Tutorial Article

Overview of the use of antimicrobials for the treatment of bacterial infections in horses

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Summary

Use of antimicrobial drugs is central to the treatment of primary and secondary bacterial infection in horses. When selecting an antimicrobial to treat confirmed or suspected bacterial infection multiple factors should be considered, including: the likely infectious agent; distribution and dosage of selected drugs; mechanisms of action; and potential side effects. Many of these issues will be covered in subsequent articles in this series. The aim of this paper is to aid the clinician in the rational selection of antimicrobials by reviewing the mode of action, spectrum of activity, pharmacokinetics, pharmacodynamics, indications and potential side effects of the main classes of antimicrobial drugs. Extralabel use of drugs is common in veterinary medicine due to a lack of licensed products. This increases the importance of a thorough understanding of antimicrobials and their possible adverse effects.

Beta lactams

Penicillin G

Mode of action

Penicillins are bactericidal antimicrobials that interfere with the final steps of bacterial cell wall synthesis by binding to transpeptidase and other penicillin-binding proteins (PBPs). This inhibits the synthesis and incorporation of peptidoglycan into the bacterial wall, leading to cell lysis (Giguere *et al.* 2006).

Spectrum of activity

Penicillin G has excellent activity against Gram-positive bacteria, with the exception of some *Staphylococcus* spp., α-*Streptococcus* spp. and *Rhodococcus equi* (Adamson *et al.* 1985; Hirsh and Jang 1987; Giguere *et al.* 2006). Penicillin has a limited Gram-negative spectrum that includes some *Pasteurella* spp. and *Actinobacillus* spp., and good anaerobic coverage with the exception of *Bacteroides fragilis* (Hirsh and Jang 1987). Penicillin is inactivated by β-lactamase enzymes produced by many *Staphylococcus* spp., most Gram-negative enteric organisms and many *Bacteroides* spp.

Dosage

- Sodium or potassium salts of penicillin G: 22,000–44,000 iu/kg bwt i.v. or i.m. q. 4–6 h.
- Procaine penicillin G (PPG): 22,000 iu/kg bwt i.m. q.12–24 h.

Pharmacokinetics and pharmacodynamics

Penicillins are organic acids that are highly ionised in plasma. They distribute widely throughout plasma but penetrate biological membranes poorly due to low lipid solubility. Penetration of biological membranes is enhanced by inflammation and penicillin may penetrate an inflamed or compromised blood-brain barrier. Penicillin does not penetrate abscesses or sites of tissue necrosis well, and has a reduced activity in the acid environments that accompany these disease processes. Elimination is via active renal tubular secretion leading to high urinary concentrations of active drug.

Penicillins exert their effects via 'time-dependent' killing; therefore, optimal efficacy is achieved only when plasma concentrations exceed the MIC of the infecting organism at all times during the dosage interval. This necessitates frequent dosing, because soluble forms typically have an elimination half-life of less than 1 h (Durr 1976; Horspool and McKellar 1995). Complexing of penicillin G with procaine for i.m. administration results in gradual release of penicillin G into the serum at detectable levels for 24 h; however, peak serum concentrations are low (Uboh *et al.* 2000). Procaine has been detected in urine 425 h after administration of multiple doses of procaine penicillin G, which limits its usefulness in

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performance horses (Stevenson *et al.* 1992; Giguere *et al.* 2006). Benzathine penicillin G (another sustained release injectable formulation) achieves such low plasma concentrations that its use cannot be recommended.

Indications

Penicillin is useful for the treatment of many Gram-positive and mixed infections. It is a first line choice for streptococcal infections, such as strangles (*Streptococcus equi* infection) or upper and lower respiratory infection caused by *S. zooepidemicus* (Sweeney *et al.* 2005). Penicillin is also indicated for treatment of some clostridial infections, including clostridial myositis, botulism and tetanus (Green *et al.* 1994). The high concentrations achieved in urine make penicillin G useful in the treatment of urinary tract infection. Penicillin G acts synergistically with the aminoglycosides, making it a common first line choice in combination with gentamicin when broad-spectrum antimicrobial coverage is required, such as in the treatment of peritonitis, pleuropneumonia, cholangiohepatitis, systemic sepsis or endocarditis. This combination is also useful for the treatment of orthopaedic infections such as osteomyelitis and septic arthritis when penicillinase-producing *Staphylococcus* spp. or *Enterobacteriaceae* are not involved (Meijer *et al.* 2000).

Adverse effects

1. Procaine reactions caused by inadvertent intravascular injection of PPG during i.m. injection lead to excitement, seizure-like activity and sometimes death (Nielsen *et al.* 1988; Olsen *et al.* 2007). Repeated injections, improper storage of PPG (heat increases dissociation of procaine) and possibly low plasma esterase activity increase the likelihood of a reaction (Chapman *et al.* 1992; Olsen *et al.* 2007).
2. Muscle soreness and focal myositis with increased serum concentrations of muscle enzymes, are common sequelae to prolonged courses of i.m. treatment with procaine penicillin G.
3. Allergy occurs occasionally and can cause serious anaphylactic reactions that lead to respiratory difficulty, diarrhoea and, rarely, death (Olsen *et al.* 2007).
4. Development of IgG antibodies that bind to erythrocytes may rarely cause a severe and life-threatening haemolytic anaemia, which typically resolves following discontinuation of therapy (Blue *et al.* 1987; McConnico *et al.* 1992; Wilkerson *et al.* 2000).
5. Rapid i.v. administration of potassium penicillin can lead to clinical signs of head shaking/rubbing, lip smacking, teeth grinding, salivation, lacrimation, increased borborygmus, mild colic/agitation and passage of soft/liquid faeces. Potassium penicillin has been shown to have prokinetic effects on the large intestine (Roussel *et al.* 2003).
6. Antimicrobial-associated colitis may develop after initiating therapy, as with many other classes of antimicrobials (Baverud *et al.* 2003).

Ampicillin and amoxicillin

Mode of action

Ampicillin and amoxicillin are aminobenzyl penicillins that, like penicillin G, bind to PBPs and are bactericidal.

Spectrum of activity

Compared to penicillin G, ampicillin and amoxicillin are better able to penetrate the outer cell wall of Gram-negative bacteria giving them better activity against bacteria such as *E. coli*, *Proteus* spp. and *Salmonella* spp. However, both drugs remain susceptible to inactivation by β-lactamases and are slightly less active than penicillin G against susceptible Gram-positive bacteria (Giguere *et al.* 2006). Plasmid-mediated resistance by Gram-negative bacteria has increased greatly over time, thereby decreasing their spectrum of activity.

Dosage

- Ampicillin sodium: 10–40 mg/kg bwt i.v. q. 6–8 h.
- Ampicillin trihydrate: 20 mg/kg bwt i.m. q. 12 h - poor serum levels obtained.

Pharmacokinetics and pharmacodynamics

Distribution is similar to penicillin, excretion is predominantly by the renal route (primarily tubular secretion), and bacterial killing is time-dependent.

Indications

Ampicillin can be used as an alternative to penicillin in many of the clinical situations listed above. It is a first line choice when combined with amikacin for the treatment of neonatal sepsis (Wilson *et al.* 1988a; Wilson and Madigan 1989; Wichtel *et al.* 1999; Henson and Barton 2001; Marsh and Palmer 2001).

Adverse effects

1. Amoxicillin trihydrate is irritant when injected i.m. and achieves only low serum concentrations (Wilson *et al.* 1988a).
2. Antimicrobial-associated colitis may develop during therapy (Baverud *et al.* 2003).

Other β-lactams

Antipseudomonal penicillins (Wise 1997) are occasionally used in horses and include ticarcillin, carbenicillin and piperacillin. These drugs can penetrate the outer cell wall of Gram-negative bacteria, including *Pseudomonas* spp. They remain susceptible to β-lactamase inactivation, a phenomenon that can be overcome, at least partially, by combining ticarcillin with clavulanic acid. Compared to other penicillins,

antipseudomonal penicillins have reduced activity against Gram-positive organisms. Expense limits their use to the treatment of systemic or uterine infection with *P. aeruginosa* or penicillinase-producing *Staphylococcus* spp., neonatal septicaemia involving aminoglycoside-resistant Gram-negative bacteria, or patients with physiological or toxic conditions that preclude use of aminoglycosides (Sweeney *et al.* 1984, 1988a,b; Wilson *et al.* 1991).

Isoxazolyl penicillins including oxacillin, cloxacillin, dicloxacillin, methicillin and nafcillin are resistant to cleavage by many β-lactamases, including those elaborated by coagulase-positive *Staphylococcus* spp. Their spectrum of activity is largely restricted to Gram-positive aerobic bacteria, but their potency against penicillin-susceptible bacteria is lower than that of penicillin G. The major indication for their use is the treatment of systemic or local infection with penicillin-resistant *Staphylococcus* spp. Oxacillin is the antibiotic of this class most often used in horses and is relatively safe.

Imipenem is a carbapenem antimicrobial that is occasionally indicated for the treatment of neonatal sepsis caused by organisms resistant to other antimicrobials. It is a bactericidal drug that has an extremely broad spectrum of activity and is given at a dose of 10–20 mg/kg bwt i.v. q. 6 h in combination with cilastatin (Orsini *et al.* 2005a; Giguere *et al.* 2006). Its use in veterinary medicine should be reserved for infections documented to be resistant to other antimicrobials.

Cephalosporins

Cephalosporins have historically been classified into generations according to the order in which they were discovered (first to fourth). This is the terminology still most commonly accepted in veterinary medicine. However, an alternative classification scheme into 7 groups based on route of administration and antimicrobial activity is utilised in human medicine and may become more widely accepted in veterinary medicine in the future (Wise 1997).

Ceftiofur

Mode of action

Ceftiofur is a bactericidal third-generation cephalosporin that binds to PBPs and prevents bacterial cell wall synthesis (Folz *et al.* 1992; Mahrt 1992; Meyer *et al.* 1992; Cervantes *et al.* 1993; Jaglan *et al.* 1994; Giguere *et al.* 2006).

Spectrum of activity

Ceftiofur has a broad antimicrobial spectrum that includes Gram-positive and Gram-negative aerobes, including *Enterobacteriaceae*, and many anaerobes, including *Clostridium* spp. and *Fusobacterium* spp. (Yancey *et al.* 1987; Salmon *et al.* 1996; Samitz *et al.* 1996). *Pasteurella* spp. are highly susceptible. Resistant bacteria include *Bacteroides* spp., *Enterococcus* spp., *Rhodococcus equi* and *Pseudomonas aeruginosa*.

Dosage

- The label dose is 2.2–4.4 mg/kg bwt i.m. q. 24 h (for the approved indication of treating infection with β-haemolytic *Streptococcus* spp.).
- A dose of 2.2 mg/kg bwt i.v., i.m. or subcut. q. 12 h is used commonly.
- For neonatal septicaemia, the dose is 5–10 mg/kg bwt i.v., i.m. or subcut. q. 8–12 h.

Pharmacokinetics and pharmacodynamics

Ceftiofur is hydrolysed by the liver to desfuroylceftiofur, an active metabolite that is highly protein bound and protected from rapid renal elimination (Giguere *et al.* 2006). Ceftiofur is labelled for i.m. dosing. However, recent studies have shown similar plasma concentration profiles following i.m., i.v. and subcut. injection (Slovis *et al.* 2006).

