Introduction

Antimicrobial resistance (AMR) in previously susceptible bacterial species is an ever-increasing problem in both human and veterinary medicine. The guidelines of European Antimicrobial Advice Ad Hoc Expert Group recommend that trimethoprim-sulfonamide combinations, trimethoprim-sulfadiazine, or trimethoprim-sulfamethoxazole (hereafter referred to as TMPS) can be used with prudence, as they are at present not considered to significantly impact the development of AMR in humans. Consistent with this, TMPS is currently not subject to special restrictions for veterinary use in food-producing or companion animals and is commonly used in adult horses. However, some equine practitioners are reluctant to use TMPS as a sole treatment in foals, both with or without bacteriologic culture, due to controversy on susceptibility test results and/or beliefs about insufficient efficacy of the drug.

Partially influencing the choice of TMPS as the first-line drug is the fact that the availability of these formulations among countries is variable. The oral formulation is available in most countries as a powder or paste. The intravenous formulation is not FDA approved nor commercially available for use in horses in the US. On the contrary, the intravenous formulation is readily available and frequently used in other countries in Europe, Australia, Asia, and the Middle East. Unavailability of an intravenous formulation might further reduce the likelihood of TMPS being selected as a first-line drug over concerns of any delay in attainment of therapeutic concentrations with oral administration, although not supported by the available published pharmacokinetic data (in the authors’ experience).

The aims of this review are as follows: (1) to review the general characteristics of TMPS combinations for use in foals, (2) to review the scientific evidence of TMPS efficacy in foals, and (3) to discuss under which indications TMPS is a valid antimicrobial treatment in foals.

Keywords: foal, antimicrobial, trimethoprim, sulfonamides, treatment
guidelines for antimicrobial treatment in foals are based on resistance patterns observed at a limited number of specific geographical locations, and resistance determinations frequently originate from a single veterinary institution per publication. It is well known that resistance patterns differ among geographical areas and hospitals, making widespread application of the available information challenging.

Current recommendations for initial empiric antimicrobial treatment in foals are administration of a combination of an aminoglycoside (amikacin sulfate or gentamicin sulfate) with a penicillin (sodium ampicillin, procaine benzyl penicillin, sodium penicillin) or a third- or fourth-generation cephalosporin (ceftriaxone, cefquinome), alone or in combination with an aminoglycoside. These protocols provide broad-spectrum bactericidal treatment targeted against the most common pathogens encountered in infectious diseases affecting foals. However, the widespread use of these specific antimicrobials is without consequence and susceptibility of amikacin, gentamicin, and ceftiofur in bacterial isolates collected from foals has decreased over time. Additionally, only ampicillin and penicillin are regarded as non-protected antimicrobials. Cephalosporins (third and fourth generation) and aminoglycosides are classified as critically important to human health by the World Health Organization, meaning that their use should be avoided in animals.

Another factor affecting initial selection is the route of administration. In critically ill foals, the choice of antimicrobial treatment is, among other factors, dependent on the recommendation to administer antimicrobials IV, rather than IM or PO, due to potentially decreased muscle perfusion and gastrointestinal absorption. While this requires consideration for critically ill patients, this recommendation does not preclude the use of IM or PO administration in noncritical disease states.

**Trimethoprim-sulfonamide**

**Characteristics**

The mechanism of action of TMPS is the combined action of trimethoprim and sulfonamides both targeting the folate synthesis of bacterial cells. Trimethoprim blocks the reduction of dihydrofolate to tetrahydrofolate, the active form of folic acid, and sulfonamides interrupt folate synthesis by competing with para-amino benzoic acid (PABA) in the synthesis of dihydrofolate. Since folate is not produced by mammalian cells, the formulation only affects bacterial or protozoal cells. However, purulent and necrotic tissues contain folate and provide PABA to bacterial cells, thereby overcoming the influence of competitive inhibition of TMPS. Therefore, TMPS is not ideal for treatment of infections with associated purulent and necrotic tissues.

One of the reasons for hesitancy to use TMPS is the perception that it is bacteriostatic. However, the combination between the bacteriostatic trimethoprim and bacteriostatic sulfadiazine or sulfamethoxazole is synergistic and produces a bactericidal antimicrobial drug when combined in a ratio ratio product to produce a 1:20 ratio in human serum after PO or parenteral administration. The synergistic bactericidal effect of the 2 drugs has also been suggested to reduce the development of AMR.

