

Rational Selection of Antimicrobials for Use in Horses

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1. Introduction

Antibiotics frequently play an important central or adjunctive role in the therapeutic management of horses and foals with a variety of illnesses, including those requiring critical care, because diseases caused by primary or secondary bacterial infection are commonly encountered and may contribute to failure of single or multiple organs. However, it should be understood that supportive therapy usually plays a role at least as important as antimicrobials in promoting a positive outcome, and that the adverse effects of antimicrobial drugs individually or in combination may actually lead to negative consequences. Antibiotic use should be based on sound rational principles involving thorough patient evaluation, good clinical judgment, overall medical knowledge, information regarding the individual patient and the infecting agent(s), selection of an appropriate drug, and formulation of a dosage regimen appropriate to the patient and its caretaker after assessment of the potential benefits and risks of that therapy.¹

The ultimate aim of antibiotic treatment is to inflict an insult on infecting bacteria sufficient to kill the organism or render it susceptible to inactivation by natural host defenses or the local microenvironment without adversely affecting the patient.¹ The

following discussion emphasizes important aspects of antimicrobial use in horses, including the bacterial species likely to be involved in particular disease syndromes, susceptibility profiles of bacterial isolates, and the antimicrobial spectrum, mode of action, indications, dose, and adverse effects of selected commonly used antibiotics. Knowledge regarding adverse effects is particularly important because the relative sparsity of antimicrobials approved for parenteral and oral use in horses frequently makes extra-label use necessary. Consequently, much of the responsibility for adverse events rests with the prescribing clinician.

2. Basic Principles of Antimicrobial Therapy

The following principles should serve as a guide for antimicrobial use in horses, but not all can be followed in the critical care patient.¹⁻⁴ In particular, the identity and susceptibility of the etiologic agent is rarely known when therapy is initiated, extra-label drug use is frequently necessary, and combination therapy with more than one antibiotic is often indicated in critical care patients.

- An infectious agent must be involved in the disease process for antimicrobial therapy to be effective.

NOTES

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- Antimicrobial therapy is necessary to rid the host of the disease
 - The identity of the infecting organism is known or at least reasonably suspected
 - a. Cytologic examination and culture of appropriate samples
 - The organism(s) is (are) susceptible to the drug(s) selected as determined by
 - a. MIC—quantitative susceptibility test (preferred because this information is helpful for selecting dose)
 - b. Kirby Bauer—qualitative susceptibility test
 - Host defense mechanisms must contribute to the patient's recovery
 - Therapeutic concentrations of the drug will be achieved at the site of infection and the microenvironment at this site will support activity of the drug
 - Appropriate dose, dosage interval, administration route, and duration of therapy are used as dictated by
 - a. Pharmacokinetic, pharmacodynamic, and toxic properties of the drug
 - b. Resolution of disease process as determined by clinical status of the patient and laboratory monitoring
 - Concurrent use of more than one antimicrobial drug is appropriate in limited situations
 - a. Life threatening conditions (insufficient time to wait for culture and susceptibility results)
 - b. Mixed infections—more than one drug is needed to provide appropriate antimicrobial spectrum
 - c. Need for synergistic activity
 - Causes of therapeutic failure should be investigated
 - a. The disease process did not have a bacterial etiology
 - b. Ineffective concentrations of antimicrobial at the site of infection
 - c. Infection in an inaccessible location or one with a poor blood supply
 - d. Microenvironment at the site of infection is not conducive to antimicrobial activity
 - e. Pathogens were or have become resistant to the chosen antimicrobial
 - f. Changes in the microbial environment at the site of infection
 - g. Continued contamination of the infection site
 - h. Infection is no longer contributing to the clinical signs
 - Need for extra-label drug use (drug, dose, route, duration) should be considered and reconsidered
 - a. Few antimicrobial drugs are licensed for parenteral administration to horses; therefore extra-label use is often necessary
 - b. Antimicrobials approved for IV use in horses: ampicillin, sulfadimethoxine, trimethoprim/sulfadiazine 48% suspension
 - c. Antibiotics approved for IM use: procaine penicillin G, benzathine penicillin G, ceftiofur (Naxcel), ampicillin
 - d. Antibiotics approved for oral use: trimethoprim/sulfadiazine (Tribrissen, Uniprim)
 - e. Antibiotics approved for intrauterine use: amikacin, gentamicin, ticarcillin
 - Adverse reactions should be recognized, investigated and reported to the manufacturer of the drug and, in the US, to the FDA/Center for Veterinary Medicine (1-888-332-8387 or 1-888-FDA-VETS; www.fda.gov/cvm/), or to the Veterinary Practitioners' Reporting Network (USPPRN) of the US Pharmacopeia (1-800-487-7776 or 1-800-4-USPPRN; www.usp.org/).
- In critical care situations, there is insufficient time to wait for results of culture and susceptibility testing of samples before initiating antimicrobial therapy. The appropriate approach is therefore to
- Collect and submit appropriate samples
 - Begin treatment based on knowledge of bacteria most likely to be involved in certain syndromes/clinical presentations and their most likely susceptibility patterns
 - Adjust therapy (antimicrobial, dose, route, frequency) based on initial response, physiologic status, adverse effects, or results of initial culture and susceptibility tests

3. Bacteria Associated with Disease Syndromes in Horses⁵

The major pathogens of horses vary by body system, age, use, geographic location, and the type of facility on which the horses reside. In referral centers, nosocomial infection with resistant bacteria including *Salmonella* sp, other enteric species, and *Staphylococcus* sp influence the situation and antibiotic-associated colitis involving *Clostridium* sp or *Salmonella* sp is an ever-present concern. In general, the following are the most commonly encountered pathogens of horses: β -hemolytic *Streptococcus* sp, *Actinobacillus* sp, *Pasteurella* sp, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* sp, *Pseudomonas aeruginosa*, *Bordetella bronchiseptica*, *Staphylococcus* sp, non-hemolytic *Streptococcus* sp, *Rhodococcus equi* (in foals), and anaerobic bacteria, particularly *Bacteroides* sp and *Clostridium* sp.

4. Empirical Selection of Antimicrobials Based on Bacterial Species and Likely Susceptibility Pattern

Antimicrobial susceptibility profiles for Gram-positive and Gram-negative aerobic bacteria isolated from horses during 1998 at the Veterinary Medical Teaching Hospital, University of California, Davis, are shown in Tables 1 and 2. Susceptibility patterns of bacteria such as β -hemolytic *Streptococcus* sp, *Actinobacillus* sp, *Pasteurella* sp and anaerobes, with the exception of *Bacteroides* sp,

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Table 1. Susceptibility of Gram-Positive Bacteria Isolated from Horses at the University of California, Davis during 1998 to Antimicrobial Agents^a

Organism (Number tested)	Percent Susceptible to Antimicrobial														
	PENG	AMP	OX	AMXCLA	CEPH	CEFTIO	CEFOX	ERYTH	RIF	TET	TMS	GENT	AMIK	CHLOR	ENRO
MIC breakpoint (µg/ml)	8	8	2	8	8	2	8	0.5	1	4	2	4	16	8	0.5
for <i>Staphylococcus</i> sp	0.003			4											
for <i>Streptococcus</i> sp		0.25					0.25			2				4	
<i>Staphylococcus aureus</i> (33)	30		67	88	91	69	36	76	94	36	55	48	94	97	94
Coag. negative <i>Staph</i> (31)	13		77	100	97	77	61	97	97	81	74	74	100	94	96
<i>Strep. zoepidemicus</i> (14)	100			100	100	100	100	100		71	100	7	0	100	
<i>Rhodococcus equi</i> (8)					39	100	100	63	88	25	100	100	87	63	
<i>Enterococcus faecalis</i> (10)		100		100			40			90				90	
<i>Enterococcus faecium</i> (10)		90		90			10			70				80	

^aData compiled by Fitchorn J, Jang S, Hirsh D and reprinted with permission.
 PENG = Penicillin G; AMP = Ampicillin; OX = Oxacillin; AMXCLA = Amoxicillin/clavulanic acid; TICLA = Ticarcillin/clavulanic acid; CEPH = Cephalothin; CEFTIO = Ceftriaxone; CEFOX = Cefoxime; ERYTH = Erythromycin; RIF = Rifampin; TET = Tetracycline; TMS = Trimethoprim/sulfonamide; GENT = Gentamicin; AMIK = Amikacin; CHLOR = Chloramphenicol; ENRO = Enrofloxacin.

