Equine Veterinary Education

EQUINE VETERINARY EDUCATION
Equine vet. Educ. (2022) **34** (1) 49-56
doi: 10.1111/eve.13467

Review Article

Systemic antimicrobial therapy in foals

***E. F. Floyd*†*, *C. A. Easton-Jones*† and *M. J. P. Theelen*‡§**

†*Rossdales Equine Hospital, Newmarket, Suffolk, UK;* ‡*Department of Clinical Sciences (Equine Internal Medicine), Faculty of Veterinary Medicine, Utrecht University, Utrecht; and* §*Department of Biomolecular Health Sciences (Clinical Infectiology), Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands*
**Corresponding author email: emily.floyd@rossdales.com*

Keywords: horse; antibiotic; antimicrobial; foal; sepsis

Summary

Antimicrobial agents are commonly used in neonatal foals for the treatment or prevention of sepsis. However, due to concerns about the development of antimicrobial resistance and increasing pressure on veterinarians to rationalise antimicrobial use, we should be trying to reduce the unnecessary use of antimicrobials. This article reviews many of the important considerations when selecting an antimicrobial for use in neonatal foals. Firstly, we consider general differences in neonatal pharmacology and physiology. Secondly, we review common antimicrobial drugs and their indications. Finally, we review antimicrobial stewardship.

Part 1: General considerations for antimicrobial selection in foals

There are several important differences between foals and adult horses which must be considered when selecting antimicrobial drugs for use in foals. Neonatal foals have a proportionally greater body water content than adult horses. In the first week of life, foals have a body water content of 71–83% compared to 60–70% in adult horses (Andrews *et al*. 1997; Fielding *et al*. 2011). Fluid dynamics differ further between mature horses and foals as a result of foals having a relatively smaller intracellular fluid compartment and larger extracellular fluid compartment as well as higher blood and plasma volumes (Carlson *et al*. 1979; Fielding *et al*. 2003; Fielding *et al*. 2011). This greater body water content means higher dosages of hydrophilic drugs such as aminoglycosides are necessary in foals whereas the dosages of lipophilic drugs are less affected (Corley and Hollis, 2009).

Drug metabolism also alters as organ function matures. The rate of hepatic metabolism and renal excretion generally increases with age. This means that protocols that are extrapolated from adult dosing may not always be appropriate, especially for young foals. For example, standard oral dosing of trimediazine sulphadiazine at 24 mg/kg achieved higher plasma levels in 1- to 10-day-old foals than would be achieved in adult horses (Swain O'Fallon *et al*. 2020). The rate of elimination of intravenous chloramphenicol has been shown to increase in foals over the first 6 weeks of life, with more prolonged elimination times in premature foals (Adamson *et al*. 1991).

Foals also differ from adult horses with regard to their gut flora as they are not yet hindgut fermenters. In foals, a healthy gastrointestinal tract with appropriate microbiota is important to allow the foal to transition into a healthy weanling. Recent studies have tracked the changes in faecal microbiota as the gut transitions from a diet of milk to becoming a hindgut fermenter (De La Torre *et al*. 2019; Lindenberg *et al*. 2019). In the first 7 days of life, the gut microbiota of foals is very transient with large inter-individual variability. A more uniform composition between foals is established by Day 20, with an increase in fibre fermenting species developing between Day 20 and Day 50 (Lindenberg *et al*. 2019). These studies suggest that the composition of bacterial populations in the foal's gut changes gradually in an age-dependent manner. These differences in microbiota allow foals to tolerate a wider range of antimicrobials, such as the macrolides, that would result in severe colitis in adult horses. However, currently no literature is available in horses regarding potential long-term effects on gut microbiota composition as a result of antimicrobials administered in early life.

The majority of pharmacokinetic studies are performed in healthy foals. The bioavailability of drugs can be altered in sick foals where disease processes, organ dysfunction, hypovolaemia and administration of other drugs can affect drug absorption and metabolism. In septic foals, for example enteral absorption of antimicrobials is often reduced as a result of hypoxic damage and reduced perfusion of the gut (Corley and Hollis 2009). Furthermore, some antimicrobials used in adult horses such as enrofloxacin are unsuitable for use in foals due to specific toxicities. The impact of these factors on the risk of antimicrobial toxicity and the steps that can be taken to monitor for these side effects will be discussed later in this article.

Common bacterial infections in foals and considerations for antimicrobial selection

Sepsis is the most common cause of foal death during the first 7 days of life. Failure of passive transfer of colostral immunity is an important risk factor. The 'open gut' of the foal which enables pinocytosis of colostral antibodies also allows direct access for bacteria from the environment and the gastrointestinal tract into the circulation. Sepsis is the result of failure of the immune response to respond adequately to infection with downstream sequelae including conditions such as septic arthritis, physitis, osteomyelitis, meningitis and umbilical infections in some foals. Antimicrobial therapy is central to the treatment of sepsis along with intravenous fluid therapy and other supportive care. When initially selecting antimicrobials for the treatment of sepsis, it is important to select broad spectrum, intravenously administered bactericidal drugs (Magdesian 2017). Empirical selection of broad-spectrum antimicrobials is necessary initially for septic foals as there is a time delay of several days until blood culture results are reported and false-negative results are

often obtained (Wilson 1989). Bactericidal drugs are necessary due to septic foals having a naive immune system compared to adults. The route of administration affects the plasma concentrations of antimicrobial drugs. The intravenous route is recommended as sick foals are often haemodynamically compromised leading to reduced perfusion of the gut and muscle and reduced absorption of drugs administered via the oral or intramuscular routes. The importance of rapid antimicrobial administration in sepsis is well recognised in humans, with earlier administration of antimicrobials associated with an improved outcome (Puskarich *et al*. 2011). Delaying the initiation of antimicrobial treatment in these foals while awaiting culture results is clinically recognised to increase the likelihood of septic shock or the sequelae described above developing. Survival rates have been shown to be improved when an empirically selected antimicrobial regime includes an antimicrobial to which isolated bacteria are susceptible (Theelen *et al*. 2019).

