Treating neonatal foal infections represents numerous challenges to equine practitioners. These infections may be systemic or localized, and progress rapidly due to impaired cellular and humoral immune responses associated with age and/or failure of passive transfer. The equine neonatal period (first 2 weeks of life) represents a unique period of pharmacology, that changes quickly afterwards towards the same characteristics as the adult. Also, neonatal foals are “therapeutic orphans” in that there is a relative paucity of neonatal pharmacology research, and neonates are typically not included in clinical trials.

Equine neonates have unique characteristics compared to adults, including increased oral drug absorption, lower binding to plasma proteins (particularly albumin), lower ratio of body-fat to fluids (affects distribution of lipophilic antimicrobials – e.g. macrolides, fluoroquinolones, trimethoprim), larger volume-of-distribution (Vd) (affects distribution of hydrophilic antimicrobials – e.g. aminoglycosides, β-lactams), increased blood-brain barrier permeability, incomplete drug metabolism pathways, acidic urine ( favouring tubular reabsorption and extending drug half-life). Variations in the neonate’s rate of maturation of these physiological variables account for these pharmacodynamic differences. Incomplete glomerular development, low perfusion pressure and inadequate osmotic load contribute to reduced renal efficiency, and prolonged elimination half-life in neonates. These variations of different elimination processes (hepatic metabolic pathways and renal excretion mechanisms) make the prediction of dosage intervals unreliable.

Septic equine neonates have reduced effectiveness of antimicrobials. Hypoxia in premature and neonatal foals decreases antibiotic clearance rates (ClB), and prolongs drug half-life (T1/2). Due to hypoxic-induced renal vasoconstriction, leading to reduced GFR. These changes may also be due to increased capillary permeability coupled with aggressive fluid therapy. Fever has been found associated with decreased serum gentamicin. ClB of aminoglycosides was lower (indicating impaired renal function) and prolonged T1/2 in uraemic compared with non-uraemic neonatal foals. Furthermore, many critically ill neonates are neutropenic, affecting both antimicrobial clinical efficacy and post-antibiotic effects. Hepatic disease or changes in hepatic blood flow (low cardiac output or raised intra-abdominal pressure) contributes to the variability of drug clearance.

Antimicrobials alone may be involved in septic shock by stimulating the release bacterial cell wall endotoxin. Foals receiving β-lactams alone, specifically ceftiofur, had increased endotoxin concentrations 12 hours later. Combined β-lactam and aminoglycoside did not result in increased endotoxin release.

### β-lactam antimicrobials

The lower acidic pH of the neonate’s stomach and the nature of milk ingesta, combined with greater permeability of the upper small intestine, favours oral drug absorption. For example, oral amoxicillin was 30-50% bioavailable in neonatal foals compared with 5-15% in adult horses. Pivampicillin, a pro-drug of ampicillin, has oral bioavailability of 40-53% in neonatal foals. Parental ceftiofur and cefquinome have also been investigated as safe and effective pharmacokinetics in neonatal foals, using higher doses and frequency of administration compared to adults.
With regard to bacterial meningitis, greater therapeutic success is more likely by administering IV cefotaxime TID or ceftriaxone BID at 15-25 mg/kg, for both. Aminoglycosides, due to their polar nature, do not attain effective concentrations in CSF.

**Aminoglycosides:** These are a mainstay for treating gram-negative infections in neonatal foals because of their rapid bactericidal effects, narrow-spectrum of clinical efficacy, relatively low resistance rates, and synergism with β-lactams. Following parenteral administration, gentamicin distribution is virtually restricted to extracellular fluid, and elimination takes place solely by glomerular filtration. The longer half-life of gentamicin, in neonatal foals is due to the larger apparent V_d.11 There disadvantages is that there is significant inter-individual variability in aminoglycoside pharmacokinetics8. Sepsis-associated alterations of vascular permeability, vascular tone, and renal function are likely responsible for this variability10, 14. Also, aminoglycosides exhibit a low therapeutic index, where there is little difference between a therapeutic and toxic dose.4 Kidneys are the main site of toxic side effects, where there is reabsorption by the proximal renal tubular epithelial cells, leading to accumulation of the drug of up to 50 times the serum concentration within the renal cortex.11 Neonatal kidneys may be more sensitive to these side effects.

Due to the differences in neonatal foal pharmacokinetics, compared to adults, then gentamicin doses greater than 6.6 mg/kg IV or IM SID are recommended.11 Given the neonatal inter-individual variability, relative narrow margin of safety, then doses above 10mg/kg in the neonatal period are difficult to justify within the neonatal period, unless appropriate tools are available to measure peak-and-trough plasma gentamicin concentrations, and/or sensitive markers of kidney damage (e.g. urine GGT/creatinine ratio).

Other issues related to gentamicin are that they are de-activated in an acidic environment, low oxygen environment or the presence of elevated inflammatory debris. One study examined amikacin in normal neonatal foals at 21mg/kg IV SID for 10 days. No renal toxicity was noted in these foals after 10 days; however, significant age-related changes were found, with amikacin T_{1/2} decreasing from 3.62±0.79 hours at 1 day of age to 1.89±0.66 hours at 10 days of age, amikacin Cl_B increasing from 1.59±0.44 (ml/min)/kg at 1 day of age to 2.71±0.61 (ml/min)/kg at 10 days of age, and amikacin V_d decreasing from 442.4±63.1 ml/kg at day 1 to 373±67.7 ml/kg at 10 days of age.13