**Administration, distribution, metabolism, and excretion**

Trimethoprim-sulfonamide combinations can be administered to horses PO or IV. Intramuscular injections are not recommended due to tissue irritation related to the alkaline pH (10 to 12). Both trimethoprim and sulfonamides are time-dependent antimicrobials that are well absorbed following PO administration. Distribution is more rapid after IV administration compared to PO administration, although this difference is only significant relative to the sulfonamides, not the trimethoprim. Further, this aspect is of questionable clinical relevance, as absorption following PO administration remains rapid (time to peak drug concentration [**T**<sub>max</sub>] = 1.5 to 3.0 hours).

In contrast, the antimicrobial serum concentrations stays above MIC90 (the lowest concentration at which growth of 90% of the isolates are inhibited) for bacteria isolated from equine infections for a longer time after PO administration compared to IV administration. Clinically, this might have benefits for improved efficacy following PO administration because, despite the delayed absorption, the prolonged exposure of bacteria to therapeutic concentrations is beneficial for time-dependent antimicrobials such as TMPS.

After absorption, TMPS is well distributed, with good intracellular penetration. Adequate antimicrobial concentrations in adult horses have been described in plasma, synovial fluid, peritoneal fluid, subcutaneous tissue, endometrial tissue, CSF, CNS tissue, and urine. Complete data are lacking on its distribution into the pulmonary epithelial lining fluid; however, adequate concentrations are reached within pulmonary macrophages. The pharmacokinetic properties of TMPS are not affected by inflammation. Both trimethoprim and sulfonamides are metabolized in the liver and excreted by the kidney. The recommended frequency of administration is controversial. Although some producers advocate once-daily administration (UNIPRIM, Neogen Corp; Norodine Equine Oral Paste, Norbrook Laboratories Ltd; and Hippotrim vet, Elanco Denmark), this is not supported by the published pharmacokinetic studies. On the contrary, twice-daily administration has been established as the optimum dosing interval.

**Spectrum, antimicrobial susceptibility, and development of resistance**

The reported susceptibility of bacterial isolates from foals to TMPS and susceptibility compared to other antimicrobials from recent literature are summarized (Table 1).
Table 1—Susceptibility of bacterial isolates from foals to potentiated sulfonamides according to geographical location and pathology. The percentage is the expression of the number of susceptible isolates from bacteriology and susceptibility reports provided by the referenced publication.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Location</th>
<th>Most common isolate</th>
<th>Gram+ bacteria</th>
<th>Gram− bacteria</th>
<th>Escherichia coli</th>
<th>All isolates</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Pennsylvania, US</td>
<td><em>E. coli</em>, 28.5%</td>
<td>—</td>
<td>—</td>
<td>57%</td>
<td>—</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Australia</td>
<td><em>E. coli</em>, 31.4%</td>
<td>64%</td>
<td>47%</td>
<td>63%</td>
<td>67%</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Virginia, US</td>
<td><em>Staphylococcus</em>, 17%; <em>E. coli</em>, 17%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>55%</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>California, US</td>
<td>—</td>
<td>69.4%</td>
<td>87.3%</td>
<td>—</td>
<td>72.8%</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>New Zealand</td>
<td><em>Streptococcus</em> spp, 25%</td>
<td>43%</td>
<td>72%</td>
<td>33%</td>
<td>65%</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Australia</td>
<td><em>Staphylococcus</em> spp, 17%</td>
<td>—</td>
<td>61%</td>
<td>—</td>
<td>—</td>
<td>72</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>New Zealand</td>
<td><em>Streptococcus</em> spp, 40%</td>
<td>58.8%</td>
<td>56.8%</td>
<td>53.6%</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>Umbilical</td>
<td>Italy</td>
<td><em>Streptococcus</em>, 32.5%</td>
<td>40%</td>
<td>3.4%</td>
<td>—</td>
<td>18.3%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Pennsylvania, US</td>
<td><em>Enterococcus</em>, 29.3%</td>
<td>82%</td>
<td>100%</td>
<td>50%</td>
<td>81%</td>
<td>54</td>
</tr>
</tbody>
</table>

Data originated primarily from the US, Australia, and New Zealand and might not reflect resistance patterns in other parts of the world. No data are available from countries where the concepts of antimicrobial stewardship were applied early on in equine practice such as the Scandinavian and other northern European countries and, as such, where decreased selection pressure for resistance is likely to have preserved inherent susceptibility.