A number of studies have been published summarising the most common bacterial isolates in neonatal foals with sepsis and their susceptibility patterns (Brewer and Koterba 1990; Marsh and Palmer 2001a,b; Corley and Hollis 2009; Theelen *et al*. 2014a,b; Theelen *et al*. 2019). Both Gram-negative and Gram-positive bacteria are often isolated from foals with sepsis. The most common isolate obtained from septic foals is *Escherichia coli*. Other Gram-negative bacteria that are often identified include enterics such as *Enterobacter* spp. and *Klebsiella* spp. Nonenteric Gram-negative bacteria commonly isolated include *Actinobacillus* spp. and *Pasteurella* spp. Gram-positive bacteria that are frequently reported in septic foals include *Streptococcus* spp., *Enterococcus* spp. and *Staphylococcus* spp (Magdesian 2017). Polymicrobic infections occur frequently in foals with sepsis, and it is possible to have mixed infections of Gram-negative and Gram-positive bacteria (Brewer and Koterba 1990; Gayle *et al*. 1998).

There is evidence from a study in California comparing isolates in neonatal septic foals at one hospital over a period of 30 years that while Gram-negative bacteria remain the most common isolates, the prevalence of Gram-positive bacteria is increasing. *Enterococcus* spp. isolates were also cultured more frequently in recent years (Theelen *et al*. 2014b). The increase in *Enterococcus* spp. prevalence is concerning as they can act as a donor of antimicrobial resistance genes to other bacteria. Hospitalisation also appears to have an impact upon the bacteria isolated and the susceptibility of the strains. When cultures were compared between hospital admission samples and those taken after 48 h of hospitalisation, there was found to be an increase in the prevalence of several bacterial species including species often involved in healthcare-associated infections such as *Acinetobacter* spp., *Klebsiella* spp., *Pseudomonas* spp. and *Serratia* spp. These results provide a rationale for repeating bacteriological culture and susceptibility testing of hospitalised foals and emphasise the importance of hospital hygiene in equine neonatal intensive care units (Theelen *et al*. 2020). It is clear from the studies already published that bacterial susceptibility is also region- and hospital-dependent, therefore local monitoring of this information to guide antimicrobial selection is recommended (Marsh and Palmer 2001a,b; Theelen *et al*. 2014a).

Despite the necessity of antimicrobial treatment in neonates to avoid septic shock, there are currently no studies investigating the long-term implications of administering antimicrobials to foals. In human medicine, studies have shown an association between the use of antimicrobials in children and the development of allergies, arthritis, inflammatory bowel disease, asthma, multiple sclerosis, obesity and diabetes (Schulfer and Blaser 2015). There is a recognition that the first year of life is vital for the development of a child's intestinal microbiota and that early exposure to antibiotics alters the microbiota and increases the risk of developing inflammatory bowel diseases in later life (Ponder and Long 2013). Alterations in gut microbiota have been noted in adult horses after antimicrobial administration but this has not been investigated in foals (Costa *et al*. 2015). Despite the lack of studies examining the long-term implications of early antimicrobial administration in foals, these results from humans and mature horses support careful consideration when prescribing antimicrobials in foals.

Part 2: Specific antimicrobial drugs – indications and considerations

Beta-lactams: penicillin and ampicillin

Beta-lactam antimicrobials are time-dependent, bactericidal drugs that inhibit cell wall synthesis. These drugs are hydrophilic which means they distribute widely throughout plasma but do not penetrate lipophilic cell membranes well. In general, they have good Gram-positive spectrum of activity, with lesser Gram-negative and anaerobic coverage. They are often used synergistically with the aminoglycosides to provide broad-spectrum coverage (Haggett 2008).

Procaine penicillin G can be administered intramuscularly. However, this route of administration is associated with a risk of penicillin reactions (Olsen *et al*. 2007) and is often poorly tolerated due to low muscle mass. Procaine penicillin G also achieves low plasma concentrations in adult horses (Uboh *et al*. 2000), and this problem is likely worsened in foals with poor perfusion leading to reduced drug absorption from the tissue. Intravenous salts (sodium or potassium) of penicillin G are better suited to use in foals as they achieve higher and more reliable plasma levels.

The aminopenicillin, ampicillin, generally provides slightly better Gram-negative coverage than penicillin G (Magdesian 2017) and has the added advantage that sensitivity to *Enterococcus spp* is generally better (Theelen 2014a). Ampicillin is generally considered to be the first-line choice for treatment of neonatal sepsis in combination with an aminoglycoside (Theelen 2014a).

Anti-pseudomonal penicillins

These drugs can penetrate the outer cell wall of Gram-negative bacteria, including *Pseudomonas* spp. They can also overcome β-lactamase inactivation when administered with clavulanic acid. They can be considered an alternative for treatment of foals with sepsis or Gram-negative infection in which the use of aminoglycosides is contraindicated due to renal dysfunction. Ticarcillin clavulanate has been used widely but is no longer commercially available. The authors have used piperacillin G tazobactam in neonatal foals but there are no published reports of the use of this drug and the dosage has been extrapolated from other species.

Oral penicillins

Amoxicillin clavulanate can be used orally for the treatment of bacterial infections in young foals (up to 4 months of age) as it can attain adequate plasma levels (Love *et al*. 1981). This drug can be considered to be good oral treatment for specific infections such as neonatal pneumonia.

Beta-lactam antimicrobials: carbapenems

These drugs have probably the widest spectrum of activity of all antimicrobials and imipenem has been studied in horses (Orsini *et al*. 2005). This drug is of critical importance to human health and should not be used in neonatal foals unless in exceptional circumstances and only after bacteriological culture and susceptibility testing has proven no other alternatives for treatment.

