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In mares with placentitis does the duration of antibiotic treatment affect foal outcome?

A Knowledge Summary by

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ISSN: **2396-9776**
Published: **03 Jul 2020**
in: **Vol 5, Issue 3**
DOI: **10.18849/VE.V5I3.309**
Reviewed by: **Margaret Nolan (PhD) and Kayleigh Barker (BVetMed(Hons) Cert AVP Stud Med MRCVS)**
Next Review Date: **09 Aug 2019**

KNOWLEDGE SUMMARY

PICO question

In mares with placentitis does treatment with long-term antibiotics result in improved foal viability when compared to repeated short courses of 7 to 10 days?

Clinical bottom line

Category of research question

Treatment

The number and type of study designs reviewed

The literature search identified six publications that included length of antibiotic treatment and foetal outcome. The publications consisted of four non-randomised non-blinded controlled trials and two randomised non-blinded controlled trials

Strength of evidence

Collectively there was weak evidence to support either an intermittent or continuous antibiotic protocol in the treatment of placentitis in mares

Outcomes reported

The literature involved experimental induction of ascending placentitis with foal survival or viability as the outcome

Conclusion

Further research is required into the diagnosis of placentitis, length of treatment and choice of antibiotic/s to penetrate the uterus in a diseased state

How to apply this evidence in practice

The application of evidence into practice should take into account multiple factors, not limited to: individual clinical expertise, patient's circumstances and owners' values, country, location or clinic where you work, the individual case in front of you, the availability of therapies and resources.

Knowledge Summaries are a resource to help reinforce or inform decision-making. They do not override the responsibility or judgement of the practitioner to do what is best for the animal in their care.

Clinical Scenario

Placentitis in mares is typically characterised by premature udder development or vaginal discharge from mid to late gestation and carries a high risk of abortion or birth of a compromised foal (Macpherson et al., 2013; and Waldridge & Pugh, 2001). The cause of placentitis and agent/s involved however are often unknown and treatment, regardless of cause, usually involves antibiotics, anti-inflammatories, and progesterone (Cummins et al., 2008; and Waldridge & Pugh, 2001). Microbial agents thought to be involved in placentitis include bacterial species such as *Streptococcus equi* subsp. *zooepidemicus,(S. zooepidemicus*) and *Escherica coli* (Canisso et al.,

2015; and Curcio et al., 2017). Fungal infections have also been reported including *Aspergillosis (Canisso et al., 2015)*. When mares are diagnosed with placentitis antibiotics may be prescribed either for the remaining length of pregnancy or in a pulsatile manner (LeBlanc, 2010; Christensen et al., 2010; Curcio et al., 2017; Bailey et al., 2010; and Ryan et al., 2008). Pulsatile therapy frequently recommends mares to receive antibiotics for 10 consecutive days a month starting at 7 months gestation (LeBlanc, 2010). No scientific data is currently available to confirm the efficacy of this treatment protocol (LeBlanc, 2010). Some evidence suggests that prolonged treatment is unable to eliminate bacteria and intermittent use may support suppression of bacterial growth (Bailey et al., 2010). Clinicians are reliant on experimental models and anecdotal evidence in making appropriate decisions regarding antibiotic choice and antibiotic length. There are currently a lack of studies comparing short- and long-term antibiotic use as a direct measurement of foal survival from mares with placentitis.

Abbreviations

CCFA – ceftiofur crystalline free acid
CFU – colony forming units
CTUP – combined thickness of the utero-placental unit
IV – intravenous administration
PO – oral administration
TMS – trimethoprim/sulphonamide
IM – intramuscular

The evidence

The literature search identified six publications that included antibiotic length of treatment and foetal outcome. The publications consisted of four non-randomised non-blinded controlled trials of level 4 (lower quality controlled trials) (OCEBM Levels of Evidence Working Group) (Macpherson et al., 2013; Christensen et al., 2010; Murchie et al., 2006; and Ryan et al., 2008). This included one pilot study (Ryan et al., 2008) and one short report presented at a conference (Christensen et al., 2010). Two publications were randomised non-blinded controlled trials of level 2b (lower quality randomised controlled trials) (Bailey et al., 2010; and Curcio et al., 2017). All studies involved experimental induction of ascending placentitis with *S. zooepidemicus*. Pony mares were used in 4/6 studies with one study involving light bred horses (Christensen et al., 2010) and one study using Criollo type mares (Curcio et al., 2017). All horses were in late gestation either unspecified gestational days (Christensen et al., 2010) or between 269 to 300 days gestation (Macpherson et al., 2013); 280–295 days; (Ryan et al., 2008) 290 days; (Bailey et al., 2010) 280–295; (Murchie et al., 2006) 269–288; and (Curcio et al., 2017) 300 days. The number of mares included in the studies were low ranging from five (Murchie et al., 2006) to 33 (Christensen et al., 2010) with number of mares per treatment group ranging from two (Murchie et al., 2006) to 12 (Bailey et al., 2010) limiting clinical extrapolation.