Trimethoprim-sulfonamide combinations are considered broad-spectrum antimicrobials. The MIC90 values are available for some pathogens including *Streptococcus equi* (0.5/9.5 µg/mL for trimethoprim/sulfadiazine), but generally, specific veterinary susceptibility breakpoints such as the Clinical and Laboratory Standards Institute or European Committee on Antimicrobial Susceptibility Testing are lacking. General antimicrobial susceptibility is often extrapolated from human data, without known relevance for veterinary medicine. Additionally, the use of different laboratory methods (disk diffusion vs serial dilution methods, potential presence of PABA in low-quality agar/broths) can give diverging results from different laboratories.

Several pathogens, including *Mycobacterium* spp, *Enterococcus* spp, and *Pseudomonas* spp, have innate resistance to TMPS. Acquired resistance is commonly seen in *Staphylococcus* spp and anaerobic pathogens. Surprisingly, isolates of methicillin-resistant *Staphylococcus* aureus are generally sensitive to TMPS, both in humans and animals. Extended-spectrum β-lactamase-producing *Enterobacteriales* are generally resistant.

Reports of antimicrobial susceptibility to TMPS over time are conflicting. Reports of bacterial culture and susceptibility results in the literature are sparse. In the early available literature, AMR to TMPS was reported to be low until the 1990s. The current literature is inconsistent, with some studies showing an increase in AMR over time and others showing stable antimicrobial susceptibility over time for bacterial isolates cultured from equine infections. The available data highlight the diversity of AMR in different geographic locations and institutions. For example, the susceptibility of equine isolates of *Escherichia coli* and *Staphylococcus* spp to TMPS was reported to be 46.9% and 68.6%, respectively, in isolates in South Africa but 73.8% and 94%, respectively, in isolates in France. The difference in susceptibility patterns might be explained in part by the nature of antimicrobial use in the geographical area sampled, but lack of standardized methods for susceptibility determinations, especially for sulfonamides, must be considered as well.

**Trimethoprim-sulfonamide in foals**

**Pharmacokinetics in foals**

Pharmacokinetic parameters in foals are dependent on the foal’s age. Foals are born with a relatively mature metabolism, and from a physiologic standpoint, the equine neonatal period has been suggested to be as short as the first 7 days. From a pharmacokinetic and physiologic point of view, foals can be considered adults or adult-like as early as 6 to 12 weeks old. Therefore, after 3 months of age, foals are considered young adults and can be administered adult dosages.

During the first 24 hours of life, the gastrointestinal tract is permeable to allow colostral antibody absorption, and an increased oral absorption of drugs might also occur; however, no clinical studies have confirmed this. Hepatic metabolism is significantly decreased in neonates due to a lack of development of hepatic smooth endoplasmic reticulum. This affects the metabolism of trimethoprim and sulfonamides, resulting in a prolonged half-life and decreased clearance of TMPS, especially in the first 24 hours of life and up to the first 3 to 4 weeks of life. Frequent nursing might also affect oral drug absorption. Although several studies have demonstrated that there is no major influence of fed state on the absorption of TMPS in adult horses, no studies have been performed on nursing foals. Given the rapid gastrointestinal transit of milk compared to solid food and the lack of impact of solid food on adult horses, the impact of nursing is likely to be insignificant.

Two pharmacokinetic studies on TMPS in foals were published recently. One evaluated PO administration in 1-day-old foals using a dose of 24 mg/kg (67 mg/mL of trimethoprim and 333 mg/mL of sulfadiazine) every 12 hours. The other evaluated IV administration in 3-day-old foals using a dose of 15 mg/kg (2.5 mg/kg of trimethoprim and 12.5 mg/kg sulfadiazine) every 12 hours. Basic pharmacokinetic values of these studies and comparison with data from studies on adult horses are presented (Table 2).
The clinical implications of pharmacokinetic values presented in Table 2 include the peak drug concentrations, $T_{\text{max}}$, (indicating the rate of absorption), area under the curve (indicating the total amount of absorption), volume of distribution (an indicator of the extent of drug distribution throughout the body), and rate of elimination. Like adult horses, $^{15,16}$ the $T_{\text{max}}$ and the rate of elimination were longer after PO administration compared to IV administration in foals. This means that after PO administration in foals, TMPS takes longer to reach a steady state over the MIC90, but its concentration stays above MIC90 for a longer period between doses compared to IV administration. After twice-daily (24 mg/kg) PO administration to neonatal foals, the mean serum concentration of both trimethoprim and sulfadiazine remained constant above MIC90 (0.5/9.5 $\mu$g/mL trimethoprim/sulfadiazine) after the second administration (at 12 hours).$^{16}$