Cephalosporins

These drugs are bactericidal and time-dependent with a broad spectrum of activity. They distribute widely throughout plasma and the extracellular compartment but have poor intracellular penetration. These drugs have been widely used in neonates due to their broad spectrum of activity, ease of administration and lack of major side effects. However, these drugs are classified as 'highest priority critically important antimicrobials' by the World Health Organization, and consequently, there is increasing pressure to reduce their usage in equine practice. There are five generations of cephalosporins. All generations have good Gram-positive coverage with increasing Gram-negative activity in the later generations.

Ceftiofur

Ceftiofur, a third-generation cephalosporin approved for use in horses in some parts of the world, is the cephalosporin most widely studied in neonatal foals. It is indicated for the treatment of neonatal sepsis when other nonprotected drugs are inappropriate, usually in the case of renal dysfunction. A significant proportion of isolates from foals with neonatal sepsis are reported to be resistant to ceftiofur, and hence, ampicillin and gentamicin or amikacin is generally a better first-line choice (Marsh and Palmar 2001a; Sanchez *et al*. 2008). The label dose of ceftiofur (2.2 mg/kg) is appropriate for the label indication of treatment of respiratory disease caused by *Streptococcus zooepidemicus*, a highly susceptible organism. A dose rate above 2 mg/kg is required to ensure that adequate blood MIC concentrations are obtained to exceed the MIC for less susceptible organisms such as *E. coli* (Meyer *et al*. 2009). Ceftiofur has the added advantage that it can achieve adequate plasma levels after intramuscular or subcutaneous injection (Slovis *et al*. 2006).

Other third-generation cephalosporins with a slightly broader Gram-negative spectrum can be used as an alternative to ceftiofur when culture and susceptibility results dictate. Examples include ceftriaxone and cefotaxime. Both these drugs cross the blood brain barrier and are indicated for the treatment of meningitis (Magdesian 2017).

Cephalosporins are suited to constant rate infusion due to their time-dependent mechanism of action, and this route of administration may improve efficacy by maximising time above MIC. Studies have evaluated continuous infusion of ceftiofur and cefotaxime, and this route of administration should be considered over bolus administration for hospitalised neonatal foals when cephalosporins use is indicated (Hewson *et al*. 2013; Wearn *et al*. 2013).

Aminoglycosides

Aminoglycosides are bactericidal, concentration-dependent antimicrobials with a predominantly Gram-negative spectrum. They are indicated for the treatment of specific Gram-negative infections or neonatal sepsis when used in combination with a beta-lactam. The main concern regarding their use is their potential to cause nephrotoxicity due to concentration of the drug in the renal tubular cells. This side effect occurs when repeated dosing occurs prior to excretion of the previous dose. Therapeutic drug monitoring (TDM) is recommended to reduce this risk. This relies on measuring a peak concentration to ensure drug efficacy and a trough concentration to ensure excretion (Magdesian 2017). Suggested target levels are shown in **Table 1**. If TDM is not available, then careful attention should be given to ensure an adequate dosing interval and normal renal function. Hydration status, urine output and serum creatinine concentration should be monitored closely.

Due to the high body water content of foals and the high volume of distribution, a high dose of aminoglycosides is required to reach therapeutic levels (see **Table 2**). Amikacin is less likely to be associated with renal side effects compared to gentamicin. The proportion of bacterial isolates that are susceptible to gentamicin is lower when compared to amikacin in some geographic regions (Theelen *et al*. 2019). From an antimicrobial stewardship point of view, gentamicin is preferred over amikacin. Therefore, making an informed decision on which aminoglycoside to use should be based on the local information obtained by ongoing monitoring of susceptibility results.

Aminoglycosides are also ideal drugs for regional use due to their concentration-dependent effect. Intra-articular medication or intravenous regional perfusion should be considered for foals with localised limb sepsis (Glass 2017).

Tetracyclines

Tetracyclines are bacteriostatic time-dependent antimicrobials which inhibit protein synthesis (Haggett 2008). They generally have a broad spectrum of activity but lack efficacy against some important Gram-negative bacteria and *Enterococcus spp*. Tetracyclines are lipophilic and penetrate well into tissues. This is a major advantage when treating localised infections such as septic arthritis, physitis or omphalophlebitis.

Oxytetracycline can be administered intravenously as a first-line antimicrobial for foals with localised bacterial infections. It is generally not considered an ideal first-line choice for the treatment of sepsis. At supra-therapeutic doses, oxytetracyline is used to treat flexural limb deformities in foals (Madison *et al*. 1994). Even at antimicrobial doses

TABLE 1: Suggested target plasma aminoglycoside concentrations for therapeutic drug monitoring

Drug	30-min peak (ug/mL)	8-h level (ug/mL)	20-h trough (ug/mL)
Amikacin	>53–60	15–20	<2
Gentamicin	>30–40	3–5	<1

TABLE 2: A list of antimicrobials commonly used in neonatal foals

	Dosage (mg/kg unless otherwise stated)	Route of administration	Frequency of administration (h)
Procaine penicillin G	20	IM	12
Sodium penicillin	20,000–44,000	IV	6
Sodium ampicillin	20	IV	6
Piperacillin tazobactam	30*	IV	6
Amoxicillin clavulanate	30	PO	8
Ceftiofur sodium	5–10	IV, IM, SC	12
Cefotaxime	40	IV	6
Ceftriaxone	25	IV	12
Amikacin	25	IV	24
Gentamicin	12	IV	36
Oxytetracycline	5 - 10	IV	12
Doxycycline	10	PO	12
Marbofloxacin	2	IV	24
	4	PO	
Clarithromycin	7.5	PO	12
Rifampin	5	PO	12
	10	PO	24
Trimethoprim sulfadiazine	5/25	PO	12
Metronidazole	10	IV, PO	12

* Dosage extrapolated from other species.

limb ligament laxity can occur and this can limit the use of this drug particularly in dysmature individuals. Oxytetracyline can cause acute kidney injury in foals, especially at high doses, and this drug should be used cautiously in foals with poor renal perfusion or evidence of reduced renal function (Ellero *et al*. 2020).