The outcome consistently measured between studies was 'foal viability', however the parameters determining viability varied between studies. Foal viability was described by Macpherson et al. (2013) and Bailey et al. (2010) as a foal able to right themselves, breathe without assistance, respond to stimuli and suckle. Low risk foals were determined by Curcio et al. (2017) as those able to breathe without assistance in less than 2 minutes, attain sternal recumbency in less than 5 minutes, a normal suckle reflex in 20 minutes, and able to stand with little or no assistance. Foal viability parameters were not defined in two studies (Christensen et al., 2010; and Murchie et al., 2008) and live foal rate was used in a single study (Ryan et al., 2008).

In studies with positive control (infected and not treated) any treatment improved foal outcome compared to no treatment at all (Bailey et al., 2010; and Curcio et al., 2017). The exception is Macpherson et al. (2013) that showed no difference in foal viability in untreated mares and mares receiving CCFA. There was no evidence to support that continuous antibiotics improved foal viability with similar foal viabilities seen in mares treated with TMS for 10 days in Curcio et al. (2017) at 93% (26 viable foals from 28 infected mares that received antibiotics) compared to antibiotics prescribed until abortion or parturition in Ryan et al. (2008) 64% (nine viable foals from

14 mares infected and received antibiotics), Christiansen et al. (2010) 71% (17 viable foals from 24 infected and treated pregnancies), and Bailey et al. (2010) at 83% of viable foals (10 viable foals from 12 infected and treated pregnancies). These findings support the need for ongoing research into identifying mares at risk of placentitis and once diagnosed monitoring clinical progression.

Summary of the evidence

Macpherson et al. (2013)	
Population:	Pony mares 280–295 days gestation
Sample size:	n = 12 pony mares
Intervention details:	All 12 mares were inoculated with *S. zooepidemicus* cervically. Treatment was initiated at onset of clinical signs (evidence of increase CTUP, placental separation, change in fluid character on ultrasound. Clinical signs of mammary gland development or vulvar discharge) • Group 1 (n = 3): Administered CCFA 6.6 mg/kg IM q96h • Group 2 (n = 6): Administered CCFA 6.6 mg/kg IM q96h, altrenogest and pentoxifylline (dose and scheduling not included) • Group 3 (n = 3): No treatment was given Treatment was continued until abortion or parturition
Study design:	Prospective non-blinded, non-randomised controlled trial
Outcome studied:	Length of gestation was determined from time of inoculation until parturition. A viable foal was defined as one that had the ability to right themselves, breathe without assistance, respond to stimuli, and suckle
Main findings: (relevant to PICO question):	CCFA alone (Group 1), or in combination with altrenogest and pentoxifylline (Group 2) did not improve foal survival or lengthen gestation • Group 1: No foals were viable and mean delivery occurred from 15 +/- 0.2 days after inoculation • Group 2: Two of the six foals were viable. Mean delivery was 15 +/- 10 days after inoculation • Group 3: Two of the three foals were viable. Mean delivery 34 +/- 16 days after inoculation
Limitations:	• Unknown number of CFU installed into the cervix • Unknown if strain of *S. zooepidemicus* was sensitive *in vitro* to CCFA • Small sample size • Unable to extrapolate to other forms of CCFA such as short acting intravenous administration

Ryan et al. (2008)

