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## Antimicrobial therapy for horses

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In recent years, there have been important changes in antimicrobial therapy in equine practice. New antimicrobials are available and a larger database of pharmacokinetic information allows for more accurate drug dosing. Concerns over drug residues in food animals and antimicrobial resistance has led to the development of the Canadian Veterinary Medical Association's Prudent Use Guidelines.<sup>1</sup> These guidelines stress obtaining a diagnosis and selecting appropriate antimicrobial therapy. In practice situations, it is often difficult to submit samples for microbiologic culture and antimicrobial susceptibility testing. In addition, it may not be prudent to delay treatment until such results are available. Empirical antimicrobial selection has been based on data from university teaching hospitals and veterinary diagnostic laboratories in eastern Canada, the United States, and even Europe.<sup>2-6</sup> However, these data do not necessarily reflect the pathogens and the antimicrobial susceptibility patterns from clinical cases in western Canada.

Recently, the authors analyzed the Prairie Diagnostics' database of equine bacterial submissions from the Large Animal Clinic of the Western College of Veterinary Medicine (WCVM) for the years 1998-2002. A total of 542 equine case samples were submitted during this period. Positive cultures were obtained from approximately 60% of cases and nearly 500 pathogens were identified and tested for antimicrobial susceptibility (Table 1). This information was entered into a Microsoft Access database and the results were analyzed with SPSS. This issue of *Large Animal Veterinary Rounds* reviews the results of this analysis and may suggest therapeutic direction for the practicing veterinarian.

### Bacteria associated with infections in horses

The Gram-positive bacteria, *Streptococcus equi* subspecies *zooepidemicus* was the most common cause of bacterial infection from all sites sampled (21% of isolates). This was followed by *Escherichia coli* (11%), *Actinobacillus suis* (7.5%), alpha-streptococci (6.1%) and *Actinobacillus equuli* (5.3%). Most of these isolates are commensal organisms of horses. Since the equine caseload at the WCVM has a strong primary care component, this distribution of pathogens is likely to be similar to cases seen in private practice, but it is very different when compared to data from teaching hospitals in the United States with a more tertiary care caseload, where staphylococci and Gram-negative pathogens are the most common isolates from equine infections.<sup>5,7,8</sup>

At the WCVM, infections caused by virulent pathogens such as *Staphylococcus aureus* and *Pseudomonas* species (spp) are relatively uncommon (24/493 and 42/493, respectively). These infections are associated with severe pathology and their antimicrobial susceptibility reflects previous antimicrobial use. Infections from *Streptococcus equi* subspecies *equi* are also relatively uncommon, composing only 4% of isolates. The low number of *S equi* isolates is most likely due to practitioners not submitting samples from obvious cases of "strangles." *Rhodococcus equi* (0.8%) and *Salmonella* spp (0.6%) appear to be infrequent causes of bacterial infections in horses from western Canada.

### Respiratory tract infections

Respiratory tract disease is common in horses and the respiratory tract was the most frequently sampled site in the study:

- 171 isolates were cultured from 107 transtracheal washes
- 39 isolates cultured from 24 nasal swabs



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**Table 1: Antimicrobial susceptibilities (% of isolates) from equine infections (1998-2002)**

Organism	No. of Isolates	Amp	Pen	Amp/Sulb	Cef	Ceph	Enro	Amik	Gent	Eryth	Tet	TMS
<i>Actinobacillus equuli</i>	26	92	80	100	100	100	100	56	92	46	96	92
<i>Actinobacillus</i> spp.	16	94	76	91	94	93	100	67	81	12	88	94
<i>Actinobacillus suis</i>	37	81	46	100	100	97	97	40	73	30	84	97
<i>Actinobacter</i> spp.	6	80	17	100	83	67	100		100	33	67	100
<i>E coli</i> (hemolytic)	4	50	0		100	50	100	100	100	0	100	75
<i>E coli</i> (non-hemolytic)	53	62	0	85	96	51	92	100	86	4	69	60
<i>Enterobacter</i> spp.	23	36	4	71	91	35	96	80	91	13	52	83
<i>Enterococcus</i> spp.	16	94	94	100	25	31	38	50	81	50	62	56
<i>Klebsiella</i> spp.	5	0	0	100	100	60	100	100	80	0	60	100
<i>Klebsiella pneumonia</i>	5	0	0	75	80	80	60	100	80	0	80	60
<i>Pasteurella</i> spp.	11	100	91	100	100	100	100	100	100	100	100	100
<i>Proteus vulgaris</i>	6	17	0	67	100	0	100	100	100	0	17	67
<i>Pseudomonas</i> spp.	21	29	19	63	40	19	67	100	71	10	48	57
<i>Pseudomonas aeruginosa</i>	21	5	0	12	10	0	21	100	55	0	0	0
<i>Rhodococcus equi</i>	4	75	50	100	75	50	100	100	100	100	75	50
<i>Salmonella</i> spp.	3	100	0		100	100	100	100	100	0	67	100
<i>Serratia</i> spp.	9	22	0	50	89	11	78	100	100	0	11	89
<i>Staphylococcus aureus</i>	24	43	43	94	96	100	95	100	100	78	96	100
<i>Staphylococcus intermedius</i>	5	60	60	100	100	100	100		100	80	100	100
<i>Staphylococcus</i> spp.	22	50	45	93	86	95	95	100	86	86	77	91
<i>Staphylococcus equi</i>	18	100	100	100	100	100	93	0	93	100	89	72
alpha- <i>Streptococcus</i> spp.	30	87	87	83	100	100	78	33	100	90	90	76
<i>Streptococcus zooepidemicus</i>	104	95	97	87	100	100	91	9	93	92	53	47

