Antimicrobial Treatment of Neonatal Foals

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ABSTRACT: It is common in clinical practice to treat neonatal foals with antimicrobials for a variety of clinical abnormalities, including neonatal septicemia and umbilical, pulmonary, or orthopedic infections. The selection and use of antimicrobials in neonatal foals are often challenging because of their unique physiologic and developmental attributes. In general, neonates (i.e., foals less than 14 days of age) require broad-spectrum, bactericidal antimicrobials. Because of the predominant nature of organisms causing infections in foals, a combination of a penicillin-class antimicrobial and an aminoglycoside is usually ideal. Therapeutic drug monitoring of an aminoglycoside is important to minimize toxicity. Additional treatment modalities, such as joint lavage and respiratory nebulization, can also augment traditional systemic antimicrobial therapy.

The equine neonate commonly requires antimicrobial treatment to combat a variety of infectious conditions, as infections can be acquired in the prenatal (i.e., in utero) or postnatal period. In the postnatal period, failure of passive transfer is considered to be a contributing factor. Prematurity, dysmaturity, and dystocia may also play a role in the development of sepsis. These serious infections can be rapidly fatal, particularly in neonatal patients with compromised immune response. In neonatal foals, immunoglobulin levels may be decreased because of failure of passive transfer, because complement concentrations are lower than in adults, and because septic foals are often neutropenic. In addition, neonatal sepsis and infections tend to be rapidly progressive. Therefore, prompt and appropriate treatment with antimicrobials is crucial to a successful outcome. The use and selection of antimicrobials in the neonate can be challenging, however, and require consideration of several issues.

FACTORS DETERMINING ANTIMICROBIAL DRUG SELECTION

A basic principle of antimicrobial treatment in neonatal foals is the use of broad-spectrum, bactericidal drugs. In addition to the cost of antimicrobial agents, several specific factors must be considered when selecting and using antimicrobial drugs in neonates:

- Likely pathogen involved
- Site of infection
• Route of administration
• Drug metabolism
• Potential for toxicity
• Length of treatment

Culture and Sensitivity Testing
Antimicrobial choices should always be based on the results of appropriate culture and sensitivity testing. Thus bacteriologic sampling of body fluid or tissue is necessary. In a foal with suspected sepsis, the ideal sample is a blood culture, which should be obtained before an antimicrobial is administered. Blood culturing should be done after surgically preparing skin over an appropriate vein (e.g., jugular, saphenous, cephalic). The sample should be collected with a sterile syringe and needle using aseptic technique. Alternatively, the blood sample can be obtained during catheter placement, again by surgically preparing the area and using aseptic technique. Regardless of which method is used, proper preparation of the site is key, as cultures taken from an improperly or inadequately prepared site have little to no value because of the high degree of contamination. After collection, the blood should be transferred to a blood culture bottle for incubation.

If antimicrobials were administered before blood collection, the sample should be placed in an antimicrobial removal device (Septi-check TSB with resin, Becton Dickinson) to allow antimicrobials to be adsorbed into a resin, thereby enhancing recovery of bacteria from the sample. Other valuable sources for bacterial culture are peritoneal, pleural, cerebrospinal, and synovial fluid. Culture material can also be obtained via transtracheal aspiration, as long as the foal is not in respiratory distress, in which case the procedure should be avoided.

Culture results should be carefully evaluated, as false-negative results can occur. Culture of blood or body fluids from foals with polymicrobial infections may recover only some of the organisms. In foals with septic joints and systemic sepsis, for example, both blood and synovial fluid should be cultured to increase the probability of identifying all pathogens.

Initiating Preliminary Treatment Based on Likely Pathogen
Because microbial culture takes time, preliminary treatment must begin before definitive culture results are available. Thus a presumptive judgment about the most likely pathogen involved must be made. Most neonatal infections are caused by organisms in the foal’s environment. Understandably, gram-negative bacteria are by far the most common pathogens involving neonates, and numerous studies have reported that Escherichia coli is the most common isolate.1,2 More than 50% of neonatal infections are caused by E. coli and other gram-negative pathogens, such as Enterobacter and Klebsiella spp.1 In one study,3 gram-positive organisms, particularly Staphylococcus and Streptococcus spp, were also cultured from septic foals.3 Less commonly encountered organisms are Clostridium, Salmonella, Pseudomonas, and Actinobacillus spp. In addition to pathogenic infections, polymicrobial infections are common.4

Given the frequency of gram-negative bacterial infections, aminoglycosides are key in the treatment of septic neonatal foals, although extended-spectrum penicillin drugs have value as well. Our practice is to include an aminoglycoside in the therapy of all foals with non-azotemic sepsis until the culture results are completed and more precise antimicrobial choices can be made. It has been shown that bacterial killing by aminoglycosides is enhanced by adding a penicillin-class antimicrobial.5,6 Hence, combinations of a penicillin-class drug and an aminoglycoside are commonly used.