Population:	Pony mares (unspecified breed) approximately 290 days gestation
Sample size:	n = 18 ponies
Intervention details:	Mares were infected intra-cervically with approximately 2 x 106 CFU of S. zooepidemicus tested sensitive to TMS in vitro. All horses commenced treatment upon signs of vaginal discharge and or placental changes (within 36 hours of inoculation). Treatment was maintained through to delivery and 7 days post-partum Experiment 1 (n = 6): • Group 1 (n = 3): Trimethoprim/sulfamethoxazole (30 mg/kg body weight q12h) • Group 2 (n = 3): As Group 1 combined with altrenogest (2.0 mg/50 kg body weight q24h) Experiment 2 (n = 12): • Group 3 (n = 4): As Group 1 • Group 4 (n = 4): As Group 1 plus dexamethasone once a day over 6 days starting at 40 mg, then decreasing after 2 days to 35 mg for 2 days, then 25 mg for 2 days • Group 5 (n = 4): Non-infected controls
Study design:	Prospective non-blinded, non-randomised controlled trial, pilot study
Outcome studied:	• Live foal • Macrophage cytokine mRNA, relaxin and progesterone by serial blood examinations collected prior to infection and at 12, 24, 48, and 72 hours post infection. Blood samples were then taken 3 times a week until delivery • Transrectal ultrasound of foetal and placenta well-being (unspecified)
Main findings: (relevant to PICO question):	Experiment 1: • Group 1 (n = 3): Two aborted at 11, and 12 days post inoculation. One carried a near-term viable foal • Group 2 (n = 3): One aborted at 14 days post inoculation. Remaining two carried near-term viable foal Experiment 2: • Group 3 (n = 4) and 4 (n = 4): One mare from each group aborted a dead fetus. Remaining six produced live pre-term foals • Group 5 (n = 4): Control mares all delivered normal viable foals
Limitations:	• Small sample size • The strain of *S.zooepidemicus* used was tested sensitive to TMS and may not be known in a clinical setting • No positive control of inoculated and not treated • No specifications to foal viability

Christensen et al. (2010)

Population:	Pregnant light breed horses
Sample size:	n = 33 horses
Intervention details:	Group 1: (n = 27) Inoculated intra-cervically with *streptococcus equi* subsp *zooepidemicus* (2–10 x 10^6 CFU). All treatments were commenced on signs of vaginal discharge or placental changes (within 48 hrs of inoculation) and continued until delivery • Group 1A (n = 6): TMS 30 mg/kg BID PO • Group 1B (n = 6): As Group A and dexamethasone given over 6 days with decreasing doses every 2 days 40 mg, 35 mg, 25 mg QD IV • Group 1C (n=6): As Group A and acetylsalicylic acid 50 mg/kg BID PO for 6 days • Group 1D (n = 6): As Group C and altrenogest 2.2 mg/50 kg QD PO • Group 1E (n = 3): Infected controls Group 2: (n = 6) Non-infected controls
Study design:	Prospective non-blinded, non-randomised controlled trial, short report
Outcome studied:	Delivery of a viable foal
Main findings: (relevant to PICO question):	All infected mares that did not receive treatment aborted within 9 days of inoculation. All mares not infected delivered viable foals • Group 1A (TMS): 4/6 foals survived • Group 1B (TMS and dexamethasone): 4/6 foals survived • Group 1C (TMS and acetylsalicylic acid): 5/6 foals survived • Group 1D (TMS, acetylsalicyclic acid, and altrenogest): 4/6 foals survived • Group 1E (infected controls): no foals survived out of three • Group 2 (uninfected controls): 6/6 foals survived Mean gestational age at delivery was shorter in all infected mares than control negative mares. Antibiotic therapy substantially improved pregnancy outcome
Limitations:	• Limited number of horses makes statistical power poor between groups • Limited details provided in short study • Viability of foals not defined

Bailey et al. (2010)

Population:	Normal pregnant pony mares 280–295 days gestation. Normal determined by systemic parameters, CTUP, echo density of foetal fluids, foetal activity, and foetal heart rate
Sample size:	n = 17 ponies
Intervention details:	All mares inoculated with 10^7 CFU *S. zooepidemicus* known sensitive to TMS *in vitro* • Group 1 (n = 5): Infected untreated controls • Group 2 (n = 12): Infected and given trimethoprim/sulfamethoxazole (TMS 30 mg/kg body weight BID PO), altrenogest (ALT 0.088 mg/kg body weight QD PO) and pentoxifylline (PTX 8.5 mg/kg body weight BID PO). Treatment continued until abortion or parturition
Study design:	Prospective non-blinded, randomised controlled trial
Outcome studied:	Delivery of a viable foal defined as a foal able to right themselves, breathe without mechanical assistance, respond to stimulation and suckle
Main findings: (relevant to PICO question):	• Mares that were treated (Group 2) were significantly more likely to deliver a viable foal (10/12 deemed viable) than mares that were not treated (Group 1 no viable foals) • 10 of the foals in Group 2 had negative blood cultures whilst all foals in Group 1 (untreated group) had positive cultures from either blood, stomach contents or thoracic fluid TMS combined with pentoxifylline and altrenogest may improve the viability of foals with experimentally induced placentitis
Limitations:	• Bacteria tested sensitive to TMS • Supraphysiologic dose of bacteria administered intra-cervically to induce disease • Limited number of horses in study • Randomisation method not described