Doxycycline is well absorbed after oral administration to young foals and due to its relatively broad spectrum of activity and good tissue penetration is an excellent choice for the treatment of localised infections such as pneumonia and omphalophlebitis (Corley 2009).

Fluoroquinolones

Fluoroquinolones are considered 'protected' drugs in equine practice and should not be used for first-line therapy (British Equine Veterinary Association 2012; World Health Organization 2019). In general, the fluoroquinolones have limited Gram-positive activity (predominantly *Staphylococcus spp*) with excellent Gram-negative coverage. They are liphophilic drugs with excellent tissue penetration.

The main limitation of their use in neonates is their propensity to cause toxicity to developing articular cartilage (Vivrette *et al*. 2001). This effect is thought to be less when using marbofloxacin compared to enrofloxacin.

Due to their excellent tissue penetration, the main indication for the use of marbofloxacin is the treatment of localised infections when culture and sensitivity results show no alternative options for treatment. Marbofloxacin has also been used to treat macrolide-resistant *Rhodococcus* equi infections.

Macrolides

The main indication for the use of macrolides is for the treatment of *Rhodococcus* infections (Giguère 2017). These drugs have a narrow, predominantly Gram-positive spectrum of activity but are highly lipophilic with excellent intracellular penetration. They can occasionally be used for the treatment of other localised infections, but only in the absence of other options based on culture and sensitivity. These drugs should be administered carefully as there is a risk of severe or fatal enterocolitis in the mare if they ingest small amounts of the drug. This risk seems to be greatest when using earlier generation macrolides such as erythromycin (Båverud *et al*. 1998). Enterocolitis can also occur as a side effect of treatment with any macrolide (Giguère 2017). This risk is greater in older foals with a more mature gut flora. Macrolides use is also associated with a reduced ability to sweat (anhydrosis or hypohydrosis). Foals undergoing treatment should be kept cool in hot weather as they are unable to thermoregulate effectively (Stieler *et al*. 2016).

Rifampin

Rifampin has a narrow spectrum of activity which is predominantly Gram-positive. The drug is highly lipophilic and penetrates well into tissues. The drug is most often used in combination with a macrolide antimicrobial for the treatment of *Rhodococcus equi* pneumonia (Giguère 2017) but can also be used to treat other localised infections. Co-administration of rifampin with clarithromycin leads to decreased plasma and pulmonary epithelial fluid cell concentrations of clarithromycin (Peters *et al*. 2012) due to inhibition of intestinal uptake transporters. This has caused debate about whether this combination of drugs is appropriate. However, as co-therapy is thought to reduce the chance of bacteria acquiring rifampin resistance and because plasma levels above the MIC for most common pathogens can still be reached, combination therapy should be used. Drug interactions between other macrolides and rifampin are variable and when gamithromycin and rifampin are combined, plasma concentrations of gamithromycin are actually increased (Berlin *et al*. 2018). Rifampin should not be used as a sole agent due to rapid acquisition of resistance (Haggett 2008) and can be combined with other oral medications such as doxycycline or trimethoprim sulfadiazine for treatment of osteomyelitis or umbilical infections. Historically, rifampin has been administered twice daily but a recent study suggested that once daily administration may be adequate (Berlin *et al*. 2017).

Potentiated sulphonamides

Trimethoprim sulfadiazine is a broad-spectrum bacteriostatic drug. Levels of resistance are relatively high in some geographic regions (Theelen 2019). The drug has lack of efficacy against *Enterococcus spp*. (Magdesian 2017) and is poorly active in purulent material (Haggett 2008). The drug is useful for first-line treatment, for example in cases of mild pneumonia. Trimethoprim sulfadiazine, however, is not a good choice in foals with suspected sepsis.

Metronidazole

Metronidazole is indicated for the treatment of anaerobic infection including clostridial infections. The drug has a longer elimination half-life in foals compared with adults and should be used at a lower dose (Swain *et al*. 2014).

Discontinuation of therapy

Once antimicrobial treatment has been started, it is important to evaluate whether or not the treatment is effective. Clinical improvement of the foal and improvement of laboratory test results are the most reliable indicators. Besides repeated clinical evaluation of the patient, repeated blood analysis, such as white blood count, serum amyloid A and fibrinogen, or repeated diagnostic imaging to monitor disease resolution can be helpful in determining when antimicrobial treatment can be discontinued. In cases that fail to improve, collection of follow-up samples for bacteriological culture and susceptibility testing can be useful. Isolation rates and antimicrobial susceptibility profiles from bacteria isolated from foals with sepsis after > 48h of hospitalisation differ significantly from those collected at hospital admission (Theelen *et al*. 2020). This demonstrates that previous test results should not be used for selection of alternative drugs for treatment if initial treatment is unsuccessful. This study also showed it was not possible to predict antimicrobial susceptibility of bacteria isolated from foals after > 48h of hospitalisation and, therefore, no general empirical recommendation could be made for treatment of foals with sepsis which did not respond well to the initial antimicrobial therapy. Repeated bacteriological culture and susceptibility testing is necessary in these cases to make an informed decision in each individual patient.