Table 2. Susceptibility of Gram-Negative Bacteria Isolated from Horses at the University of California, Davis during 1998 to Antimicrobial Agents^a

Organism (Number tested)	Percent Susceptible to Antimicrobial													
	PENG	AMP	AMXCLA	TICLA	CEPH	CEFTIO	CEFOX	ERYTH	TET	TMS	GENT	AMIK	CHLOR	ENRO
MIC Breakpoint (µg/ml)	4	8	8	16	8	2	8	0.5	4	2	4	16	8	0.5/25
<i>E. coli</i> (74)	68	14	93	94	73	94	97		71	60	86	100	91	100
<i>Klebsiella pneumoniae</i> (15)			79	87	66	100	100		54	67	67	100	80	100
<i>Serratia marcescens</i> (4)			0	0	0	75	100		50	0	0	0	0	100
<i>Actinobacillus suis</i> -like (26)	100	89	100	100	100	100	100	30	96	96	100	100	100	100
<i>Actinobacillus equuli</i> (7)	100	100	100	100	100	100	100	28	86	86	100	100	100	100
<i>Actinobacillus ligniersii</i> (2)	100	100	100	100	100	100	100	0	100	100	100	100	100	100
<i>Pasteurella</i> sp (6)	100	100	100	100	100	83	83	33	100	100	100	100	100	83
<i>Salmonella</i> sp (18)	30	100	100	67	100	100	100		73	34	49	100	36	100
<i>Salmonella agona</i> (13)	0	100	100	54	100	100	100		92	15	54	100	0	100
<i>S. typhimurium</i> (11)	82	100	100	91	100	100	100		82	82	82	100	82	100

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are somewhat predictable and do not show great variation between different geographic locations. In contrast, Enterobacteriaceae, *Pseudomonas* sp, *Bordetella* sp, coagulase-positive *Staphylococcus* sp, alpha-hemolytic *Streptococcus* sp, and *Bacteroides fragilis* have either unpredictable susceptibility or are predictably resistant to particular antibiotics or classes of antibiotics.³ It is thus particularly important to perform susceptibility tests on these isolates. While it is acknowledged that there may be substantial variation in susceptibility patterns of bacteria between different geographical locations, and organisms isolated from patients in hospitals or on farms where antibiotics are used frequently are likely to show more resistance than bacteria isolated from horses on premises on which antimicrobial use is not prevalent, Tables 1 and 2 should provide a reasonable guide to the expected susceptibility patterns of the equine pathogens.

5. Suggested Choices of Antimicrobials Based on Susceptibility of Bacterial Isolates

β-hemolytic *Streptococcus* sp

First choice: penicillin G

Second choices: ampicillin, ceftiofur, cefazolin

Alternate choices: trimethoprim/sulfonamide (TMS), erythromycin, rifampin, chloramphenicol

Coagulase-positive *Staphylococcus* sp

First choices: cefazolin, rifampin, amikacin, enrofloxacin

Alternate choices: oxacillin, chloramphenicol, ceftiofur, erythromycin

Coagulase-negative *Staphylococcus* sp

First choices: cefazolin, rifampin, amikacin

Alternate choices: chloramphenicol, enrofloxacin, ceftiofur, gentamicin, tetracycline, oxacillin

Enterococcus sp

First choice: ampicillin

Alternate choices: chloramphenicol, tetracycline

Rhodococcus equi

First choice: erythromycin + rifampin

Alternate choices: erythromycin or arithromycin alone or gentamicin + rifampin

Corynebacterium pseudotuberculosis

First choice: penicillin G

Alternate choices: TMS, erythromycin, rifampin, ceftiofur

Actinobacillus sp/*Pasteurella* sp

First choices: TMS, gentamicin, ampicillin, ceftiofur

Alternate choices: penicillin G, tetracycline, chloramphenicol

Escherichia coli

First choice: amikacin

Alternate choices: ceftiofur, gentamicin, enrofloxacin, chloramphenicol, ticarcillin/clavulanic acid

Salmonella sp

First choices: amikacin or ceftiofur (or other third-generation cephalosporins)

Second choices: cefazolin, enrofloxacin

Alternate choices: gentamicin, tetracycline, ampicillin, ticarcillin/clavulanic acid, chloramphenicol, TMS

Bordetella bronchiseptica

First choice: TMS

Alternate choices: gentamicin, tetracycline

Klebsiella pneumoniae

First choice: amikacin

Second choices: ceftiofur, enrofloxacin, ticarcillin/clavulanic acid

Alternate choices: gentamicin, chloramphenicol, TMS

Pseudomonas aeruginosa

First choice: amikacin

Alternate choices: ticarcillin/clavulanic acid, gentamicin, imipenem

Bacteroides sp (other than *B. fragilis*) are showing increased evidence for β -lactamase production

First choice: metronidazole

Second choice: chloramphenicol

Alternate choices: Penicillin G or Tetracycline or Ceftiofur

Bacteroides fragilis (most isolates produce β -lactamase)

First choice: metronidazole

Alternate choices: chloramphenicol, tetracycline

Clostridium sp, *Fusobacterium* sp, *Peptostreptococcus* sp (Gram-positive anaerobes)

First choices: penicillin G, metronidazole

Alternate choices: chloramphenicol, tetracycline, ceftiofur

6. Selection of Antimicrobials for Initiating Treatment Based on the Most Likely Etiologic Agent and Probability of Susceptibility to Antimicrobial Agents

Neonatal Septicemia

A high proportion of septicemic foals are infected with Gram-negative bacteria, including *E. coli* in about 50%, *Actinobacillus suis*-like sp, *Klebsiella pneumoniae*, *Actinobacillus equuli*, *Enterobacter* sp, *Citrobacter* sp, and *Salmonella* sp.⁶ As many as 50% of septicemic foals have polymicrobial infection with more than one Gram-negative species or with a Gram-negative bacterium along with a Gram-positive species, usually *Streptococcus zooepidemicus*, *Enterococcus* sp, or *Staphylococcus* sp.⁶ Anaerobic bacteria are rarely involved in neonatal septicemia, except secondary to enterocolitis caused by *Clostridium perfringens*.

Suggested Antimicrobial Protocols

Treatment protocols for neonatal septicemia must include antimicrobials with a high level of activity against Gram-negative enteric bacteria. Use of bactericidal agents that do not require extensive

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hepatic metabolism is preferred, as is the parenteral route of administration.

First choice: amikacin + ampicillin

Alternate choices: amikacin + penicillin G; amikacin + cefazolin; gentamicin + ampicillin, penicillin G, or cefazolin; ceftiofur or other third-generation cephalosporin; ticarcillin/clavulanic acid; imipenem (for resistant infections); TMS may be appropriate for continued oral therapy of infections caused by susceptible organisms.

Pneumonia

Pneumonia in neonatal foals frequently occurs in association with septicemia; therefore, the predominant bacterial isolates and antimicrobials recommended for use are the same as those listed above for neonatal septicemia. Polymicrobial infection is common, as it is in older foals in which the most frequent bacterial isolate is *S. zooepidemicus*, followed closely by Gram-negative non-enteric bacteria (*Actinobacillus suis*-like sp and *Pasteurella* sp). *E. coli*, *Klebsiella pneumoniae*, other enteric bacteria, *Pseudomonas aeruginosa*, and *Staphylococcus* sp are less commonly involved. *Rhodococcus equi* is frequently the most common etiologic agent on farms on which infection is endemic.

Suggested Antimicrobial Protocols

Except in instances in which *R. equi* is the suspected pathogen, the following guidelines for choice of antimicrobials to initiate treatment apply:

First choice: penicillin G, ceftiofur, TMS

Alternate choices: penicillin G, ampicillin + gentamicin

When *R. equi* is the suspected or confirmed pathogen:

First choice: erythromycin or azithromycin + rifampin

Alternate choices: rifampin + gentamicin; erythromycin alone; azithromycin

The distribution of bacterial species isolated from adult horses with pneumonia is similar to that described for older foals, except that *R. equi* is rarely involved and anaerobic bacteria are much more commonly isolated from pneumonic adult horses than from pneumonic foals (see Pleuropneumonia).

Acute Pleuropneumonia

Polymicrobial infection is common in horses with pleuropneumonia and frequently involves combinations of Gram-positive aerobes (*S. zooepidemicus*), Gram-negative aerobes (*Actinobacillus suis*-like sp *Pasteurella* sp *E. coli*, or *Klebsiella pneumoniae*) and anaerobes (*Bacteroides fragilis*, *Bacteroides* sp, *Fusobacterium* sp, or *Peptostreptococcus* sp).^{7,8}

Consequently, antimicrobials used in treatment regimens should provide a broad spectrum of activity. Treatment regimens should also take into account the fact that anaerobic bacteria are involved in approximately 50% of cases and the most important anaerobe, *Bacteroides fragilis* has a high likelihood of resistance to penicillins and cephalosporins, including ceftiofur.⁹ *Mycoplasma* sp is the etiologic agent in sporadic cases, in which case use of oxytetracycline, enrofloxacin, erythromycin, or azithromycin may be necessary.¹⁰

Suggested Antimicrobial Protocols

First choice: penicillin G or ampicillin + gentamicin ± metronidazole

Alternate choices: penicillin or ampicillin + amikacin ± metronidazole; ceftiofur ± metronidazole

Special circumstances or continued therapy: Chloramphenicol; TMS; Oxytetracycline; Enrofloxacin

Peritonitis

Since abdominal surgery and enteric disease are frequently predisposing factors in the development of peritonitis, Gram-negative enteric bacteria (especially *E. coli* and *Klebsiella pneumoniae*) are found in almost 50% of cases. Obligate anaerobic bacteria are also commonly isolated from the peritoneal cavity.⁵ *Actinobacillus* sp can cause peritonitis without other apparent predisposing factors, and β-hemolytic *Streptococcus* sp and *Corynebacterium pseudotuberculosis* may be involved, particularly when diffuse peritonitis occurs in association with an internal abdominal abscess. *Clostridium perfringens* may induce peritonitis in foals in association with necrotizing enterocolitis.