The synergy between penicillin-class antimicrobials and aminoglycosides is likely the result of increased uptake of the aminoglycoside by the bacterium because of penicillin-mediated damage to the bacterial cell wall.5 This combination provides a broad spectrum of coverage and bactericidal action with maximum and efficient killing. Numerous drug combinations are satisfactory, including combining penicillin, ampicillin, ticarcillin, or ceftiofur with gentamicin or amikacin. Some drug combinations should be avoided, however, because they have been shown to be antagonistic in vitro. These include penicillin–tetracycline, penicillin–oxytetracycline, and penicillin–chloramphenicol.5

In treating humans with severe sepsis, the use of some β-lactam antimicrobials has been associated with liberation of endotoxin, worsening of clinical signs, and fever. This appears to vary with the organism involved and drug being used.7,8 In an in-vitro model of foal septicaemia, β-lactam antibiotics resulted in greater liberation of endotoxin than aminoglycosides.9 In addition, there was an increase in tumor necrosis factor–α (TNF-α) activity associated with endotoxin elaboration.9 It seems prudent, therefore, to include treatment to protect the foal from endotoxia when treating with antimicrobials in the β-lactam group.

Site of Infection
Another important factor to consider in selecting antimicrobials for administration to foals is the site of infection. Bacterial sepsis is commonly associated with...
localized infection in pulmonary tissue, brain and meninges, joints, or umbilical remnants. An important principle of antimicrobial use is that the drug must be present in the infected tissues in an adequate concentration to kill the organism. Therefore, it is important to consider the tissue involved because it affects the duration, dose, and type of antimicrobial needed. For example, umbilical remnants are poorly vascularized structures and antimicrobial delivery to these tissues is often inefficient. If there is documented or suspected umbilical sepsis, prompt surgical removal may be advisable.

Orthopedic infections are not uncommon in sick neonates, and prompt and aggressive treatment can be very rewarding. All foals with orthopedic infections should receive systemic antimicrobials, but joint infections should also be treated with intraarticular antimicrobials following vigorous joint lavage. Joint lavage removes bacteria and inflammatory debris and is absolutely crucial to overall recovery of such conditions. A valuable antimicrobial for intraarticular treatment is amikacin (250 mg), although other antimicrobials can be used if the results of bacterial sensitivity testing dictate. Lavage can be repeated daily or every other day, as needed. Refractory joint infections may benefit from the use of intraarticular antimicrobial-impregnated beads, intramedullary antimicrobial infusion, or synovectomy and surgical debridement. These treatment modalities usually require referral to a tertiary care facility.

Meningeal infections require special considerations because of the blood–brain barrier. Many drugs, including aminoglycosides, penetrate this barrier poorly and thus have little use in the treatment of meningitis. While inflammation may allow some increased penetration of some drugs into the central nervous system (CNS), clinicians should not rely on this phenomenon when treating foals with meningitis. Drugs with good penetration of the blood–brain barrier are chloramphenicol, sulfamethoxazole, and third-generation cephalosporins (e.g., ceftazidime, cefotaxime). Cefotaxime has been successfully used at a dose of 40 mg/kg tid or qid in foals with meningitis. Ceftazidime (40 mg/kg q6–8h) has been used by one of the authors (M. F.) to successfully treat foals with confirmed septic meningitis. Ceftriaxone is considered by many to be a third-generation cephalosporin as well; however, its penetration of the blood–brain barrier has not been reported in foals. In normal adult horses, ceftriaxone was not detected in the cerebrospinal fluid after repeated intramuscular (IM) administration. One major drawback in using the third-generation cephalosporins is cost, which may be limiting in some cases.