Murchie et al. (2006)	
Population:	Late gestational pony mares aged 4–15 years, weighing 190–290 kgs, with gestation age 269–288 days
Sample size:	n = 5 ponies
Intervention details:	• Study 1 (n = 5): All mares had microdialysis probes inserted into their allantoic fluid. All mares received penicillin G 22,000 u/kg, every 6 hrs gentamicin 6.6 mg/kg body weight QD and flunixin meglumine 1 mg/kg body weight QD. All treatments were given intravenously. Samples were taken serially immediately before injection then 5, 15, 30, 45, 60, 90 minutes then 2, 4, 6, 12, 18, 20, 22, and 24 hours after drug administration • Study 2 (n = 2): Experimental placentitis was induced by intracervical inoculation with *S. zooepidemicus* 1 x 10^7 CFU 10 days after Study 1. Mares were treated 4 days after inoculation as described above for 7 days

Study design:	Prospective non-blinded, non-randomised controlled trial
Outcome studied:	• Objective to monitor drug concentrations in allantoic fluid of pregnant pony mares using *in vivo* microdialysis and establish if this method is useful for determining allantoic concentrations of drugs in normal mares and those with placentitis • Foal viability after allantoic fluid samples in both infected and non-infected mares
Main findings: (relevant to PICO question):	Study 1: • Penicillin G and gentamicin were detected in allantoic fluid Study 2: • Placental drug transfer may be altered if active placental infection is present • Potential for increased dose intervals for penicillin G and increased dose rate of gentamicin to effectively combat placental infections in mares • Both mares that were infected aborted non-viable foals one at 291 days and one at 307 days gestation
Limitations:	• Small sample size of two mares in Study 2 make conclusions regarding efficacy of 7 days treatment difficult to surmise • Intervention procedure of allantoic sampling may also have compromised foetal well-being with only two out of five viable foals born at 32 and 45 days after experimentation, whilst one mare that had allantocentesis performed and was not inoculated aborted at 315 days gestation

Curcio et al. (2017)	
Population:	27 multiparous Criollo or Criollo type mares approximately 300 days gestation, 10 +/- 2-years-old, parity of 3 +/- 0.5, body weight 437 +/- 22 kg with no history of subfertility or late term pregnancy abnormality
Sample size:	n = 46 pregnancies from 2012 to 2014
Intervention details:	Group 1 (n = 8): Control not infected Group 2 (n= 38): Infected with 10^7 CFU *S. zooepidemicus* • Group 2A (n = 8): TMS 30 mg/kg body weight BID intravenously and flunixin (1.1 mg/kg QD IV) • Group 2B (n = 8): As Group A with altrenogest 0.088 mg/kg intramuscular every 7 days for two treatments • Group 2C (n = 6): As Group A with estradiol cypionate (EC) 10 mg/mare intramuscular every 3 days for three treatments • Group 2D (n = 6): As Group A with altrenogest as described in Group B and ECP as described in Group C • Group 2E (n = 10): Infected no treatment All treatments were initiated 48 hours after inoculation and continued for 10 days

Study design:	Randomised non-blinded controlled trial

Outcome studied:	• Time of induction to delivery
	• Serum steroid concentrations in response to treatment
	• Foal viability was separated into low and high risk
	• Foals defined as low risk if:
	  ○ Able to breathe without assistance in under 2 minutes
	  ○ Assume sternal recumbency in less than 5 mins
	  ○ Exhibit normal suckle reflex in 20 minutes
	  ○ Stand with no or minimal assistance
	• Foals defined as high risk if:
	  ○ Signs of immaturity (silky hair coat, floppy ears, delayed sucking)
	  ○ Evidence of sepsis