Suggested Antimicrobial Protocols

First choice: penicillin or ampicillin + gentamicin

Alternate choices: ceftiofur; penicillin or ampicillin + amikacin

Internal Abdominal Abscess

Because resolution of peritonitis frequently involves encapsulation and development of adhesions to wall off infection, any of the infectious agents listed for peritonitis may cause internal abdominal abscesses. However, *S. zooepidemicus* and *S. equi* are the most common causes of internal abscesses in most geographic locations, except in western states where *C. pseudotuberculosis* is endemic, in which case the latter organism is involved at least as often as β-hemolytic *Streptococcus* sp.^{11,12}

Suggested Antimicrobial Protocols

Except where there is a history of abdominal surgery or recent enteric disease, antibiotics active against Gram-positive aerobic bacteria should be selected to initiate treatment of internal abscess.

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First choice: penicillin G or ampicillin + rifampin

Alternate choices: penicillin G alone; ceftiofur; penicillin G + gentamicin; rifampin + TMS; penicillin G + TMS

Rifampin is recommended because of its high level of activity against causal Gram-positive organisms, excellent ability to penetrate and remain active within the environment present in abscesses, and oral route of administration. Because of the poor lipid solubility of penicillin and ampicillin, they penetrate abscesses poorly unless a high serum to tissue concentration gradient is achieved by IV administration of high doses to initiate treatment.

Septic Arthritis

Septic arthritis, physitis, and polysynovitis in neonatal foals most often occurs in association with or as a sequel to septicemia; therefore, the bacterial species involved and recommended antimicrobials are the same as those listed for septicemia. *Streptococcus zooepidemicus* is more commonly isolated from older foals than from foals less than 3 weeks of age and may be the sole etiologic agent in these cases. *Rhodococcus equi* should be considered in cases of septic arthritis, synovitis, or osteomyelitis in foals aged 1 to 8 months on farms with endemic *R. equi* infection, particularly when the individual foal has also shown signs of *R. equi* pneumonia. When *R. equi* is the suspected or confirmed pathogen, treatment with erythromycin or azithromycin + rifampin is indicated.

Septic arthritis or synovitis in adult horses most often occurs secondary to trauma, intrasynovial injection, or surgical intervention.¹³ The mechanism by which infection was introduced influences the distribution of bacterial species isolated. *Staphylococcus* sp account for more than 50% of the isolates from synovial structures infected by injection or surgery, whereas Gram-negative enteric bacteria and anaerobes predominate in synovial structures infected via a wound.¹³ *Pseudomonas* sp, β -hemolytic *Streptococcus* sp, non-hemolytic *Streptococcus* sp, and *Actinobacillus* sp are also commonly isolated from infected synovial structures. Polymicrobial infection is common in joints that become infected via a wound.¹³

Suggested Antimicrobial Protocols

The high likelihood of involvement of penicillinase-producing *Staphylococcus* sp and *Enterobacteriaceae* should be considered when initiating treatment of septic arthritis or septic tenosynovitis in adult horses.

First choice: cefazolin or cephalothin + amikacin

Alternate choices: cefazolin or cephalothin + gentamicin; oxacillin + gentamicin or amikacin; rifampin + amikacin; enrofloxacin

In all cases of septic arthritis or synovitis, lavage with or without arthroscopic debridement is important to remove inflammatory debris from the synovial cavity. Thereafter, instillation of appropriate antimicrobials, usually amikacin, gentamicin, or a third-generation cephalosporin, is indicated.¹⁴ More effective inactivation of bacteria in synovial cavities and bone may be accomplished using the technique of regional limb perfusion.^{15,16} This technique involves application of a tourniquet proximal to the involved structure, followed by intravenous or intraosseous injection of the appropriate antimicrobial to create local concentrations of an antimicrobial that are much higher than can be achieved through conventional parenteral or oral dosing. Alternate approaches, particularly in horses with septic osteomyelitis or physitis lesions that have been debrided surgically, include local instillation of antibiotic-impregnated sponges or polymethyl methacrylate beads that release the antimicrobial into the local environment.^{17,18}

Osteomyelitis and Orthopedic Infection

Selection of antimicrobials for treatment of osteomyelitis secondary to trauma or surgical intervention follows the same principles as outlined above for septic arthritis in adult horses because the distribution and species of bacteria isolated are similar in the two conditions. Enterobacteriaceae, *Streptococcus* sp, and *Staphylococcus* sp each account for 20 to 25% of bacterial isolates.¹⁹

Urinary Tract Infection

Infection of the urinary tract most often manifests as cystitis and generally occurs secondary to infection that ascends via the urethra. Consequently, Gram-negative enteric bacteria, particularly *E. coli*, are involved in more than 50% of cases and *Pseudomonas aeruginosa* is isolated from approximately 10%. Gram-positive bacteria, predominantly β -hemolytic *Streptococcus* sp and *Staphylococcus* sp, can be isolated from approximately 20% of cases, often in association with Gram-negative organisms.

Suggested Antimicrobial Protocols

A high proportion of the administered dose of most β -lactam and aminoglycoside antibiotics and TMS is eliminated in the active form in urine. Therefore, concentrations of these antibiotics in urine are generally much higher than those achieved in serum, allowing them to kill bacteria that would otherwise be considered resistant by virtue of a minimal inhibitor concentration (MIC) higher than the standard breakpoint for susceptibility. This concept, termed conditional susceptibility, can be exploited in the treatment of infections of the urinary tract.

First choice: gentamicin + penicillin G or ampicillin

Alternate choices: TMS; gentamicin alone; ceftiofur

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Cellulitis

Cellulitis involving the limbs may be clinically indistinguishable from acute lymphangitis because both conditions result in marked swelling, heat, pain, and lameness. It is frequently not possible to isolate bacteria from such cases because a successful therapeutic outcome relies upon aggressive antimicrobial therapy early in the disease course before development of abscesses or skin sloughs that provide material for culture. Coagulase-positive *Staphylococcus* sp are most often involved, especially in racehorses,²⁰ while β -hemolytic *Streptococcus* sp, coagulase-negative *Staphylococcus* sp, Gram-negative aerobic bacteria, and anaerobic bacteria are involved less often. In areas of the western US where *C. pseudotuberculosis* infection is endemic, this organism is an important cause of external abscesses and limb cellulitis, as well as sporadic cases of ulcerative lymphangitis.¹¹ Anaerobic bacteria, particularly *Clostridium perfringens* and *C. septicum*, are important causes of cellulitis when it occurs in association with myositis secondary to contaminated intramuscular injections or deep puncture wounds involving muscle.

Suggested Antimicrobial Protocols

Treatment protocols for limb cellulitis should take into account the high likelihood that penicillinase-producing *Staphylococcus* sp are involved and the fact that the condition can progress rapidly and lead to serious complications including laminitis, skin slough and death.

First choice: cephalothin or cefazolin + amikacin

Alternate choices: enrofloxacin; penicillin or ampicillin + amikacin; cephalothin or cefazolin (preferably with gentamicin); oxacillin + amikacin or gentamicin; rifampin + gentamicin

Treatment protocols for cellulitis in association with septic myositis secondary to IM injections should include antimicrobials with activity against *Clostridium* sp.

First choice: penicillin or ampicillin + gentamicin + metronidazole. Fasciotomy, drainage of abscesses, and debridement of necrotic tissue are also important therapeutic measures.

Mastitis

Mastitis occurs sporadically in lactating, non-lactating, and nulliparous mares and fillies.²¹ *S. zooepidemicus* is the most common etiologic agent, being involved in approximately 40% of cases. Gram-negative enteric bacteria (*E. coli*, *Klebsiella pneumoniae*, *Enterobacter* sp) are isolated from approximately 20% of cases, Gram-negative non-enteric bacteria (*Actinobacillus* sp or *Pasteurella* sp) from 15%, and *Staphylococcus* sp from about 10%.²¹

Suggested Antimicrobial Protocols

First choices: ceftiofur

Alternate choices: penicillin or ampicillin + gentamicin; TMS, penicillin, ampicillin + amikacin; cephalothin or cefazolin

Acute Colitis in Adult Horses

In many instances, the etiology of acute colitis is not determined. *Clostridium difficile*, and to a lesser extent *C. perfringens*, should be considered the likely cause of colitis in horses that have a history of antimicrobial administration, particularly if the resulting diarrhea has a foul "spoiled fish" odor.^{22,23} *Salmonella* sp also cause diarrhea in stressed horses, particularly those that have undergone surgery or have experienced another stressful illness and have been treated with antimicrobials, but can also cause outbreaks of diarrhea in otherwise healthy horses.²⁴ *Ehrlichia risticii* should be suspected when signs of colitis occur in horses, particularly pastured horses, residing in endemic areas during the summer and fall.

