (Dias and De Lacerda Neto 2013). In cases refractive to medical therapy, surgery can be considered (JV thrombectomy), although this tends to be reserved for cases where perseverance of sepsis and persistent clinical signs (impaired venous drainage of the head or central nervous system oedema) are an issue (Ryu et al. 2004). Our foal lacked such clinical signs at discharge,

and we presumed a good long-term outcome with possibility of recanalisation, and relatively minor impact on future performance (Moreau and Lavoie 2009).

In conclusion, PTE is a potentially fatal and probably underdiagnosed debilitating condition. It is unpredictable in incidence and difficult to diagnose. An understanding of the aetiology, risk factors and careful monitoring of the site are required. Focal venous trauma (i.e. i.v. catheter placement) and a hypercoagulable state both make thrombus formation more likely. Measures such as systemic control of inflammation and infection, focal decrease of irritation and trauma, and appropriate application of thrombolytic medication are indispensable.

## Authors' declaration of interests

## Ethical animal research

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## Authorship

Both authors contributed equally to this case report. The primary author prepared the majority of the first draft of the manuscript and assisted in patient care. The secondary author drafted sections of the manuscript, revised sections of the case report and was primarily responsible for patient care.

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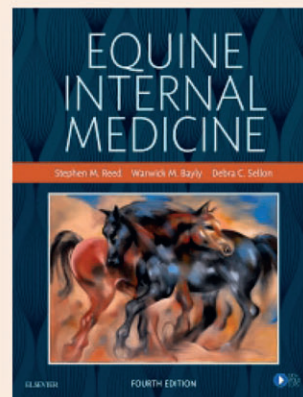Vivrette, S.L., Bostian, A., Bermingham, E. and Papich, M.G. (2001) Quinolone-induced arthropathy in neonatal foals. *Proc. Am. Assoc. Equine Practnrs.* **47**, 376-377.