Main findings: (relevant to PICO question):	• Time from inoculation to delivery was not significantly different between Group 1 control mares and Group 2D mares receiving supplemental EC (mean 35 and 46 days respectively) • Time from inoculation to delivery was significantly shorter in mares receiving other treatments in Groups 2B, 2C, and 2D compared to control mares. However, delivery was shortest in mares not receiving any treatment (Group 2) • Foal survival at parturition and 7 days of age were similar amongst treated Groups 2A–2E to control (Group 1) ranging between 66.7–100% • There was no significant difference in the number of high risk foals in Group 2D compared to control mares (Group 1) • There was a significant difference in the number of high risk foals in Groups 2A–2C and 2E compared to control (Group 1) • Mares in Group 2E had significantly higher number of dystocia's and premature parturitions
Limitations:	• Unknown if the same mares were used over multiple seasons, which order of treatments were received, and if those inoculated were known to no longer be infected • Unknown if strain cultured was sensitive to TMS *in vitro* • Small treatment groups

Appraisal, application and reflection

Placentitis is a common condition estimated to affect 3–5% of Thoroughbred pregnancies and can be challenging for the clinician to diagnose and treat (Canisso et al., 2015). Current treatment protocols recommend a multifactorial approach involving antibiotics, anti-inflammatories and progesterone (Murchie et al., 2006; and Waldridge & Pugh, 2001). Two different antibiotic regimes have been proposed in the treatment of placentits; 1) pulse antibiotics involving 10 consecutive days each month until parturition; and 2) continuous antibiotics until parturition. The purpose of this Knowledge Summary was to evaluate the evidence comparing the treatment length of antibiotics and foal viability as no studies reported the use of pulse antibiotic therapy.

Six studies met the inclusion criteria and all the studies involved experimental induction of ascending placentitis using *S. zooepidemicus*. Two studies Curcio et al. (2017) and Bailey et al. (2010) provide the most comparable in terms of length of antibiotic treatment. Curcio et al. (2017) treated for 10 days with an average time from

inoculation to parturition of treated mares 23.7 days and foal survival of 93% (26/28). Bailey et al. (2010) treated until abortion or delivery with average time from inoculation to parturition 31 days with 83% (10/12) of treated mares producing viable foals. Treatment commenced later in the study by Curcio et al. (2017) with the average gestation of mares approximately 300 days, whilst mares in the study by Bailey et al. (2010) were 280–295 days gestation. Viability of the foals and mean gestational lengths were similar between the studies, regardless of duration of antibiotics (both over 320 days gestation). Clinically it is recognised that chronic insidious placentitis carriers a better prognosis compared to acute disease as the foal has time to mature. The aim of placentitis treatment may be to delay parturition and allow foetal maturation as opposed to eliminating bacteria.

All the studies used supraphysiological doses of *S. zooepidemicus* to initiate placentitis. The amount of colony forming units were unspecified in two studies (Murchie et al., 2006; and Bailey et al., 2010) whilst the remaining studies varied. Ryan et al. (2008) inoculated 2 x 10^6 CFU, whilst Christiansen et al. (2010) had a variable dose between 2–10 x 10^6 CFU, Macpherson et al. (2013) and Curcio et al. (2017) used a higher dose of 1 x 10^7 CFU. Clinical ascending placentitis is thought to be insidious in onset and reflective of mare perineal or cervical conformation (Waldridge & Pugh, 2001) and experimental inoculation may limit clinical extrapolation of results. The strain used was tested sensitive to the antibiotics prescribed *in vitro* (TMS) in Ryan et al. (2008) and Bailey et al. (2010), however was not specified if it was sensitive to the antibiotics prescribed in the other studies. No studies commented on culture and sensitivity of vaginal discharge post inoculation or uterine fluid post foaling/aborting.