In conclusion, PO administration is preferred if the foal is believed to have a functional and perfused gastrointestinal system. The first dose can be given IV to ensure a more rapid achievement of maximum antimicrobial serum concentration.$^{16}$

### Dose selection for foals

In a study using IV administration of 15 mg/kg of TMPS every 12 hours, serum concentrations failed to reach a steady state over MIC90 for $E$ coli (0.5/9.5 $\mu$g/mL) and $S$ equi (0.5/9.5 $\mu$g/mL).$^{23,35}$ The authors suggest that this dosage would still be sufficient for some $Staphylococcus$ spp and $Streptococcus$ spp with a reported MIC90 of 0.25 $\mu$g/mL for trimethoprim.$^{35}$ In another study$^{34}$ using PO administration of 24 mg/kg every 12 hours, the antimicrobial serum concentration of trimethoprim and sulfadiazine remained at steady state at or above MIC90 for $E$ coli, $S$ equi, and $S$ aureus for the entire interdosing interval. Considering the importance of $E$ coli in foal diseases, the recommended dosage in foals prior to appropriate clinical trials should therefore be 24 mg/kg every 12 hours IV or PO.$^{34}$ This contrasts with current recommendations of a dosage of 30 mg/kg every 12 hours based on the adult dosage prior to published pharmacokinetic studies in foals.$^{6}$ The use of this lower dose compared to the adult recommendation is advisable in foals due to the higher area under the curve, lower hepatic metabolism, and increased permeability of the blood-brain barrier in young animals compared to adults.$^{36}$

### Adverse effects in foals

The safety margin of the recommended dosage of TMPS in adult horses is high. No increase in adverse effects was reported after administration of a 5-times-higher dosage than the current recommendations. Similar studies have not been performed in foals. There has been 1 report documenting neurological adverse effects, circling, and continuous chewing after an adult dose of TMPS was accidentally administered to a foal.$^{37}$

The influence of TMPS on the intestinal microflora in adult horses has been described, and TMPS administration is associated with antimicrobial-associated diarrhea and alteration of the hindgut antimicrobial flora.$^{38,39}$ Nevertheless, it has been proposed that the incidence of postantimicrobial diarrhea after TMPS is not higher compared to other frequently used antimicrobials.$^{40}$ Gastrointestinal adverse effects after antimicrobial treatment are considered less likely in foals < 60 days of age than in adult horses because of their less developed gastrointestinal flora.$^{41}$ Additionally, TMPS did not cause any gastrointestinal adverse effects when given to foals in published pharmacokinetic studies.$^{34,35}$

### Drug interactions

Interactions between TMPS administered IV and $\alpha$-2 agonists$^{42}$ can occur in foals (in the authors’ experience). In adult horses, severe reactions ranging from excitement to arrhythmias and sudden death have been reported after IV injection of detomidine followed by immediate IV injection of TMPS.$^{43}$ As far as the authors are aware, there are no reports describing similar adverse effects with $\alpha$-2 agonists if the TMPS is administered PO.