Suggested Antimicrobial Protocols

In general, administration of antimicrobials should be discontinued in horses that develop diarrhea during a course of antimicrobial therapy. Antimicrobial treatment is generally not indicated for the treatment of undifferentiated colitis, except in horses with profound neutropenia, persistent high fever, or other evidence of severe compromise to the integrity of the bowel wall. In these instances, the antibiotic of choice is gentamicin (6.6 mg/kg SID) administered IV for a short (3 to 5 day) course, provided renal function is adequate and fluid deficits are addressed by IV fluid therapy. When *C. difficile* or *C. perfringens* are the suspected or confirmed etiologic agents, oral administration of metronidazole (15 mg/kg PO TID) is the treatment of choice. Whereas a high proportion of *C. difficile* isolates are susceptible to metronidazole in most geographic areas, a substantial number of those isolated at UC Davis have proven to be resistant to metronidazole,²⁵ necessitating carefully controlled use of other antimicrobials such as vancomycin under these special circumstances. Administration of oxytetracycline (6.6 mg/kg IV SID) is the treatment of choice when *E. risticii* is the suspected or confirmed cause of colitis.

7. Activity and Properties of Selected Antimicrobials

Penicillin G⁴

Spectrum of Activity and Mode of Action

Penicillin G, like other penicillins and cephalosporins, exerts a bactericidal effect by inhibiting penicillin-binding proteins (PBPs) and therefore synthesis and incorporation of peptidoglycan into the cell wall of susceptible bacteria.⁴ The anti-

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crobial spectrum of penicillin G includes most Gram-positive aerobes with the exception of about 50% of coagulase-positive *Staphylococcus* sp, alpha-*Streptococcus* sp, and *Rhodococcus equi*.^{5,26} Most isolates of *Actinobacillus* sp and *Pasteurella* sp from horses are also susceptible. Enterobacteriaceae are generally resistant. Gram-positive anaerobes and many *Bacteroides* sp isolates (Gram-negative anaerobes), but not *Bacteroides fragilis*, are susceptible.⁵

Dosage and Pharmacokinetics

Sodium or potassium salts of penicillin G: 10,000 to 40,000 IU/kg q 4–6 h IV or IM

Procaine penicillin G (PPG): 22,000 IU/kg q 12–24 h IM

Benzathine penicillin G: not recommended because of low plasma concentrations achieved

The polar nature of penicillin G and other penicillins gives them a volume of distribution similar to the extracellular fluid volume and results in low lipid solubility and poor tissue penetration unless high doses are used to achieve a high serum to tissue concentration gradient.⁴ The soluble dosage forms have a short serum elimination half-life of less than 1 hour,^{27,28} and because β -lactams do not exert a significant inhibitory post-antibiotic effect on susceptible bacteria, frequent dosing or constant infusion is necessary to maintain concentrations above the MIC of susceptible bacteria (so called “time-dependent” killing).^{29,30} Complexing of penicillin G with procaine for IM administration maintains detectable serum concentrations for at least 24 hours but peak serum concentrations are low.³¹ This limits the antimicrobial spectrum and penetration into tissue sites of infection. Penicillins are excreted by active renal tubular secretion and therefore achieve high concentrations of active drug in the urine.⁴ For this reason, they are useful for treating urinary tract infections caused by organisms that may not otherwise be considered susceptible.

Limitations

1. Parenteral administration is necessary for all dosage forms of penicillin G. The bioavailability of penicillin V administered intragastically to horses is less than 10%.^{32,33}
2. The soluble sodium and potassium salts are unstable in solution and reconstitution of fresh drug is necessary before dosing.
3. The activity of penicillins is reduced in acid environments such as occur in abscesses and sites of tissue necrosis. Penicillin G is inactivated by β -lactamase enzymes elaborated by many *Staphylococcus* sp, most Gram-negative enteric organisms, and many *Bacteroides* sp, including *B. fragilis*.

4. Procaine has been detected in urine for 425 hours after administration of multiple doses of PPG;³⁴ thus administration of PPG to performance horses has the potential to result in a positive procaine blood test for at least 14 days.

Adverse Effects

1. Penicillin allergy is rare in horses but can cause serious anaphylactic reactions leading to respiratory difficulty and/or diarrhea.
2. Reactions lasting up to 5 minutes and characterized by excitement, seizure activity, and sometimes death have been observed during or shortly after IM injection of PPG.³⁵ These reactions are more common after several days of therapy, particularly if one injection site is used repeatedly. These reactions may reflect accidental IV administration of PPG, or a reaction to free procaine. The concentration of free procaine in bottles of PPG increase following exposure to heat such as would occur with bottles kept in a car or truck during the summer.³⁶
3. Many horses develop muscle soreness and focal myositis during prolonged courses of IM treatment with PPG.
4. Many horses develop measurable levels of anti-penicillin antibodies of the IgM class of limited significance following treatment with penicillin. Some horses also elaborate IgG antibodies that become bound to the surface of erythrocytes and will develop a Coombs' test positive immune-mediated hemolytic anemia which may be severe and life-threatening but usually resolves when penicillin treatment is discontinued.^{37–39}
5. Reactions to potassium penicillin G are frequently observed when this formulation is injected IV, particularly when administration is rapid. Reactions seen during or after administration include head shaking/rubbing, lip smacking, teeth grinding, salivation, lacrimation, increased borborygmus, mild colic/agitation, and passage of soft/liquid feces. Signs often recur with subsequent doses but can usually be eliminated by administration of the drug by infusion over at least 30 minutes. Similar reactions have not been reported with rapid IV administration of sodium penicillin G or sodium ampicillin.

Ampicillin and Amoxicillin⁴

Ampicillin and amoxicillin are aminobenzyl penicillins which, when first introduced onto the market, had a substantially broader spectrum of activity than penicillin G against Gram-negative bacteria including *E. coli*, *Proteus mirabilis*, and *Salmonella* sp, by virtue of their improved ability to penetrate the outer membrane of Gram-negative bacteria.

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Both ampicillin and amoxicillin are susceptible to inactivation by β -lactamases and are slightly less active than penicillin G against susceptible Gram-positive bacteria.⁴ The progressive increase in plasmid-mediated resistance, which induces production of β -lactamases by Gram-negative bacteria, has reduced the activity of ampicillin and amoxicillin to the point where they now show only a slight advantage over penicillin G in terms of spectrum of activity. Rapid IV injection of ampicillin sodium is well tolerated, a clear advantage over potassium penicillin G. Ampicillin sodium administered IV has an elimination half-life of less than 1 hour,⁴⁰ thus doses of 10 to 40 mg/kg q 6 to 8 h are recommended, depending on the susceptibility of the infecting organism. The trihydrate formulations of ampicillin and amoxicillin are designed for IM injection and give a depot effect similar to that seen with procaine penicillin G. However, the low serum concentrations achieved limits the spectrum of activity. Amoxicillin trihydrate is irritant and stings when injected IM.⁴¹ For these reasons, procaine penicillin G or ceftiofur are preferred when IM administration of a β -lactam antibiotic is indicated.

Isoxazolyl (Penicillinase-Resistant) Penicillins⁴

Beta-lactamase enzymes (penicillinases and cephalosporinases) are a heterogeneous group of compounds elaborated by many coagulase-positive staphylococci, Gram-negative bacteria, and some anaerobic bacteria. They inactivate β -lactam antibiotics by cleaving the β -lactam ring. Two approaches have been taken to overcome this problem, namely co-administration of β -lactamase inhibitors with a penicillinase susceptible penicillin or the use of a penicillinase-resistant penicillin. Isoxazolyl penicillins include **oxacillin**, **cloxacillin**, **dicloxacillin**, **methicillin**, and **nafcillin**.⁴ By virtue of their chemical structure, these compounds resist cleavage by many β -lactamases, including almost all of those elaborated by coagulase-positive *Staphylococcus* sp. Their spectrum of activity is largely restricted to Gram-positive aerobic bacteria but their potency against penicillin-sensitive bacteria is lower than that of penicillin G. While nafcillin has greater in vitro activity than oxacillin and cloxacillin, and all have higher activity than methicillin, differences in protein binding result in similar in vivo activity. The major indication for the use of isoxazolyl penicillins in horses is the treatment of systemic or local infections with penicillin-resistant *Staphylococcus* sp, the most important of which is limb cellulitis, particularly in racehorses. Oxacillin is the drug most often chosen and is used at a dose of 20 to 40 mg/kg IV q 6 to 8 h, usually in combination with an aminoglycoside antibiotic to extend the spectrum of activity. Oxacillin is considered to be a relatively safe drug in horses. In contrast, nafcillin administered by bolus IV injection at the same dose as oxacillin, appears to be highly irritant and may induce severe thrombophlebitis.

