Placentitis Associated Neonatal Problems and the Effect of Therapeutic Interventions

Palmer JE, Sertich PL, Cornman BI, Wilkins PA, Boston RC

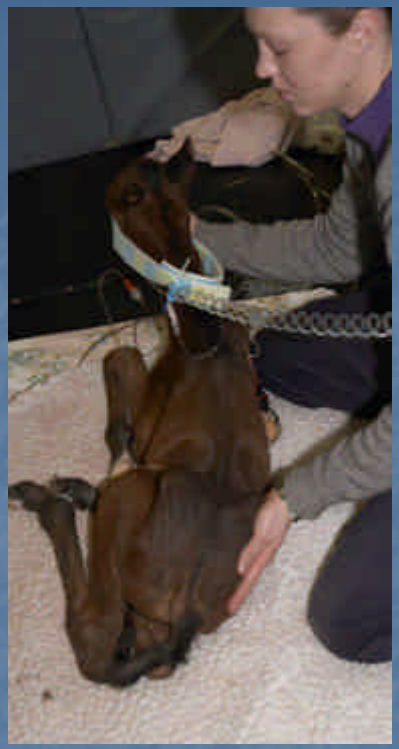
New Bolton Center
School of Veterinary Medicine
University of Pennsylvania

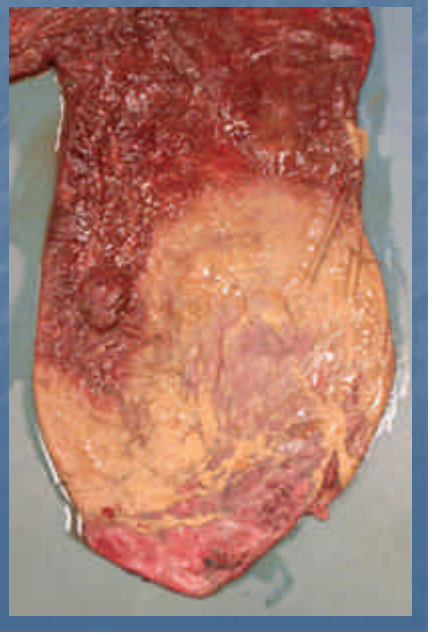
Etiology of Neonatal Diseases

- Neonatal Encephalopathy
- Neonatal Nephropathy
- Neonatal Gastroenteropathy
- Prematurity
- IUGR
- Sepsis
  - Bacteremia

Role of Placentitis

- Risk factor for neonatal diseases
- Disrupt the fetal environment
  - Change placental metabolism
  - Change nutrient transfer
  - Inflammatory mediators
    - Cytokines
    - Others
- Negative effects
- Positive effects





Role of Placentitis

- Many neonatal diseases
  - Multiple etiologies
  - Disruption of fetal life
    - Predispose to neonatal disease
    - Origin of the neonatal disease
- Same process - different organs
  - Neonatal Encephalopathy
  - Neonatal Nephropathy
  - Neonatal Gastroenteropathy

Role of Placentitis

- Direct manifestation of placental dysfunction
  - Prematurity
  - IUGR
- Neonatal manifestation
  - Sepsis
  - Bacteremia

Hypothesis

- The occurrence of neonatal diseases is influenced by fetal exposure to placentitis
- Treatment of placentitis will protect against the development of neonatal diseases

Methods

- Observational retrospective study
- Population
  - Hospitalized mare/foals 2000-2005
    - Foals referred for critical care
    - High Risk Pregnancy cases
  - Fetal membranes examined
  - Foal examined
  - Data source – clinician notes
    - Placental evaluation – PLS
    - Foal evaluation – JEP

Methods

- Presence of placentitis
  - Gross findings
  - Histologic findings
  - Retained fetal membranes
    - > 3 hours postpartum
- Prepartum therapy
- Occurrence of birth problems
  - Prolonged Stage II
  - Premature placental separation (PPS)
  - Need for birth resuscitation

Methods

- Occurrence of neonatal problems
  - Neonatal Encephalitis (NE)
  - Neonatal Nephropathy (NN)
  - Neonatal Gastroenteropathy (NG)
  - Clinical prematurity
  - IUGR
  - Sepsis
  - Bacteremia