Amp: ampicillin; Pen: penicillin; Amp/Sulb: ampicillin/sulbactam; Cef: ceftiofur; Ceph: cephalothin; Enro: enrofloxacin; Amik: amikacin; Gent: gentamicin; Eryth: erythromycin; Tet: tetracycline; TMS; trimethoprim/sulfonamide

- 25 isolates cultured from 19 guttural pouch washes
- a few isolates were also obtained from cultures of lung and pleural fluid.

From all sites except the guttural pouch, the most common isolate involved was *S zooepidemicus* (22%). The next most common pathogens were *A suis* (12%), *A equuli* (7%) and alpha-streptococci (7%). In guttural pouch washes, *S equi* was isolated most often (24%), followed by *A suis*, *S zooepidemicus* and *A equuli*. In chronic cases of pleuropneumonia with considerable respiratory pathology, opportunistic pathogens such as *Pseudomonas* spp, *Enterobacter*, *Serratia* spp, and *Staphylococcus aureus* were cultured. The role of *S zooepidemicus* and *S equi* in equine respiratory tract infections has been well documented.<sup>3,9-16</sup> *S zooepidemicus* is considered normal flora of the upper respiratory tract and *S equi* is known to cause persistent, asymptomatic, guttural pouch infection in horses.<sup>17,18</sup>

Penicillin, ceftiofur and trimethoprim/sulfonamides (TMS) are the usual first line treatment choices for streptococcal infections in horses (Table 2).<sup>8</sup> The results of the WCVM study support the use of penicillin and ceftiofur for treatment of bacterial sinusitis and guttural pouch infections since there was a high degree of susceptibility to these antimicrobials. Of the *S zooepidemicus* isolates, 97% were susceptible to penicillin and

100% were susceptible to ceftiofur. Of the *S equi* isolates, 100% were susceptible to both penicillin and ceftiofur. Only 47% of *S zooepidemicus* and 72% of *S equi* isolates were susceptible to TMS. The susceptibility of *S zooepidemicus* to TMS is much less at the WCVM than that reported at veterinary teaching hospitals in other countries.<sup>4,5,7,8</sup> The availability of TMS products for horses varies between countries and this influences bacterial susceptibility to these products. Because of the availability of injectable formulations and the convenience of oral dosing, TMS is frequently administered to horses in western Canada. This may explain the high level of resistance documented in the WCVM isolates.

Other antimicrobials with good activity against *S zooepidemicus* were ampicillin (95%), cephalothin (100%), and erythromycin (92%). Only 53% of isolates were susceptible to oxytetracycline. For *S equi* isolates, 100% were susceptible to ampicillin, cephalothin, erythromycin, and ampicillin/sulbactam, while 89% were susceptible to oxytetracycline.