In addition, acute renal failure has been observed in dogs given nafcillin perioperatively at our clinic. Nafcillin sodium is labeled for slow IV infusion in humans. It should be diluted to at least one liter and administered slowly over at least 30 minutes when used in horses in the event that oxacillin is unavailable.

Beta-Lactamase Inhibitors and Anti-Pseudomonal Penicillins⁴

Clavulanic acid (clavulanate) and **sulbactam** are β -lactam antibiotics that have a low level of antimicrobial activity but a very high affinity for many, but not all, β -lactamases.⁴ When β -lactamase inhibitors are administered concurrently with susceptible β -lactam antibiotics, time-dependent binding of β -lactamases by the inhibitor protects susceptible penicillins from inactivation resulting in restoration of their spectrum of activity. Antibiotic formulations containing amoxicillin/clavulanic acid, ticarcillin/clavulanic acid, and ampicillin/sulbactam are marketed for veterinary use in North America and have proven to be useful for the treatment of infections caused by penicillinase-producing *Staphylococcus* sp, many Enterobacteriaceae and *Bacteroides* sp in several species. Since ampicillin, amoxicillin, and ticarcillin possess good activity against Gram-positive bacteria, combinations of these antibiotics with β -lactamase inhibitors can be used to provide broad-spectrum antibiotic activity.⁴²⁻⁴⁵

Ticarcillin is an anti-pseudomonal carboxypenicillin that is active against many isolates of *Pseudomonas aeruginosa* and several other Gram-negative bacteria, with the exception of *Klebsiella* sp, *Enterobacter* sp, *Citrobacter* sp, and *Serratia* sp. Whereas approximately 50% of *P. aeruginosa* isolates are resistant to ticarcillin by virtue of production of β -lactamases, most of the β -lactamases produced by this organism are not inactivated by clavulanic acid. Therefore, *P. aeruginosa* isolates that are resistant to ticarcillin are usually also resistant to ticarcillin/clavulanic acid.⁴² Conversely, a number of isolates of *Klebsiella pneumoniae* and some other Enterobacteriaceae are made susceptible to ticarcillin by co-administration of clavulanic acid.⁴⁶ Since the ticarcillin/clavulanic acid combination is expensive, indications for its use in the horse are limited and include systemic or uterine infections with *P. aeruginosa* or penicillinase-producing *Staphylococcus* sp, and neonatal septicemia involving aminoglycoside-resistant Gram-negative bacteria or patients with physiologic or toxic conditions that preclude aminoglycoside use.⁴²⁻⁴⁴

Oral Penicillins

Absorption of **penicillin V**, **ampicillin**, and **amoxicillin** after oral administration to horses is poor, except in neonatal foals. The bioavailability of penicillin V is <5%, that of ampicillin is <10%, and that of amoxicillin is variable, but ranges from 5% to 20%.^{32,33,41,47-50} In addition, feeding further

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reduces absorption. Absorption and elimination of the bioavailable fraction is rapid and the half-life of elimination is about 1 hour. It would be necessary to administer very high doses (50 to 100 mg/kg) of these antibiotics at frequent intervals to achieve therapeutic serum concentrations. Unabsorbed drug remaining in the GI tract would likely cause disturbances in the colonic flora and may initiate fatal pseudomembranous colitis.³³ For this reason, oral administration of available penicillins in adult horses is not recommended.

Several esters of ampicillin, including **pivampicillin**, **bacampicillin**, and **talampicillin** have been developed for oral administration to other species. These esters are resistant to degradation by gastric acid and pass to the small intestine as inactive pro-drugs that become hydrolyzed to active ampicillin during absorption from the GI tract. For this reason, the bioavailability (30% to 40%) is much higher than that achieved by ampicillin and the majority of unabsorbed drug remaining in the GI lumen is probably inactive and less likely than ampicillin to disrupt the colonic flora.⁴⁷⁻⁵² Of interest is the finding that the absorption of pivampicillin in horses is improved by feeding.⁴⁸ Further development of pivampicillin or bacampicillin as oral dosage forms for horses would prove very useful to equine clinicians but these drugs are not yet available in the US.

Ceftiofur

Ceftiofur is a third-generation cephalosporin antibiotic approved for use in horses and food-producing animals.^{4,53-57}

Spectrum of Activity

Ceftiofur has a broad antimicrobial spectrum that includes Gram-positive and Gram-negative aerobes, including Enterobacteriaceae, and many anaerobes, including *Clostridium* sp and *Fusobacterium* sp.^{9,58,59} *Pasteurella* sp are highly susceptible and generally have a lower MIC than Enterobacteriaceae. Resistant bacteria include *Bacteroides* sp, *Enterococcus* sp, *Rhodococcus equi*, and *Pseudomonas aeruginosa*.

Dosage and Pharmacokinetics

The efficacy of ceftiofur has been demonstrated in an equine "shipping fever" model and in several field trials with naturally occurring equine respiratory disease, in which it was shown to be equal or superior to ampicillin and potentiated sulfonamide preparations.⁵³ The approved label claim in the USA includes only respiratory tract infections caused by β -hemolytic *Streptococcus* sp. Like *Pasteurella* sp isolated from cattle, β -hemolytic *Streptococcus* sp isolated from horses are highly susceptible to ceftiofur (MIC usually <0.25 μ g/ml). This is, in part, the reason why the label dose is so much lower than that routinely recommended for other third-generation cephalosporins. The MIC of susceptible

enteric bacteria such as *E. coli* is usually in the range of 0.25 to 1.0 μ g/ml.

1. The label dose for the label indication is 2.2 to 4.4 mg/kg q 24 h IM.
2. Doses of 5–10 mg/kg q 12 h IV or IM have been used successfully to treat foals with septicemia caused by Gram-negative bacteria.
3. IV or IM administration has been used in the clinical setting, although the kinetic profile of ceftiofur is slightly better when the drug is administered IM rather than IV. This may reflect the fact that administered ceftiofur sodium is rapidly hydrolyzed to the equally active compound, desfuroylceftiofur, which is then highly bound to plasma proteins that protect it from rapid renal elimination. Ceftiofur shows good penetration into body fluids, joints, and pulmonary tissue sites of infection, but does not enter the cerebral spinal fluid in effective concentrations in the absence of meningeal inflammation.
4. The pharmacokinetics of ceftiofur are highly complex, and results of studies are further influenced by the assay methods used to measure concentrations in plasma. A more prolonged elimination half-life is found when an HPLC assay which measures free and protein bound ceftiofur and metabolites is used rather than a microbiologic assay that measures microbially active concentrations of free ceftiofur and its active desfuroylceftiofur metabolite.
5. Despite a label claim that includes only infections caused by β -hemolytic *Streptococcus* sp, the high susceptibility of this organism to penicillin G and the relatively low cost of procaine penicillin G make it the drug of choice in most instances. Third-generation cephalosporins such as ceftiofur are best reserved for treatment of infections caused by organisms resistant to penicillin G, potentiated sulfonamides, or aminoglycosides. However, the IM route of administration of this drug, lack of risk of "penicillin reactions" and positive procaine drug tests, and its broad spectrum of activity which includes Enterobacteriaceae make ceftiofur very useful for treating neonatal sepsis and polymicrobial infections such as bacterial pneumonia in adult horses.

Limitations and Adverse Effects

1. Ceftiofur sodium is unstable in solution and must be reconstituted before dosing. Once reconstituted, it should be used within 12 hours if kept at room temperature but can be maintained for up to 7 days if refrigerated or up to 8 weeks if frozen.
2. Diarrhea and pseudomembranous colitis have been observed in horses treated with higher

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than label doses of ceftiofur, although routinely recommended doses are reasonably safe.⁵⁴

3. Minor injection site discomfort and irritation occur with repeated administration.⁵⁴

Aminoglycosides⁴

Spectrum of Activity

Aminoglycosides exert a bactericidal effect on susceptible bacteria by interfering with ribosomal protein synthesis.⁴ To exert this effect, the drug must first be transported into the bacterial cell, in part by diffusion and in part by an active transport mechanism that is inhibited in anaerobic conditions but which is facilitated by damage to the bacterial cell wall created by other antibiotics. This is the mechanism underlying synergy between aminoglycosides and β -lactam antibiotics. Extensive resistance to kanamycin and streptomycin has rendered these drugs much less useful than gentamicin and amikacin, which are consequently the most commonly used aminoglycosides in horses and have indications for treating a variety of Gram-negative infections in many body systems. Amikacin and gentamicin both show excellent activity against Gram-negative aerobes, including Enterobacteriaceae.^{5,26} Some *Mycobacterium* sp and *Mycoplasma* sp are also susceptible. Activity against Gram-positive aerobes is generally poor, although many coagulase-positive *Staphylococcus* sp are susceptible to amikacin and, to a slightly lesser extent, gentamicin.^{5,26} Obligate anaerobes and facultative anaerobes under anaerobic conditions are resistant to aminoglycosides. In terms of potency, spectrum of activity, and stability to enzymes involved in plasmid-mediated resistance, the order of activity of aminoglycosides is amikacin > tobramycin \geq gentamicin > kanamycin = neomycin \geq streptomycin.⁴ Bacteria resistant to an aminoglycoside higher in the order are generally also resistant to all aminoglycosides that appear lower in the order. One exception is the finding that gentamicin is inherently more active than amikacin against non-enteric organisms such as *Actinobacillus* sp and *Pasteurella* sp.⁵ Whereas amikacin has a broader spectrum of activity against Enterobacteriaceae, the MIC of organisms that are susceptible to gentamicin is often 2- to 4-fold lower than amikacin, indicating that gentamicin is inherently more potent than amikacin.^{5,26} The recommended dose of gentamicin is, therefore, about one-third of that used for amikacin.