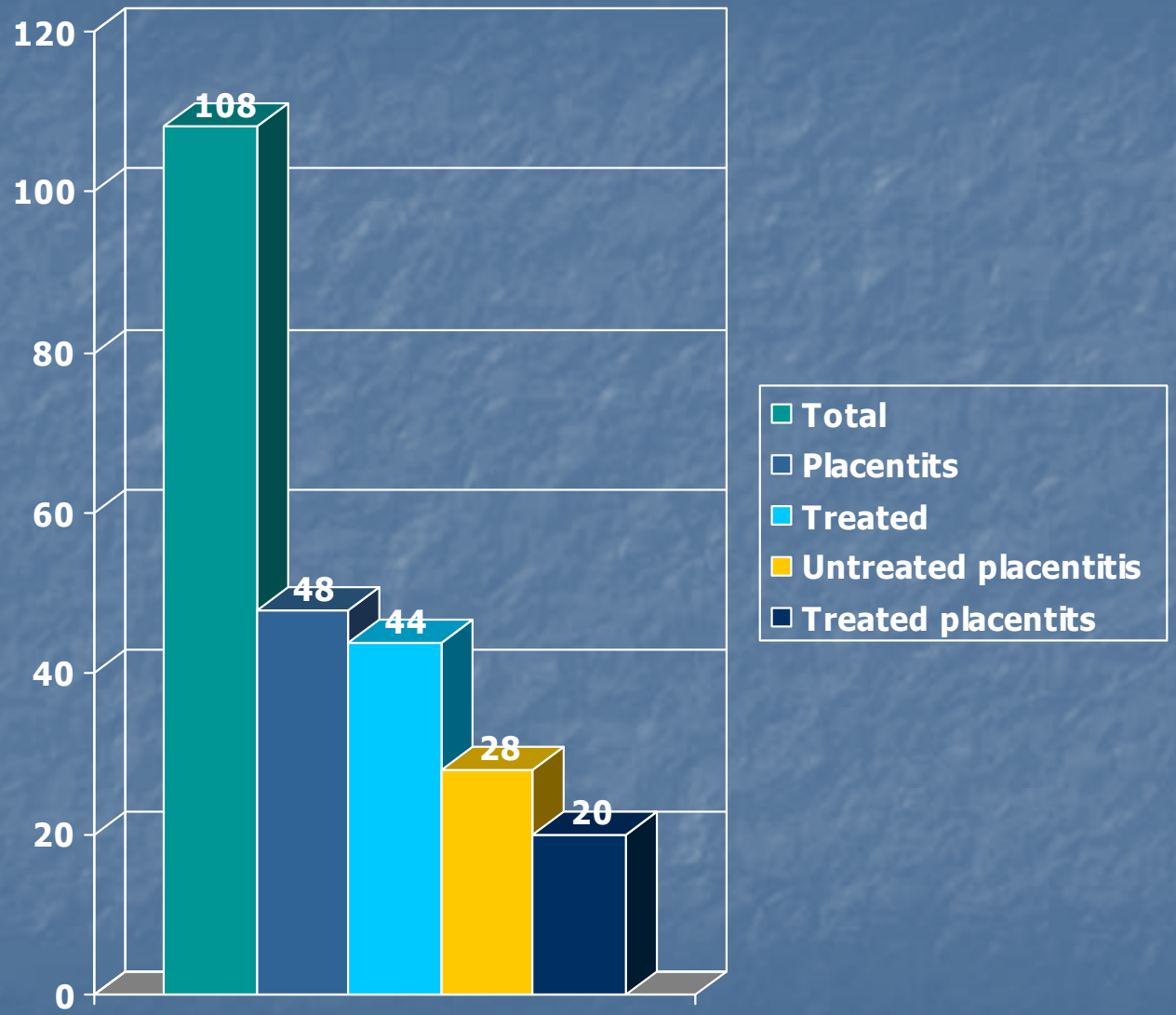
Statistical Analysis

- Logistic regression
  - Odds of occurrence of neonatal disease states
    - Based on presence or absence of placentitis
  - Interaction of treatment and outcome
- Kruskal-Wallis analysis
- Fishers Exact test
- Significance level
  - $p \leq 0.05$
  - Trend p 0.05-0.10
  - Odds ratio confidence interval 95%

Results

- 108 cases
- Placentitis - 44% (48/108)
  - Gross - 56% (27 cases)
  - Histologic 60% (29 cases)
  - Retention 33% (16 cases)
- Prepartum treatment 41% (44/108)
  - Placentitis cases treated 42% (20/48)

Placentitis and Treatment



Possible Confounders

- Diagnosis of "Placentitis"
  - No definitive diagnosis during gestation
  - Placentitis could resolve during gestation
- Severe placentitis not included
- Birth problems
  - Prolonged stage II labor (5/71)
    - > 30 minutes
  - Premature placental separation (27/97)
  - Need for birth resuscitation (20/108)