With pulmonary infections, inhaled nebulized antimicrobials can be beneficial, particularly in foals with meconium aspiration syndrome. A parenteral dose of gentamicin can be nebulized with 20 ml of saline using an ultrasonic nebulizer (DeVilbiss UltraNeb99, Sunrise Medical) and a tight-fitting face mask (Equine Aeromask Foal Size, Canadian Monaghan) to achieve high antimicrobial concentrations in the airways. An additional benefit of nebulization may be enhanced clearance of mucus and inflammatory debris, although this has not been confirmed by objective means. It is important to recognize that nebulized antimicrobials should not be used alone in systemically ill foals. They should always be combined with parenteral administration of an appropriate antimicrobial.

**Route of Administration**

The route of administration is also a consideration when selecting antimicrobials. Orally administered drugs are attractive for clients, but many septic foals are intolerant of oral intake, thereby limiting the usefulness of oral antimicrobials. In addition, few oral antimicrobials for use in foals are available. Penicillin V and amoxicillin have been used in neonatal foals, but their antimicrobial spectrum is limited and the serum concentrations achieved at standard doses are poor. Most antimicrobials can be administered IM, but foals have very little muscle mass and injection sites can become swollen and painful very quickly. This often makes such therapy difficult for owners to maintain. Placement of a catheter allows IV medication to be administered without these complications. An IV catheter must be carefully maintained, however, and such maintenance may be beyond the ability of some clients or facilities. In those circumstances, hospitalization may be the best option.

**Drug Metabolism**

The absorption and disposition (i.e., distribution, metabolism, excretion) of antimicrobial drugs differ significantly in neonates compared with adult horses, resulting in the need for dosing regimens unique to these patients. Factors that contribute to these differences include greater gastrointestinal absorption capacity, higher percentage of total body water (which results in a larger volume of distribution for many drugs), and decreased protein binding because of relative hypoalbuminemia. Immature hepatic and renal functions result in reduced drug metabolism and excretion compared with adults. Thus it is important to recognize that neonatal foals are not simply “small adults.”

Many pathophysiologic processes that commonly occur in equine neonates can also alter drug absorption...
and disposition. Hypoxia and prematurity decrease the elimination rate constant and clearance and increase the half-life of amikacin in equine neonates. Sepsis (with its attendant effects on renal blood flow, cardiac output, and tissue perfusion), fever, anemia, azotemia, and diarrhea have all been demonstrated to alter aminoglycoside clearance. Septic foals often receive multiple concurrent drug therapies, some of which may alter the disposition of antimicrobial agents. Phenylbutazone, aspirin, and dexamethasone, among other drugs, alter gentamicin elimination.

**Potential Toxicity**

Toxicity of antimicrobials must also be considered. Some potentially valuable drugs, particularly enrofloxacin, are specifically toxic in the neonate and their use in these patients should be discouraged. Although aminoglycosides are invaluable in treating neonatal sepsis, careful monitoring is necessary to optimize efficacy and minimize toxicity. Urinalysis, blood urea nitrogen, and serum creatinine measurements have low sensitivity and are generally poor means of monitoring for nephrotoxicity associated with aminoglycosides. Significant renal toxicity must exist before these parameters become altered. Monitoring aminoglycoside clearance and trough concentrations is considered to be superior to monitoring serum creatinine concentrations because aminoglycoside concentrations can indicate abnormal clearance before renal lesions develop and doses can be altered appropriately before nephrotoxicity progresses.

**Length of Treatment**

The final consideration in antimicrobial treatment of foals is when to stop therapy. While this may seem self-evident, it is often a challenging decision following critical illness. Premature withdrawal of antimicrobials can lead to recurrence of problems, some of which may be serious. In general, for soft tissue infections, antimicrobial therapy should continue until signs of local infection are no longer clinically present and systemic signs of infection such as temperature, complete blood cell count, and fibrinogen concentration have been normal for 72 hours. In foals with meningitis, however, antimicrobial therapy should continue for 3 to 4 weeks, regardless of clinical or clinicopathologic findings. This is necessary to completely eradicate bacteria within the choroidplexus from which bacteria can sometimes be shed for several weeks following treatment. Similarly, foals with osteomyelitis frequently require prolonged antimicrobial therapy. Careful clinical assessment and radiographic monitoring are required in these cases.