Ceftiofur penetrates into body fluids, joints, synovial fluid and pulmonary tissue well, but does not enter the CSF in effective concentrations. Elimination is via glomerular filtration and active tubular secretion. Cephalosporins exert time-dependent bacterial killing.

Indications

Despite being labelled solely for the treatment of infections caused by β-haemolytic *Streptococcus* spp., ceftiofur has a broad spectrum of activity and is useful for the treatment of other Gram-positive, Gram-negative or mixed infections. Uses include treatment of strangles, pneumonia, some abscesses and skin infections, cystitis or other urinary tract infection and joint infection. Ceftiofur can be used with an aminoglycoside to treat mixed infections in which greater Gram-negative coverage is required; for example, peritonitis, cholangiohepatitis or septic arthritis. Ceftiour by the i.v. route is useful in horses that become refractory to i.m. injection of procaine penicillin G. Regional limb perfusion and intra-articular injection of ceftiofur have been shown to provide synovial concentrations that exceed the MIC for many common organisms for 24 h, making ceftiofur useful for the treatment of septic arthritis (Mills *et al.* 2000; Pille *et al.* 2005; Lescun *et al.* 2006). Ceftiofur administered via nebulisation to calves has been shown to be more effective than systemic administration in the treatment of *Pasteurella* spp. pneumonia (Sustronck *et al.* 1995; Vermeersch *et al.* 1996). Anecdotal reports suggest that this route may also be useful in horses.

Adverse effects

1. Diarrhoea and colitis have been observed in horses treated with high doses of ceftiofur (Mahrt 1992).
2. Minor injection site discomfort and irritation occur with repeated administration (Mahrt 1992).

Other cephalosporins

First generation cephalosporins are predominantly effective against Gram-positive organisms. Cefazolin and cefalotin are first generation cephalosporins that have limited applications in equine medicine (Ruoff and Sams 1985). Second and third generation drugs generally have better Gram-negative activity. Cefotaxime and ceftriaxone are third generation cephalosporins that penetrate the blood brain barrier well and have been used for the treatment of bacterial meningitis (Pellegrini-Masini and Livesey 2006). Cefotaxime has also been used successfully to treat neonatal sepsis (Rohdich 2006; Thomas *et al.* 2006). Fourth generation cephalopsorins have a broad spectrum of activity. Ceftazidime (third generation) and other fourth generation drugs including cefquinome have antipseudomonal activity and are resistant to beta-lactamases. Cefepime is a fourth generation drug that has been shown to cross the blood brain barrier in human neonates (Ellis *et al.* 2007) and has been shown to reach therapeutic levels after i.v. administration in foals (Gardner and Papich 2001).

Aminoglycosides (gentamicin and amikacin)

Mode of action

Aminoglycosides are bactericidal antimicrobials that are actively pumped across cell membranes. Once inside the cell, they bind to the 30S ribosomal subunit and interfere with protein synthesis, ultimately leading to bacterial cell death. Active uptake of aminoglycosides is reduced in oxygen poor environments and uptake is enhanced by β-lactams that interfere with bacterial cell wall synthesis (Giguere *et al.* 2006). Aminoglycosides work best in alkaline environments and have a reduced activity at sites of tissue damage in which the pH falls (Giguere *et al.* 2006).

Spectrum of activity

Aminoglycoside activity is predominantly limited to aerobic Gram-negative bacteria (Adamson *et al.* 1985; Hirsh and Jang 1987). Anaerobes and Gram-positive bacteria, with the exception of some coagulase positive *Staphylococcus* spp., are usually resistant (Adamson *et al.* 1985; Hirsh and Jang 1987). Some *Mycoplasma* spp. and *Mycobacteria* spp. are susceptibile (Giguere *et al.* 2006).

Dosage

- Gentamicin: 6.6 mg/kg bwt i.v. q. 24 h.
- Amikacin: 21–25 mg/kg bwt i.v. q. 24 h.
- Higher (or lower) doses based on results of therapeutic drug monitoring

Pharmacokinetics and pharmacodynamics

Aminoglycosides are highly polar bases that distribute in a volume similar to the extracellular fluid volume. Their penetration into cells and tissues is generally poor (Pedersoli *et al.* 1980; Golenz *et al.* 1994; Magdesian *et al.* 1997, 1998; Jones *et al.* 1998). Elimination is by glomerular filtration leading to high concentrations of active drug in urine. Aminoglycosides concentrate in renal tubular epithelial cells (Brown *et al.* 1982; Giguere *et al.* 2006). They exert a significant post antibiotic effect and kill bacteria in a concentration-dependent manner. (Karlowsky *et al.* 1994). Dosing regimens that accomplish high peak concentration, high AUC, high peak concentration to MIC ratio and low trough concentration are desirable and can be optimised through therapeutic drug monitoring.

Indications

Aminoglycosides are used to treat Gram-negative infections in horses and are frequently combined with β-lactams for a synergistic effect and to offer broad spectrum antimicrobial coverage; for example, in the treatment of pleuropneumonia, septic arthritis or osteomyelitis. Amikacin is usually reserved for the treatment of infection with organisms resistant to gentamicin, or for the treatment of Gram-negative neonatal sepsis, due to its lower potential for nephrotoxicity and superior activity against *Enterobacteracea*. Gentamicin has better activity than amikacin against streptococci and nonenteric Gram-negative organisms (Hirsh and Jang 1987), and both drugs generally have good activity against *Pseudomonas* spp. Both amikacin and gentamicin have been used successfully to treat septic arthritis and other localised infections by implanting antibiotic-impregnated collagen sponges or polymethacrylate beads, intra-articular administration or regional perfusion with drug (Whithair *et al.* 1992; Farnsworth *et al.* 2001; Lescun *et al.* 2006). These routes of administration achieve high local concentrations with a reduced risk of side effects. Deactivation in low oxygen and acidic environments and poor penetration reduces the ability of aminoglycosides to effectively treat bacterial infection in necrotic tissue or abscesses.

Adverse effects

1. Nephrotoxicity (acute tubular nephrosis) is the most important side effect of aminoglycosides and occurs because the active drug concentrates in renal tubular epithelial cells. Prevention of toxicity involves using recommended dosage regimens, minimising the duration of therapy, maintaining hydration and renal perfusion, minimising 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 plus periodic urinalysis and monitoring of serum concentrations of BUN and creatinine are recommended (Giguere *et al.* 2006).
2. Ototoxicity is reported occasionally (Riviere and Coppoc 1981; Riviere *et al.* 1983; Nostrandt *et al.* 1991).

3. Neuromuscular blockade mediated through inhibition of acetylcholine at nicotinic cholinergic receptors can occur, most often in association with the concurrent use of anaesthetic agents. Treatment involves i.v. administration of calcium chloride or gluconate, plus neostigmine or edrophonium. Aminoglycosides should not be given to animals with botulism.
4. Muscle irritation can occur with i.m. injections; therefore, i.v. administration is preferred.

Trimethoprim-sulphonamide combinations (potentiated sulphonamides)

Mode of action

Sulphonamides prevent incorporation of para-aminobenzoic acid (PABA) into folic acid in bacterial cells. Bacteria, unlike mammals, are unable to use preformed folate, hence this competitive inhibition prevents the formation of bacterial DNA. When used alone, sulphonamides are considered to be bacteriostatic, but they act synergistically with diaminopyrimidines such as trimethoprim (TMP) to create a bactericidal combination. Trimethoprim inhibits dihydrofolate reductase, the subsequent enzymic step in folate synthesis (van Duijkeren *et al.* 1994; Giguere *et al.* 2006).

Spectrum of activity

Potentiated sulphonamides have a broad-spectrum of activity against many Gram-positive and Gram-negative aerobes (Amyes and Smith 1974; Adamson *et al.* 1985; Hirsh and Jang 1987; van Duijkeren *et al.* 1994). However, *Pseudomonas* spp., *Mycoplasma* spp. and many isolates of *Klebsiella* spp. are resistant. The *in vivo* activity of potentiated sulphonamides against anaerobic bacteria is poor despite *in vitro* susceptibility test results to the contrary (Hirsh and Jang 1987). This discrepancy may result from the high levels of folate present in sites of anaerobic infection secondary to cell death. Bacterial resistance to potentiated sulphonamides is common and limits their usefulness (Wilson and Madigan 1989; Marsh and Palmer 2001).

Dosage

- 15–24 mg/kg bwt i.v. q. 8–12 h, slowly.
- (24–)30 mg/kg bwt *per os* q. 12 h.

Pharmacokinetics and pharmacodynamics

Trimethoprim and, to a lesser extent, sulphadiazine and sulphamethoxazole, are highly lipid soluble and distribute well throughout the body (Bogan *et al.* 1984; Brown *et al.* 1988; van Duijkeren *et al.* 1994). They achieve high intracellular concentrations and cross the blood-brain barrier (Green *et al.* 1990, 1992). Pus and necrotic tissue inactivate potentiated sulphonamides because they provide PABA to bacterial cells, thereby overcoming their mechanism of competitive inhibition (Giguere *et al.* 2006). The ratio of TMP to sulphonamides is important and was originally matched at a 1:5 ratio for administration to man. In horses, the more rapid elimination of TMP relative to sulphonamides leads to suboptimal drug ratios at the site of action (van Duijkeren *et al.* 1994) and makes twice daily administration necessary. Oral bioavailability is generally good, although absorption is slowed and reduced by feeding (Bogan *et al.* 1984; van Duijkeren *et al.* 1994).

Some hepatic metabolism of both drugs occurs, and elimination is by renal excretion of active drug and metabolites, leading to high concentrations in the urine (Brown *et al.* 1988; van Duijkeren *et al.* 1994). The antimicrobial activity and pharmacokinetic properties of sulphadiazine in horses are superior to those of sulphamethoxazole (Giguere *et al.* 2006). Potentiated sulphonamides kill bacteria in a time-dependent manner.

Indications

The broad spectrum of activity, wide availability, relatively low cost, and oral route of administration leads to potentiated sulphonamides being used commonly in equine practice. They are useful in the treatment of bacterial infection of the upper and lower respiratory tract, although some streptococci, including *S. equi*, are relatively resistant (Ensink *et al.* 2003, 2005). Good penetrability also makes potentiated sulphonamides useful for treating septic arthritis, osteomyelitis, peritonitis and meningitis. However, widespread resistance, and in some countries, lack of availability of a parenteral formulation, leads more commonly to their use as a follow-up treatment once the acute phase of infection has been controlled with other antimicrobials. Inactivation by pus makes these drugs less useful for treating abscesses; however, potentiated sulphonamides have been used successfully in combination with rifampin to treat internal abscesses (Pusterla *et al.* 2007). Urinary excretion makes potentiated sulphonamides useful for the treatment of urinary tract infections (Brown *et al.* 1988; van Duijkeren *et al.* 1994). They also penetrate the reproductive tract and cross the placenta well, making them useful in the treatment of placentitis, retained fetal membranes or epididymitis. Sulphadiazine or sulphamethoxazole have been used successfully in combination with the diaminopyrimidine, pyrimethamine, to treat equine protozoal myelitis (MacKay *et al.* 2000).