When and how antibiotics were prescribed varied between studies. Two studies used TMS at 30 mg/kg body weight PO every 12 hours (Christensen et al., 2010; and Bailey et al., 2010). Curcio et al. (2017) used the same dose rate, however delivered the TMS IV every 12 hours and Ryan et al. (2008) did not specify dose rate or administration route of TMS. A single study used penicillin G (22,000 u/Kg), and gentamicin (6.6 mg/kg) (Murchie et al., 2006) and a single study evaluated CCFA the active metabolite of ceftiofur at 6.6 mg/kg IM repeated after 96 hours (Macpherson et al., 2013). Four studies specified that antibiotics were commenced when clinical signs of placentitis occurred which varied between 36 hours (Ryan et al., 2008) to 48 hours (Christensen et al., 2010) or was not specified (Macpherson et al., 2013; and Bailey et al., 2010). Clinical signs attributed to placentitis included vaginal discharge (Christensen et al., 2010; and Ryan et al., 2008) or elevated CTUP (Christensen et al., 2010). Murchie et al. (2006) initiated antibiotics 4 days post inoculation regardless of clinical signs observed, and Curcio et al. (2017) initiated antibiotics 48 hours after inoculation regardless of clinical signs observed. The length of antibiotic treatment varied amongst the studies with four of the studies continuing antibiotics until parturition (Christensen et al., 2010, Bailey et al., 2010, Macpherson et al., 2017; and Ryan et al., 2008), whilst Murchie et al. (2006) treated for 7 days and Curcio et al. (2017) treated for 10 days. No studies evaluated examined physical, chemical, or ultrasonographic parameters of mares or foals whilst the mares were on antibiotic treatment.

The study by Ryan et al. (2008) additionally evaluated the use of antibiotics in mares with placentitis after abortion or foaling. Post mortem investigation of the non-viable foals found evidence *S. zooepidemicus* in foal lungs from mares that were treated with antibiotics and those that were not. The majority of foals in the study by Ryan et al. (2008) born from treated mares had negative blood cultures (10/12 foals treated with antibiotics had negative blood cultures). Uterine cultures taken from mares immediately post foaling or aborting that were on antibiotics were less predictable, with two thirds of mares (8/12 mares) returning a positive uterine culture to *S. zooepidemicus* despite the administration of antibiotics for over 4 weeks. It was proposed by Ryan et al. (2008) that early initiation of treatment was able to inhibit bacterial growth and subsequent inflammation. As treatment was initiated at onset of clinical signs, delayed antibiotic administration may only suppress bacterial growth. Further research is required into when to start antibiotic treatment and improve detection of mares with suspected placentitis.

Methods to monitor foetal well-being to aid in determining when to treat placentitis is limited. Curcio et al. (2017) noted that 4/10 mares that were inoculated failed to develop vaginal discharge and 3/10 mares failed to show an increase in CTUP or evidence of placental separation on rectal ultrasound. Further studies into the

correlation of foetal circulation including heart rate, cord pressure (Vincze et al., 2019) and thickness of the placenta measured both abdominally and rectally may aid in earlier identification of mares with placentitis (Curcio et al., 2017). Decreasing progesterone and rising oestrogen levels have been correlated with poor prognosis of foetal survival (Curcio et al., 2017). Allantocentesis samples have also been used to assess foetal health, however further investigation is warranted into the technique (Murchie et al., 2008).

All studies involved a multi-model approach to treatment with combined therapeutic regimes. 5/6 studies included altrenogest (Macpherson et al., 2013; Christensen et al., 2010; Curcio et al., 2017; Bailey et al., 2010; and Ryan et al., 2008), single studies evaluated flunixin (Murchie et al., 2006), acetylcystine (Christensen et al., 2010), and estradiol cypionate (Curcio et al., 2017). Two studies examined pentoxifylline (Bailey et al., 2010; and Macpherson et al., 2017), and two studies examined dexamethasone (Christensen et al., 2010; and Ryan et al., 2008). The evaluation of these agents into the treatment of placentitis is beyond the scope of this article.

The use of antibiotics in a pulsatile manner has been explored in dogs with chronic pyoderma (Carlotti et al., 2004). In the canine model cephalexin (15 mg/kg twice a day) was prescribed for 2 days of the week and was compared against a placebo. The study found that pulse 'weekend' therapy was effective in reducing the time between relapses in canine idiopathic pyoderma and no resistance was noted in the 12 month period. It has been proposed that bacterial resistance to antibiotics may be limited in pulse antibiotic therapy as it minimises the time microbes are exposed to antibiotics and the selection of resistance (Baker et al., 2018). It was noted that in pulse therapy a bactericidal drug is advised with high concentrations to minimise pathogen abundance (Baker et al., 2018; and Carlotti et al., 2004). More research is required into what drugs and clinical scenarios pulse antibiotic therapy may be implemented.