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**Table 2—Comparison of pharmacokinetic variables from clinical trials in foals and adult horses after PO and IV administration.**

<table>
<thead>
<tr>
<th></th>
<th>Foal PO administration (24 mg/kg)$^{34}$</th>
<th>Foal IV administration (15 mg/kg)$^{15}$</th>
<th>Adult PO administration$^{16}$ (30 mg/kg)</th>
<th>Adult IV administration$^{16}$ (15 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trimethoprim</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax ($\mu$g/mL)</td>
<td>1.92 ± 0.25</td>
<td>1.25</td>
<td>1.06</td>
<td>2.42</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.4 ± 0.4</td>
<td>0.08</td>
<td>3.5</td>
<td>—</td>
</tr>
<tr>
<td>AUC ($\mu$g•h/mL)</td>
<td>21.1 ± 5.3</td>
<td>11.5</td>
<td>15.4</td>
<td>4.9</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>6.5 ± 2.0</td>
<td>2.9</td>
<td>5.1</td>
<td>2.8</td>
</tr>
<tr>
<td>$V_d$ (L/kg)</td>
<td>—</td>
<td>1.99</td>
<td>—</td>
<td>1.96</td>
</tr>
<tr>
<td><strong>Sulfadiazine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax ($\mu$g/mL)</td>
<td>37.8 ± 13.4</td>
<td>20.5</td>
<td>22.4</td>
<td>52.7</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.4 ± 0.6</td>
<td>0.08</td>
<td>1.7</td>
<td>—</td>
</tr>
<tr>
<td>AUC ($\mu$g•h/mL)</td>
<td>667 ± 424</td>
<td>246.8</td>
<td>420.8</td>
<td>159.5</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>10.8 ± 6.1</td>
<td>4.1</td>
<td>8.2</td>
<td>4.6</td>
</tr>
<tr>
<td>$V_d$ (L/kg)</td>
<td>—</td>
<td>0.61</td>
<td>—</td>
<td>0.5</td>
</tr>
</tbody>
</table>

AUC = Area under the curve. Cmax = Maximum concentration. $t_{1/2}$ = Elimination half-life. Tmax = Time to peak drug concentration. $V_d$ = Volume of distribution.
The combination of rifampicin and TMPS is not recommended due to the induction of metabolic P450 enzyme by rifampicin accelerating the metabolism of TMPS. Additionally, rifampicin is categorized as a highly critical antimicrobial for human medicine.

**Use of TMPS for specific foal diseases**

-Prophylactic perioperative antimicrobial treatment—Elective surgeries performed in foals include umbilical herniorrhaphy and surgical correction of limb deformities. Although reported infection rates associated with elective surgeries in foals are low and the benefits of perioperative antimicrobials in clean surgeries are questionable, many equine clinicians administer perioperative antimicrobials due to the perceived higher risk of environmental contamination and increased susceptibility to infections in this population.

Available first-line antimicrobials for foals include amoxicillin, ampicillin, penicillin, tetracyclines, and TMPS. Among these, TMPS has been suggested to provide the best antimicrobial coverage. These foals typically have short hospitalization times and, therefore, low risk of acquiring nosocomial infections additionally supporting the use of TMPS. On the basis of the pharmacokinetic properties of TMPS and prolonged period before reaching concentrations above MIC90 for common pathogens after PO administration, IV administration is recommended for preoperative use. Where intravenous formulations are not available, PO administration of TMPS should be at least 3 hours prior to surgery to ensure attainment of appropriately timed therapeutic concentrations.

It is also important to recognize the potentially fatal side effects associated with combined administration of IV TMPS and α-2 agonists commonly used as premedication prior to anesthesia. In young foals, premedication with benzodiazepines might be sufficient to avoid the use of α-2 agonists before induction of general anesthesia. Other drugs that can be used to avoid α-2 agonists when administering TMPS preoperatively include opioids, phenothiazine, barbiturates, and propofol.

-Neonatal sepsis—Sepsis in neonatal foals is a common cause of mortality and morbidity worldwide. Initial treatment should include broad-spectrum antimicrobials targeting the most frequently isolated gram-negative bacteria such as *E. coli*, *Klebsiella* spp., and *Actinobacillus* spp, but also gram-positive isolates such as *Streptococcus* spp and *Staphylococcus* spp. Polymicrobial infections occur and are associated with decreased survival. A correlation between outcome and initiation of appropriate empirical antimicrobial treatment has been suggested but not demonstrated in a recent study.

The authors propose that the pharmacokinetic characteristics of TMPS make it suitable for treatment of bacterial sepsis in areas with documented susceptibility of bacterial isolates. It provides broad antimicrobial activity with excellent tissue penetration and high intracellular concentrations. Further, the authors propose that TMPS is an excellent option for prolonged treatment due to the possibility of PO administration, allowing for easy administration on farm.