Adverse effects

1. Reversible neutropenia without a left shift, likely due to suppression of folate synthesis, has been noted during prolonged courses of treatment. Supplementation with folinic acid in the form of Brewer's yeast may speed resolution.
2. Trimethoprim-sulphonamide combinations disturb the gastrointestinal flora to a limited degree, but can cause colitis and diarrhoea on occasion.
3. Tremor, excitement, ataxia, collapse and, rarely, death have been encountered during or shortly after i.v.

administration of both the approved aqueous solution and aqueous suspension formulations of trimethoprim/sulphadiazine, particularly with rapid i.v. administration (van Duijkeren *et al.* 1994)
4. Concurrent use of detomidine or other α-2 agonists and i.v. TMS formulations should be avoided because this combination has been associated with dysrhythmia, hypotension and death (van Duijkeren *et al.* 1994).

Rifampin

Mode of action

Rifampin exerts a bactericidal action on susceptible bacteria by inhibiting RNA polymerase, the enzyme that catalyses transcription of RNA to DNA (Giguere *et al.* 2006).

Spectrum of activity

Rifampin has a narrow antimicrobial spectrum that includes Gram-positive aerobes, some Gram-negative nonenteric aerobes and most anaerobes (Wilson *et al.* 1988b). Rifampin has excellent activity against *Staphylococcus aureus*, *Rhodococcus equi*, *Mycobacterium* spp., *Corynebacterium* spp. and *Streptococcus* spp. (Wilson *et al.* 1988b) and acts synergistically with the macrolides.

Dosage

- 5 mg/kg bwt *per os* q. 12 h.
- Higher doses (7.5–10 mg/kg bwt *per os* q. 12 h) are sometimes used in the treatment of *R. equi* pneumonia.

Pharmacokinetics and pharmacodynamics

Rifampin is highly lipophilic, has a wide volume of distribution, and excellent penetration into tissues and cells, including phagocytes. Rifampin remains active intracellularly and in acid environments.

Oral availability is generally good but variable (Burrows *et al.* 1985, 1992; Wilson *et al.* 1988b; Kohn *et al.* 1993), and rifampin is highly protein bound in plasma. Hepatic metabolism of the drug occurs and rifampin induces hepatic enzymes. The exact mechanism of excretion of rifampin in horses is not well understood, but the drug and its metabolites are probably excreted via bile with some minor urinary excretion (Giguere *et al.* 2006).

Indications

Major indications for the use of rifampin in horses are treatment of *R. equi* pneumonia, internal abscesses caused by *Corynebacterium* spp. or *Streptococcus* spp., limb cellulitis, and infections caused by penicillinase-producing *Staphylococcus* spp. (Pratt *et al.* 2005; Barr 2006). Rifampin should always be used in combination with antimicrobials of another class because bacteria rapidly develop resistance to rifampin when it is used as a sole agent. Rifampin has been used with macrolides or aminoglycosides to treat *R. equi* pneumonia in foals, or with penicillin, ceftiofur or potentiated sulphonamides to treat internal abscesses. Rifampin should not be used in combination with fluroquinolones due to *in vitro* evidence of antagonism (Michelet *et al.* 1997).

Adverse effects

1. Causes rusty orange staining of urine, mucous membranes, secretions and clothing.
2. Rifampin has a bitter taste and can cause anorexia.
3. Benign faecal softening is common with the use of rifampin, but fatal colitis has also been reported, especially when the drug is used in combination with other antimicrobials (Båverud *et al.* 1998). Staggering the introduction of different antimicrobial classes into the treatment regimen when initiating therapy is sometimes suggested in geographic areas where antimicrobial-associated colitis is prevalent.
4. Rifampin may cause a false elevation in concentrations of some liver enzymes measured on automated chemistry analysers, and can potentially affect elimination of other drugs metabolised by the liver.

Macrolides

Erythromycin, clarithromycin and azithromycin

Mode of action

Macrolides inhibit bacterial protein synthesis by reversibly binding to the 50S ribosomal subunit, which leads to inhibition of transpeptidation and translocation, and incomplete protein synthesis. Macrolides are usually considered to be bacteriostatic but may be bactericidal at high doses.

Spectrum of activity

Macrolides are predominantly active against Gram-positive aerobes (*R. equi* is highly susceptible). They have intermediate activity against some Gram-negative nonenteric aerobes (including *Actinobacillus* spp. and *Pasteurella* spp.) and some anaerobes (including *Clostridium* spp., *Bacteroides* spp., except *B. fragilis*, and some *Fusobacterium* spp.) (Adamson *et al.* 1985). Azithromycin has better activity than erythromycin against anaerobic bacteria and Gram-negative aerobes (Jacks *et al.* 2003).

Dosage

- Erythromycin: 20–25 mg/kg bwt *per os* q. 6–8 h (estolate or microencapsulated base are the preferred formulations).
- Azithromycin: 10 mg/kg bwt *per os* q. 24 h initially, followed by 10 mg/kg bwt q. 48 h.
- Clarithromycin: 7.5 mg/kg bwt *per os* q. 12 h.

Tulathromycin is a newer injectable macrolide that has been used in experimental studies and may become available for clinical use in the future (Scheuch *et al.* 2007).

Pharmacokinetics and pharmacodynamics

Macrolides have high lipid solubility and hence are widely distributed in the body and show excellent penetration of cells and tissues. High concentrations of macrolides can be detected in bronchoalveolar fluid cells after oral administration (Jacks *et al.* 2001).

Oral bioavailability of erythromycin is generally poor and dependent on formulation and feeding. Some formulations, including nonencapsulated erythromycin base, are degraded by gastric acid. Erythromycin estolate has the highest bioavailability (mean of 36%) in fasted foals and the microencapsulated base has the next highest (Lakritz *et al.* 2000a,b). Azithromycin and clarithromycin can be used at a longer dosing interval than erythromycin because they are more stable compounds, have better oral bioavailability, slower elimination, and reach higher and more persistent concentrations in phagocytes (Jacks *et al.* 2001; Suarez-Mier *et al.* 2007).

Erythromycin is more extensively metabolised by the liver than is azithromycin (Giguere *et al.* 2006). Excretion is predominantly via bile.

Indications

The major indication for the use of macrolides is the treatment of *R. equi* infection in foals (Giguere *et al.* 2004). Azithromycin has also been used to treat proliferative enteropathy caused by *Lawsonia intracellularis* (Feary *et al.* 2007).

Adverse effects

1. Macrolides should not be used orally in adult horses because of the association with severe and fatal colitis (Gustafsson *et al.* 1997; Båverud *et al.* 1998; Stratton-Phelps *et al.* 2000). Diarrhoea, and occasionally severe colitis, can also be a side effect in foals.
2. Fatal colitis has been reported in mares while their foals were 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 foal's muzzle (Gustafsson *et al.* 1997; Båverud *et al.* 1998).
3. Fever/hyperthermia and severe, often fatal, respiratory distress have been observed in foals treated with erythromycin during hot weather (Stratton-Phelps *et al.* 2000). Extreme care should therefore be taken when using macrolides during hot weather. Close observation and provision of shade are essential and foals should not be left outside on hot sunny days.
4. Erythromycin has been shown to inhibit chemotaxis and migration of neutrophils into sites of inflammation in pulmonary airways and perhaps other sites (Lakritz *et al.* 1997). 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 has the potential to 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 (Lakritz *et al.* 1993, 1997).
5. Hepatobiliary toxicity, interference with elimination of other drugs metabolised by the liver and interference with liver enzyme assays are reported to be considerations with erythromycin use but are rarely of clinical significance.

Fluoroquinolone antibiotics

Enrofloxacin

Mode of action

Fluoroquinolones are bactericidal antimicrobials that act by inhibiting the DNA gyrase responsible for supercoiling strands of bacterial DNA. Inhibition of this enzyme leads to abnormal spatial DNA configuration and degradation of DNA by exonucleases (Giguere *et al.* 2006).

Spectrum of activity

Fluoroquinolones are predominantly active against Gram-negative aerobes, including Enterobacteriaceae and *Pseudomonas aeruginosa*, and against *Mycoplasma* spp., *Rickettsia* spp. and *Ehrlichia* spp. They have limited Gram-positive coverage, with the exception of many *Staphylococcus* spp. (Haines *et al.* 2000). Activity against anaerobes is limited (Giguere *et al.* 2006).

Dosage

Enrofloxacin is the only fluoroquinolone currently in clinical use in horses.

- 5.0 mg/kg bwt i.v. q. 24 h.
- 5–7.5 mg/kg bwt *per os* q. 24 h.

Suggested doses exist in the literature for other fluoroquinolones, but safety data is lacking (Bousquet-Melou *et al.* 2002; Davis *et al.* 2006a; Fernandez-Varon *et al.* 2006). Ciprofloxacin should not be used in the horse due to its high propensity to cause fatal colitis (W.D. Wilson, personal communication).

Pharmacokinetics and pharmacodynamics

Fluoroquinolones are bactericidal antimicrobials that kill bacteria in a concentration-dependent manner and have high lipid solubility. High concentrations are achieved in liver, spleen and kidney; moderate levels in skin, muscle, heart, stomach, intestine, uterus, mammary gland, bone and bladder; and low levels in CSF and the eye (Giguere and Belanger 1997).

Oral bioavailability is generally good (60–80%), depending on formulation (Giguere *et al.* 1996; Langston *et al.* 1996; Haines *et al.* 2000). After absorption, 20–25% of enrofloxacin is de-ethylated to ciprofloxacin, which has slightly higher antimicrobial activity than enrofloxacin (Kaartinen *et al.* 1997). Fluroquinolones are eliminated predominantly in the urine with minor biliary excretion of parent drug and active metabolites (Giguere *et al.* 1996; Giguere and Belanger 1997).

Indications

Enrofloxacin is indicated for treatment of bacterial diseases caused by Gram-negative organisms or *Staphylococcus* spp. Enrofloxacin can be combined with β-lactams to provide broad spectrum antimicrobial coverage. Good penetration of bone and lung makes the drug useful for treatment of osteomyelitis, septic arthritis and Gram-negative bacterial pneumonia. Urinary excretion makes the drug useful for treatment of urinary tract infection, and high concentrations in the liver make enrofloxacin a first line choice for the treatment of cholangiohepatitis (Peek and Divers 2000). Excellent efficacy against *Staphylococcus* spp. makes enrofloxacin a useful drug for treating superficial pyoderma and cellulitis. However, in human medicine fluoroquinolones have been associated with an increased incidence of MRSA infection and hence their use should be carefully considered (Weber *et al.* 2003). Enrofloxacin also appears to have good activity against *Corynebacterium pseudotuberculosis*. In conjunction with its good intracellular penetration, this property may make it a useful drug for treating internal abscesses. Distal limb perfusion with enrofloxacin has been used successfully to treat septic arthritis; however, its propensity to cause tissue irritation may limit its use (Parra-Sanchez *et al.* 2006).