Part 3: Surveillance of antimicrobial drug use and development of resistance

Frequent use of antimicrobial drugs leads to the development of antimicrobial resistance over time, and this trend is also observed for bacteria isolated from foals with sepsis (Sanchez *et al*. 2008; Theelen *et al*. 2014). The opposite was also seen: susceptibility to 'older' drugs that were no longer used increased over time (Theelen *et al*. 2014). This supports the central notion in antimicrobial stewardship programmes that reduced use of an antimicrobial drug can contribute to maintaining the efficacy of that antimicrobial drug over time. Antimicrobial stewardship programmes are being developed and implemented in human as well as veterinary medicine in order to sustain the efficacy of antimicrobial drugs in the light of increasing development and spread of resistance. Surveillance of antimicrobial drug use and development of resistance are key concepts in any antimicrobial stewardship strategy. Since antimicrobial drug prescription varies between different geographic regions, based on common practices and local regulation, development of antimicrobial resistance also varies between different geographic regions. Susceptibility patterns from bacteria isolated from (neonatal) foals also differ between geographic regions (Brewer and Koterba 1990; Gayle *et al*. 1998; Marsh and Palmer 2001a,b; Russell *et al*. 2008; Sanchez *et al*. 2008; Hollis *et al*. 2008; Theelen *et al*. 2014; Hytychová and Bezdeková 2015; Toombs-Ruane *et al*. 2016). Utilising studies obtained from different countries with different antimicrobial usages and over different time periods to make decisions regarding antimicrobial treatment in individual patients may therefore result in inappropriate treatment and potentially poor corresponding outcome. This highlights the importance of incorporating continuous surveillance of antimicrobial drug use and development of resistance in each practice or hospital.

For surveillance of antimicrobial drug use, procurement or prescription data can be used. The former is easier to obtain but does not allow for differentiation between patient types or, in mixed practices, species. Prescription data can be obtained from many patient management systems and allows for detailed analysis of prescription policy between species, different types of patients and even between different veterinarians. Systematic collection of these data also allows for benchmarking between practices which can stimulate veterinarians to further reduce the use of antimicrobials in their practice.

Monitoring development of antimicrobial resistance starts with implementing the policy of collecting samples for bacteriological culture and susceptibility testing in each case and not only in refractory cases. Furthermore, systematic recording of bacteriological culture and susceptibility testing results is essential in order to be able to detect changes in prevalence and antimicrobial susceptibility over time. It is therefore advisable to assign this task to a designated person within the practice and to discuss trends on a regular basis within the entire team to increase awareness and engagement.

Two different methods for antimicrobial susceptibility testing are used: disk diffusion (Kirby Bauer) or microdilution susceptibility testing. In disk diffusion susceptibility testing, antibiotic discs are placed on agar plates inoculated with bacteria. Interpretation criteria for inhibition zones are used to determine antimicrobial susceptibility. The results of this method of testing are reported as S (susceptible), I (intermediate) or R (resistant). In microdilution susceptibility testing the wells in the microtiter plates are inoculated with a broth containing the bacteria as well as varying concentrations of the antimicrobial drugs of interest. After the incubation time, each well is checked for bacterial growth. By using this procedure, it is possible to determine the Minimum Inhibitory Concentration (MIC; the lowest concentration of antimicrobial drug that inhibits bacterial growth) for each antimicrobial drug that was tested. Interpretation breakpoints are used to determine susceptibility. If the MIC is below the breakpoint, an organism is considered to be susceptible (S); if the MIC is above the breakpoint, an organism is considered to be resistant (R). Microdilution is currently considered the gold standard of susceptibility testing. This method allows for early detection of increasing MIC values, which might still be well below the breakpoint meaning the isolate is still susceptible but are an early indicator of development of antimicrobial resistance (Theelen 2014). From a surveillance point of view, microdilution susceptibility is therefore preferred over disk diffusion susceptibility testing.

Practical guidelines for antimicrobial stewardship in foals

Antimicrobial stewardship involves the judicious use of antimicrobials balanced against the requirement to treat the presenting clinical condition (Raidal 2019). The same principles apply to human medicine as well as veterinary medicine, including equine medicine. This requires a multifactorial approach combining reduction of resistant reservoirs, improved diagnostic techniques for bacterial infection, improved infection control measures, improved preventative health measures and greater insight into the aetiology of infections to reduce dependence on antimicrobials and limit the emergence of antimicrobial

resistance. Recently, several excellent papers have been published on antimicrobial stewardship in equine medicine (Raidal 2019; Prescott 2021). In these papers, guidelines are formulated that can be applied in equine practice. A recent study on antimicrobial stewardship in small animal medicine clearly demonstrated the positive effect of implementing an antimicrobial stewardship programme in small animal clinics by reducing the total amount of antimicrobials used and showing a shift in type of drugs used from 'protected' antimicrobials such as cephalosporins and fluoroquinolones to more 'first-line' antimicrobials such as penicillins (Hopman *et al*. 2019). Developing and incorporating an antimicrobial stewardship strategy are therefore important for all veterinary practices in order to reduce the use of antimicrobial drugs. Future research and development of new improved diagnostic techniques will hopefully contribute to a decreased need for use of antimicrobials. In the meantime, many aspects related to antimicrobial stewardship can be applied in daily practice. In the following paragraph, we will discuss how antimicrobial stewardship guidelines can be applied practically in (neonatal) foal medicine.