**SPECIFIC PROPERTIES OF DRUGS IN ANTIMICROBIAL GROUPS**

**β-Lactam Group**

**Penicillins**

The penicillins are bactericidal and act by inhibiting cross-linking within the bacterial cell wall. They are inexpensive and are characterized by a gram-positive spectrum, good soft tissue penetration, and low toxicity. Penicillin G is the most common penicillin used in equine medicine. Sodium or potassium penicillin G can be administered either IV or IM every 6 hours. Procaine penicillin G can be administered IM every 12 hours. Recommended dose rates for penicillin G are 20,000 to 50,000 IU/kg. When used at an appropriate dose and combined with an aminoglycoside, penicillin G is a reasonable first-choice drug while waiting for culture and sensitivity results.

**Semisynthetic Pencillins**

Ampicillin and amoxicillin are semisynthetic penicillins with an extended spectrum that includes some gram-negative organisms. In one study, ampicillin was one of the most effective antimicrobials for treating *Streptococcus* infections and one of the poorest for treating *Staphylococcus* and gram-negative infections. When ampicillin was administered IM at 11 mg/kg, effective blood concentrations were observed for up to 6 hours. Ampicillin trihydrate administered at 20 mg/kg PO q8h resulted in serum concentrations adequate for only very sensitive *Streptococcus* spp. Given that streptococcal infections are more common than staphylococcal infections in septic equine neonates, IV ampicillin is a good empiric choice if combined with an effective aminoglycoside.

Amoxicillin is also available as either an oral or IM preparation, but absorption is apparently poor in horses, leading to blood concentrations adequate only in treating infections caused by bacteria that are particularly sensitive. Thus amoxicillin has a very little role in the treatment of septic neonatal foals.

Ticarcillin and ticarcillin–clavulanate combinations are effective extended-spectrum penicillins used to treat sepsis in foals. Recommended dose rates are 40 to 60 mg/kg IV q6h and 50 mg/kg IV q6h, respectively. As with the other members of the penicillin group, there is marked synergy with aminoglycosides. Ticarcillin, however, is much more expensive than penicillin G or ampicillin.

**Cephalosporins**

Cephalosporins are closely related to the penicillins in structure and function. As a group, the cephalosporins have fairly broad-spectrum activity, low
potential for toxicity, and good tissue penetration. Some members are penicillinase resistant. Modification of the basic structure has led to a number of different members of the group, with resultant variation in basic characteristics.

First-generation cephalosporins include cephalothin, cephapirin, and cefazolin. This subgroup has primarily a gram-positive spectrum and is penicillinase resistant. Second-generation cephalosporins have an increased gram-negative spectrum, with decreased gram-positive activity, and are represented by cefaclor and cefoxitin, among others. Third-generation cephalosporins include ceftiofur, cefotaxime, and ceftazidime. This subgroup has a greatly enhanced gram-negative spectrum and diminished gram-positive activity. Some members, ceftazidime in particular, also demonstrate good CNS penetration. Third-generation cephalosporins have many attractive features and are valuable drugs in the treatment of neonatal sepsis. However, an in-vitro model of foal sepsis showed that treatment with ceftiofur resulted in release of a large amount of endotoxin from the bacteria, which was associated with increased TNF-α production. This has not been documented in vivo but suggests that antitoxin treatment should be used concurrently with ceftiofur. In one report, ceftriaxone and ceftazidime were effective in over 90% of all isolates. However, these drugs are expensive and should be reserved for specific cases. Third-generation cephalosporins, such as ceftiofur, are common alternatives to aminoglycosides in the initial antimicrobial therapy of azotemic neonates. A fourth generation of cephalosporins is now available and is represented by cefepine. This compound has increased efficacy against gram-negative organisms as well as activity against Pseudomonas spp. However, there are no reports of its use in foals.

Aminoglycosides

Aminoglycoside antimicrobials have bactericidal activity and exert their effect by inhibiting bacterial cell protein synthesis. Members of this drug class are excreted unchanged in the urine, have poor oral absorption and poor CNS penetration, and are nephrotoxic. A benefit is that, according to one trial, treatment with amikacin resulted in minimal endotoxin release from cultured E. coli in an in-vitro model of foal sepsis while providing good microbial killing. In humans and laboratory animals, risk factors known to enhance aminoglycoside nephrotoxicity are prior renal insufficiency, increased dose or frequency of administration, hypovolemia, dehydration, metabolic acidosis, and concurrent exposure to any other nephrotoxins. Gentamicin and amikacin are the two most common aminoglycosides used in equine medicine. Recent research has demonstrated the value of once-daily aminoglycoside therapy in adult horses, but dose regimens in adult horses (e.g., gentamicin 6.6 mg/kg IV sid) are usually inappropriate for neonates. The higher volume of distribution in neonates results in significantly lower peak serum concentrations compared with adults. Also there is wide variation in the clearance of these drugs in sick equine neonates. These factors make it difficult to predict the dose and frequency of administration that a particular individual foal may require to achieve the target serum peak and trough concentrations. Thus use of a standard, or “off-the-shelf,” dose regimen for aminoglycosides in the ill neonate is likely to result in suboptimal efficacy and/or predispose the foal to nephrotoxicity. The only reliable method of determining dose regimens for aminoglycosides in the ill neonate is to monitor drug therapy.