Adverse effects

1. Fluoroquinolones cause noninflammatory arthropathy in immature animals (Specht and Frederick 1991). Signs include joint swelling and lameness, reflecting disruption of the extracellular matrix of collagen, and resultant erosions/blisters on weightbearing surfaces of articular cartilage. Foals appear to be highly susceptible to these adverse effects, particularly when they are weightbearing and active (Specht and Frederick 1991).
2. Weakening and rupture of tendons, particularly the Achilles tendon, has been reported in man during treatment with fluoroquinolones. Experimental studies suggest that fluoroquinolones have an adverse effect on equine tendon fibres (Yoon *et al.* 2004). Mild plantar desmitis and superficial digital flexor tendonitis have been reported in adults receiving high doses (Bertone *et al.* 1998).
3. Ataxia and other neurological signs have been noted during or following rapid i.v. bolus administration (Bertone *et al.* 1998). Thus, a slow rate of i.v. administration of enrofloxacin formulations is recommended
4. Intramuscular injection is not recommended because it causes unacceptable tissue reactions (Kaartinen *et al.* 1997).
5. Oral enrofloxacin, especially in the paste formulation, has been associated with severe oral ulceration (Epstein *et al.* 2004).
6. Enrofloxacin, especially in oral formulation, has been associated with colitis.

Tetracyclines (oxytetracycline and doxycycline)

Mode of action

Tetracyclines inhibit bacterial protein synthesis by reversible binding to the 30S ribosomal subunit (Giguere *et al.* 2006). Uptake into cells is via active carrier-mediated transport. Tetracyclines are generally considered to be bacteriostatic, but may be bactericidal at high concentrations.

Spectrum of activity

Tetracyclines have a broad spectrum of activity that includes many Gram-positive and Gram-negative aerobes, with the exception of *Proteus* spp. and *Pseudomonas* spp. Activity against enterococci, streptococci and staphylococci is variable. Anaerobic coverage is generally good, but both *Bacteroides* spp. and *Clostridium* spp. have a variable susceptibility (Giguere *et al.* 2006). Ehrlichial, anaplasmal and rickettsial organisms are highly susceptible (Madigan and Pusterla 2000).

Dosage

- Oxytetracycline: 5–10 mg/kg bwt i.v. q. 12 h.
- Doxycycline: 10 mg/kg bwt *per os* q. 12 h.

Pharmacokinetics and pharmacodynamics

Tetracyclines are well distributed to most tissues, with the exception of the CNS. After i.v. administration of oxytetracycline therapeutic concentrations can be detected in peritoneal and synovial fluid and urine (Brown *et al.* 1981). After oral administration of doxcycline to foals therapeutic concentrations can be detected in peritoneal and synovial fluid, as well as in broncho-alveolar lavage cells and urine (Womble *et al.* 2007).

Oral bioavailability of oxytetracyline is poor (White and Prior 1982) and associated with disturbance of GI flora, thereby precluding the oral route of administration. Bioavailability of doxycycline dosed at 10 mg/kg bwt *per os* appears to be adequate in foals (Womble *et al.* 2007) but is more variable in adult horses, leading researchers to suggest that a dose of 20 mg/kg bwt is necessary to achieve therapeutic serum concentrations (Davis *et al.* 2006b). Plasma protein binding of oxytetracycline is approximately 50% (Pilloud 1973) and close to 90% for doxycycline.

Oxytetracycline undergoes significant entero-hepatic recycling and is finally eliminated in the urine via glomerular filtration. Doxycycline is primarily excreted in the faeces (Giguere *et al.* 2006).

Indications

Oxytetracyline is indicated for the treatment of anaplasmosis (*Anaplasma phagocytophilum*) (Madigan and Pusterla 2000), Potomac horse fever (*Neorickettsia risticii*) (Palmer 1993), Lyme disease (*Borrelia burgdorferi*) (Chang *et al.* 2005) and leptospirosis (Bernard 1993). Oxytetracycline is also indicated occasionally as a broad spectrum antimicrobial for the treatment of other generalised bacterial infections. Its use is limited by concerns over adverse side effects, the need for i.v. dosing and widespread resistance. Tetracyclines have been used successfully to treat proliferative enteropathy in foals caused by *Lawsonia intracellularlis* (Sampieri *et al.* 2006).

Doxycycline can be used as an alternative to i.v. oxytetracyline for treating the above conditions. The oral route of administration and lower risk of adverse renal side effects make doxycycline attractive for the treatment of generalised or focal bacterial infection, although effectiveness in adult horses is limited by variable bioavailability and widespread bacterial resistance. Therapeutic concentrations are achieved in broncho-alveolar lavage fluid of foals, suggesting that doxycycline may be useful for treating lower respiratory disease caused by β-haemolytic streptococci and possibly *Rhodococcus* spp. (Womble *et al.* 2007).

There is much interest in the use of doxcycline for its nonantibacterial effects, which include attenuation of matrix metalloprotease activity, anti-fibrotic, anti-collagenase and anti-inflammatory effects (Koivunen *et al.* 1997; Arnoczky *et al.* 2004; Fujita *et al.* 2006). This may give doxycycline a place in the treatment for pulmonary fibrosis, recurrent airway obstruction and other conditions. Oxytetracycline is also used for the treatment of flexural limb deformity in foals (Kasper *et al.* 1995).

Adverse effects

1. Renal tubular necrosis can occur following i.v. administration of oxytetracycline, particularly when administered to animals that are hypovolaemic, endotoxaemic, haemoglobinuric or myoglobinuric (Riond and Riviere 1989; Vivrette *et al.* 1993).
2. Rapid i.v. administration of oxytetracycline can result in hypotension and collapse, likely mediated via calcium chelation and neuromuscular blockade of the myocardium (Gyrd-Hansen *et al.* 1981). Intravenous use of doxycycline is contraindicated because it results in fatal cardiovascular effects (Riond *et al.* 1992).
3. Tetracyclines bind to calcium and are deposited in bone and teeth, leading to discolouration (Giguere *et al.* 2006).
4. Oxytetracycline disturbs GI flora, sometimes leading to fatal antimicrobial-associated colitis (Andersson *et al.* 1971; Baker and Leyland 1973; Cook 1973; Owen *et al.* 1983; Keir *et al.* 1999). This risk is reduced by using appropriate doses and avoiding use in anorexic, highly stressed individuals.
5. Intramuscular use of long acting preparations has been associated with severe muscle reactions and is not recommended (Dowling and Russell 2000).

Chloramphenicol

Mode of action

Chloramphenicol is a bacteriostatic antimicrobial that binds irreversibly to the 50S ribosomal subunit, thereby inhibiting peptidyl transferase and bacterial protein synthesis.

Spectrum of activity

Chloramphenicol has a very wide spectrum of activity that includes Gram-positive and Gram-negative aerobes and anaerobes. Mycobacteria are resistant to chloramphenicol, and many Gram-negative bacteria acquire plasmid-mediated resistance with time (Giguere *et al.* 2006).

Dosage

- Chloramphenicol palmitate 30–50 mg/kg bwt *per os* q. 6–8 h.
- Chloramphenicol sodium succinate (if available) 25–50 mg/kg bwt i.v. q. 6–8 h.

Pharmacokinetics and pharmacodynamics

Chloramphenicol is highly lipid soluble and distributes widely throughout the body. Therapeutic concentrations are achieved in many tissues, including liver, kidney, synovial fluid, peritoneal fluid and CSF (Gronwall *et al.* 1986).

Oral bioavailability in foals is high at 83% (Brumbaugh *et al.* 1983). Bioavailability in adults is lower and more variable (Gronwall *et al.* 1986) and there is some evidence that repeated administration results in progressively lower serum concentrations. The short elimination half-life of the drug following i.v. administration, and expense, limit i.v. use (Brown *et al.* 1984).

Chloramphenicol is eliminated by hepatic metabolism following conjugation with glucoronic acid. Inactive metabolites are excreted in the urine (Giguere *et al.* 2006). The elimination half-life is prolonged in newborn foals due to immaturity of hepatic metabolic pathways (Adamson *et al.* 1991).

Indications

Chloramphenicol is used for the treatment of many bacterial infections, including pneumonia, peritonitis, internal abscess, otitis media/interna or cellultis, in which broad spectrum antibiosis is required. Its ability to penetrate the blood-brain barrier provides an indication for the treatment of a variety of CNS disorders such as cerebral abscess or meningitis (Pellegrini-Masini and Livesey 2006). Its bacteriostatic mode of action typically precludes its use as a first-line choice when rapid bacterial killing is required.

Adverse effects

1. Bone marrow depression can occur in human patients who come into contact with the drug. Idiosyncratic fatal aplastic anaemia has been reported at a frequency of between 1:25,000 and 1:60,000 individuals who use or contact the drug (Del Giacco *et al.* 1981; Page 1991). This effect is not dose related; consequently, chloramphenicol use is banned in farm animals in most countries, and in all animals in others. Personnel handling the drug should be advised to wear gloves, a mask and eye protection.
2. Dose-dependent suppression of protein synthesis can occur, leading to anaemia and pancytopenia (Giguere *et al.* 2006).
3. Chloramphenicol use can decrease the clearance of other drugs, including phenylbutazone, phenytoin, barbiturates and xylazine (Burrows *et al.* 1989; Grubb *et al.* 1997).
4. Chloramphenicol may suppress antibody production, hence concurrent vaccination is not recommended (Giguere *et al.* 2006).

Metronidazole

Mode of action

Metronidazole, like other nitroimidazoles, is a bactericidal antimicrobial that acts by causing extensive breakage in DNA strands and inhibition of the DNA repair enzyme, DNAase 1 (Giguere *et al.* 2006).

Spectrum of activity

The narrow spectrum of activity includes almost all anaerobic bacteria and many protozoa.

Dosage

- 15 mg/kg bwt *per os* q. 8 h for clostridial enteritis.
- 20 mg/kg bwt *per os* or *per rectum* q. 8 h for other anaerobic infections.
- 20 mg/kg bwt i.v. q. 8 h.

Pharmacokinetics and pharmacodynamics

Metronidazole is widely distributed in the body and penetrates tissues well (Sweeney *et al.* 1986; Baggot *et al.* 1988; Specht *et al.* 1992; Steinman *et al.* 2000). Metronidazole can be detected in bone, peritoneal and synovial fluid, abscesses, and the CNS following oral or i.v. administration.

Oral bioavailability is high and absorption is rapid (Sweeney *et al.* 1986; Baggot *et al.* 1988; Specht *et al.* 1992; Steinman *et al.* 2000). Administration *per rectum* can be used in horses in which oral administration is contraindicated, although serum concentrations are lower than after oral administration (Garber *et al.* 1993; Steinman *et al.* 2000).

Elimination is via hepatic metabolism followed by urinary excretion of active drug and inactive metabolites.

Indications

The major indication for use of metronidazole in horses is the treatment of infections, such as clostridial myositis, caused by anaerobic bacteria or, in combination with other antibiotics, treatment of polymicrobic infections such as pleuropneumonia that may involve anaerobic bacteria (Sweeney *et al.* 1991). Oral use for treating colitis caused by *Clostridium* spp. (McGorum *et al.* 1998; Magdesian *et al.* 2002) and topical use to treat thrush and canker are additional indications.