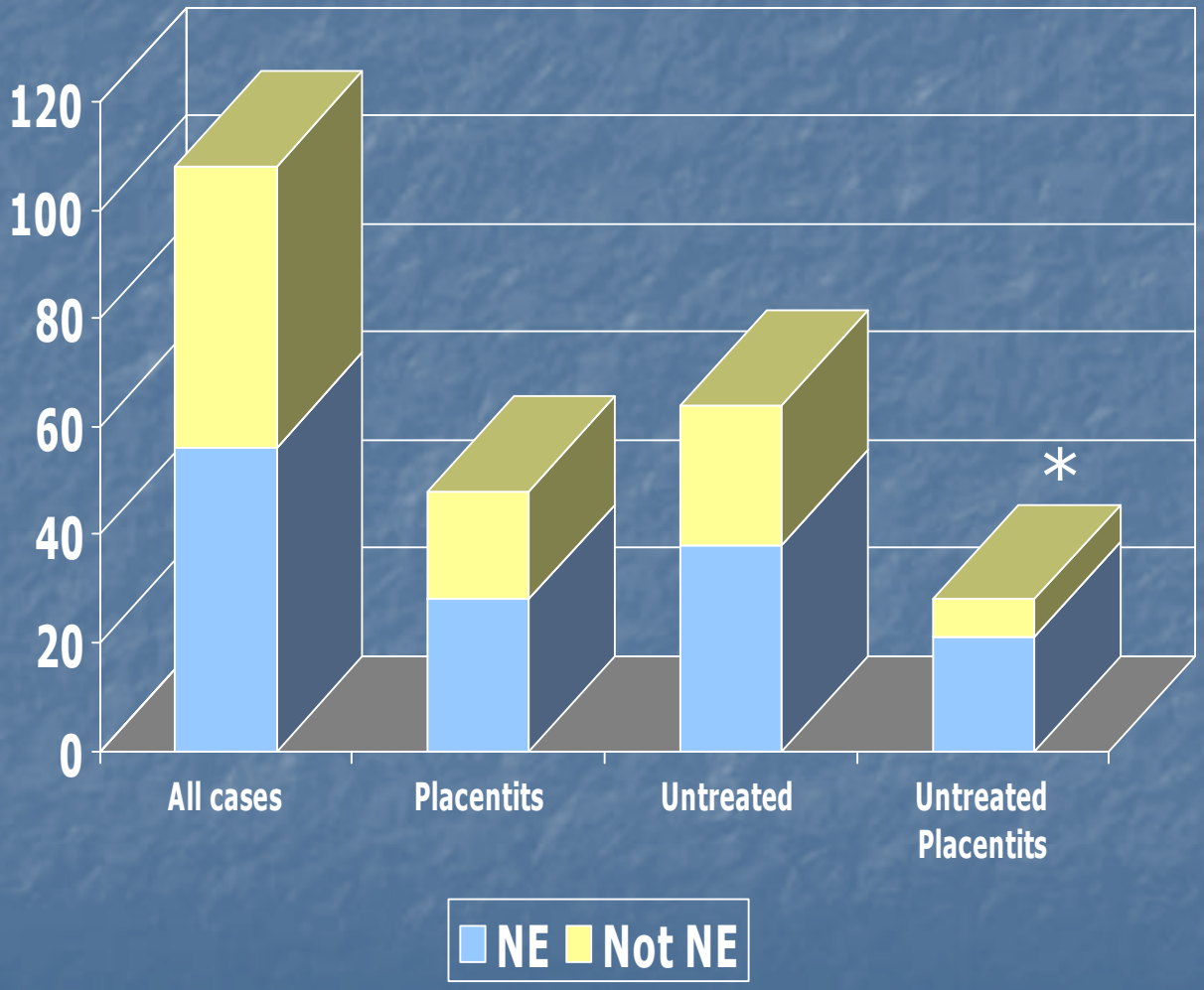
Clinical Diagnosis

- NE 52% - 56/108
- NN 40% - 43/108
- NG 37% - 40/108
- Clinical prematurity 4.6% - 5/108
- IUGR 9% - 10/108
- Sepsis 56% - 61/108
- Bacteremia 18% - 19/108
- Normal 27% - 29/108
  - None of these problems
  - Other neonatal problems
    - Musculoskeletal problems
    - Neonatal isoerythrolysis.

Placentitis, Treatment and Disease

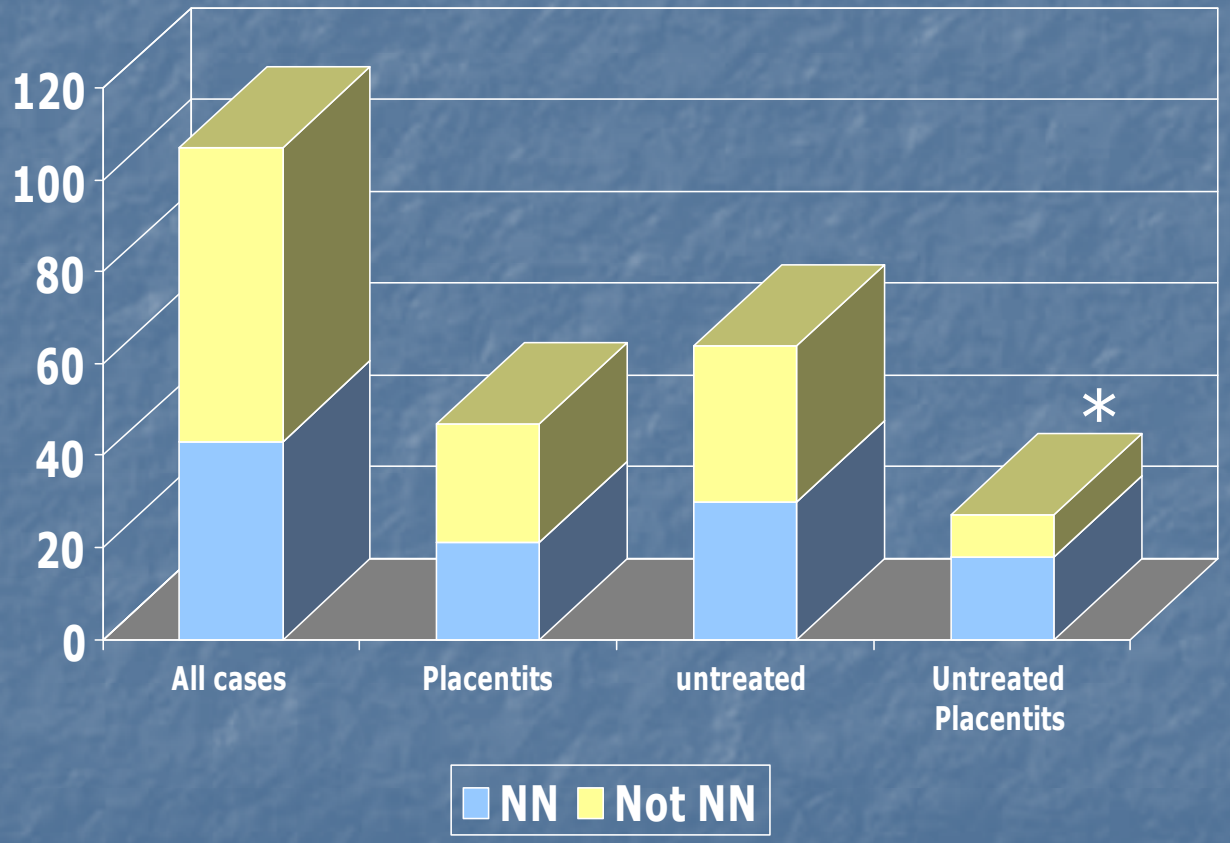
- No association of NE, NN or NG
  - With placentitis
  - With prepartum treatment
    - Regardless of the occurrence of placentitis
- Untreated placentitis
  - NE – p = 0.028, OR 3.4, 95% CI 1.1-9.8
  - NN – p = 0.011, OR 4, 95% CI 1.4-11.5
  - NG – p = 0.031, OR 3.1, 95% CI 1.1-8.6
  - Sepsis – p = 0.087, OR 2.8, 95% CI 0.86-9.1
  - Bacteremia – p = 0.018, OR 4.8, 95% CI 1.3-17.9