Trimethoprim–Sulfamethoxazole

Trimethoprim–sulfamethoxazole combinations are common, inexpensive, oral antimicrobial agents. The combination is considered bactericidal and is characterized by renal excretion and minimal toxic potential. Unfortunately, bacterial resistance is apparently widespread, so this combination should not be the first-choice antimicrobial therapy in neonatal foals.

Fluoroquinolones

The fluoroquinolones of veterinary importance are enrofloxacin and orbifloxacin. This is a very effective family of antimicrobials, but significant potential for arthropathy is associated with their use. In a pharmacokinetic study in foals, Bermingham et al suggested that enrofloxacin be dosed at 10 mg/kg PO sid to achieve anticipated therapeutic concentrations. In three of four foals receiving 10 mg/kg PO sid, lameness with joint distention was noted by day 4 to 6. Postmortem evaluation documented articular cartilage loss with synovitis. In our opinion, these compounds should be reserved for situations in which there is no alternative and then used only with the informed consent of the owner.

SUMMARY

A combination of a penicillin-class drug and an aminoglycoside is appropriate empiric systemic antimicrobial therapy for most nonazotemic equine neonates. Further therapy should be based on bacterial culture and sensitivity results of appropriate samples, with consideration of route of administration, drug absorption and disposition, tissue penetration, toxicity, and cost. The combination of systemic and local (e.g., intraarticular)
antimicrobial therapies may be indicated in some circumstances. The unique physiology and pathophysiology of the neonate necessitate careful laboratory monitoring to optimize antimicrobial use.

REFERENCES

ARTICLE #5 CE TEST

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### 1. The organism(s) most commonly associated with infection of septic neonates is
a. E. coli
b. Salmonella spp.
c. Klebsiella spp.
d. Streptococcus spp.

### 2. Which of the following would be a good empiric choice in treating ill neonatal foals?
- a. erythromycin
- b. ampicillin–amikacin
- c. chloramphenicol–penicillin
d. enrofloxacin

### 3. The most accurate and effective means of monitoring aminoglycoside toxicity in foals is
- a. serial monitoring of blood urea nitrogen and creatinine.
b. urine analysis.
c. renal ultrasonography.
d. monitoring of aminoglycoside blood levels.

4. Enrofloxacin has been shown to have what important toxic action in foals?
a. nephrotoxicity
b. intraarticular cartilage damage
c. no significant toxicity
d. growth retardation

5. Which of the following is not an important consideration in selecting antimicrobials for neonatal foals?
a. most likely pathogen
b. site of infection
c. duration of infection
d. potential toxicity

6. Which of the following is correct regarding aminoglycoside administration to neonatal foals?
a. Typical adult dosages are appropriate.
b. Excretion in ill foals varies.
c. Trough levels of gentamicin of 5 µg/ml are acceptable.
d. When trough levels are excessive, the treatment interval should be decreased.

7. A third-generation cephalosporin that has good CNS penetration is
a. cefazolin.
b. ceftazidime.
c. ampicillin.
d. enrofloxacin.

8. Penicillins and aminoglycosides are synergistic, a phenomenon which is believed to be caused by
a. aminoglycosides increasing plasma levels of penicillins.
b. aminoglycosides inactivating penicillinase.
c. penicillins inhibiting the enzymes that confer resistance to aminoglycosides.
d. penicillins enhancing bacterial uptake of aminoglycosides.

9. Aminoglycosides would have the least value in treating which of the following?
a. meningitis
b. kidney or bladder infection
c. sepsis
d. joint infection

10. Antimicrobial treatment of a neonatal foal with a soft tissue infection can be stopped
a. after 72 hours.
b. when the temperature, complete blood cell count, and fibrinogen level are normal.
c. when the temperature, complete blood cell count, and fibrinogen level are normal for 72 hours.
d. after 6 days of treatment.