



Nocardioform Placentitis

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Definition

Nocardioform placentitis (NP) is a pathologically unique form of focal mucoid placentitis. It is characterized by infection with gram-positive branching bacteria in the ventral aspect of the fetal side (i.e., chorioallantois) of the feto-maternal interface, creating a lymphoplasmacytic mucoid lesion with a typical pungent/soil odor.

NP is caused by actinomycetes, most commonly *Amycolatopsis* spp. (*A. kentuckyensis*, *A. lexingtonensis*, *A. pretoriensis*), *Crossiella equi*, and less commonly *Streptomyces* spp. (*S. atriruber*, and *S. silaceus*). In rare cases (2-7%), *Crossiella equi* and *Amycolatopsis* spp. coinfection is isolated.

Additionally, other unidentified species of actinomycete gram-positive branching bacilli are also reported in fetal membranes submitted for pathological evaluations, as many as 4-14% of suspected cases are negative to the common NP pathogens on PCR and culture screening despite having the typical characteristic pathological lesions.

NP was first diagnosed in central Kentucky in the mid-80s. Since its first description, the occurrence of NP has varied from sporadic cases to outbreak years in the region. Previously, *Crossiella equi* was the primary isolate associated with NP; however, in the 2011 and 2020 outbreaks, *Amycolatopsis* spp. isolates were twice as common as *Crossiella equi* isolates. Outside Kentucky and the United States, NP has been primarily reported as isolated cases, rarely as outbreaks and with *Amycolatopsis* spp as the exclusive etiological agent.

Clinical Features

- Clinical signs in affected mares are variable and may be absent.
- Premature mammary gland development may be observed in as much as 55% of mares affected with NP.
- Vaginal discharge is rarely observed, except in rare and severe cases, as most lesions are ventrally located at the uterine horns/body and typically have no involvement with the cervical star.



- Transabdominal ultrasound findings consist of hyperechoic exudate accumulation accompanied by separation of the chorionic surface from the endometrial surface with or without pockets of debris and fluid. Changes in the sonographic appearance of the allantoic and amniotic fluids are usually minimal, except in advanced and severe cases.
- Transrectal ultrasound findings may reveal edematous chorioallantois and rarely exudate may be seen in multifocal lesions extending caudally to the cervix.

Four outcomes have been described in mares experiencing NP:

- **Abortion**
- **Stillbirth**
- **Delivery of a weak premature or term foal.** These foals are malnourished and often have incomplete ossification of cuboidal bones, likely secondary to placental insufficiency. Gestation length is reduced by 20 days on average in NP cases.
- **Delivery of a healthy normal foal.** Healthy neonates born from mares affected with NP often have lower birth weight than non-affected foals. Of interest, WBC count and transfer of passive immunity are not affected in viable NP foals.

Placental Lesions

The size of placental lesions is significantly correlated with neonate viability, but placental weight is not affected by NP. Despite rather impressive focal to multifocal chorionic villi blunting and coverage with a thick, tenacious mucoid material with a characteristic putrid soil smell, the amnion and umbilical cord are not typically affected by NP.

NP lesions are typically restricted to the chorioallantois, more specifically the chorionic surface. In some cases, nodular masses with/without cystic formations (adenomatous cystic hyperplasia) are also seen on the allantoic surface. Most cases of NP have a singular focal well-demarcated lesion of varying size seen most frequently at the uterine body or base of the uterine horns. However, multifocal lesions closer to the caudal uterine body have also been reported.

A variation of NP includes a focal to extensive avillic area, which grossly is not covered with any exudate, but histologically the typical lesions are present. While cystic adenomatous hyperplasia of the chorioallantois is occasionally present, it is not specific to NP.



This lesion is found in different types of chronic placentitis and sometimes in otherwise healthy pregnancies.

Incubation Period

The incubation period of NP is unknown. Results of one study suggested that potential exposure to the bacteria associated with NP occurs during the summer and early fall in the Northern Hemisphere. Since mares appear to be infected during this time window, and clinical signs and pregnancy loss are typically observed after 3 to 5 months, it has been suggested that 3-5 months is the minimum time from exposure to clinical signs.

Risk Factors

- There is a strong association between weather conditions during mid-late pregnancy and an increased occurrence of NP. Specifically, exposure to low rainfall and high temperatures during August and September in central Kentucky when most mares are in mid-gestation results in an increased incidence of abortion later in pregnancy.
- Mares suffering from NP were older than contemporaneous health controls in one study; however, parity, last breeding, and a previous history of NP did not affect the odds for recurrence of NP in the subsequent season. Furthermore, the occurrence of NP did not affect postpartum fertility in Thoroughbred mares.

Transmission

Despite extensive investigations, the transmission and pathogenesis remain unknown at this time. At present, there is no evidence for mare-to-mare transmission.