-Historically, the reason TMPS has not been used to treat septic foals is the reported low susceptibility of *E. coli*. However, a study of septic foals in Sweden reported a 94% susceptibility of *E. coli* isolates to TMPS. In the same time period, a 69% susceptibility was reported among equine strains of *E. coli* in California. This disparity in susceptibility demonstrates that susceptibility patterns should not be generalized and that region-specific data are important in evidence-based decision-making.

The susceptibility to TMPS of other gram-negative isolates, such as *Actinobacillus* spp and *Klebsiella* spp, is generally good. Gram-positive isolates are generally susceptible, albeit with regional variations. 

The general AMR of *Enterococcus* spp that are occasionally isolated from septic foals is high. Although they have been reported to have higher susceptibility to TMPS than to β-lactams in some instances, *Enterococcus* spp should always be considered resistant to treatment with TMPS. When comparing TMPS to other antimicrobial drugs frequently administered to foals, the literature from Oceania and the US shows that the overall susceptibility of cultured bacterial isolates to TMPS is average (55% to 73%; Table 1).

Septic foals frequently require hospitalization, which exposes them to hospital-acquired pathogens that are known to be commonly resistant to TMPS. Considering this, TMPS is a suboptimal choice for initial treatment in foals expected to have a prolonged period of hospitalization.

-Septic arthritis and osteomyelitis—The most common bacterial isolates reported from septic arthritis and osteomyelitis in foals are similar to those isolated from septic foals. Trimethoprim-sulfonamide combinations are a well-established treatment for osteomyelitis and septic synovitis in humans. They penetrate synovial cavities and bone well and achieve concentrations in bone 6 times higher than in serum. Therefore, TMPS is a good choice as an empirical treatment in combination with surgical debridement and lavage. However, due to impaired action in the presence of necrotic tissue, TMPS is not recommended for osteomyelitis, where debridement is impossible due to anatomical location or financial constraints.

-Umbilical infection and patent urachus—Environmental and fecal pathogens are the most common agents causing umbilical infections. However, the isolates are also often similar to those from septic foals, the most common being *Streptococcus* spp, *Enterococcus* spp, and *E. coli*. Because TMPS has reduced effects in purulent and necrotic material, it cannot be recommended for umbilical abscesses or extended umbilical infections unless it is combined with surgical removal and drainage. On the other hand, TMPS reaches high concentrations in urine, which would make it a good choice to treat a patent urachus (in absence of umbilical abscessation or widespread infection of the internal umbilical structures).
Diarrhea (in systemically affected foals, excluding foal heat diarrhea)—Bacteremia is present in approximately half of neonatal foals admitted to hospital facilities for treatment of diarrhea. Therefore, it is advisable to initiate antimicrobial treatment in foals suffering from diarrhea to avoid complications associated with bacteremia rather than as primary treatment of the diarrhea. Trimethoprim-sulphonamide combinations are an established treatment for diarrhea in both calves and humans. The most frequent bacterial species isolated from blood cultures from diarrheic foals are Enterococcus (innate resistance to TMPS), followed by Pantoaea agglomerans, E coli, and Salmonella spp and Actinobacillus spp. These isolates had a combined antimicrobial susceptibility to TMPS at 81%, with E coli and Salmonella spp being the least sensitive. Actinobacillus spp generally have a high susceptibility to TMPS. Based on these studies, TMPS has good antimicrobial effects on the most frequent bacterial species isolated from blood cultures in these foals. In addition to treating sepsis from translocated bacteria, some foals require antimicrobials targeting bacteria in the gut lumen or in the gut wall. In adult horses, TMPS has been detected in feces after both PO and IV administration. Foals are less sensitive to antimicrobial-induced alterations of the bacterial flora compared to adult horses, and alterations are quickly restored after discontinuation of antimicrobial treatment (as short as after 2 days in foals compared to 30 days in adult horses).

Pneumonia—Pneumonia in foals has different etiologies depending on the age of the foal. In neonates, it is most commonly secondary to sepsis (hematogenous spread) or aspiration pneumonia. In neonates presented with pneumonia, antimicrobial treatment should be directed toward bacterial species frequently isolated from foals suffering from sepsis.