Dosage and Pharmacokinetics

Aminoglycosides are not absorbed after oral administration and must therefore be administered parenterally by IV or IM injection. These polar organic bases are restricted in their distribution to a volume equivalent to the extracellular fluid volume,⁶⁰⁻⁶⁴ thus penetration into cells and tissues is generally poor.⁴ Elimination is by glomerular filtration of active drug, which therefore appears in high concen-

tration in urine and accounts for the high utility of aminoglycosides for treating urinary tract infections.^{4,65} Unlike penicillins and cephalosporins, aminoglycosides exert a significant post-antibiotic effect.⁶⁶ Killing of susceptible bacteria by aminoglycosides is "concentration-dependent" and correlates more closely with the peak concentration achieved, the area under the plasma concentration-time curve, and the ratio of the peak concentration of the drug to the MIC of the infecting organism, than with the length of time during the dosage interval that aminoglycoside concentrations remain above MIC.⁶⁷ Aminoglycosides are concentrated in renal tubular epithelium through a saturable transport mechanism during therapy. Nephrotoxicity depends on persistence of the drug in renal tubular epithelium and is governed by the amount of time during the dosage interval that serum concentrations remain above a putative nephrotoxic threshold concentration. In recent years it has been documented that administration of the total daily dose of an aminoglycoside once daily is safer and more effective in humans than administration of the same total daily dose divided into 3 equal doses at 8-hour intervals as in traditional dosage regimens.^{68,69} Once-daily dosage regimens for amikacin (21 mg/kg) and gentamicin (7 mg/kg) IV or IM are now routinely used at our clinic and elsewhere and have proven to be safe and effective.^{61,62,70}

Limitations

1. The need for parenteral dosing.
2. Amikacin and gentamicin cause irritation when administered IM; therefore, IV dosing is preferred.
3. Use by routes other than intrauterine constitutes extra-label drug use.
4. Lack of activity against anaerobic bacteria and *Streptococcus* sp.

Adverse Effects

All aminoglycoside antibiotics have the potential to induce nephrotoxicity (acute tubular nephrosis), neuromuscular blockade, and ototoxicity (vestibular and cochlear damage), although ototoxicity is recognized infrequently in horses.⁷¹⁻⁷³ The general order of nephrotoxicity is neomycin > gentamicin > kanamycin and amikacin > streptomycin and tobramycin. With the exception of neomycin, therapy with aminoglycosides is usually well tolerated unless treatment is prolonged or risk factors are present. Prevention of aminoglycoside toxicity involves using recommended dosage regimens, minimizing the duration of therapy, maintaining hydration and optimal renal perfusion, minimizing concurrent use of other nephrotoxic drugs such as NSAIDs, and seeking alternative drugs in patients with pre-existing renal tubular disease. Dosage adjustment based on measured peak and trough plasma antibiotic concentrations, along

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with periodic urinalysis and monitoring of serum concentrations of blood urea nitrogen (BUN) and creatinine are recommended. Aminoglycoside use is contraindicated in patients with botulism.

Trimethoprim-Sulfonamide Combinations (Potentiated Sulfonamides)^{4,74}

Spectrum of Activity

Potentiated sulfonamides are considered bactericidal by virtue of inhibition of sequential steps in the synthesis of folate and, therefore, DNA. Trimethoprim and other diaminopyrimidines such as ormetoprim and pyrimethamine inhibit the dihydrofolate reductase enzyme and exert a synergistic action with sulfonamides which competitively inhibit incorporation of PABA into folic acid.^{4,74} Potentiated sulfonamides have a broad-spectrum activity against many Gram-positive and Gram-negative aerobes.^{5,26,74,75} However, *Pseudomonas* sp, *Mycoplasma* sp, and many isolates of *Klebsiella* sp are resistant. The in vivo activity of potentiated sulfonamides against anaerobic bacteria is poor despite susceptibility test results to the contrary.⁵ This may result from the high levels of folate present in sites of anaerobic infection secondary to cell death. Sulfadiazine or sulfamethoxazole are commonly used in combination with pyrimethamine to treat equine protozoal myelitis caused by *Sarcocystis neurona*.

Dosage and Pharmacokinetics

1. A dose of 15–24 mg/kg q 8–12 h IV is recommended in those countries in which aqueous injectable solutions are available. Similar doses are used for the TMP/sulfadiazine aqueous suspension (Tribrissen® 48%) that was recently reintroduced for IV use in horses in the USA. This formulation should be administered slowly.
2. Oral tablets, paste, or powders containing TMP with sulfadiazine or sulfamethoxazole in a 1:5 ratio are used at doses of 20 to 30 mg/kg of drug combination BID.

The pharmacokinetic and antimicrobial profile of sulfadiazine is superior to that of sulfamethoxazole, although generic formulations of TMP/sulfamethoxazole are commonly used in horses in an extra-label manner. Trimethoprim and, to a lesser extent, sulfadiazine and sulfamethoxazole, are well distributed in the body due to their high lipid solubility.^{74,76,77} They achieve high intracellular concentrations and cross the blood–brain barrier.⁷⁸ Widespread distribution is reflected in a volume of distribution for TMP that exceeds 1 l/kg.^{74,76} The pharmacokinetics of TMP and sulfonamides are well matched in humans but, in horses, the rapid elimination of trimethoprim leads to more prolonged persistence of the sulfonamide, resulting

in higher than optimal ratios of the drugs in infection sites.⁷⁴ For this reason, potentiated sulfonamides should be administered at least twice daily in horses. Absorption of TMP and sulfonamides from the GI tract of horses is good, although the absorption of TMP is reduced substantially by feeding and the absorption of sulfonamides is delayed by feeding.^{74,77} Elimination of trimethoprim and sulfonamides involves both renal excretion of active drug and hepatic metabolism followed by elimination of metabolites in the urine. Sufficient concentrations of active drug appear in urine to make potentiated sulfonamide preparations useful for treating urinary tract infections.^{74,76}

Limitations

1. Lack of clinical activity against anaerobic bacteria.
2. Some β -*Streptococcus* sp appear to be resistant despite susceptibility results to the contrary.

Adverse Effects

1. Reversible neutropenia without a left shift has been noted during prolonged courses of treatment. This likely results from suppression of folate synthesis and resolves following termination of therapy. Supplementation with folic acid in the form of Brewer's yeast may further speed resolution.
2. TMP/sulfonamide combinations are generally thought to minimally disturb the gastrointestinal flora of horses.⁷⁹ Therefore antibiotic-associated colitis and diarrhea are not commonly encountered. However, serious pseudomembranous colitis and death have been observed on occasion. Geographic, dietary, and other factors such as prior treatment with other antibiotics or surgical stress, may influence colonic flora (particularly *Clostridium difficile*) and predispose horses to the development of pseudomembranous colitis.
3. Tremors, excitement, ataxia, collapse, and rare deaths have been encountered during or shortly after intravenous administration of both the approved aqueous solution and aqueous suspension formulations of trimethoprim/sulfadiazine, particularly when the rate of administration is rapid.⁷⁴ Thus, a slow rate of administration is recommended when TMS is used IV.
4. Concurrent use of detomidine and intravenous TMS formulations should be avoided because this combination has been associated with dysrhythmias, hypotension, and death.⁷⁴

Rifampin⁴

Spectrum of Activity

Rifampin exerts a bactericidal action on susceptible bacteria by inhibiting RNA polymerase, the enzyme

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that catalyses transcription of RNA to DNA.⁴ Since Gram-negative bacteria are relatively impervious to this enzyme, most are resistant.⁸⁰ Thus the narrow antimicrobial spectrum of rifampin includes Gram-positive aerobes, most Gram-positive and Gram-negative anaerobes, and some Gram-negative non-enteric aerobes.⁸⁰ Rifampin is one of the most active known antimicrobials against *Staphylococcus aureus* and shows excellent activity against *Rhodococcus equi*, *Mycobacterium* sp, *Corynebacterium* sp, and *Streptococcus* sp.⁸⁰ The major indications for the use of rifampin in horses are treatment of *R. equi* pneumonia, internal abscesses caused by *Corynebacterium* sp, and *Streptococcus* sp, and infections caused by penicillinase producing *Staphylococcus* sp.