Neonatal Encephalopathy



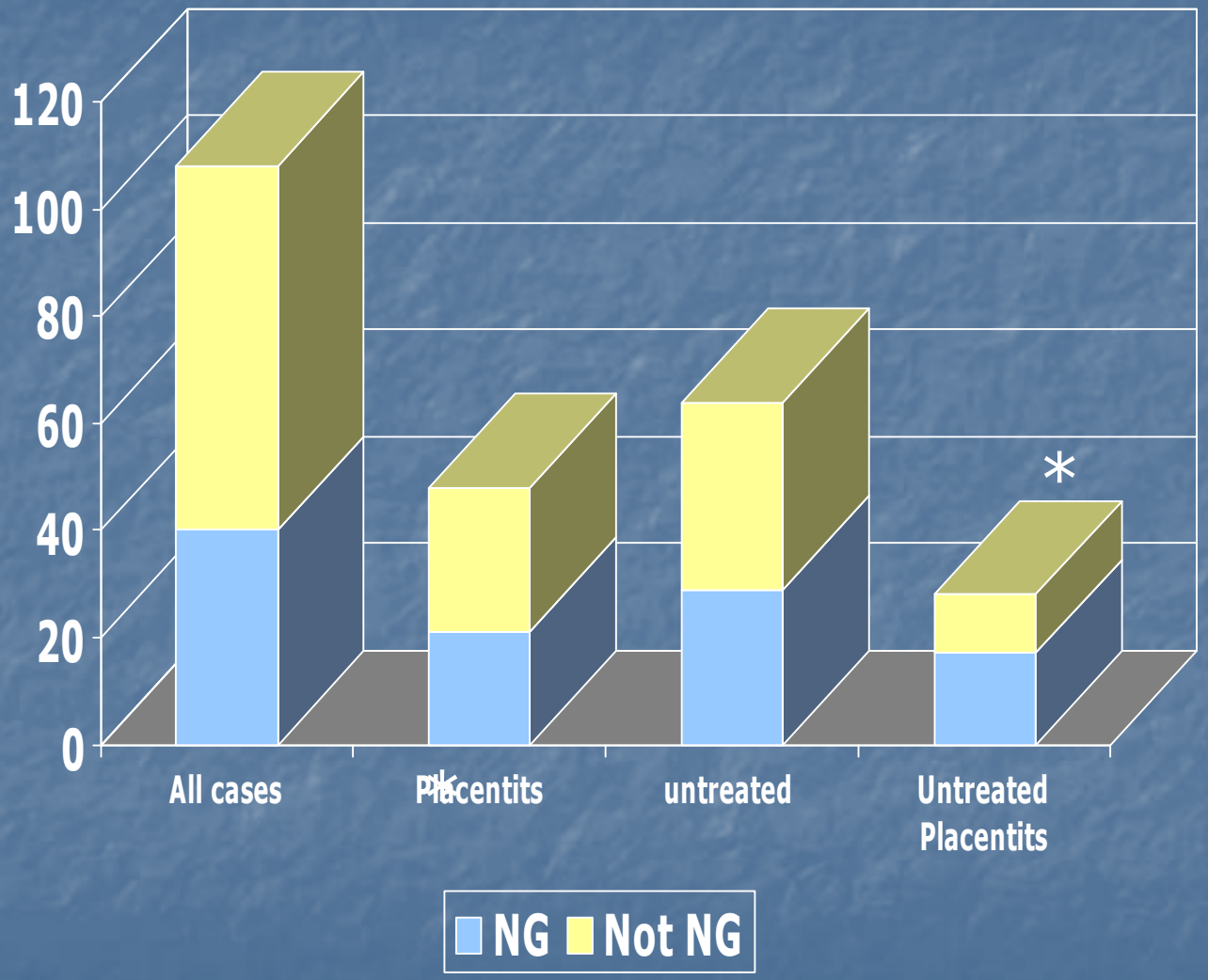
p = 0.028, OR 3.4, 95% CI 1.1-9.8

Neonatal Nephropathy



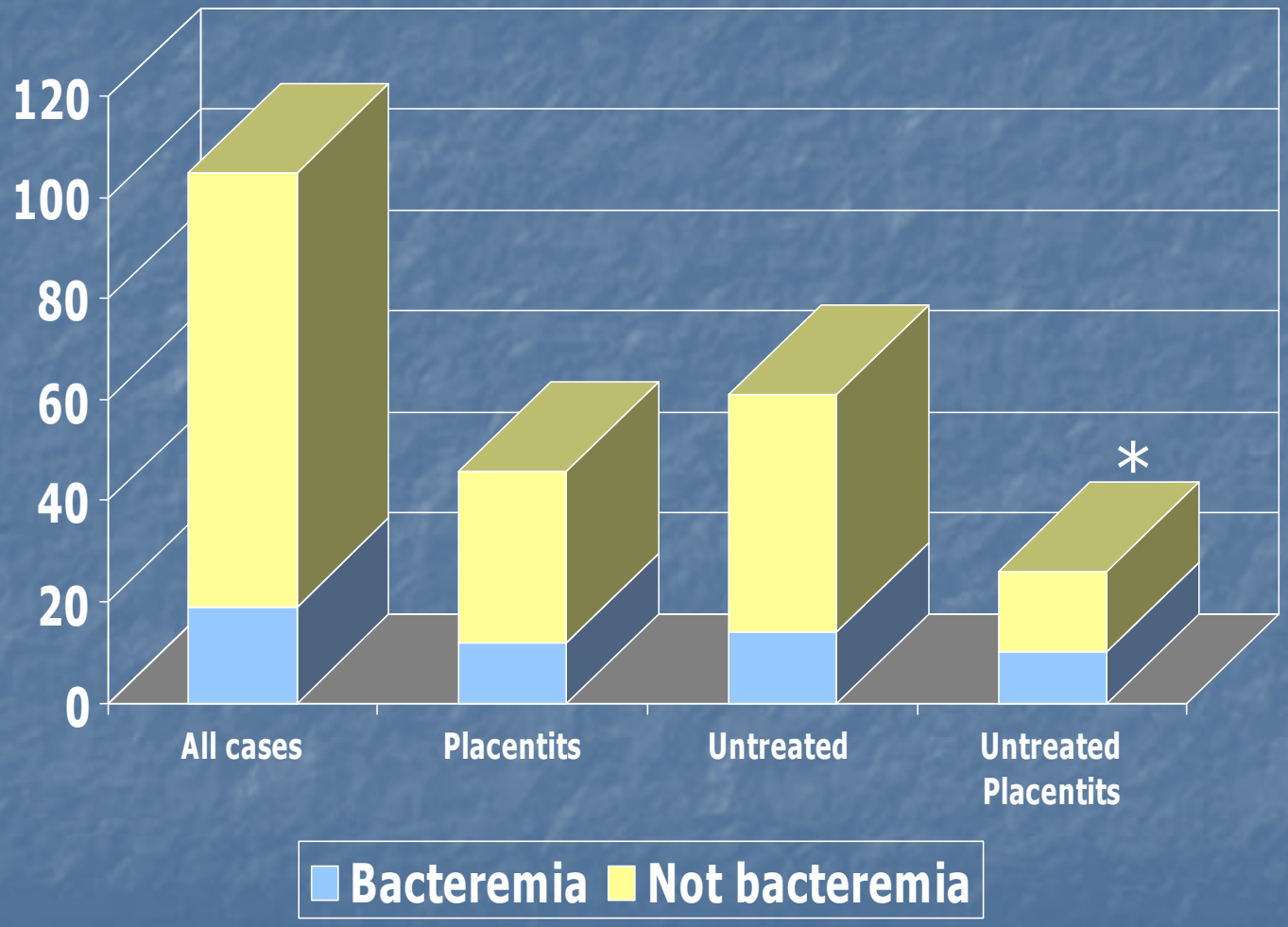
p = 0.011, OR 4, 95% CI 1.4-11.5

Neonatal Gastroenteropathy



p = 0.031, OR 3.1, 95% CI 1.1-8.6

Bacteremia



p = 0.018, OR 4.8, 95% CI 1.3-17.9

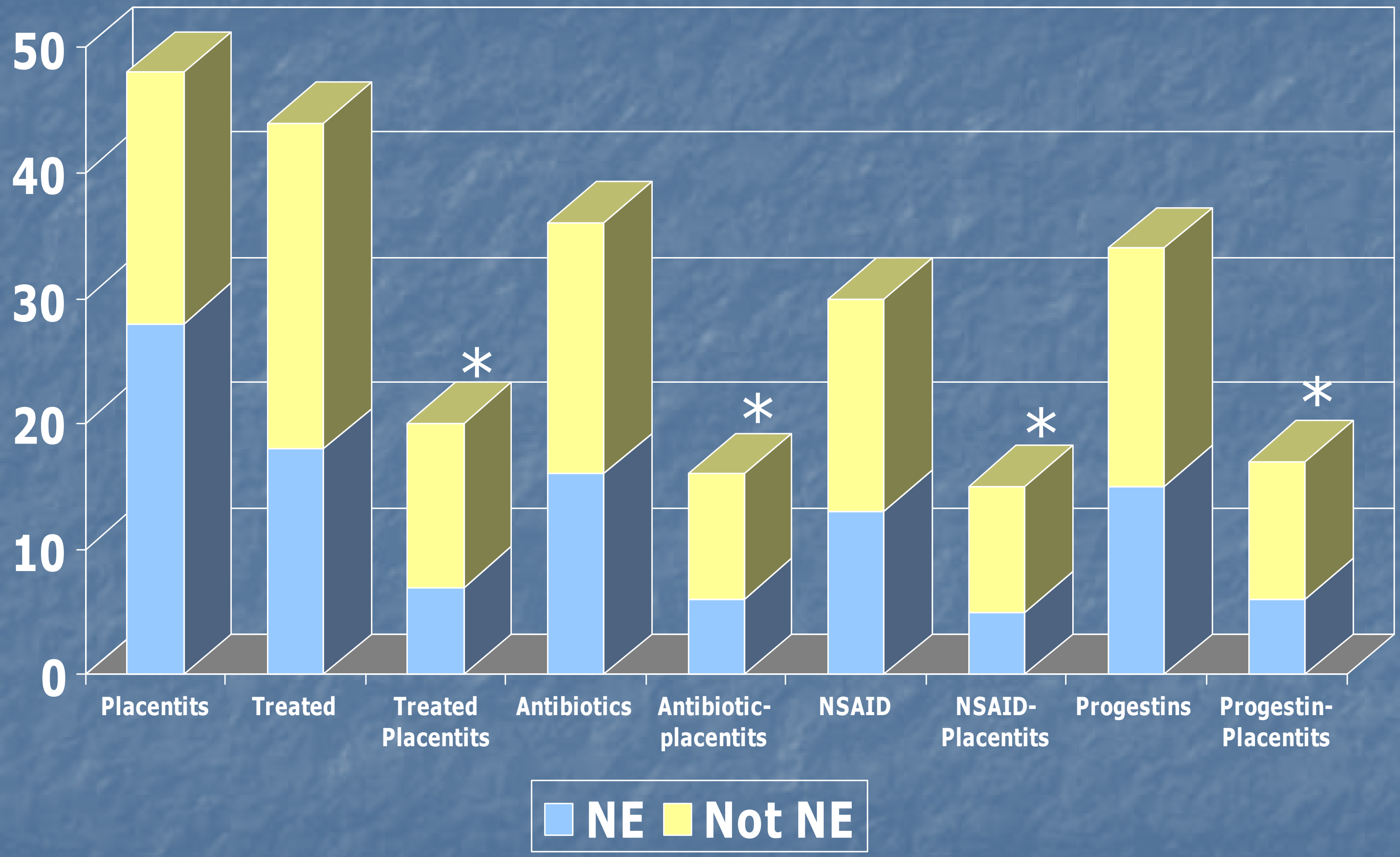
Sepsis
Bacteremia

- Sepsis
  - No association with placentitis
  - Untreated placentitis
    - p = 0.087, OR = 2.8, CI 0.86 - 9.1
  - Treatment in all mares protect against?
    - p = 0.057, OR 0.4, 95% CI 0.12 -1.03
  - Treatment of placentitis not protective
- Bacteremia
  - Trend association with placentitis
    - p = 0.055, OR 2.8 95% CI 0.98 – 7.74
  - Untreated placentitis
    - p = 0.018, OR 4.8, 95% CI 1.3-17.9
  - Treatment of placentitis not protective