Multiple types of placentitis have been described in the literature including ascending, focal mucoid (nocardioform), diffuse (haematogenous) and multifocal (Canisso et al., 2015). All the above studies involved an experimental model to induce ascending placentitis and the extrapolation to other forms is limited. Placentitis treatment remains frustrating for the clinician to treat with limited ability to perform culture and sensitivity against the potential organism/s involved. Current literature supports the use of antibiotics in the combined treatment of placentitis but does not provide evidence of the length of time they should be prescribed for. Further investigation of placentitis may involve correlating foetal and placental well-being to foal survival to be used as a measure of ceasing or altering treatment regimes.

Methodology Section

Search Strategy	
Databases searched and dates covered:	Search terms were applied in PubMed Central accessed on NCBI website (1910–2019), CAB Abstracts database accessed on OVID platform (1973–2019)
Search terms:	**CAB Abstracts:** 1. (equine* or horse* or equus or equid* or mare or mares or broodmare or broodmares or 'brood mare' or 'brood mares' or pony or ponies).mp. or exp equidae/ or exp equus/ or exp horses/ or exp mares/) 2. (Placentitis or placenta or pregnancy or fetus or foetus).mp. or exp placentitis/ or exp pregnancy/) 3. (antibiotic or antibiotics or antimicrobial or antimicrobials or anti-microbial or anti-microbials or antibacterial or antibacterials or 'antiinfective agent' or 'antiinfective agents' or 'anti-infective agent' or 'anti-infective agents' or penicillin or gentamicin or ceftiofur or excede).mp. or exp

	antibacterial agents/ or exp antibiotics/ or exp antiinfective agents/) 4. 1 and 2 and 3 **PubMed:** 1. (equine OR horse OR mare OR mares OR broodmare OR brood mare OR pony OR ponies) 2. (Placentitis or placenta or pregnancy or fetus or foetus) 3. (antibiotic or antibiotics or antimicrobial or antimicrobials or anti-microbial or anti-microbials or antibacterial or antibacterials or 'antiinfective agent' or 'antiinfective agents' or 'anti-infective agent' or 'anti-infective agents' or penicillin or gentamicin or ceftiofur or excede) 4. 1 and 2 and 3
Dates searches performed:	9 August 2019

Exclusion / Inclusion Criteria	
Exclusion:	Non-English language, narrative or non-systematic review articles, unpublished data, pharmacokinetic, or *in vitro* experimental studies
Inclusion:	Any reported use of antibiotics in the treatment of placentitis in mares

Search Outcome

Database	Number of results	Excluded – non-English language publication	Excluded – systematic review or non-equine	Excluded – did not state duration of antibiotic	Excluded – single case report	Total relevant papers
CAB Abstracts	285	18	214	4	38	11
PubMed	263	10	216	2	30	5
Total relevant papers when duplicates removed						**6**

CONFLICT OF INTEREST

The author declares no conflicts of interest.