Antimicrobial stewardship starts with prevention of disease. Hygiene protocols, both at farms and in the hospital, should be optimised to prevent infections, thereby decreasing the need to use antimicrobials to treat infections. This is especially important in the perinatal period as foals are susceptible to sepsis. Hygiene protocols should include hand hygiene, aseptic protocols and isolation of patients with contagious conditions. Furthermore, bacterial infections can be avoided by preventative medicine measures, such as excellent prepartum and foaling management, assuring adequate colostrum intake in neonatal foals and by vaccination. Once infection has occurred, it is important to make an evidence-based decision about whether or not a foal should be treated with antimicrobials in each individual case. Many cases do not need antimicrobial treatment, such as mild cases of diarrhoea or foals with colic. Recently, a study demonstrated that a policy change to treat foals with *Rhodococcus equi* pneumonia in the later stage of the disease reduced antimicrobial usage without increasing mortality (Arnold-Lehna *et al*. 2020). Appropriate aseptic sample collection technique is also important in this light to avoid sample contamination and overtreatment. The duration of antimicrobial therapy should be appropriate. Excessive duration of treatment should be avoided. Clinical and blood parameters can be used to evaluate the need for continuation of treatment. Removal of the infected source can reduce the need for long-term antimicrobials. For example, abscess drainage or surgical removal of infected tissue can take away the need to treat a foal with antimicrobials. Antimicrobials must only be used with veterinary involvement. Owners should not have access to antimicrobial drugs without consulting a veterinarian. As discussed previously, continuous monitoring of bacteriological culture and sensitivity results in each practice is essential to collect information on the local situation regarding prevalence and susceptibility of bacteria. Antimicrobials should be classified as 'first line', 'alternative' and 'protected' options, based on local culture and susceptibility results. Documents ranking antimicrobials based on risk management of antimicrobial resistance are available and should be used as guidance for selection of antimicrobial drugs for treatment in veterinary medicine, such as the World Health Organization 'List of Critically Important Antimicrobials for Human Medicine' and the PROTECT ME toolkit developed by the British Equine Veterinary Association (British Equine Veterinary Association 2012; World Health Organization 2019). Antimicrobials that are of critical importance to human health, such as 3rd-, 4th- and 5th-generation cephalosporins, fluoroquinolones and carbapenems (World Health Organization 2019) should be classified as 'protected' and their use should always be justified by bacteriological culture and susceptibility testing results demonstrating that no other alternatives are available. Treatment should be modified based on culture and susceptibility results for individual patients, when possible. Dose and route of administration should be appropriate to the condition being treated to make sure antimicrobials reach sufficiently high concentrations to be effective at the location of the infection. Local delivery methods (e.g. intra-articular administration in a septic joint) can be used to allow for high antimicrobial concentrations at the site of infection, which is especially useful in cases where concentration-dependent antimicrobials are used as bacterial killing is directly proportional to the ratio of peak drug concentration to the MIC of the infecting bacteria. Isolation of patients infected by multi-drug resistant bacteria is important to reduce the risk of spread of resistance. Monitoring antimicrobial drug use in a practice provides the opportunity of comparing data between individual years and/or veterinarians within a practice or even between practices (benchmarking). Benchmarking can have a positive effect on reducing the total amount of antimicrobials used (Hopman *et al*. 2019). Post educational training for veterinarians on antimicrobial resistance and practice-wide discussions on guidelines should be organised in order to improve alignment. Client education on antimicrobial resistance can assist in reducing client pressure on veterinarians to prescribe antimicrobials. This can be achieved through sharing information by the use of posters or leaflets for clients.

Prophylactic use of antimicrobials in foals in the first few days of life has been advocated in the past to prevent infections but given the current rise of antimicrobial resistance and the worldwide call for reducing antimicrobial use, should not be used. Antimicrobial prophylaxis should not be used as a substitute for good animal health management. Prevention of infections by improving hygiene on breeding farms is key. In each case, the requirement to treat the presenting clinical condition with antimicrobials should be balanced against the potential for development or spread of resistance (Raidal 2019). Empirical use of antimicrobials is justified in initial treatment protocols for rapidly progressive, life-threatening conditions such as sepsis in foals, while awaiting the results of culture and susceptibility tests to increase the chance of survival (Theelen *et al*. 2019). Selection of antimicrobial drugs in these cases should be based on knowledge of the bacterial agents most likely involved with the disease process and knowledge of local resistance patterns combined with antimicrobial guidelines favouring antimicrobial drugs with the lowest risk of development and spread of resistance.

Conclusions

It is important to realise that results of bacteriological culture and susceptibility testing may differ between geographic regions. Temporal trends in susceptibility and resistance also

occur. Continuous local monitoring of culture and susceptibility results is therefore of utmost importance to ensure that empirical selection of drugs for treatment is based on contemporaneous and locally applicable susceptibility results. Bacteriological culture and susceptibility testing in individual cases therefore might not only benefit the individual patient, but also provides the basis for empirical drug selection in future cases.

Foals treated at NICU facilities are at risk for healthcare-associated infections (Theelen *et al*. 2020). Hygiene is important to prevent infection and spread of resistant bacteria. Repeated bacteriological culturing and susceptibility testing is advisable in hospitalised foals to detect ongoing or healthcare-associated infections at an early stage to provide guidance for potentially changing antimicrobial therapy.

Choosing antimicrobials for treatment of equine neonates is complex. Selecting antimicrobial drugs is more complicated than matching 'drugs and bugs'. Knowledge about the drugs, the microbiological aspects and the clinical situation of the patient are all necessary to make an appropriate decision and improve the chance of a positive outcome for the foal. The challenge is not to always play it safe, just because it is easy, but to make a well-considered decision in each individual case. Judicious use of antimicrobials is important to prevent development of resistance. In order for the veterinary profession to take responsibility and contribute to the worldwide battle against antimicrobial resistance, all veterinary practices should develop and implement a practice-wide antimicrobial stewardship strategy.

Authors' declarations of interest

No conflicts of interest have been declared.

Ethical animal research

Not applicable to this review article.

Source of funding

None.

Authorship

The manuscript has been written in equal parts by all three authors. All authors have reviewed and formatted the final version.

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.

Andrews, F.M., Nadeau, J.A., Saabye, L. and Saxton, A.M. (1997) Measurement of total body water content in horses, using deuterium oxide dilution. *Am. J. Vet. Res.* **58**, 1060-1064.

Arnold-Lehna, D., Venner, M., Berghaus, L.J., Berghaus, R. and Giguère, S. (2020) Changing policy to treat foals with *Rhodococcus equi* pneumonia in the later course of disease decreases antimicrobial usage without increasing mortality rate. *Equine Vet. J.* **52**, 531-537.