Pleuropneumonia is often polymicrobial in horses; the initial colonization of the lower respiratory tract with *S zooepidemicus* is followed by an invasion of Gram-negative and anaerobic pathogens.<sup>3,11</sup> The Gram-negative bacteria *A suis* and *A equuli* were the most common isolates from pneumonia and

**Table 2: Suggested antimicrobial protocols for respiratory disease**

**Bacterial sinusitis, "strangles," guttural pouch empyema**

- Sodium or potassium penicillin G: (10,000-40,000 IU/kg q 6 hr IV or IM)
- Procaine penicillin G: (22,000 IU/kg q 12 hr IM)
- Ceftiofur: (2.2-4.4 mg/kg q 24 hr IM)

**Alternate choices**

- Sodium ampicillin (10-40 mg/kg q 6 hr IV)
- Cephalothin or cefazolin (11 mg/kg q 6 hr IV)
- Erythromycin (estolate, ethylsuccinate or stearate) (20-25 mg/kg q 8 hr PO)

**Pneumonia (uncomplicated)**

- Penicillin G or sodium ampicillin or ceftiofur

**Pleuropneumonia**

- Penicillin G or sodium ampicillin or ceftiofur
- Gentamicin (4.4-6.6 mg/kg q 24 hr IV, SC, IM)
- Metronidazole (20-25 mg/kg q 8 hr PO)  
or
- Penicillin G or ampicillin or ceftiofur
- Enrofloxacin (5 mg/kg IV or 10 mg/kg PO q 24 hr)
- Metronidazole

pleuropneumonia cases after *S. zooepidemicus*. This is in contrast to a previous study that found *E. coli* and *Pasteurella* spp to be the most common Gram-negative isolates.<sup>3</sup> More virulent pathogens such as *Pseudomonas* spp, *Serratia* spp and *Staphylococcus aureus* were isolated from more chronic cases with severe pathology. Because most infections are polymicrobial, antimicrobial therapy needs to target streptococci, Gram-negative, and anaerobic therapy. No single antimicrobial product tested provides this coverage; therefore, combination therapy is required for effective therapy.

Of all isolates tested, *Actinobacillus* spp had the greatest susceptibility to TMS, with >90% of isolates being susceptible. However, susceptibility to TMS of the other Gram-negative isolates (*E. coli*, *Pseudomonas*, *Enterobacter*, *Serratia*, and *Klebsiella* spp) varied considerably. Less than half of *A. suis* isolates were susceptible to penicillin. The *Pasteurella* spp isolates were highly susceptible to all tested antimicrobials, with 91% susceptible even to penicillin. Enrofloxacin or gentamicin showed the greatest activity against the respiratory pathogens isolated at the WCVI, however, neither drug is efficacious against obligate anaerobes and there was variable susceptibility of *Pseudomonas* and *Klebsiella* spp to both drugs.

Previous studies have reported a high incidence of anaerobic infections in horses with pneumonia or pleuropneumonia (25%–46%).<sup>3,19</sup> Anaerobes are likely to be present in those cases with a putrid breath odour, although the lack of a putrid odour does not rule-out the possibility of an anaerobic infection.<sup>19</sup> In the WCVI study, only 7 anaerobes were isolated

from transtracheal washes, and these tended to be from cases with advanced disease. Two of the isolates were *Bacteroides* spp. Antimicrobial therapy targeted against anaerobes is relatively easy and inexpensive; a previous study has suggested improved survival rates of horses with pleuropneumonia if attention is given to treatment of anaerobes.<sup>19</sup> The role of *Mycoplasma* spp in equine respiratory tract infections is uncertain, but it appears to be an opportunistic infection.<sup>20,21</sup> *Mycoplasma* spp were isolated from only 6 horses with respiratory disease at the WCVI and all of the cases were part of chronic, mixed infections.

Bacterial pneumonia is most commonly caused by *S. zooepidemicus*. Uncomplicated cases are likely to respond to penicillin or a cephalosporin. From the WCVI data, the most logical treatment choice for pleuropneumonia is a combination of penicillin, ampicillin, or ceftiofur with gentamicin or enrofloxacin. Oral metronidazole may be added for its ability to penetrate abscessed tissue and its excellent activity against *Bacteroides fragilis*, which has become increasingly resistant to penicillins and cephalosporins.<sup>22</sup> Culture and susceptibility testing from a transtracheal wash or pleural fluid sample should always be performed because of the variable susceptibilities of the Gram-negative bacteria. Follow-up samples should be considered as bacterial populations and susceptibility patterns may shift as a disease progresses. The use of gentamicin or enrofloxacin for respiratory infections in horses is extralabel, but consistent with prudent-use guidelines. Practitioners should be familiar with the potential for adverse effects from either of these drugs and should receive appropriate consent from clients before initiating therapy.<sup>8</sup>

## Reproductive tract infections

The second most common site for bacterial culture was the reproductive tract of mares. A total of 43 isolates were cultured from 33 uterine samples and 7 isolates were cultured from 6 vaginal samples. Like the respiratory tract, the majority of isolates were *S. zooepidemicus* (28%). The next most common pathogen was *E. coli* (22%). *Pseudomonas* spp was only cultured from one uterine sample and one vaginal swab. Except for the low prevalence of *Pseudomonas* spp, these results are comparable with previous studies from other teaching hospitals.<sup>23-26</sup>