Adverse effects

1. Neurological side effects characterised by depression, weakness, ataxia, vestibular signs, seizures and peripheral neuropathy have been observed on occasion in horses treated concurrently with metronidazole and other drugs (Bertone and Horspool 2004).
2. Anorexia can occur after oral administration, most often related to the bad taste (Sweeney *et al.* 1991). Rinsing out the mouth with water 15–30 min after administration often helps overcome this problem.
3. Nitroimidazoles have been shown to be carcinogenic in laboratory animals (Giguere *et al.* 2006).
4. Metronidazole has been inconclusively associated with teratogenesis in pregnant women and hence it should be used cautiously in the first trimester in pregnant mares.

Vancomycin

Mode of action

Vancomycin is a bactericidal antimicrobial that interferes with the synthesis of bacterial cell wall peptidoglycan.

Spectrum of activity

Vancomycin is active against *Clostridium* spp. and also has a narrow Gram-positive aerobic spectrum that includes many resistant staphylococcal and enterococcal organisms. Most Gram-negative organisms are resistant to vancomycin.

Dosage

- 4.5–7.5 mg/kg bwt i.v. q. 8 h.
- 4 mg/kg bwt loading dose, 2 mg/kg bwt *per os* q. 8 h for treating enteric clostridiosis.

Pharmacokinetics and pharmacodynamics

Vancomycin has relatively poor tissue distribution, but therapeutic concentrations can be detected in synovial fluid after i.v. administration (Orsini *et al.* 1992). The primary route of excretion is renal via glomerular filtration (Giguere *et al.* 2006). Oral bioavailability is poor; therefore, oral administration is used only for treating enteric metronidazole-resistant clostridial infection.

TABLE 1: Summary of commonly used antimicrobial agents

Drug	Class	Gram + spectrum	Gram - spectrum	Anaerobic spectrum	Dose	Dosage interval (h)	Route	Site of effect	Adverse effects	Propensity to cause antibiotic induced-colitis	Cidal vs. static	Time or concentration dependent
Procaine penicillin G	β-lactam	+++	+	++	22,000 iu/kg bwt	12–24	i.m.	PBPs, cell wall synthesis	Procaine reactions allergy, myositis haemolytic anaemia	+	Cidal	Time
Sodium or potassium penicillin G	β-lactam	+++	+	++	22,000-44,000 iu/kg bwt	4-6	i.v.	PBPs, cell wall synthesis	Allergy, agitation mild colic	+	Cidal	Time
Ampicillin sodium	β-lactam	++	++	++	10–40 mg/kg bwt	6–8	i.v.	PBPs, cell wall synthesis		+	Cidal	Time
Ceftiofur	β-lactam	+++	+++	++	Adults 2.2 mg/kg bwt Foals 5–10 mg/kg bwt	12–24	i.m., i.v., subcut.	PBPs, cell wall synthesis	Myositis	+	Cidal	Time
Cefotaxime	β-lactam	+++	+++	++	40 mg/kg bwt	6	i.v.	PBPs, cell wall synthesis		+	Cidal	Time
Gentamicin	Aminoglycoside	+/-	+++		6.6 mg/kg bwt	24	i.v.	30S subunit, protein synthesis	Nephrotoxicity ototoxicity	+/-	Cidal	Concentration
Amikacin	Aminoglycoside		+++		21–25 mg/kg bwt	24	i.v.	30S subunit, protein synthesis	Nephrotoxicity	+/-	Cidal	Concentration
Trimethoprim sulphamethoxale/ sulphadiazine	Potentiated sulphonamide	+++	+++	++	30 mg/kg bwt 15–24 mg/kg bwt	12 12	*per os* i.v.	Folate synthesis	Neutropenia ataxia, arrhythmias, death (i.v.)	+	Cidal	Concentration
Rifampin	Rifamycin	+++	+	++	5 mg/kg bwt	12	*per os*	RNA polymerase	Orange discolouration	+	Cidal	Concentration
Erythromycin	Macrolide	+++	+	+	25 mg/kg bwt	6–8	*per os*	50S subunit, protein synthesis	Colitis in mares hyperthermia	+	Static	Concentration
Azithromycin	Macrolide	+++	+	+	10 mg/kg bwt	24	*per os*	50S subunit, protein synthesis	Colitis in mares hyperthermia	+	Static	Concentration
Clarithromycin	Macrolide	+++	++	++	7.5 mg	12	*per os*	50S subunit, protein synthesis	Colitis in mares hyperthermia	+	Static	Concentration
Enrofloxacin	Fluoroquinolone	+	+++		5–7.5 mg/kg bwt	24	*per os*, i.v.	DNA gyrase, DNA supercoiling	Arthropathy oral ulceration neurological signs tendon rupture	+	Cidal	Time
Oxytetracycline	Tetracycline	+++	+++	+++	5–10 mg/kg bwt	12	i.v.	30S subunit, protein synthesis	Renal tubular necrosis hypotension, collapse bone/tooth discolouration	+	Static	Concentration
Doxycycline	Tetracycline	+++	+++	+++	10 mg/kg bwt	12	*per os*	30S subunit, protein synthesis	Bone/tooth discolouration	+	Static	Concentration
Chloramphenicol		+++	+++	+++	30–50 mg/kg bwt	8	*per os*	30S subunit, protein synthesis	Aplastic anaemia in man anaemia and pancytopenia	+/-	Static	Concentration
Metronidazole	Nitroimidazole			+++	15–20 mg/kg bwt	8	*per os*, i.v.	DNA breakage and inhibition of repair	Neurological signs anorexia carcinogenic?	+	Cidal	Concentration
Vancomycin	Glycopeptide	+++			4.5–7.5 mg/kg bwt 4 mg/kg bwt once then 2 mg/kg bwt	8 8	i.v. *per os*	Cell wall synthesis	Tissue irritant ototoxicity? nephrotoxicity?	+/-	Cidal	Concentration

Indications

Few indications exist for use of vancomycin in veterinary medicine, and its use is controversial because vancomycin is considered a last resort treatment for methicillin-resistant staphylococcal infection in man. Vancomycin has been used in horses to treat enteritis caused by metronidazole-resistant strains of *Clostrium difficil*e and infections caused by methicillin-resistant staphylococci and enterococci (Orsini *et al.* 2005b).

Adverse effects

1. The i.v. formulation is highly irritant and should be administered over at least 30 min.
2. Ototoxicity and nephrotoxicity have been reported in man.

Conclusion

A summary of the major antimicrobials used in horses is provided in **Table 1**. This should aid the veterinarian in selecting an appropriate antimicrobial to treat a confirmed or suspected bacterial infection by highlighting the spectrum of activity, mechanism of action, route of administration, dosage and dosing interval, and important potential side effects of the major antimicrobials. A basic understanding of the mechanisms of actions, advantages and limitations of each class of antimicrobials will aid the practioner in the rational selection of antimicrobials for a wide variety of clinical problems.

References

Adamson, P.J., Wilson, W.D., Baggot, J.D., Hietala, S.K. and Mihalyi, J.E. (1991) Influence of age on the disposition kinetics of chloramphenicol in equine neonates. *Am. J. vet. Res.* **52**, 426-431.

Adamson, P.J., Wilson, W.D., Hirsh, D.C., Baggot, J.D. and Martin, L.D. (1985) Susceptibility of equine bacterial isolates to antimicrobial agents. *Am. J. vet. Res.* **46**, 447-450.

Amyes, S.G. and Smith, J.T. (1974) Trimethoprim-sensitivity testing and thymineless mutants. *J. med. Microbiol.* **7**, 143-153.

Andersson, G., Ekman, L., Mansson, I., Persson, S., Rubarth, S. and Tufvesson, G. (1971) Lethal complications following administration of oxytetracycline in the horse. *Nord. Vet.* **23**, 9-22.

Arnoczky, S.P., Lavagnino, M., Gardner, K.L., Tian, T., Vaupel, Z.M. and Stick, J.A. (2004) *In vitro* effects of oxytetracycline on matrix metalloproteinase-1 mRNA expression and on collagen gel contraction by cultured myofibroblasts obtained from the accessory ligament of foals. *Am. J. vet. Res.* **65**, 491-496.

Baggot, J.D., Wilson, W.D. and Hietala, S. (1988) Clinical pharmacokinetics of metronidazole in horses. *J. vet. Pharmacol. Therap.* **11**, 417-420.

Baker, J.R. and Leyland, A. (1973) Diarrhoea in the horse associated with stress and tetracycline therapy. *Vet. Rec.* **93**, 583-584.

Barr, B.S. (2006) *Rhodococcus equi* pneumonia in a foal. *Vet. Clin. N. Am.: Equine Pract.* **22**, 239-246.

Båverud, V., Franklin, A., Gunnarsson, A., Gustafsson, A. and Hellander-Edman, A. (1998) *Clostridium difficile* associated with acute colitis in mares when their foals are treated with erythromycin and rifampicin for *Rhodococcus equi* pneumonia. *Equine vet. J.* **30**, 482-488.

Baverud, V., Gustafsson, A., Franklin, A., Aspan, A. and Gunnarsson, A. (2003) *Clostridium difficile*: prevalence in horses and environment, and antimicrobial susceptibility. *Equine vet. J.* **35**, 465-471.

Bernard, W.V. (1993) Leptospirosis. *Vet. Clin. N. Am.: Equine Pract.* **9**, 435-444.

Bertone, A.L., Tremaine, W.H., Macoris, D.G., Simmons, E.J., Ewert, K.M. and Weisbrode, S.E. (1998) Effect of the chronic systemic administration of an injectable enrofloxcain solution on physical, musculoskeletal, and histologic parameters in adult horses. *Proc. Am. Ass. equine Practnrs.* **44**, 252-253.

Bertone, J. and Horspool, L (2004) *Equine Clinical Pharmacology*, Elsevier Health Sciences.

Blue, J.T., Dinsmore, R.P. and Anderson, K.L. (1987) Immune-mediated hemolytic anemia induced by penicillin in horses. *Cornell Vet.* **77**, 263-276.

Bogan, J.A., Galbraith, A., Baxter, P., Ali, N.M. and Marriner, S.E. (1984) Effect of feeding on the fate of orally administered phenylbutazone, trimethoprim and sulphadiazine in the horse. *Vet. Rec.* **115**, 599-600.

Bousquet-Melou, A., Bernard, S., Schneider, M. and Toutain, P.L. (2002) Pharmacokinetics of marbofloxacin in horses. *Equine vet. J.* **34**, 366-372.

Brown, M.P., Gronwall, R. and Castro, L. (1988) Pharmacokinetics and body fluid and endometrial concentrations of trimethoprim-sulfamethoxazole in mares. *Am. J. vet. Res.* **49**, 918-922.

Brown, M.P., Kelly, R.H., Gronwall, R.R. and Stover, S.M. (1984) Chloramphenicol sodium succinate in the horse: serum, synovial, peritoneal, and urine concentrations after single-dose intravenous administration. *Am. J. vet. Res.* **45**, 578-580.

Brown, M.P., Stover, S.M., Kelly, R.H. and Farver, T.B. (1982) Gentamicin sulfate in the horse: serum, synovial, peritoneal, and urine concentrations after single dose intramuscular administration. *J. vet. Pharmacol. Therap.* **5**, 119-122.

