Synovial sepsis diagnostics and antimicrobial resistance: a one-health perspective

Garett B. Pearson, DVM*; Machiel P. Ysebaert, DVM, MS; Brittany Papa, BS; Heidi L. Reesink, VMD, PhD, DACVS

Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY

*Corresponding author: Dr. Pearson (gbp34@cornell.edu)

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ABSTRACT
This article, as part of the Currents in One Health series, reviews the current state of diagnostics for synovial sepsis. Synovial sepsis is a condition that affects veterinary and human medicine and requires coordinated efforts from both parties, as well as environmental considerations to accurately diagnose and preserve effective treatments. The article discusses best practices to identify the causative agent in septic synovitis, trends in bacterial identification and antimicrobial resistance patterns across common bacterial species, and a one-health perspective to optimize diagnostics across species. Antimicrobial resistance is a challenge facing both human and veterinary medicine and requires mindful and attentive prescribing to reduce the development of antimicrobial resistance and preserve antimicrobials for future application. The current standard of care for bacterial identification in veterinary practice is culture and antimicrobial susceptibility; however, positive culture rates from synovial sepsis cases often remain <50%. Recent developments in advanced bacterial identification present opportunities for improved bacterial identification in synovial sepsis. Increased bacterial isolation will also help guide empirical antimicrobial therapy. Utilizing information and recommendations from both the human and veterinary literature will improve timely and accurate bacterial identification and therefore rapid and effective treatment of synovial sepsis across species and limit the development of antimicrobial resistance.

Keywords: equine, synovial sepsis, antimicrobial resistance, multidrug resistance, bacterial culture

Septic synovitis is an infection of any synovial structure, including joints, tendon sheaths, and bursas, causing inflammation and potentially irreversible damage to the affected structure. Infection within the synovial structure may be due to hematogenous spread of the infective organism, synovial injection or surgery, or traumatic injury or a wound or may be idiopathic. Synovial sepsis is seen in humans, dogs, and horses, with an associated mortality rate reported in all species of up to 9.5% to 11%. Potential sequelae include irreversible cartilage damage and rapidly progressing osteoarthritis in joints, with the additional complications of fibrosis and adhesion formation within tendon sheaths and bursae. These sequelae can lead to persistent lameness that can be performance limiting and negatively impact quality of life. Clinical suspicion of septic synovitis is typically based on history; clinical signs, including swelling, pain, and inflammation around the affected structure; lameness; diagnostic imaging; and synovial fluid analysis. Definitive diagnosis is based on identifying the causative agent in a synovial fluid sample. In veterinary medicine, this is typically done by direct visualization of bacteria on synovial fluid cytology or, more commonly, isolation by synovial fluid culture. However, positive culture rates across species are variable (25% to 70%). Advances in bacterial isolation including matrix-assisted laser desorption ionization–time-of-flight mass spectrometry and 16S rRNA sequencing provide a promising future for a more accurate and timely diagnosis when combined with culture and antimicrobial susceptibility in cases of synovial sepsis. Increased bacterial isolation will also help guide empirical antimicrobial therapy. Utilizing information and recommendations from both the human and veterinary literature will improve timely and accurate bacterial identification and therefore rapid and effective treatment of synovial sepsis across species.
initiated and can be based on the most likely organisms considering the etiology of the infection. However, adjusting antimicrobial therapy on the basis of isolated organism and antimicrobial susceptibility patterns is imperative to the successful treatment of septic synovitis. Antimicrobial resistance (AMR) within bacteria commonly associated with septic synovitis affects both veterinarians and physicians and presents an important challenge to successful treatment. Antimicrobial stewardship should be a priority when treating infected synovial structures, and knowledge of antimicrobials available for use in veterinary practice and which to avoid and reserve for resistant infections in humans is imperative for veterinarians to reduce occurrence and propagation of AMR. In addition to human and veterinary origins, the environment can serve not only as a route for bacterial acquisition but also as a source of resistance factors from environmental microbiota. Continued evaluation of factors affecting positive culture rate, alternative methods of bacterial isolation, periodic reporting of commonly isolated organisms, and identification of emerging AMR within populations affected by septic synovitis will help veterinarians and physicians improve the likelihood of a positive outcome when treating cases of septic synovitis. Ensuring most accurate and judicious antimicrobial therapy will reduce AMR pathogens and conserve effectiveness of higher-tier antimicrobials for use when necessary.