Treatment of Placentitis

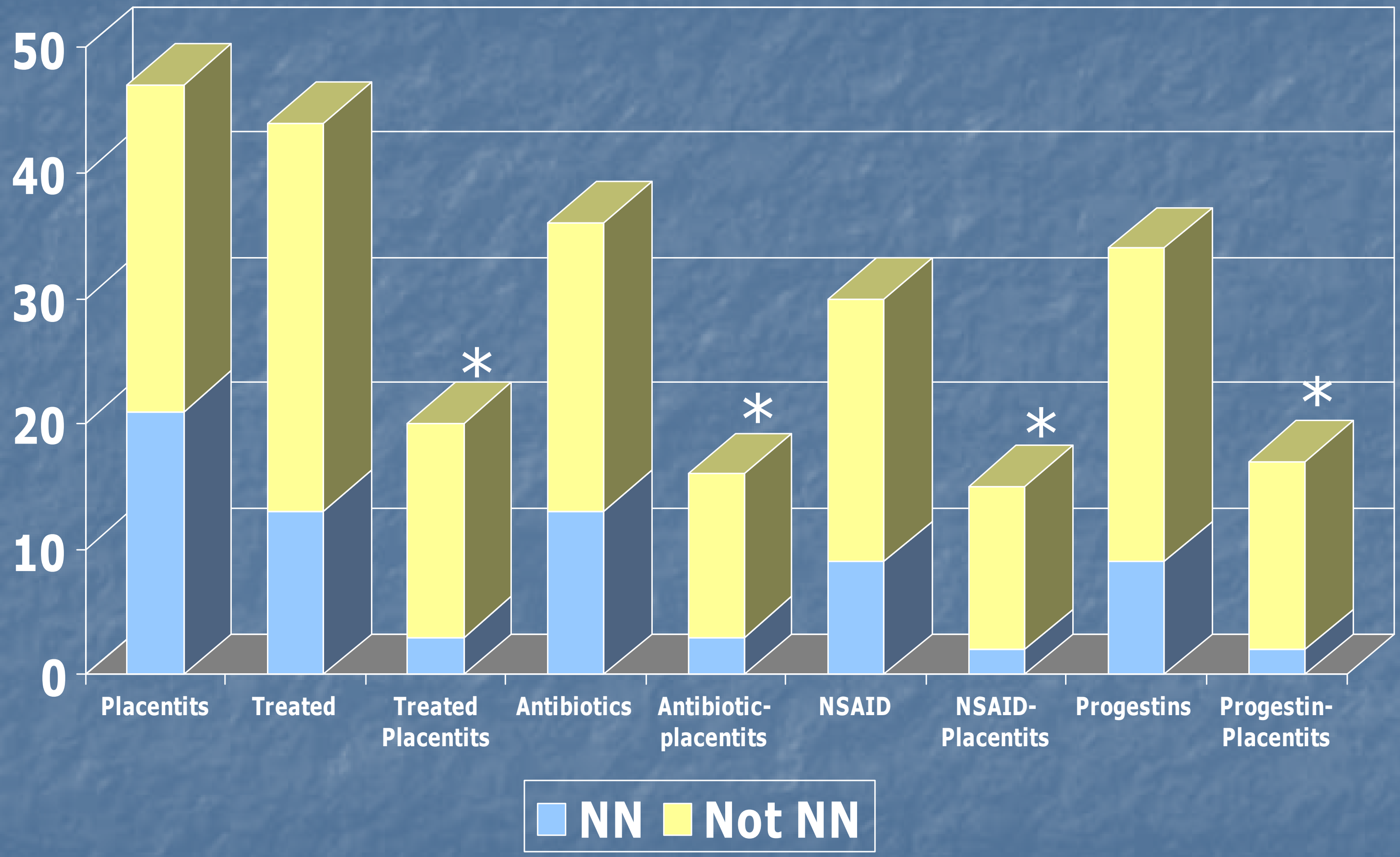
- Antimicrobials – 36 cases
  - TMS - 34 cases
  - Gentamycin/Penicillin – 3 cases
- NSAIDs – 30 cases
  - Flunixin melamine – 29 cases
  - Phenylbutazone – 1 case
- Progestins – 30 cases
  - Altrenogest
- Intranasal oxygen – 9 cases
- Vitamin E – 6 cases
- Pentoxifylline – 2 cases