Dosage and Pharmacokinetics

1. Oral doses of 2.5 to 7.5 mg/kg PO q 12 h are recommended and have a bioavailability of about 70%, although substantial inter-individual variation exists.⁸⁰⁻⁸³ Doses of 5.0–7.5 mg/kg q 12 h are usually used initially in combination with erythromycin to treat *R. equi* pneumonia. The dose can be reduced after a good initial response to therapy has been observed.
2. Wide distribution and excellent penetration of tissues and cell membranes facilitate killing of bacteria at sites of infection. Rifampin penetrates phagocytic cells, is active intracellularly, and retains antimicrobial activity at acid pH, allowing sterilization of abscesses.
3. Rifampin is synergistic with erythromycin, the drug most often administered concurrently, and can be used with penicillins and with potentiated sulfonamides.⁸⁴ Slight antagonism of antimicrobial effect has been noted in vitro with gentamicin but this is likely of minor clinical importance.⁸⁴ Rifampin has been used successfully in combination with gentamicin in our clinic to treat *R. equi* pneumonia in foals.

Limitations

1. No approved, easily administered oral dosage forms are available for horses. Capsules for human use are expensive, unpalatable, and not easily prepared into a suitable oral paste.
2. Poor solubility in aqueous media limits the availability of injectable dosage forms.
3. Narrow spectrum of antimicrobial activity.
4. Bacteria may rapidly gain resistance to rifampin during therapy; therefore the drug should only be used in combination with other antimicrobial agents that will kill resistant mutants.
5. Feeding reduces absorption of rifampin from the gastrointestinal tract.

Adverse Effects

1. Causes rusty orange staining of urine, mucous membranes, secretions, and clothing.
2. Suspensions constituted from oral capsules taste bad, even when mixed with molasses or corn syrup. Horses may be reluctant to swallow the administered dose. The bad taste of rifampin remaining in the mouth may cause horses to become anorectic during therapy. It is therefore important to administer the drug far back on the tongue and make sure the horse swallows. Rinsing the mouth before feeding reduces this negative effect on appetite, as with other orally administered medications in horses.
3. Many horses develop slight softening of the feces while on treatment with rifampin. This is not usually a major concern. However, explosive diarrhea with rapid loss of sodium, potassium, and chloride occurs on occasion and can be life threatening, especially during hot weather. This problem has been observed in foals and adult horses when rifampin is used in combination with erythromycin, penicillin G, or TMP/sulfonamide.
4. Rifampin may cause a false elevation in concentrations of some liver enzymes measured on automated chemistry analyzers and can potentially affect elimination of other drugs metabolized by the liver.

*Erythromycin⁴**Mechanism of Action and Spectrum of Activity*

Erythromycin, like other macrolide antibiotics, has a macrocyclic lactone ring structure attached to two or more sugar moieties. Killing of susceptible bacteria is mediated through binding to subunits of the 50S ribosome resulting in inhibition of translocation and protein synthesis. Erythromycin is usually considered to be bacteriostatic but may be bactericidal at high concentration. Erythromycin is active against Gram-positive aerobes (*R. equi* is highly susceptible); some *Actinobacillus* sp and *Pasteurella* sp; some anaerobic bacteria including *Clostridium* sp, *Bacteroides* sp (except *B. fragilis*), and some *Fusobacterium* sp.²⁶ Intermediate susceptibility is shown by *Ehrlichia* sp and *Bordetella* sp. Resistant organisms include Enterobacteriaceae, *Mycobacterium* sp, *Mycoplasma* sp, and *Chlamydia* sp.²⁶ The major indication for use of erythromycin is the treatment of *R. equi* pneumonia.

Dosage and Pharmacokinetics

1. Oral doses of 20 to 25 mg/kg q 8 h are recommended. A 12-hour dosing interval may be appropriate for erythromycin estolate after several days of dosing at an 8-hour interval.⁸⁵ Erythromycin stearate or esters

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(estolate or ethylsuccinate) are the preferred oral dosage forms in humans because they are less susceptible than erythromycin base and salts to degradation by gastric acid. Erythromycin stearate undergoes hydrolysis in the intestine to form erythromycin base, while the erythromycin esters are absorbed intact and are then hydrolyzed to active erythromycin base after absorption.⁸⁵ Oral administration of the less expensive free base or phosphate salt of erythromycin has proven to be effective for treating foals with *R. equi* pneumonia, either when used alone or in combination with rifampin, despite the finding that bioavailability ranges from 10–40%.⁸⁵⁻⁸⁷ Similarly, erythromycin ethylsuccinate is poorly absorbed in foals. Feeding prior to administration reduces bioavailability of all dosage forms evaluated.⁸⁶ Bioavailability in adult horses is probably even lower than in foals, although differences in experimental design in published studies preclude definitive conclusions.⁸⁵⁻⁸⁸ The bioavailability of microencapsulated erythromycin base and erythromycin estolate in foals is higher than that of other dosage forms, making these the two recommended formulations for treating *R. equi* pneumonia.^{85,86,89}

2. In the unusual event that parenteral dosing of erythromycin is necessary, the lactobionate salt is used at a dose of 5 to 10 mg/kg q 8–12 h by *slow* intravenous infusion.
3. High lipid solubility of erythromycin and other macrolides ensures wide distribution in the body and excellent penetration of cells and tissues. Intracellular concentrations of active erythromycin in phagocytes greatly exceed serum concentrations and persist for a longer duration.
4. Erythromycin is active intracellularly and at acid pH, and is synergistic with rifampin.

Limitations

1. The acid susceptibility of erythromycin base, phosphate and some esters limits absorption of active drug and may predispose to side effects. Serum concentrations of the microbially inactive anhydroerythromycin acid breakdown product are higher than concentrations of active erythromycin base after administration of the base and phosphate formulations.⁸⁵⁻⁸⁷ Anhydroerythromycin may be responsible for some of the observed side effects.
2. Frequent dosing is necessary.
3. Intravenous formulations (lactobionate and gluceptate) are expensive and poorly tolerated.

Adverse Effects

1. Like other macrolide antibiotics, erythromycin can cause gastrointestinal disturbances, diarrhea, and fatal pseudomembranous colitis.⁹⁰⁻⁹² The poor absorption of orally administered drug, and excretion of active erythromycin and metabolites in bile, likely result in substantial concentrations of active erythromycin reaching the colon to initiate disturbances in flora. For this reason, erythromycin use by the oral route in adult horses should be avoided if possible. Fatal colitis has been reported in mares while their foals are being treated orally with erythromycin, presumably due to ingestion of small amounts of active drug during coprophagic activity, or from contamination of feeders or water buckets with drug remaining on the foals' muzzle.^{91,92}
2. The motilin-like activity of erythromycin stimulates gastrointestinal motility.⁹³ This effect has been exploited clinically for the treatment of adynamic ileus, particularly that seen in post-operative colic patients, by using low-dose (2 mg/kg) IV infusions of erythromycin lactobionate. This effect may also be responsible for signs of mild colic and diarrhea in some horses treated orally with erythromycin. Rapid IV administration of antimicrobial doses of erythromycin lactobionate (5–10 mg/kg) causes severe reactions characterized by excitement, disorientation, ataxia, tachycardia, diarrhea, lacrimation, sweating, urination, and other signs of autonomic stimulation, including collapse.⁸⁵⁻⁸⁷ Therefore, erythromycin lactobionate should be administered slowly as an IV infusion.
3. Fever/hyperthermia and severe, often fatal, respiratory distress have been observed in foals treated with erythromycin during hot weather.⁹⁰ The mechanism underlying this reaction is unknown, but it likely results from derangement of the hypothalamic temperature "set-point" and may be predisposed by pre-existing lung disease. This reaction is of acute or peracute onset and is generally seen between the second and fourth day of treatment, although it can occur at any time (even shortly after treatment is discontinued) if adverse environmental conditions of high ambient temperature prevail.⁹⁰ Tachypnea and hyperthermia (up to 110°F) are observed early in the course of condition. If the core body temperature can be brought down quickly using cold water/alcohol baths, fans, and cold water enemas, affected foals may recover rapidly and fully. Otherwise, an acute respiratory distress syndrome with underlying bronchointerstitial pneumonia and systemic signs of heat stroke develops and frequently

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proves fatal. Extreme care should therefore be taken when erythromycin is used to treat foals during hot weather. Close observation and provision of shade are essential. Foals on erythromycin treatment should not be left outside on hot sunny days, and good ventilation, fans, or air conditioning should be used to control indoor temperatures.⁹⁰

4. Erythromycin has been shown to inhibit chemotaxis and migration of neutrophils into inflammatory sites in pulmonary airways and perhaps other sites.⁹⁴ This effect can prove highly beneficial in the treatment of neutrophil-mediated hyperreactive airway disease, such as occurs commonly in foals with chronic bacterial pneumonia. However, this effect may predispose to superinfection of the lung with resistant Enterobacteriaceae, *Pneumocystis carinii*, and perhaps other pathogens that may play a role in induction of an acute respiratory distress syndrome.
5. Hepatobiliary toxicity, interference with elimination of other drugs metabolized by the liver, and interference with liver enzyme assays are reported to be considerations with erythromycin use but are rarely of clinical significance.
6. Erythromycin formulations approved for IM use in ruminants and pigs are generally non-aqueous, buffered, alcohol or propylene glycol-based preparations which cause severe local pain and tissue reactions when administered IM to horses and can prove fatal when administered IV. Use of these formulations in horses is, therefore, contraindicated.