Commonly Isolated Organisms

In 1992, gram-negative bacteria were isolated more frequently than gram-positive in cases of equine septic synovitis. Over the last 10 years, gram-positive organisms have been cultured more frequently from synovial fluid and synovial membrane samples than gram-negative, suggesting a shift over time toward more gram-positive synovial infections or an enhanced ability to culture gram-positive organisms. However, when foals are considered separately from adults, a higher proportion of gram-negative organisms are cultured, likely due to the hematogenous nature of synovial sepsis in foals. The most common equine synovial sepsis isolates during the last decade include *Streptococcus* spp, *Staphylococcus* spp, and *Enterobacteriaceae* spp. *Streptococcus equi* subsp. *zooepidemicus* was the most common *Streptococcus* species isolated, *Staphylococcus aureus* was the most common *Staphylococcus* species isolated, and *Escherichia coli* was the most common *Enterobacteriaceae* isolated. In the last decade, the most common isolates from canine synovial fluid and synovial membrane samples were *Staphylococcus* species, *Streptococcus* species, and *Pseudomonas aeruginosa*. These same species have been reported in canines in previous decades, though *E coli* and *Pasteurella multocida* were also common. In cattle, *Streptococcus* species, *Staphylococcus* species, and *Enterobacteriaceae* are also commonly isolated, though *Mycoplasma* species and *Trueperella pyogenes* are also reported in high proportions in some studies. In humans, *Staphylococcus aureus* and *Streptococcus* species are the most common isolates from cases of nongonococcal septic arthritis, with *E coli* and *P aeruginosa* implicated in a smaller number of cases. To summarize, *Staphylococcus* and *Streptococcus* species are the most commonly isolated bacteria across many species.

Direct culture of synovial fluid has a high rate of false-negative results. Because of this, many cases of synovial sepsis are diagnosed on the basis of synovial fluid cytologic analysis, without a positive bacterial culture. In horses, synovial fluid with a total nucleated cell count > 30.0 X 10^6/L, > 80% neutrophils, and or total protein > 40 g/L is considered infected; however, these parameters may not be met in cases of early sepsis, sepsis after a corticosteroid injection, a draining synovial structure, or infection with a low virulence organism. Gram stain can be used to diagnose synovial sepsis from the presence of intracellular bacteria. Visualization of bacteria is useful for selection of empirical antimicrobial therapy even without direct susceptibility results; however, the absence of bacteria on a Gram-stained smear does not rule out synovial sepsis. Thus, microscopy is often not beneficial in selection of empirical antimicrobial therapy in the absence of positive bacterial culture, and there is a need for improved techniques for bacterial culture from synovial fluid. Diagnostic limitations in cases of synovial sepsis highlight the importance of continued reporting of commonly isolated organisms with pertinent case information to help guide empirical therapy. If empirical therapy is appropriately prescribed, the likelihood of exposing bacteria to ineffective antimicrobials and development of further AMR could be minimized. In addition to scientific reports, centralized databases to which clinicians or laboratories can report case information, isolated organisms, antimicrobial use, and antimicrobial efficacy has the potential to benefit clinicians both within and across species.