REFERENCES

1. Bailey, C. S., Macpherson, M. L., Pozor, M. A., Troedsson, M. H., Benson, S., Giguere, S., Sanchez, L. C., LeBlanc, M. M. & Vickroy, T. W. (2010). Treatment efficacy of trimethoprim sulfamethoxazole, pentoxifylline and altrenogest in experimentally induced equine placentitis. *Theriogenology,* 74(3)**,** 402–12. DOI: http://dx.doi.org/10.1016/j.theriogenology.2010.02.023
2. Baker, C. M., Ferrari, M. J. & Shea, K. (2018). Beyond dose: Pulsed antibiotic treatment schedules can maintain individual benefit while reducing resistance. *Scientific Reports,* 8(1). DOI: http://dx.doi.org/10.1038/s41598-018-24006-w
3. Canisso, I. F., Ball, B. A., Cray, C., Squires, E. L. & Troedsson, M. H. (2015). Use of a Qualitative Horse-Side Test to Measure Serum Amyloid A in Mares With Experimentally Induced Ascending Placentitis. *Journal of Equine Veterinary Science,* 35(1)**,** 54–59. DOI: http://dx.doi.org/10.1016/j.jevs.2014.11.007
4. Carlotti, D. N., Jasmin, P., Gardey, L. & Ssanquer, A. (2004). Evaluation of cephalexin intermittent therapy (weekend therapy) in the control of recurrent idiopathic pyoderma in dogs: a randomized, double-blinded, placebo-controlled study. *Veterinary Dermatology,* 15(s1)**,** 1–19. DOI: http://dx.doi.org/10.1111/j.1365-3164.2004.00410_2-4.x
5. Christensen, D. L., Moulton, K., Hopper, R., Walters, F. K., Cooley, A. J., LeBlanc, M. & Ryan, P. (2010). Evidence-based medicine approach to develop efficacious therapies for late-gestation mares presenting with uterine infections using and experimentally induced placentitis model. *Animal Reproduction Science,* 121**,** 345–346.
6. Cummins, C., Carrington, S., Fitzpatrick, E. & Duggan, V. (2008). Ascending placentitis in the mare: a review. *Irish Veterinary Journal,* 61(5)**,** 307–313. DOI: http://dx.doi.org/10.1186/2046-0481-61-5-307
7. Curcio, B. R., canisso, I. F., Pazinato, F. M., Borba, L. A., Feijo, L. S., Muller, V., Finger, I. S., Toribio, R. E. & Nogueira, C. E. W. (2017). Estradiol cypionate aided treatment for experimentally induced ascending placentitis in mares. *Special Issue: The David E. Bartlett Award for Lifetime Achievement in Theriogenology.,* 9**,** 454. DOI: http://dx.doi.org/10.1016/j.theriogenology.2017.03.010
8. LeBlanc, M. M. (2010). Ascending placentitis in the mare: an update. *Reproduction in Domestic Animals,* 45**,** 28–34. DOI: http://dx.doi.org/10.1111/j.1439-0531.2010.01633.x
9. Macpherson, M. L., Giguere, S., Hatzel, J. N., Pozor, M., Benson, S., Diaw, M., Sanchez, L. C., Vickroy, T. W., Tell, L., Wetzlich, S. & Sims, J. (2013). Disposition of desfuroylceftiofur acetamide in serum, placental tissue, fetal fluids, and fetal tissues after administration of ceftiofur crystalline free acid (CCFA) to pony mares with placentitis. *Journal of Veterinary Pharmacology Therapeutics,* 36(1)**,** 59–67. DOI: http://dx.doi.org/10.1111/j.1365-2885.2012.01392.x
10. Macpherson, M. L., Giguere, S., Pozor, M. A., Runcan, E., Vickroy, T. W., Benson, S. A., Troedsson, M. H. T., Hatzel, J. N., Larson, J., Vanden Berg, E., Kelleman, A. A., Sanchez, L. C. & LeBlanc, M. M. (2017). Pharmacokinetics of ceftiofur sodium in equine pregnancy. *Journal of Veterinary Pharmacology Therapeutics,* 40(6)**,** 656–662. DOI: http://dx.doi.org/10.1111/jvp.12399
11. Murchie, T. A., Macpherson, M. L., LeBlanc, M. M., Luznar, S. & Vickroy, T. W. (2006). Continuous monitoring of penicillin G and gentamicin in allantoic fluid of pregnant pony mares by in vivo microdialysis. *Equine Veterinary Journal,* 38(6)**,** 520–525. DOI: http://dx.doi.org/10.2746/042516406X156136
12. Murchie, T. A., Macpherson, M. L., LeBlanc, M. M., Luznar, S. & Vickroy, T. W. (2008). Detection of gentamicin and penicillin concentrations in allantoic fluid of pregnant pony mares by in vivo microdialysis. *Havemeyer Foundation Monograph Series***,** 33.
13. Ryan, P., Crouch, J., Sykes, D., Moulton, K., Christiansen, D., Hopper, R., Read, R., Bennett, W. & LeBlanc, M. M. (2008). Experimentally induced placentitis in late gestation mares with Streptococcus equi zooepidemicus: prevention of pre-term birth. *Havemeyer Foundation Monograph Series***,** 35–36.

14. Vincze, B., Baska, F., Papp, M. & Szenci, O. (2019). Introduction of a new fetal examination protocol for on-field and clinical equine practice. *Theriogenology,* 125**,** 210–215. DOI: http://dx.doi.org/10.1016/j.theriogenology.2018.11.004
15. Waldridge, B. M. & Pugh, D. G. (2001). Equine placentitis. *Compendium on Continuing Education for the Practicing Veterinarian,* 23**,** 573–575.

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