Brown, M.P., Stover, S.M., Kelly, R.H., Farver, T.B. and Knight, H.D. (1981) Oxytetracycline hydrochloride in the horse: serum, synovial, peritoneal and urine concentrations after single dose intravenous administration. *J. vet. Pharmacol. Therap.* **4**, 7-10.

Brumbaugh, G.W., Martens, R.J., Knight, H.D. and Martin, M.T. (1983) Pharmacokinetics of chloramphenicol in the neonatal horse. *J. vet. Pharmacol. Therap.* **6**, 219-227.

Burrows, G.E., MacAllister, C.G., Beckstrom, D.A. and Nick, J.T. (1985) Rifampin in the horse: comparison of intravenous, intramuscular, and oral administrations. *Am. J. vet. Res.* **46**, 442-446.

Burrows, G.E., MacAllister, C.G., Tripp, P. and Black, J. (1989) Interactions between chloramphenicol, acepromazine, phenylbutazone, rifampin and thiamylal in the horse. *Equine vet. J.* **21,** 34-38.

Burrows, G.E., MacAllister, C.G., Ewing, P., Stair, E. and Burrows, S.L. (1992) Rifampin disposition in the horse: effects of repeated dosage of rifampin or phenylbutazone. *J. vet. Pharmacol. Therap.* **15**, 305-308.

Cervantes, C.C., Brown, M.P., Gronwall, R. and Merritt, K. (1993) Pharmacokinetics and concentrations of ceftiofur sodium in body fluids and endometrium after repeated intramuscular injections in mares. *Am. J. vet. Res.* **54**, 573-575.

Chang, Y.F., Ku, Y.W., Chang, C.F., Chang, C.D., McDonough, S.P., Divers, T., Pough, M. and Torres, A. (2005) Antibiotic treatment of experimentally Borrelia burgdorferi-infected ponies. *Vet. Microbiol.* **107**, 285-294.

Chapman, C.B., Courage, P., Nielsen, I.L., Sitaram, B.R. and Huntington, P.J. (1992) The role of procaine in adverse reactions to procaine penicillin in horses *Aust. vet. J.* **69**, 129-133 [erratum *Aust. vet. J.* **69**, 193].

Cook, W. (1973) Diarrhoea in the horse associated with stress and tetracycline therapy. *Vet. Rec.* **93**, 15-17.

Davis, J.L., Papich, M.G. and Weingarten, A. (2006a) The pharmacokinetics of orbifloxacin in the horse following oral and intravenous administration. *J. vet. Pharmacol. Therap.* **29**, 191-197.

Davis, J.L., Salmon, J.H. and Papich, M.G. (2006b) Pharmacokinetics and tissue distribution of doxycycline after oral administration of single and multiple doses in horses. *Am. J. vet. Res.* **67**, 310-316.

Del Giacco, G.S., Petrini, M.T., Jannelli, S. and Carcassi, U. (1981) Fatal bone marrow hypoplasia in a shepherd using chloramphenicol spray. *Lancet* **1**, 945.

Dowling, P.M. and Russell, A.M. (2000) Pharmacokinetics of a long-acting oxytetracycline-polyethylene glycol formulation in horses. *J. vet. Pharmacol. Therap.* **23**, 107-110.

Durr, A. (1976) Comparison of the pharmacokinetics of penicillin G and ampicillin in the horse. *Res. vet. Sci.* **20**, 24-29.

Ellis, J.M., Rivera, L., Reyes, G., Castillo, F., Marte, P., Tejada, M. and Salazar, J.C. (2007) Cefepime cerebrospinal fluid concentrations in neonatal bacterial meningitis. *Ann. Pharmacotherapy* **41**, 900-901.

Ensink, J.M., Bosch, G. and van Duijkeren, E. (2005) Clinical efficacy of prophylactic administration of trimethoprim/sulfadiazine in a *Streptococcus equi* subsp. *zooepidemicus* infection model in ponies. *J. vet. Pharmacol. Therap.* **28**, 45-49.

Ensink, J.M., Smit, J.A. and van Duijkeren, E. (2003) Clinical efficacy of trimethoprim/sulfadiazine and procaine penicillin G in a *Streptococcus equi* subsp. *zooepidemicus* infection model in ponies. *J. vet. Pharmacol. Therap.* **26**, 247-252.

Epstein, K., Cohen, N., Boothe, D., Nieuwoudt, C. and Chandler, J. (2004) Pharmacokinetics, stability, and retrospective analysis of use of an oral gel formulation of the bovine injectable enrofloxacin in horses. *Vet. Ther.* **5**, 155-167.

Farnsworth, K.D., White, N.A., 2nd and Robertson, J. (2001) The effect of implanting gentamicin-impregnated polymethylmethacrylate beads in the tarsocrural joint of the horse. *Vet. Surg.* **30**, 126-131.

Feary, D.J., Gebhart, C.J. and Pusterla, N. (2007) Lawsonia intracellularis proliferative enteropathy in a foal. *Schweizer Arch. Tierheilk.* **149**, 129-133.

Fernandez-Varon, E., Ayala, I., Marin, P., Carrion, A., Martos, N., Escudero, E. and Carceles, C.M. (2006) Pharmacokinetics of danofloxacin in horses after intravenous, intramuscular and intragastric administration. *Equine vet. J.* **38**, 342-346.

Folz, S.D., Hanson, B.J., Griffin, A.K., Dinvald, L.L., Swerczek, T.W., Walker, R.D. and Foreman, J.H. (1992) Treatment of respiratory infections in horses with ceftiofur sodium. *Equine vet. J.* **24**, 300-304 [erratum *Equine vet. J.* **24**, 366].

Fujita, M., Ye, Q., Ouchi, H., Harada, E., Inoshima, I., Kuwano, K. and Nakanishi, Y. (2006) Doxycycline attenuated pulmonary fibrosis induced by bleomycin in mice. *Antimicrob. Agents Chemotherapy* **50**, 739-743.

Garber, J.L., Brown, M.P., Gronwall, R.R. and Merritt, K. (1993) Pharmacokinetics of metronidazole after rectal administration in horses. *Am. J. vet. Res.* **54**, 2060-2063.

Gardner, S.Y. and Papich, M.G. (2001) Comparison of cefepime pharmacokinetics in neonatal foals and adult dogs. *J. vet. Pharmacol. Therap.* **24**, 187-192.

Giguere, S. and Belanger, M. (1997) Concentration of enrofloxacin in equine tissues after long term oral administration. *J. vet. Pharmacol. Therap.* **20**, 402-404.

Giguere, S., Sweeney, R.W. and Belanger, M. (1996) Pharmacokinetics of enrofloxacin in adult horses and concentration of the drug in serum, body fluids, and endometrial tissues after repeated intragastrically administered doses. *Am. J. vet. Res.* **57**, 1025-1030.

Giguere, S., Prescott, J.F., Baggot, J.D. and Walker, R.D. (2006) *Antimicrobial Therapy in Veterinary Medicine*, 4th edn., Iowa State University Press, Ames, Iowa. p 606.

Giguere, S., Jacks, S., Roberts, G.D., Hernandez, J., Long, M.T. and Ellis, C. (2004) Retrospective comparison of azithromycin, clarithromycin, and erythromycin for the treatment of foals with *Rhodococcus equi* pneumonia. *J. vet. intern. Med.* **18**, 568-573.

Golenz, M.R., Wilson, W.D., Carlson, G.P., Craychee, T.J., Mihalyi, J.E. and Knox, L. (1994) Effect of route of administration and age on the pharmacokinetics of amikacin administered by the intravenous and intraosseous routes to 3 and 5-day-old foals. *Equine vet. J.* **26**, 367-373.

Green, S.L., Little, C.B., Baird, J.D., Tremblay, R.R. and Smith-Maxie, L.L. (1994) Tetanus in the horse: a review of 20 cases (1970 to 1990). *J. vet. intern. Med.* **8**, 128-132.

Green, S.L., Mayhew, I.G., Brown, M.P., Gronwall, R.R. and Montieth, G. (1990) Concentrations of trimethoprim and sulfamethoxazole in cerebrospinal fluid and serum in mares with and without a dimethyl sulfoxide pretreatment. *Can. J. vet. Res.* **54**, 215-222.

Green, S.L., Mayhew, I.G., Brown, M.P., Gronwall, R.R. and Montieth, G. (1992) Concentrations of trimethoprim and sulfamethoxazole in cerebrospinal fluid and serum in mares with and without a dimethyl sulfoxide pretreatment. *J. vet. Pharmacol. Therap.* **15**, 309-313.

Gronwall, R., Brown, M.P., Merritt, A.M. and Stone, H.W. (1986) Body fluid concentrations and pharmacokinetics of chloramphenicol given to mares intravenously or by repeated gavage. *Am. J. vet. Res.* **47**, 2591-2595.

Grubb, T.L., Muir, W.W., 3rd, Bertone, A.L., Beluche, L.A. and Garcia-Calderon, M. (1997) Use of yohimbine to reverse prolonged effects of xylazine hydrochloride in a horse being treated with chloramphenicol. *J. Am. vet. med. Ass.* **210**, 1771-1773.

Gustafsson, A., Baverud, V., Gunnarsson, A., Horn af Rantzien, M., Lindholm, A. and Franklin, A. (1997) The association of erythromycin ethylsuccinate with acute colitis in horses in Sweden. *Equine vet. J.* **29**, 314-318.

Gyrd-Hansen, N., Rasmussen, F. and Smith, M. (1981) Cardiovascular effects of intravenous administration of tetracycline in cattle. *J. vet. Pharmacol. Therap.* **4**, 15-25.

Haines, G.R., Brown, M.P., Gronwall, R.R. and Merritt, K.A. (2000) Serum concentrations and pharmacokinetics of enrofloxacin after intravenous and intragastric administration to mares. *Can. J. vet. Res.* **64**, 171-177.

Henson, S. and Barton, M. (2001) Bacterial isolates and antibiotic sensitivity patterns from septicemic neonatal foals: a 15 year retrospective study (1986-2000). In: *Dorothy R. Havemeyer Foundation Neonatal Septicemia Workshop*, Havemeyer Foundation, Talloires, France.

Hirsh, D.C. and Jang, S.S. (1987) Antimicrobic susceptibility of bacterial pathogens from horses. *Vet. Clin. N. Am.: Equine Pract.* **3**, 181-190.

Horspool, L.J.I. and McKellar, Q.A. (1995) Disposition of penicillin G sodium following intravenous and oral administration to *Equidae*. *Br. Vet. J.* **151**, 401-412.

Jacks, S., Giguere, S., Gronwall, P.R., Brown, M.P. and Merritt, K.A. (2001) Pharmacokinetics of azithromycin and concentration in body fluids and bronchoalveolar cells in foals. *Am. J. vet. Res.* **62**, 1870-1875.

Jacks, S.S., Giguere, S. and Nguyen, A. (2003) In vitro susceptibilities of *Rhodococcus equi* and other common equine pathogens to azithromycin, clarithromycin, and 20 other antimicrobials. *Antimicrob. Agents Chemotherapy* **47**, 1742-1745.

Jaglan, P.S., Roof, R.D., Yein, F.S., Arnold, T.S., Brown, S.A. and Gilbertson, T.J. (1994) Concentration of ceftiofur metabolites in

the plasma and lungs of horses following intramuscular treatment. *J. vet. Pharmacol. Therap.* **17**, 24-30.