Other Macrolide Antibiotics

Azithromycin, roxithromycin, clarithromycin, dirithromycin, flurithromycin, and other new macrolides which show enhanced absorption from the GI tract, longer elimination half-life, more persistent tissue concentration, and broader antimicrobial spectrum have been developed for use in humans and show great promise for use in animals, including horses.⁴ Unpublished observations indicate that the absorption of azithromycin in foals is superior to that of erythromycin^a and that an oral dose of 10 mg/kg SID for 5 days followed by the same dose every other day until lesions resolve has proven to be successful for the treatment of *R. equi* pneumonia and pneumonia caused by other susceptible pathogens.^b

Fluoroquinolone Antibiotics⁴

Antibiotics of the fluoroquinolone class include enrofloxacin, ciprofloxacin, orbifloxacin, marbofloxacin, norfloxacin, danofloxacin, and several others.⁴ These antimicrobials are bactericidal DNA gyrase inhibitors that were developed as oral or parenteral dosage forms for use in humans and certain domestic species. Nalidixic acid, the first of the quinolones, is now rarely used. Enrofloxacin

(Baytril, Bayer Corp.) is approved for use in small animals and cattle in the US and is occasionally used in an extra-label manner to treat infections in horses using the IV or oral routes. The cattle formulation (Baytril 100, Bayer Corp), an aqueous solution in L-arginine designed for IM injection, has been shown to be effective and generally well tolerated when administered IV or IM to horses, although some horses experience pain and swelling at the injection site.^b

Spectrum of Activity

Fluoroquinolones show excellent activity against Gram-negative aerobes, including Enterobacteriaceae and *Pseudomonas aeruginosa*, and against *Mycoplasma* sp, *Rickettsia* sp, and *Ehrlichia* sp.^{4,95} These antimicrobials are generally less active against Gram-positive aerobes, although many isolates of *Staphylococcus* sp are susceptible.⁹⁵ Most isolates of *R. equi* and anaerobic bacteria are resistant.⁴ Fluoroquinolones are active against intracellular organisms. After administration to horses about 20–25% of the absorbed dose is de-ethylated to ciprofloxacin, which has slightly higher antimicrobial activity than enrofloxacin.⁹⁶

Dosage and Pharmacokinetics

1. An IV dose of 5.0–5.5 mg/kg SID (Baytril® 100 or Baytril®, Bayer Corp.) and an oral dose of 7.5 mg/kg SID or 4.0 mg/kg BID (Baytril® tablets or Baytril® 3.23% Concentrate Antibacterial Solution, Bayer Corp.) are recommended based on results of pharmacokinetic studies.^{96,97} IM injection of Baytril injectable is not recommended because it causes unacceptable tissue reactions,⁹⁶ whereas Baytril 100 appears to be tolerated better when administered IM.

The elimination half-life of enrofloxacin after IV injection to horses is reported to be 4.5 to 6 hours and after IM injection to be about 12–15 hours.^{95–97} The difference reflects slow absorption after IM injection. Mean bioavailability after oral administration of crushed Baytril tablets is approximately 60%, although absorption is erratic and there is considerable inter-individual variation.^{97,98} Bioavailability after intragastric administration of Baytril 3.23% Concentrate Antibacterial Solution (Bayer Corp.) is almost 80%.⁹⁵ Volume of distribution after IV use exceeds 2 l/kg, indicating widespread distribution in the body.⁹⁶ Concentrations of bioactive enrofloxacin and metabolites in liver, spleen, and kidney are 5 to 10 times higher than those in serum after repeated oral dosing.⁹⁹ Concentrations in brain, vitreous, and aqueous humor are only 10–20% of serum concentrations, whereas concentrations in skin, muscle, heart, stomach, intestine, uterus, mammary gland, bone, and bladder are similar to

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those in serum.⁹⁹ After oral administration, concentrations of active enrofloxacin in feces are much higher than those in serum, reflecting incomplete absorption as well as biliary secretion of parent drug and active metabolites.⁹⁹ Concentrations in urine are several hundred fold higher than those in serum, indicating renal elimination of a large fraction of the dose and suggesting utility for treating urinary tract infections.⁹⁷

Limitations/Adverse Effects

1. Suboptimal activity against Gram-positive aerobes, except *Staphylococcus* sp limits indications for use in horses.
2. Ataxia and other neurologic signs have been noted during or following rapid IV bolus administration of high doses (15 mg/kg or more) of Baytril 100.¹⁰⁰ Similar signs have been observed in debilitated post surgical cases given the same formulation at the 5 mg/kg dose. Thus, a slow rate of IV administration of enrofloxacin formulations is recommended.
3. Rapid onset of non-inflammatory arthropathy when used in immature animals limits fluoroquinolone use in foals.¹⁰¹ This effect is independent of dose but is dependent on age, species, and joint stress. Signs include joint swelling and lameness and reflect disruption of the extracellular matrix of collagen and depletion of collagen that results in erosions/blisters on weight-bearing surfaces of articular cartilage. Foals appear to be highly susceptible to these adverse articular effects, particularly when they are weight bearing and active.¹⁰¹ No clinical signs or histopathologic lesions indicative of articular cartilage damage were observed in adult horses treated with high doses of enrofloxacin daily for 21 days but 2 horses did develop clinical evidence of mild plantar desmitis or superficial digital flexor tendinitis.¹⁰⁰
4. Weakening and rupture of tendons, particularly the Achilles tendon, has been reported in humans during treatment with fluoroquinolones. Cases have been observed as early as the second day of therapy but most occurred during chronic treatment of older people, particularly when corticosteroids were administered concurrently.¹⁰² This adverse effect likely has a mechanism similar to that involved in fluoroquinolone-induced arthropathy.
4. Since the potential long-term toxic effects of fluoroquinolones in adult performance horses have not been assessed, enrofloxacin should be reserved for treating Gram-negative or staphylococcal infections resistant to other antibiotics and its use in foals should be avoided, except under special circumstances.

Metronidazole⁴

Spectrum of Activity

Metronidazole, like other nitroimidazoles, acts by causing extensive breakage in DNA strands and inhibition of the DNA repair enzyme, DNAase 1.⁴ The narrow spectrum of activity includes almost all anaerobic bacteria and many protozoa.⁴ The major indication for use of metronidazole in horses is the treatment of infections caused by anaerobic bacteria or, in combination with other antibiotics, treatment of polymicrobial infections such as pleuropneumonia that may involve anaerobic bacteria.^{8,103} Oral use for treating pseudomembranous colitis caused by *Clostridium* sp,¹⁰⁴ and topical use to treat thrush and canker are additional indications.

Dosage and Pharmacokinetics

1. Oral doses of 20–25 mg/kg q 8–12 h or 15 mg/kg q 6 h are recommended.^{105,106} Absorption is rapid and bioavailability is high.^{105–108} An oral dose of 15 mg/kg q 8 h is used to treat Clostridial colitis.
2. The parenteral dose is 20 mg/kg q 8–12 h.
3. Good absorption of metronidazole after intrarectal administration has been documented in horses and offers an alternate route when oral or esophageal lesions preclude oral administration.^{107,109}
4. Metronidazole is widely distributed in the body and penetrates tissues well.^{105–108}
5. Metronidazole is compatible with penicillins and aminoglycosides when used to treat polymicrobial infections.

Limitations

1. The narrow antibacterial spectrum usually necessitates use in combination with other antibiotics.
2. No oral dosage forms are approved for use in horses in the USA, although palatable paste formulations designed for horses are available in Britain and some other countries.
3. The parenteral dosage form (a 5% solution) is expensive and, because of poor solubility of metronidazole in aqueous media, requires a large administration volume.

Adverse Effects

1. Metronidazole is considered to be a safe drug for use in horses.¹⁰³ Gastrointestinal upsets and diarrhea are encountered on occasion.
2. Neurologic side effects characterized by depression, weakness, ataxia, vestibular signs, seizures, and peripheral neuropathy have been observed on occasion in horses treated concurrently with metronidazole and other drugs. Attempts to reproduce these signs

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with high doses of metronidazole (50 mg/kg PO q 8 h) were not successful in spite of the very high serum concentrations of metronidazole achieved.

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