The role of anaerobic bacteria in endometritis is unclear at this time.<sup>27</sup> The majority of reproductive tract infections are limited to the mucosa and superficial endometrium, therefore intrauterine therapy is the preferred method of treatment. Systemic therapy should be limited to cases of postpartum metritis when the mare shows systemic illness or when a uterine biopsy suggests deep inflammation and infection. Currently, treatment regimens (including drug, dose, frequency and method of infusion) for endometritis in the mare are based more on convenience and practicality than scientific evidence.<sup>26</sup> In Canada, only gentamicin and amikacin are approved for intrauterine use in mares with endometritis. Based on the results from the WCVI study, gentamicin is the first choice for intrauterine treatment of endometritis. Since

only 9% of *S zooepidemicus* isolates were susceptible to amikacin, it should be reserved for Gram-negative infections with documented resistance to gentamicin.

### Urinary tract infections

Infection of the urinary tract in horses typically occurs as an ascending infection from skin and gastrointestinal flora.<sup>8</sup> From the horses with urinary tract infections, 18 cultures grew 26 isolates and the most common pathogen isolated was *E coli* (22%), followed by alpha streptococci (19%). Although found in <10% of urinary tract infections, isolates of *Pseudomonas* spp, *Enterococcus* spp and *Enterobacter* spp were resistant to most antimicrobials. The remaining isolates were varying Gram-positive and Gram-negative bacteria. Susceptibility results are based on achievable plasma concentrations, but most antimicrobials are eliminated in high concentrations in the urine. Therefore, susceptibility results are not always predictive of therapeutic efficacy, and drugs considered “resistant” may be clinically effective. Because some urinary tract infections were due to pathogens highly resistant to most antimicrobials, these results emphasize the need for culture and bacterial identification to determine appropriate therapy. Ceftriaxone appears to be a logical initial therapy due to its elimination in urine and activity against *E coli* and streptococci, but gentamicin or enrofloxacin may be necessary for *Pseudomonas* spp or *Enterobacter* spp infections, and ampicillin is the best choice for enterococcal infections (Table 3).

### Post-surgical infections

In a variety of post-surgical sites, 27 isolates were cultured from 15 submitted samples. A wide variety of Gram-positive and Gram-negative bacteria was isolated, with no one pathogen being identified in the majority of cases. The most common isolates were *S aureus*, *Pseudomonas aeruginosa* and non-hemolytic *E coli*. The staphylococcal and *Enterobacteriaceae* isolates indicate contamination of surgical sites with skin and fecal flora, while *Pseudomonas aeruginosa* is often an environmental opportunist that is given a selective advantage with the routine use of antimicrobials.<sup>28</sup> Although the antimicrobial susceptibility patterns of the Gram-negative isolates were highly variable, the *S aureus* isolates were highly susceptible to cephalosporins, enrofloxacin, aminoglycosides, tetracycline, and TMS. Therefore, culture and susceptibility testing is mandatory for postsurgical infections in order to select appropriate antimicrobial therapy and to identify nosocomial problems.

### Abscesses/wounds/joints/tendon Sheaths

Numerous isolates were grown from samples identified as abscesses, chronic or acute wounds. *E coli* and *S zooepidemicus* were the most common isolates. Joint and

**Table 3: Suggested antimicrobial protocols for urinary tract infections**

- Ceftriaxone (2.2-4.4 mg/kg q 24 hr IM)
- Gentamicin (4.4 mg/kg q 24 hr IV, SC, IM)
- Enrofloxacin (5 mg/kg IV or 10 mg/kg PO q 24 hr)
- Sodium ampicillin: (10-40 mg/kg q 6 hr IV)

tendon sheath fluid samples yielded 18 isolates. There was not one predominate isolate, but *A equuli*, *S zooepidemicus*, *Enterococcus* spp, and *S aureus* were the most common. Previous reports have supported the use of amikacin for musculoskeletal infections in horses because of its efficacy against staphylococci and pseudomonads.<sup>7,29-31</sup> While the WCVI results support the efficacy of amikacin against the *S aureus* isolates (100% susceptible), its activity against the other common isolates was poor. Only a few *S zooepidemicus* were susceptible to amikacin. While gentamicin was poorly effective for musculoskeletal infections in a previous study,<sup>7</sup> it was highly effective (>90%) against the pathogens from the WCVI. Therefore, gentamicin should be considered the first choice for antimicrobial therapy of equine musculoskeletal infections based on its spectrum activity and reduced cost of therapy as compared to amikacin. Ceftriaxone is also an appropriate choice, except in enterococcal infections (Table 4).