Jones, S.L., Wilson, W.D. and Milhalyi, J.E. (1998) Pharmacokinetics of gentamicin in healthy adult horses during intravenous fluid administration. *J. vet. Pharmacol. Therap.* **21**, 247-249.

Kaartinen, L., Panu, S. and Pyorala, S. (1997) Pharmacokinetics of enrofloxacin in horses after single intravenous and intramuscular administration. *Equine vet. J.* **29**, 378-381.

Karlowsky, J.A., Zhanel, G.G., Davidson, R.J. and Hoban, D.J. (1994) Once-daily aminoglycoside dosing assessed by MIC reversion time with *Pseudomonas aeruginosa. Antimicrob. Agents Chemotherapy* **38**, 1165-1168.

Kasper, C.A., Clayton, H.M., Wright, A.K., Skuba, E.V. and Petrie, L. (1995) Effects of high doses of oxytetracycline on metacarpophalangeal joint kinematics in neonatal foals. *J. Am. vet. med. Ass.* **207**, 71-73.

Keir, A.A., Stampfli, H.R. and Crawford, J. (1999) Outbreak of acute colitis on a horse farm associated with tetracycline-contaminated sweet feed. *Can. vet. J.* **40**, 718-720.

Kohn, C.W., Sams, R., Kowalski, J.J., Powers, J. and Wallace, S. (1993) Pharmacokinetics of single intravenous and single and multiple dose oral administration of rifampin in mares. *J. vet. Pharmacol. Therap.* **16**, 119-131.

Koivunen, A.L., Maisi, P., Konttinen, Y.T., Prikk, K. and Sandholm, M. (1997) Collagenolytic activity and its sensitivity to doxycycline inhibition in tracheal aspirates of horses with chronic obstructive pulmonary disease. *Acta vet. Scand.* **38**, 9-16.

Lakritz, J., Wilson, W.D., Berry, C.R., Schrenzel, M.D., Carlson, G.P. and Madigan, J.E. (1993) Bronchointerstitial pneumonia and respiratory distress in young horses: clinical, clinicopathologic, radiographic, and pathological findings in 23 cases (1984-1989). *J. vet. intern. Med./Am. Coll. Vet. Intern. Med.* **7**, 277-288.

Lakritz, J., Wilson, W.D., Marsh, A.E. and Mihalyi, J.E. (2000a) Effects of prior feeding on pharmacokinetics and estimated bioavailability after oral administration of a single dose of microencapsulated erythromycin base in healthy foals. *Am. J. vet. Res.* **61**, 1011-1015.

Lakritz, J., Wilson, W.D., Marsh, A.E. and Mihalyi, J.E. (2000b) Pharmacokinetics of erythromycin estolate and erythromycin phosphate after intragastric administration to healthy foals. *Am. J. vet. Res.* **61**, 914-919.

Lakritz, J., Wilson, W.D., Watson, J.L., Hyde, D.M., Mihalyi, J. and Plopper, C.G. (1997) Effect of treatment with erythromycin on bronchoalveolar lavage fluid cell populations in foals *Am. J. vet. Res.* **58**, 56-61 [erratum *Am. J. vet. Res.* **58**, 337].

Langston, V.C., Sedrish, S. and Boothe, D.M. (1996) Disposition of single-dose oral enrofloxacin in the horse. *J. vet. Pharmacol. Therap.* **19**, 316-319.

Lescun, T.B., Vasey, J.R., Ward, M.P. and Adams, S.B. (2006) Treatment with continuous intrasynovial antimicrobial infusion for septic synovitis in horses: 31 cases (2000-2003). *J. Am. vet. med. Ass.* **228**, 1922-1929.

MacKay, R.J., Granstrom, D.E., Saville, W.J. and Reed, S.M. (2000) Equine protozoal myeloencephalitis. *Vet. Clin. N. Am.: Equine Pract.* **16**, 405-425.

Madigan, J.E. and Pusterla, N. (2000) Ehrlichial diseases. *Vet. Clin. N. Am.: Equine Pract.* **16**, 487-499, ix.

Magdesian, K.G., Wilson, W.D. and Mihalyi, J. (1997) Pharmacokinetics and nephrotoxicity of high dose, once daily administered amikacin in neonatal foals. *Proc. Am. Ass. equine Practnrs.* **43**, 396-397.

Magdesian, K.G., Hirsh, D.C., Jang, S.S., Hansen, L.M. and Madigan, J.E. (2002) Characterization of *Clostridium difficile* isolates from foals with diarrhea: 28 cases (1993-1997). *J. Am. vet. med. Ass.* **220**, 67-73.

Magdesian, K.G., Hogan, P.M., Cohen, N.D., Brumbaugh, G.W. and Bernard, W.V. (1998) Pharmacokinetics of a high dose of gentamicin administered intravenously or intramuscularly to horses. *J. Am. vet. med. Ass.* **213**, 1007-1011.

Mahrt, C.R. (1992) Safety of ceftiofur sodium administered intramuscularly in horses. *Am. J. vet. Res.* **53**, 2201-2205.

Marsh, P.S. and Palmer, J.E. (2001) Bacterial isolates from blood and their susceptibility patterns in critically ill foals: 543 cases (1991-1998). *J. Am. vet. med. Ass.* **218**, 1608-1610.

McConnico, R.S., Roberts, M.C. and Tompkins, M. (1992) Penicillin-induced immune-mediated hemolytic anemia in a horse. *J. Am. vet. med. Ass.* **201**, 1402-1403.

McGorum, B.C., Dixon, P.M. and Smith, D.G. (1998) Use of metronidazole in equine acute idiopathic toxaemic colitis. *Vet. Rec.* **142**, 635-638.

Meijer, M.C., van Weeren, P.R. and Rijkenhuizen, A.B. (2000) Clinical experiences of treating septic arthritis in the equine by repeated joint lavage: a series of 39 cases. *J. vet. Med.* **47**, 351-365.

Meyer, J.C., Brown, M.P., Gronwall, R.R. and Merritt, K. (1992) Pharmacokinetics of ceftiofur sodium in neonatal foals after intramuscular injection. *Equine vet. J.* **24**, 485-486.

Michelet, C., Avril, J.L., Arvieux, C., Jacquelinet, C., Vu, N. and Cartier, F. (1997) Comparative activities of new fluoroquinolones, alone or in combination with amoxicillin, trimethoprim-sulfamethoxazole, or rifampin, against intracellular *Listeria monocytogenes. Antimicrob. Agents Chemotherapy* **41**, 60-65.

Mills, M.L., Rush, B.R., St Jean, G., Gaughan, E.M., Mosier, D., Gibson, E. and Freeman, L. (2000) Determination of synovial fluid and serum concentrations, and morphologic effects of intraarticular ceftiofur sodium in horses. *Vet. Surg.* **29**, 398-406.

Nielsen, I.L., Jacobs, K.A., Huntington, P.J., Chapman, C.B. and Lloyd, K.C. (1988) Adverse reaction to procaine penicillin G in horses. *Aust. vet. J.* **65**, 181-185.

Nostrandt, A.C., Pedersoli, W.M., Marshall, A.E., Ravis, W.R. and Robertson, B.T. (1991) Ototoxic potential of gentamicin in ponies. *Am. J. vet. Res.* **52**, 494-498.

Olsen, L., Ingvast-Larsson, C., Brostrom, H., Larsson, P. and Tjalve, H. (2007) Clinical signs and etiology of adverse reactions to procaine benzylpenicillin and sodium/potassium benzylpenicillin in horses. *J. vet. Pharmacol. Therap.* **30**, 201-207.

Orsini, J.A., Ramberg, C.F., Jr., Benson, C.E., Dreyfuss, D.J., Vecchione, J.A. and Kunz, C.C. (1992) Vancomycin kinetics in plasma and synovial fluid following intravenous administration in horses. *J. vet. Pharmacol. Therap.* **15**, 351-363.

Orsini, J.A., Moate, P.J., Boston, R.C., Norman, T., Engiles, J., Benson, C.E. and Poppenga, R. (2005a) Pharmacokinetics of imipenem-cilastatin following intravenous administration in healthy adult horses. *J. vet. Pharmacol. Therap.* **28**, 355-361.

Orsini, J.A., Snooks-Parsons, C., Stine, L., Haddock, M., Ramberg, C.F., Benson, C.E. and Nunamaker, D.M. (2005b) Vancomycin for the treatment of methicillin-resistant staphylococcal and enterococcal infections in 15 horses. *Can. J. vet. Res.* **69**, 278-286.

Owen, R.A., Fullerton, J. and Barnum, D.A. (1983) Effects of transportation, surgery, and antibiotic therapy in ponies infected with *Salmonella*. *Am. J. vet. Res.* **44**, 46-50.

Page, S.W. (1991) Chloramphenicol 1. Hazards of use and the current regulatory environment. *Aust. vet. J.* **68**, 1-2.

Palmer, J.E. (1993) Potomac horse fever. *Vet. Clin. N. Am.: Equine Pract.* **9**, 399-410.

Parra-Sanchez, A., Lugo, J., Boothe, D.M., Gaughan, E.M., Hanson, R.R., Duran, S. and Belknap, J.K. (2006) Pharmacokinetics and pharmacodynamics of enrofloxacin and a low dose of amikacin administered via regional intravenous limb perfusion in standing horses. *Am. J. vet. Res.* **67**, 1687-1695.

Pedersoli, W.M., Belmonte, A.A., Purohit, R.C. and Ravis, W.R. (1980) Pharmacokinetics of gentamicin in the horse. *Am. J. vet. Res.* **41**, 351-354.

Peek, S.F. and Divers, T.J. (2000) Medical treatment of cholangiohepatitis and cholelithiasis in mature horses: 9 cases (1991-1998). *Equine vet. J.* **32**, 301-306.

Pellegrini-Masini, A. and Livesey, L.C. (2006) Meningitis and encephalomyelitis in horses. *Vet. Clin. N. Am.: Equine Pract.* **22**, 553-589, x.

Pille, F., De Baere, S., Ceelen, L., Dewulf, J., Croubels, S., Gasthuys, F., De Backer, P. and Martens, A. (2005) Synovial fluid and plasma concentrations of ceftiofur after regional intravenous perfusion in the horse. *Vet. Surg.* **34**, 610-617.

Pilloud, M. (1973) Pharmacokinetics, plasma protein binding and dosage of oxytetracycline in cattle and horses. *Res. vet. Sci.* **15**, 224-230.

Pratt, S.M., Spier, S.J., Carroll, S.P., Vaughan, B., Whitcomb, M.B. and Wilson, W.D. (2005) Evaluation of clinical characteristics, diagnostic test results, and outcome in horses with internal infection caused by *Corynebacterium pseudotuberculosis*: 30 cases (1995-2003). *J. Am. vet. med. Ass.* **227**, 441-448.

Pusterla, N., Whitcomb, M.B. and Wilson, W.D. (2007) Internal abdominal abscesses caused by *Streptococcus equi* subspecies *equi* in 10 horses in California between 1989 and 2004. *Vet. Rec.* **160**, 589-592.