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.

Becvarova, I. and Buechner-Maxwell, V. (2012) Feeding the foal for immediate and long-term health. *Equine Vet. J.* **44**, 149-156.

Berlin, S., Kirschbaum, A., Spieckermann, L., Oswald, S., Keiser, M., Grube, M., Venner, M. and Siegmund, W. (2017) Pharmacological indices and pulmonary distribution of rifampicin after repeated oral administration in healthy foals. *Equine Vet. J.* **49**, 618-623.

Berlin, S., Wallstabe, S., Scheuch, E., Oswald, S., Hasan, M., Wegner, D., Grube, M., Venner, M., Ullrich, A. and Siegmund, W. (2018) Intestinal and hepatic contributions to the pharmacokinetic interaction between gamithromycin and rifampicin after single-dose and multiple-dose administration in healthy foals. *Equine Vet. J.* **50**, 525-531.

Brewer, B.D. and Koterba, A.M. (1990) Bacterial isolates and susceptibility patterns in foals in a neonatal intensive care unit. *Compend. Contin. Educ. Pract. Vet.* **12**, 1773-1781.

British Equine Veterinary Association (2012) PROTECT ME toolkit. (Accessed 25 October 2020).

Carlson, G.P., Harold, D. and Rumbaugh, G.E. (1979) Volume dilution of sodium thiocyanate as a measure of extracellular fluid volume in the horse. *Am. J. Vet. Res.* **40**, 587-589.

Corley, K.T.T. and Hollis, A.R. (2009) Antimicrobial therapy in neonatal foals. *Equine Vet. Educ.* **21**, 436-448.

Costa, M.C., Stämpfli, H.R., Arroyo, L.G., Allen-Vercoe, E., Gomes, R.G. and Weese, J.S. (2015) Changes in the equine fecal microbiota associated with the use of systemic antimicrobial drugs. *BMC Vet. Res.* **3**(**11**), 19.

De La Torre, U., Henderson, J.D., Furtado, K.L., Pedroja, M., Elenamarie, O., Mora, A., Pechanec, M.Y., Maga, E.A. and Mienaltowski, M.J. (2019) Utilizing the fecal microbiota to understand foal gut transitions from birth to weaning. *PLoS One* **30**, 14.

Ellero, N., Freccero, F., Lanci, A., Morini, M., Castagnetti, C. and Mariella, J. (2020) Rhabdomyolysis and acute renal failure associated with oxytetracycline administration in two neonatal foals affected by flexural limb deformity. *J. Vet. Sci.* **22**, 7.

Fielding, C.L., Magdesian, K.G. and Edman, J.E. (2011) Determination of body water compartments in neonatal foals by use of indicator dilution techniques and multifrequency bioelectrical impedance analysis. *Am. J. Vet. Res.* **72**, 1390-1396.

Fielding, C.L., Magdesian, K.G., Elliott, D.A., Craigmill, A.L., Wilson, W.D. and Carlson, G.P. (2003) Pharmacokinetics and clinical utility of sodium bromide (NaBr) as an estimator of extracellular fluid volume in horses. *J. Vet. Intern. Med.* **17**, 213-217.

Gayle, J.M., Cohen, N.D. and Chaffin, M.K. (1998) Factors associated with survival in septicemic foals: 65 cases (1988–1995). *J. Vet. Intern. Med.* **12**, 140-146.

Giguère, S. (2017) Treatment of infections caused by *Rhodococcus equi*. *Vet. Clin. North Am. Equine Pract.* **33**, 67-85.

Glass, K. and Watts, A.E. (2017) Septic arthritis, physitis, and osteomyelitis in foals. *Vet. Clin. North Am. Equine Pract.* **33**, 299-314.

Haggett, E.F. and Wilson, W.D. (2008) Overview of the use of antimicrobials for the treatment of bacterial infections in horses. *Equine Vet. Educ*. **20**, 433-448.

Hewson, J., Johnson, R., Arroyo, L.G., Diaz-Mendez, A., Ruiz-López, J.A., Gu, Y. and del Castillo, J.R. (2013) Comparison of continuous infusion with intermittent bolus administration of cefotaxime on blood and cavity fluid drug concentrations in neonatal foals. *J. Vet. Pharmacol. Ther.* **36**, 68-77.

Hollis, A.R., Wilkins, P.A., Palmer, J.E. and Boston, R.C. (2008) Bacteremia in equine neonatal diarrhea: a retrospective study (1990–2007). *J. Vet. Intern. Med.* **22**, 1203-1209.

Hopman, N.E.M., Portengen, L., Hulscher, M.E.J.L., Heederik, D.J.J., Verheij, T.J.M, Wagenaar, J.A., Prins, J.M., Bosje, T., Schipper, L., van Geijlswijk, I.M. and Broens, E.M. (2019) Implementation and evaluation of an Antimicrobial Stewardship Programme in

companion animal clinics: a stepped-wedge design intervention study. *PLoS One*. **14**(**11**), e0225124.

Hytychová, T. and Bezdeková, B. (2015) Retrospective evaluation of blood culture isolates and sepsis survival rate in foals in the Czech Republic: 50 cases (2011–2013). *J. Vet. Emerg. Crit. Care* **25**, 660-666.

Lindenberg, F., Krych, L., Kot, W., Fielden, J., Frøkiær, H., van Galen, G., Nielsen, D.S. and Hansen, A.K. (2019) Development of the equine gut microbiota. *Sci. Rep.* **8**, 14427.

Love, D.N., Rose, R.J., Martin, I.C. and Bailey, M. (1981) Serum levels of amoxycillin following its oral administration to Thoroughbred foals. *Equine Vet. J.* **13**, 53-55.