Diagnostic Sampling, Testing, and Handling

- Definitive diagnosis of NP is made based on pathological and microbiological evaluations of the fetal tissues post abortion or fetal membranes postpartum.
- While performing an abortion workup, both fetal membranes and fetuses should be evaluated.
- When a live foal is accompanied by fetal membranes with gross lesions, the fetal membranes should be submitted for full pathological and microbiological assessments.
- **The peripheral regions of lesions have more active ongoing inflammation than the center of the lesion, and these areas should be sampled for histopathology and microbiological evaluation.**



- Histopathological lesions of NP are characterized by an amphophilic and amorphous lymphoplasmacytic mucoid lesion. The secretions contain amorphous eosinophilic debris, sloughed chorionic epithelial cells and leukocytes, and numerous filamentous branching bacilli can be seen within the mucoid secretions observed.
- Culture of fetal and/or membrane lesions demonstrate hard colonies of Gram-positive branching bacillus.
- PCR with primers for *Amycolatopsis* spp. and *Crossiella equi* can aid in confirming the diagnosis of NP in most cases.

Treatment

Currently, attempts to create experimental NP infection have been unsuccessful, limiting assessment of therapy efficacy. Recent information from central Kentucky did not show significant benefit of therapy on foal viability or the size of NP placental lesions. Additional prospective controlled studies are needed to better assess the efficacy, length, and type of NP treatment.

Culture and sensitivity of bacteria isolated from NP lesions after foaling has shown >90% are sensitive *in vitro* to SMZs and doxycycline. Of interest, both antimicrobials are known to diffuse well into fetal fluids, but it is unknown if therapeutic concentrations are achieved at the level of the mucoid lesion. Mares suspected to have NP based on ultrasonographic lesions are usually empirically treated with one of these antimicrobials.

Anti-inflammatory treatment (NSAID or COX-2 inhibitor), progestin (altrenogest, 0.88mg/kg, q 24 h), estrogens (estradiol cypionate, 10 mg/mare, q 48 h; estradiol benzoate, 40 mg/mare, q 24 h; or estradiol-17 β , 100 mg/mare, q 24 h), and rheologic agent (pentoxifylline 8.5mg/kg, q 12 h) have been anecdotally reported to be helpful.

Shedding of Organism Following Resolution of Clinical Signs

Mares identified with NP at the time of delivery did not have residual implications on later fertility. Uterine lavage post-foaling anecdotally aids the normal process of uterine clearance and involution in NP. In one study, bacteria associated with NP were only found in one mare postpartum, and most mares rapidly cleared infection with NP.

Environmental Persistence

Although other genera of actinomycetes are well-known soil-associated microbes, environmental persistence of NP bacteria has yet to be demonstrated.



<p>Specific Control Measures</p>	<ul style="list-style-type: none"> ● Because the risk factors and transmission mechanisms for NP are unknown, specific preventative control practices have not yet been identified. ● Current practice includes screening pregnant mares and treating those with clinical and sonographic findings consistent with NP. Early lesions are challenging to detect without experience, and negative sonographic findings should be interpreted carefully.
<p>Biosecurity Issues for Receiving Animals</p>	<p>Currently, there is no documented transmission between animals. Therefore, no special biosecurity measures need to be implemented. One study screened Thoroughbred mares before and after mating for NP in central Kentucky and did not find any evidence of <i>Amycolatopsis</i> spp. or <i>Crossiella equi</i> on PCR. Mares inoculated with <i>Crossiella equi</i> 24 h post-artificial insemination or mares inseminated with <i>Streptomyces</i> spp. mixed with raw semen did not yield positive PCR the day after inoculation or result in NP in mares becoming pregnant.</p>
<p>Disinfection</p>	<p>Actinomycetes are easily killed by standard means of disinfection. Any fetal and/or placental tissues not submitted for diagnostics should be located and discarded appropriately.</p>
<p>Zoonotic Potential</p>	<p>Based on current evidence, there is no zoonotic potential.</p>
<p>Further reading</p>	<p>Donahue JM, Williams NM. Emergent causes of placentitis and abortion. <i>Vet Clin North Am Equine Pract.</i> 2000;16(3).</p> <p>Fedorka CE, Scoggin KE, Ruby RE, et al. Clinical, pathologic, and epidemiologic features of nocardioform placentitis in the mare. <i>Theriogenology.</i> 2021;171:155-161.</p> <p>Canisso IF, Ball BA, Erol E, et al. Attempts to induce nocardioform placentitis (<i>Crossiella equi</i>) experimentally in mares. <i>Equine Vet J.</i> 2015;47(1):91-95.</p> <p>El-Sheikh Ali H, Fedorka C, Ball BA. White paper updates on equine nocardioform placentitis. The Virtual Nocardioform Placentitis Workshop 9-28-2020. https://gluck.ca.uky.edu/sites/gluck.ca.uky.edu/files/general/nocardioform_placentitis_workshop_sept_2020.pdf.</p>

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