Positive Culture Rate

Previously reported positive culture rates from cases of presumptive equine synovial sepsis range from 25% to 70%. With a reported false-negative rate of 50% to 70%, to date, the only submission recommendation aimed at increasing the likelihood of a positive culture is the use of enrichment broth, such as the BACTEC blood culture vials, as the submission container. This finding has been repeated across humans, horses, and dogs and in all species has been found to increase the positive culture rate from synovial fluid samples in cases of septic synovitis. Because of this, many cases of synovial sepsis are diagnosed on the basis of synovial fluid cytologic analysis, without a positive bacterial culture. In horses, synovial fluid with a total nucleated cell count > 30.0 X 10^6/L, > 80% neutrophils, and or total protein > 40 g/L is considered infected; however, these parameters may not be met in cases of early sepsis, sepsis after a corticosteroid injection, a draining synovial structure, or infection with a low virulence organism. Gram stain can be used to diagnose synovial sepsis from the presence of intracellular bacteria. Visualization of bacteria is useful for selection of empirical antimicrobial therapy even without direct susceptibility results; however, the absence of bacteria on a Gram-stained smear does not rule out synovial sepsis. Thus, microscopy is often not beneficial in selection of empirical antimicrobial therapy in the absence of positive bacterial culture, and there is a need for improved techniques for bacterial culture from synovial fluid. Diagnostic limitations in cases of synovial sepsis highlight the importance of continued reporting of commonly isolated organisms with pertinent case information to help guide empirical therapy. If empirical therapy is appropriately prescribed, the likelihood of exposing bacteria to ineffective antimicrobials and development of further AMR could be minimized. In addition to scientific reports, centralized databases to which clinicians or laboratories can report case information, isolated organisms, antimicrobial use, and antimicrobial efficacy has the potential to benefit clinicians both within and across species.
The goal of clinical microbiology is to identify microbial isolates to identify the etiological agent and likely most effective antimicrobial therapy. In most veterinary diagnostic laboratories, bacterial identification is performed primarily by culturing the microorganism out of a clinical sample, followed by morphologic and phenotypic description of the isolate. Cultures are then compared with the standard references, such as the ATCC Bacteriology Culture Guide. Unfortunately, the characteristics of the isolates often do not perfectly match with the published tables of characteristics, nor the various designed schemes or computer programs to identify the isolates. Consequently, this leads to variation among laboratories regarding the most probable identification of strains. Moreover, when cultures are negative, identification is impossible and antimicrobial therapeutic treatment choice is nonspecific, delayed, empirical, or even erroneous, which can result in poor stewardship and/or potential clinical disastrous consequences.

A study in the 1980s demonstrated phylogenetic relationships of bacteria by comparing the stable part of the genetic code of bacterial DNA. The highly conserved genes coding for 5S, 16S, and 23S rRNA with the variable spaces are now used for taxonomic assignment and referred to as metagenomics. In metagenomics, all nucleic acids are extracted from a clinical sample, sequenced, and compared to a microbial database for exact genotypic classification, identification, and characterization of drug resistance. The theoretical advantages of the 16S rRNA approaches include a more rapid turnaround time (< 10 hours for some techniques), a higher sensitivity, and more exhaustive bacterial identification. However, further standardization of the methods for clinical implementation are still required. Even though more affordable sequencing equipment has been developed in the last decade, the technology remains expensive for individual clinical sample analysis. Variations that may have a place in the future of diagnosing septic synovitis include 16S rRNA sequencing, metagenomic next-generation sequencing, metagenomic shotgun sequencing, antigen microarrays, and mass spectrometry. More efficient clinical diagnosis of septic processes with subsequent better stewardship of antimicrobial treatment choices and clinical outcomes is becoming commonplace in human medicine with increasing implementation in veterinary medicine. In the meantime, empirical antimicrobial therapy should still be based on most likely etiologic agent deducted from case-specific information or guided by culture and susceptibility.

Figure 1—A proposed approach to improve diagnosis and treatment of synovial sepsis. Figure created with BioRender.com.