Riond, J.L. and Riviere, J.E. (1989) Effects of tetracyclines on the kidney in cattle and dogs. *J. Am. vet. med. Ass.* **195**, 995-997.

Riond, J.L., Riviere, J.E., Duckett, W.M., Atkins, C.E., Jernigan, A.D., Rikihisa, Y. and Spurlock, S.L. (1992) Cardiovascular effects and fatalities associated with intravenous administration of doxycycline to horses and ponies. *Equine vet. J.* **24**, 41-45.

Riviere, J.E. and Coppoc, G.L. (1981) Selected aspects of aminoglycoside antibiotic nephrotoxicosis. *J. Am. vet. med. Ass.* **178**, 508-509.

Riviere, J.E., Coppoc, G.L., Hinsman, E.J., Carlton, W.W. and Traver, D.S. (1983) Species dependent gentamicin pharmacokinetics and nephrotoxicity in the young horse. *Fundam. Appl. Toxicol.* **3**, 448-457.

Rohdich, N., Zschiesche, E., Heckeroth, A., Wilhelm, C., Leendertse, I., Thomas, E. and Alumni, R.R. (2006) Treatment of septicemia and severe bacterial infections in foals with a new cefquinome formulation (Cobactan IV 4.5%): A field study. In: *Intervet Innovation GmBH*, Intervet, Germany.

Roussel, A.J., Hooper, R.N., Cohen, N.D., Bye, A.D., Hicks, R.J. and Schulze, J.L. (2003) Evaluation of the effects of penicillin G potassium and potassium chloride on the motility of the large intestine in horses. *Am. J. vet. Res.* **64**, 1360-1363.

Ruoff, W.W., Jr. and Sams, R.A. (1985) Pharmacokinetics and bioavailability of cephalothin in horse mares. *Am. J. vet. Res.* **46**, 2085-2090.

Salmon, S.A., Watts, J.L. and Yancey, R.J., Jr. (1996) *In vitro* activity of ceftiofur and its primary metabolite, desfuroylceftiofur, against organisms of veterinary importance. *J. vet. diag. Invest.* **8**, 332-336.

Samitz, E.M., Jang, S.S. and Hirsh, D.C. (1996) *In vitro* susceptibilities of selected obligate anaerobic bacteria obtained from bovine and equine sources to ceftiofur. *J. vet. diag. Invest.* **8**, 121-123.

Sampieri, F., Hinchcliff, K.W. and Toribio, R.E. (2006) Tetracycline therapy of *Lawsonia intracellularis* enteropathy in foals. *Equine vet. J.* **38**, 89-92.

Scheuch, E., Spieker, J., Venner, M. and Siegmund, W. (2007) Quantitative determination of the macrolide antibiotic tulathromycin in plasma and broncho-alveolar cells of foals using tandem mass spectrometry. *J. Chromatography* **850**, 464-470.

Slovis, N.M., Wilson, W.D., Stanley, S.D., Lakritz, J., Mihalyi, J. and Kollias-Baker, C. (2006) Comparative pharmacokinetics and bioavailability of ceftiofur in horses after intravenous, intramuscular, and subcutaneous administration. *Proc. Am. Ass. equine Practnrs.* **52**, 329-330.

Specht, T.E. and Frederick, G. (1991) Quinolone-induced arthropathy in immature *Equidae* [letter]. *J. Am. vet. med. Ass.* **198**, 516.

Specht, T.E., Brown, M.P., Gronwall, R.R., Rib, W.J. and Houston, A.E. (1992) Pharmacokinetics of metronidazole and its concentration in body fluids and endometrial tissues of mares. *Am. J. vet. Res.* **53**, 1807-1812.

Steinman, A., Gips, M., Lavy, E., Sinay, I. and Soback, S. (2000) Pharmacokinetics of metronidazole in horses after intravenous, rectal and oral administration. *J. vet. Pharmacol. Therap.* **23**, 353-357.

Stevenson, A.J., Weber, M.P., Todi, F., Young, L., Beaumier, P. and Kacew, S. (1992) Plasma elimination and urinary excretion of procaine after administration of different products to Standardbred mares. *Equine vet. J.* **24**, 118-124.

Stratton-Phelps, M., Wilson, W.D. and Gardner, I.A. (2000) Risk of adverse effects in pneumonic foals treated with erythromycin versus other antibiotics: 143 cases (1986-1996). *J. Am. vet. med. Ass.* **217**, 68-73.

Suarez-Mier, G., Giguere, S. and Lee, E.A. (2007) Pulmonary disposition of erythromycin, azithromycin, and clarithromycin in foals. *J. vet. Pharmacol. Therap.* **30**, 109-115.

Sustronck, B., Deprez, P., Muylle, E., Vermeersch, H., Vandenbossche, G. and Remon, J.P. (1995) Evaluation of the nebulisation of sodium ceftiofur in the treatment of experimental *Pasteurella haemolytica* bronchopneumonia in calves. *Res. vet. Sci.* **59**, 267-271.

Sweeney, C.R., Timoney, J.F., Newton, J.R. and Hines, M.T. (2005) *Streptococcus equi* infections in horses: guidelines for treatment, control, and prevention of strangles. *J. vet. intern. Med./Am. Coll. Vet. Intern. Med.* **19**, 123-134.

Sweeney, C.R., Soma, L.R., Beech, J., Reef, V. and Simmons, R. (1984) Pharmacokinetics of ticarcillin in the horse after intravenous and intramuscular administration. *Am. J. vet. Res.* **45**, 1000-1002.

Sweeney, R.W., Beech, J. and Simmons, R.D. (1988a) Pharmacokinetics of intravenously and intramuscularly administered ticarcillin and clavulanic acid in foals. *Am. J. vet. Res.* **49**, 23-26.

Sweeney, R.W., Beech, J., Simmons, R.D. and Soma, L.R. (1988b) Pharmacokinetics of ticarcillin and clavulanic acid given in combination to adult horses by intravenous and intramuscular routes. *J. vet. Pharmacol. Therap.* **11**, 103-108.

Sweeney, R.W., Sweeney, C.R. and Weiher, J. (1991) Clinical use of metronidazole in horses: 200 cases (1984-1989). *J. Am. vet. med. Ass.* **198**, 1045-1048.

Sweeney, R.W., Sweeney, C.R., Soma, L.R., Woodward, C.B. and Charlton, C.A. (1986) Pharmacokinetics of metronidazole given to horses by intravenous and oral routes. *Am. J. vet. Res.* **47**, 1726-1729.

Thomas, E., Thomas, V. and Wilhelm, C. (2006) Antibacterial activity of cefquinome against equine bacterial pathogens. *Vet. Microbiol.* **115**, 140-147.

Uboh, C.E., Soma, L.R., Luo, Y., McNamara, E., Fennell, M.A., May, L., Teleis, D.C., Rudy, J.A. and Watson, A.O. (2000) Pharmacokinetics of penicillin G procaine versus penicillin G potassium and procaine hydrochloride in horses. *Am. J. vet. Res.* **61**, 811-815.

van Duijkeren, E., Vulto, A.G. and van Miert, A.S. (1994) Trimethoprim/sulfonamide combinations in the horse: a review. *J. vet. Pharmacol. Therap.* **17**, 64-73.

Vermeersch, H., Vandenbossche, G., Remon, J.P., Samyn, W., Vandendriessche, K., Sustronck, B., Muylle, E. and Deprez, P. (1996) Pharmacokinetics of nebulized sodium ceftiofur in calves. *J. vet. Pharmacol. Therap.* **19**, 152-154.

Vivrette, S., Cowgill, L.D., Pascoe, J., Suter, C. and Becker, T. (1993) Hemodialysis for treatment of oxytetracycline-induced acute renal failure in a neonatal foal. *J. Am. vet. med. Ass.* **203**, 105-107.

Weber, S.G., Gold, H.S., Hooper, D.C., Karchmer, A.W. and Carmeli, Y. (2003) Fluoroquinolones and the risk for methicillin-resistant *Staphylococcus aureus* in hospitalized patients. *Emerg. Infect. Dis.* **9**, 1415-1422.

White, G. and Prior, S.D. (1982) Comparative effects of oral administration of trimethoprim/sulphadiazine or oxytetracycline on the faecal flora of horses. *Vet. Rec.* **111**, 316-318.

Whithair, K.J., Bowersock, T.L., Blevins, W.E., Fessler, J.F., White, M.R. and van Sickle, D.C. (1992) Regional limb perfusion for antibiotic treatment of experimentally induced septic arthritis. *Vet. Surg.* **21**, 367-373.

Wichtel, M.E., Buys, E., DeLuca, J. and Stringel, G. (1999) Pharmacologic considerations in the treatment of neonatal septicemia and its complications. *Vet. Clin. N. Am.: Equine Pract.* **15**, 725-746.

Wilkerson, M.J., Davis, E., Shuman, W., Harkin, K., Cox, J. and Rush, B. (2000) Isotype-specific antibodies in horses and dogs with immune-mediated hemolytic anemia. *J. vet. intern. Med.* **14**, 190-196.

Wilson, W.D. and Madigan, J.E. (1989) Comparison of bacteriologic culture of blood and necropsy specimens for determining the cause of foal septicemia: 47 cases (1978-1987). *J. Am. vet. med. Ass.* **195**, 1759-1763 [erratum *J. Am. vet. med. Ass.* **196**, 438].

Wilson, W.D., Spensley, M.S., Baggot, J.D. and Hietala, S.K. (1988a) Pharmacokinetics and estimated bioavailability of amoxicillin in mares after intravenous, intramuscular, and oral administration. *Am. J. vet. Res.* **49**, 1688-1694.

Wilson, W.D., Spensley, M.S., Baggot, J.D. and Hietala, S.K. (1988b) Pharmacokinetics, bioavailability, and *in vitro* antibacterial activity of rifampin in the horse. *Am. J. vet. Res.* **49**, 2041-2046.

Wilson, W.D., Spensley, M.S., Baggot, J.D., Hietala, S.K. and Pryor, P. (1991) Pharmacokinetics and bioavailability of ticarcillin and clavulanate in foals after intravenous and intramuscular administration. *J. vet. Pharmacol. Therap.* **14**, 78-89.

Wise, R. (1997) B-lactams: cephalosporins. In: *Antibiotics and Chemotherapy*, Ed: F.E.A. O'Grady, Churchill Livingstone, New York. p 202.

Womble, A., Giguere, S. and Lee, E.A. (2007) Pharmacokinetics of oral doxycycline and concentrations in body fluids and bronchoalveolar cells of foals. *J. vet. Pharmacol. Therap.* **30**, 187-193.

Yancey, R.J., Jr., Kinney, M.L., Roberts, B.J., Goodenough, K.R., Hamel, J.C. and Ford, C.W. (1987) Ceftiofur sodium, a broad-spectrum cephalosporin: evaluation *in vitro* and *in vivo* in mice. *Am. J. vet. Res.* **48**, 1050-1053.

Yoon, J.H., Brooks, R.L., Jr., Khan, A., Pan, H., Bryan, J., Zhang, J., Budsberg, S.C., Mueller, P.O. and Halper, J. (2004) The effect of enrofloxacin on cell proliferation and proteoglycans in horse tendon cells. *Cell Biol. Toxicol.* **20**, 41-54.