NE, Placentitis and Treatment

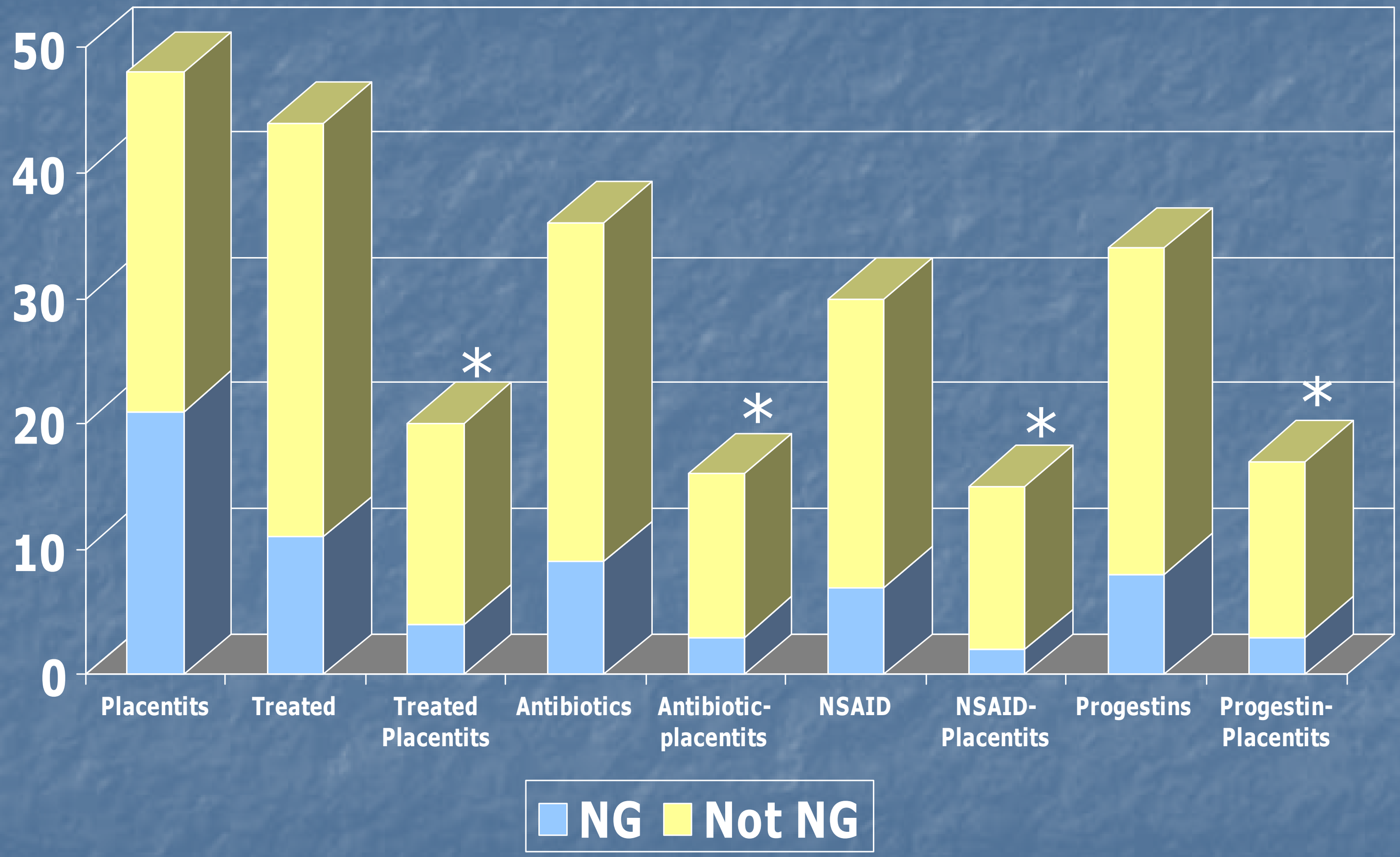


Progestins p=0.015, OR 0.12, CI 0.02-0.66

NN, Placentitis and Treatment



NG, Placentitis and Treatment



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Treatment of Placentitis

- Increases odds of a normal foal
- For normal foals
  - Any treatment
    - p=0.032, OR 7.9, CI 1.2-53
  - Antimicrobials
    - p=0.013, OR 11.2, CI 1.7-75
  - NSAIDS
    - p= 0.014, OR 14.2, CI 1.7-119
  - Progestins
    - p= 0.043OR 7.1CI 1.1-47

Treatment of Placentitis

- No significant benefit in preventing
  - Sepsis
  - Bacteremia
  - IUGR?
  - Clinical prematurity?

Confounders

- Interaction
  - Untreated placentitis
  - PPS
  - Birth resuscitation
- NE
  - Significant
    - Untreated placentitis, PPS, Birth resuscitation
  - No interaction
- NN
  - Significant
    - Untreated placentitis, PPS
  - No interaction

Confounders

- NG
  - Significant
    - Untreated placentitis, PPS , Birth resuscitation
  - No interaction
- Sepsis
  - Not significant
  - No interaction
- Bacteremia
  - Significant - Untreated placentitis
  - No interaction

Conclusions

- Strong association of untreated placentitis
  - NE, NN and NG
  - Placentitis is the etiology
- Prepartum treat of the mare for placentitis
  - Strongly protective
  - Antimicrobials, NSAIDs and progestins
- Association of untreated placentitis
  - Bacteremia
  - Trend with sepsis

Conclusions

- Treatment, independent of placentitis, trend to protect against sepsis
  - Something other than placentitis responding to treatment?
  - Treatment decrease exposure to predisposing factors?
- Treatment of mares with placentitis significantly increased the odds of having a foal without any of the neonatal problems studied
- Mares with suspect placentitis should be treated prepartum to prevent development of common neonatal diseases

PLACENTITIS ASSOCIATED NEONATAL PROBLEMS AND THE EFFECT OF THERAPEUTIC INTERVENTIONS

Palmer JE, Sertich PL, Cornman BI, Wilkins PA and Boston RC

Department of Clinical Studies, New Bolton Center,
School of Veterinary Medicine, University of Pennsylvania, Kennett Square, PA, USA

Disruption of the intrauterine environment may be the initiator of many serious neonatal diseases. The inflammatory response may directly affect placental sufficiency or the inflammatory cascade accompanying the placentitis may have secondary adverse consequences for the fetus. We report on a preliminary retrospective study of the relationship between placentitis and neonatal diseases and the effect of therapy.