Antimicrobial Resistance

AMR is a global public health threat that jeopardizes the state of modern medicine. Reducing AMR requires a coordinated one-health directive from the human, veterinary, and environmental sectors to develop or repurpose antimicrobials, utilize alternative therapies, improve diagnostics, and prevent infection. Currently, AMR costs the US medical system approximately $16 billion annually. Restrictions on the use of antimicrobials as growth promoters and reduction in antimicrobial prophylaxis are critical areas of improvement for veterinarians. The majority of antimicrobials used in both human and animal medicine are poorly metabolized, resulting in the antimicrobial being excreted into the environment unchanged. Even if the antimicrobial is released into the environment at subclinical levels, they can still contribute to the generation of AMR by upregulating the rate of mutation and gene transfer. All medical fields should be targeting antimicrobial therapy appropriately, reinforcing the importance of accurate and timely diagnostics. Continued funding and support of organizations aimed at combating AMR, such as the Innovative Medicines Initiative, the Global Antibiotic Research and Development partnership, and FIND, is necessary.
Studies have shown that up to approximately 94% of *E. coli* isolates from urinary tract infections in the US are resistant to the most common medication used to treat them.\(^\text{31}\) Trends in AMR in veterinary medicine are difficult to study because the numbers are not compiled, making generation of a study with sufficient power difficult. A study\(^\text{32}\) from 2018 reported that 66.3% of *Staphylococcus* spp cultured from horses between 1993 and 2009 were resistant to at least 1 antimicrobial, and 25% were multidrug resistant. Isolates had the highest rate of AMR to β-lactams and aminoglycosides.\(^\text{32}\) Another study\(^\text{31}\) in horses identified an increase in resistance in *E. coli* and *Streptococcus* spp to many commonly used antimicrobials including enrofloxacin, ceftiofur, gentamycin, tetracyclines, and trimethoprim sulfad from a study period of 1999 to 2012. AMR in equine practice is thought to be stable or slowly increasing over time but has been described as a tsunami in human medicine.\(^\text{34}\) However, this is likely due to underreporting and absence of studies in the equine literature. While there are still few surveillance studies in the canine literature, evidence points toward an increase in multidrug-resistant isolates.\(^\text{55–58}\) Antimicrobial stewardship is the principle of intentional practices aimed at sustaining the efficacy of antimicrobial drugs in the face of resistance.\(^\text{54}\) This is imperative to human and animal health. It is important that veterinarians practice with intention to reduce the development of AMR, not only for animal health, but for human health as well. Animals and humans share a close bond, and AMR isolates can be transferred from animals to humans.\(^\text{59–62}\) The consideration that domesticated animals could act as a source for community-acquired infections in humans is important, and AMR would only complicate this situation.\(^\text{63}\) Many antimicrobials listed as prioritized critically important by the WHO have shown increased resistance in horses.\(^\text{27,53}\) First-line treatment with medications such as third-generation cephalosporins and fluoroquinolones should be discouraged, as the efficacy of these antimicrobials should be reserved for future use. Not only is the antimicrobial selection important, but dosing should be based on pharmacokinetics studies to ensure efficacy. Exposure to subtherapeutic concentrations or inappropriate frequency of administration contributes to development of resistance.

The British Equine Veterinary Association “Protect ME” toolkit is an award-winning model of antimicrobial stewardship that was introduced in 2012 and updated in 2020 as an encouragement for equine practitioners to develop protocols and policies for the prudent use of antimicrobials. The European Medicines Agency developed a categorization of antimicrobials with route of administration to promote responsible prescription to protect human and animal health.\(^\text{55}\) Surveillance strategies for AMR bacteria have been developed to promote stewardship for antimicrobial use, but they are lacking in veterinary medicine.\(^\text{66–68}\) Based on several studies performed to characterize the antimicrobial use patterns of equine practitioners in Europe and the US, the aminoglycosides and potentiated sulfonamides appeared the most common class of antimicrobial prescribed in equine referral practices in the US.\(^\text{69,70}\)

Studies have highlighted the need for improvement in bacterial identification and susceptibility testing, perioperative antimicrobial use, and biosecurity in equine hospitals to reduce the future impact of AMR infections not only on veterinary medicine, but human medicine as well.\(^\text{54,70}\) In the US, human healthcare utilizes surveillance techniques to analyze and disseminate AMR information, enabling effective control methods, detection of trends, and guided stewardship efforts.\(^\text{71}\) To the authors’ knowledge, no such system is available in veterinary medicine.

### Closing Thoughts

Utilizing information provided from both human and veterinary literature regarding the optimization of diagnostics, continued promotion of research directed at efficient and cost-effective bacterial isolation, and continued reporting of isolates and antimicrobial susceptibility patterns are critical components to improving diagnosis and enabling timely therapy for patients of all species with septic synovitis. AMR is a global health threat that requires cooperation of both veterinary and human medicine as well as environmental consciousness. Antimicrobial stewardship and more ubiquitous reporting may help to facilitate appropriate antimicrobial prescribing and reduce development of AMR.

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