Madison, J.B., Garber, J.L., Rice, B., Stumf, A.J., Zimmer, A.E. and Ott, E.A. (1994) Effect of oxytetracycline on metacarpophalangeal and distal interphalangeal joint angles in newborn foals. *J. Am. Vet. Med. Assoc.* **204**, 246-249.

Magdesian, K.G. (2017) Antimicrobial pharmacology for the neonatal foal. *Vet. Clin. N. Am. Equine Pract.* **33**, 47-65.

Marsh, P.S. and Palmer, J.E. (2001a) Bacterial isolates from foals with diarrhea: 28 cases (1993–1997). *J. Am. Vet. Med Assoc.* **220**, 67-73.

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

Meyer, S., Giguere, S., Rodriquez, R., Zielinski, R.J., Grover, G.S. and Brown, S.A. (2009) Pharmacokinetics of intravenous ceftiofur sodium and concentration in body fluids of foals. *J. Vet. Pharmacol. Ther.* **32**, 309-316.

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. Ther.* **30**, 201-207.

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

Peters, J., Eggers, K., Oswald, S., Block, W., Lütjohann, D., Lämmer, M., Venner, M. and Siegmund, W. (2012) Clarithromycin is absorbed by an intestinal uptake mechanism that is sensitive to major inhibition by rifampicin: results of a short-term drug interaction study in foals. *Drug Metab. Dispos.* **40**, 522-528.

Ponder, A. and Long, M.D. (2013) A clinical review of recent findings in the epidemiology of inflammatory bowel disease. *Clin. Epidemiol.* **5**, 237-247.

Prescott, J.F. (2021) Outpacing the resistance tsunami: antimicrobial stewardship in equine medicine, an overview. *Equine Vet. Educ*. **33**, 539-545.

Puskarich, M. A., Trzeciak, S., Shapiro, N. I., Arnold, R. C., Horton, J. M., Studnek, J. R., Kline, J. A. and Jones, A. E. (2011) Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. *Crit. Care Med.* **39**, 2066-2071.

Raidal, S.L. (2019) Antimicrobial stewardship in equine practice. *Aust. Vet. J.* **97**, 238-242.

Russell, C.M., Axon, J.E., Blishen, A. and Begg, A.P. (2008) Blood culture isolates and antimicrobial sensitivities from 427 critically ill neonatal foals. *Aust. Vet. J.* **86**, 266-271.

Sanchez, L.C., Giguère, S. and Lester, G.D. (2008) Factors associated with survival of neonatal foals with bacteremia and racing performance of surviving Thoroughbreds: 423 Cases (1982–2007). *J. Am. Vet. Med Assoc.* **233**, 1446-1452.

Schulfer, A. and Blaser, M.J. (2015) Risks of antibiotic exposures early in life on the developing microbiome. *PLoS Pathog.* **11**.

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. Assoc. Equine Practnrs.* **52**, 329-330.

Stieler, A.L., Sanchez, L.C., Mallicote, M.F., Martabano, B.B., Burrow, J. A. and MacKay, R.J. (2016) Macrolide-induced hyperthermia in foals: role of impaired sweat responses. *Equine Vet. J.* **48**, 590-594.

Swain, E.A., Magdesian, K.G., Kass, P.H., Edman, J.E. and Knych, H.K. (2014) Pharmacokinetics of metronidazole in foals: influence of age within the neonatal period. *J. Vet. Pharmacol. Ther.* **38**, 227-234.

Swain O'Fallon, E., McCue, P., Rao, S. and Gustafson, D.L. (2020) Pharmacokinetics of a sulfadiazine and trimethoprim suspension in neonatal foals. *J. Vet. Pharmacol. Therap*. https://doi.org/10.1111/jvp.12930.

Theelen, M.J.P., Wilson, W.D., Byrne, B.A., Edman, J.M., Kass, P.H. and Magdesian, K.G. (2019) Initial antimicrobial treatment of foals with sepsis: Do our choices make a difference? *Vet. J.* **243**, 74-76.

Theelen, M.J.P., Wilson, W.D., Byrne, B.A., Edman, J.M., Kass, P.H., Mughini-Gras, L. and Magdesian, K.G. (2020) Differences in isolation rate and antimicrobial susceptibility of bacteria isolated from foals with sepsis at admission and after ≥48 hours of hospitalization. *J. Vet. Intern. Med.* **34**, 955-963.

Theelen, M.J.P., Wilson, W.D., Edman, J.M., Magdesian, K.G. and Kass, P.H. (2014a) Temporal trends in in vitro antimicrobial susceptibility patterns of bacteria isolated from foals with sepsis: 1979–2010. *Equine Vet. J.* **46**, 161-168.

Theelen, M.J.P., Wilson, W.D., Edman, J.M., Magdesian, K.G. and Kass, P.H. (2014b) Temporal trends in prevalence of bacteria isolated from foals with sepsis: 1979–2010. *Equine Vet. J.* **46**, 169-173.

Toombs-Ruane, L.J., Riley, C.B., Kendall, A.T., Hill, K.E., Benschop, J. and Rosanowski, S.M. (2016) Antimicrobial susceptibility of bacteria isolated from neonatal foal samples submitted to a New Zealand veterinary pathology laboratory (2004 to 2013). *N. Z. Vet. J.* **64**, 107-111.

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.

Vivrette, S., Bostian, A., Bermingham, E. and Papich, M. (2001) Quinolone-induced arthropathy in neonatal foals. *Proc. Am. Assoc. Equine Practnrs.* **47**, 376-377.

Wearn, J.M.G., Davis, J.L., Hodgson, D.R., Raffetto, J.A. and Crisman, M.V. (2013) Pharmacokinetics of a continuous rate infusion of ceftiofur sodium in normal foals. *J. Vet. Pharmacol. Ther.* **36**, 99-101.

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. Assoc.* **195**, 1759-1763.

World Health Organization (2019) *Critically important antimicrobials for human medicine*, 6th edn., World Health Organization, Geneva.