Clinician notes from foals and their mares from 2000 through 2005 were reviewed. Cases with complete fetal membrane evaluation by the second author (PLS) and foal evaluation by the first author (JEP) were included. Data was analyzed through logistic regression. A p-value of 5% was used to separate chance from factor driven differences in outcomes, and a p-value interval of 5% and 10% was used to highlight the presence of trends.

One hundred eight (108) cases were identified. When all cases were considered, there was no association of Neonatal Encephalitis (NE), Neonatal Nephropathy (NN) or Neonatal Gastroenteropathy (NG) with placentitis or prepartum treatment regardless of the occurrence of placentitis. However, when treatment of placentitis was considered, NE, NN and NG were significantly more likely to occur in foals born to mares with untreated placentitis. There was a trend for bacteremia to be associated with placentitis and it was also more likely in foals with untreated placentitis. Treatment of mares with any combination of antimicrobials, NSAIDs or progestins significantly protected foals against the development of NE, NN and NG. No significant benefit of treatment was seen in preventing sepsis or bacteremia. Mares with placentitis were more likely to have a normal foal if treated with antibiotics, NSAIDs or progestins.

There is a strong association of placentitis and neonatal diseases (NE, NN and NG) but only in untreated cases. This strong association supports the hypothesis that placentitis is the cause of these diseases. In addition prepartum treat of the mare for placentitis appears to strongly protect against development of these diseases. Commonly utilized therapy seemed to contribute to this protective affect. Surprisingly, treatment, independent of the presence of placentitis, showed a trend to protect against sepsis suggesting that something other than placentitis which responded to treatment could predispose the foal to sepsis. Alternately, treatment of the mare might decrease the exposure of the neonatal foal to factors that predispose to sepsis. These trends will be explored further as more cases are added to this data set. Although bacteremia was more likely in foals from mares with untreated placentitis, prepartum treatment of the mares did not protect from bacteremia. Treatment of mares with placentitis significantly increased the odds of having a foal

without any of the neonatal problems. Mares with suspect placentitis should be treated prepartum to prevent development of common neonatal diseases.