### Bacterial keratitis

Eight isolates were cultured from 8 eyes with infectious keratitis. The majority of the infections were due to *S zooepidemicus* (63%). The other isolates were alpha streptococci, *S aureus*, and *Actinobacillus* spp. Although only a small number of cultures were submitted from the WCVI, these results are different from a previous report of 63 cases of infectious keratitis in horses. In that report, 58% of cultured isolates were Gram-positive organisms and 48% were Gram-negative, with nearly 50% of the Gram-negative isolates being *Pseudomonas* spp.<sup>32</sup>

Because of the consequences of nonresponsive or inadequately treated corneal infections in horses, it is reasonable to initiate treatment with broad-spectrum antimicrobial therapy effective against staphylococci and pseudomonads.<sup>33</sup> Gentamicin or triple antibiotic preparations are good initial choices. Triple antibiotic contains

**Table 4: Suggested antimicrobial protocols for musculoskeletal infections**

- Gentamicin (4.4 mg/kg q 24 hr IV, SC, IM) or local therapy by regional perfusion or antimicrobial impregnated polymethylmethacrylate beads
- Ceftriaxone, except enterococcal infections (2.2-4.4 mg/kg q 24 hr IM)

**Table 5: Suggested antimicrobial protocols for neonatal sepsis**

- Sodium or potassium penicillin G (10,000-40,000 IU/kg q 6 hr IV or IM); or
- Sodium ampicillin (10-40 mg/kg q 6 hr IV); or
- Cephalothin or cefazolin (11 mg/kg q 6 hr IV)

**Plus:**

- Gentamicin (6.6 mg/kg q 24 hr IV); or
- Amikacin (21 mg/kg q 24 hr IV); or
- Enrofloxacin (5 mg/kg q 24 hr IV)

**Or**

- Ceftiofur (5-10 mg/kg q 12 hr IV or IM)

neomycin, bacitracin and polymixin. This combination provides broad-spectrum antimicrobial activity. Neomycin has good activity against *Staphylococcus* spp and Gram-negative bacteria. Polymixin B is rapidly bactericidal against Gram-negative bacteria including *Pseudomonas* spp. Due to systemic toxicity, polymixin B is only used topically, so it is not typically included on susceptibility reports from microbiology services. However, *Pseudomonas aeruginosa* veterinary isolates are routinely susceptible to polymixin B.<sup>34</sup> Polymixin B also binds and inactivates endotoxin, reducing inflammation and tissue destruction. Like polymixin B, bacitracin is a topical product not routinely included on susceptibility reports. Bacitracin is active against Gram-positive bacteria, with a mechanism of action similar to the  $\beta$ -lactam antibiotics. Penicillins and cephalosporins are not used as commercial ophthalmic formulations because of the risk of contact sensitization, so bacitracin is their equivalent.

### Neonatal sepsis

Too few isolates were submitted from septic neonatal foals at the WCVM for any meaningful interpretation. Previously published reports indicate that *E coli* is the most common pathogen isolated.<sup>2,5,6,35</sup> However, reports from investigators of sepsis in humans indicate the reemergence of Gram-positive bacteria such as *Enterobacter* spp and *Enterococcus* spp as causative pathogens. This is of great concern because of the tendency for these pathogens to be resistant to multiple antimicrobials.<sup>36</sup> This trend was recently documented in a study of critically ill neonatal foals from Pennsylvania.<sup>5</sup> These studies emphasize the need for culture and susceptibility testing of samples from septic neonates (Table 5).

### Conclusions

The results of this study support routine bacteriological culture and susceptibility testing for infectious equine diseases. Computerization has made it practical to review the data and such reviews need to be conducted periodically

since pathogenic organisms and their antimicrobial susceptibility change with time and may vary on the basis of location or treatment. This study demonstrates that the *in vitro* antimicrobial susceptibility can reliably be predicted for many pathogens and practitioners can use this information to select appropriate antimicrobial therapy. However, Gram-negative bacteria typically have unpredictable susceptibilities and testing is still essential for determining appropriate antimicrobial therapy for these pathogens. Final selection of the optimal antimicrobial must also consider other factors such as the site of infection, pharmacokinetics of the drug, risks of adverse side effects, cost of therapy, and effect of underlying diseases.

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