In foals older than 1 month, pneumonia can be treated as a primary disease, with the most common bacteria isolated being Streptococcus spp (identified in up to 83.1% of all cases). The reported susceptibility of Streptococcus spp to TMPS is between 80% and 100% in France, the UK, and the US. Moreover, TMPS has been shown to be effective in treating lower respiratory tract infections caused by Streptococcus spp in adult horses.

The second most common isolate is Rhodococcus equi, which has poor susceptibility to TMPS. The third most common bacteria isolated from foals with pneumonia is Actinobacillus spp (up to 58.5%), with a reported susceptibility to TMPS of 75% to 100%. A less common but well documented pathogen causing pneumonia in immunosuppressed individuals is Pneumocystis carinii, for which TMPS is the treatment of choice. The variability in sensitivity highlights the need for an appropriate diagnosis prior to the initiation of front-line treatment.

Trimethoprim-sulphonamide combinations have good intracellular penetration within alveolar macrophages. However, its distribution into other areas of the equine lung is unclear. The main sites of infection in lower airway disease are the pulmonary epithelial lining fluid and intracellularly within alveolar macrophages. The distribution of TMPS to pulmonary epithelial lining fluid and bronchial fluid has been investigated and reported in healthy horses. Unfortunately, these studies have been performed with suboptimal dosing (a single PO administration or once-daily administration). No additional studies with appropriate dosing regimens have been published. Considering this, the conclusions of these studies should not be applied to a clinical case using optimal dosing. The distribution of TMPS to lung tissue and bronchial fluid in humans and monkeys has been reported to be excellent, and further studies of both adult horses and foals are necessary. Trimethoprim-sulphonamide is not a good antimicrobial choice in foals suffering from pneumonia with lung abscesses.

Wounds—According to the European Wound Management Association, all wounds are expected to be colonized with bacteria, but only wounds that are clinically infected should be treated with antimicrobials. Instead, primary treatment should be restricted to local lavage and debridement. Type and duration of disease is also relevant in antimicrobial selection for an equine wound. Trimethoprim-sulphonamide combinations are not effective against anaerobic bacteria or in the presence of purulent and necrotic material. The most important treatment for infected wounds affected by anaerobic bacteria or large amounts of necrotic tissue is debridement and sufficient drainage of the wound. Once these crucial steps have been performed, the use of TMPS is no longer contraindicated.

The most common bacteria isolated from equine wounds and their reported susceptibility to TMPS from California, the US, and the UK are Staphylococcus spp (80.5%), E coli (46.7%), Actinobacillus spp (86%), Bacillus spp (54.9%), Enterococcus spp, Pseudomonas spp, and Streptococcus spp (81.3%). In a study from the UK, the combined susceptibility of bacterial isolates to TMPS isolated from wounds was 74% in samples from ambulatory practice and 48% in samples from referral hospitals. In many cases, isolates from wounds show higher susceptibility to TMPS than to other first-line antimicrobial drugs, such as penicillin. With these aspects in mind, TMPS appears to be a good antimicrobial choice in foals suffering from nonpurulent and non-necrotic wounds and lacerations, or following debridement.

Conclusions

Trimethoprim-sulphonamide combinations are safe to administer to foals and without reported side effects when administered at a dosage of 24 mg/kg every 12 hours PO or 15 mg/kg every 12 hours IV. The oral dosage of 24 mg/kg every 12 hours PO reaches serum/plasma concentrations above MIC90 for relevant pathogens. Bacterial susceptibility is variable and varies considerably among geographical areas and laboratory facilities. The use of α-2 agonists with intravenous TMPS should be avoided.
On the basis of the available published evidence, TMPs can be suggested as empirical treatment for the following conditions in foals: perioperative antimicrobial coverage, diarrhea (against translocating bacteria via the affected gut wall and sepsis), most pneumonia causes (except Rhodococcus spp and pulmonary abscesses), wounds, septic arthritis, osteomyelitis, and umbilical infections (without associated abscessation). In the presence of purulent or necrotic tissue, TMPs is not a treatment of choice. However, following surgical debridement and/or ligation, it can be considered a reasonable choice. Foals presented for sepsis should be administered TMPs empirically only if the general TMPs susceptibility in the respective geographic area is known to be good and in cases in which short or no hospitalization periods (i.e., lower risk of development of resistant nosocomial infections) are anticipated.

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