Equine Synovial Sepsis - A Systematic Review of the Literature

Honors Thesis

Presented to the College of Agriculture and Life Sciences,

Cornell University

in Partial Fulfillment of the Requirements for the

Biological Sciences Honors Program

by

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May 2022

ABSTRACT

For my thesis I performed a systematic review of the literature on equine synovial sepsis covering 1990-July 2021 using appropriate PICOS criteria. Of the 541 studies initially screened, 110 were retained in the final review. These were first reviewed from the perspective of the etiology of synovial sepsis, the frequency with which specific synovial structures were involved, and survival rates to discharge for foals and adults. Return to soundness and athletic performance were also analyzed for adults. The microorganisms most commonly identified and the prevalence of antimicrobial susceptibility were also reviewed. The most common cause of synovial sepsis in adults was trauma (70%) compared to hematogenous infection in foals (96%). Overall the most common form of synovial sepsis was septic arthritis, with the tarsus being the most affected joint in adults. The digital flexor tendon sheath and navicular bursa were the most commonly affected tendon sheath and bursa respectively. Survival rates to discharge ($p=0.03$) were higher in adults (83%) than foals (63%), but did not change over time ($p=0.17$). Rates of survival, return to soundness, and return to athletic performance did not differ for adults with septic arthritis, tenosynovitis, or bursitis. In adults the most common organisms isolated were *Staphylococci*, *Streptococci*, and *E.coli*, compared to *E.coli, Rhodococcus equi*, and *Actinobacillus* spp, in foals. Although antimicrobial data was limited, the prevalence of antimicrobial resistant coagulase-positive *Staphylococci* increased over the duration of the study. Prevalence of antimicrobial resistant coagulase-negative *Staphylococci* and beta-hemolytic *Streptococci* varied between antimicrobials.

INTRODUCTION

The objective of this thesis was to perform a systematic review of the literature from 1990-2021 on synovial sepsis in horses. Papers were selected using the search terms “equine OR horse AND synovial sepsis OR joint sepsis OR tenosynovitis OR bursitis”. These papers were then sorted based on age, group of affected animals (foals or adults), structures affected, microbes isolated, and antimicrobial sensitivity testing data, and the results were aggregated and analyzed to look for trends in case outcome, types of microorganisms isolated, and antimicrobial sensitivity of microbial isolates. In this thesis introduction I will first discuss the normal structure and function of the synovial membrane, important components of other synovial structures, and the damage that occurs during sepsis, before discussing the significance of synovial sepsis in equine veterinary medicine.

The Normal Synovial Membrane, Structure, and Function of Synovial Joints

Normal synovial joints (also called diarthrodial joints) consist of a number of important structures. The figure below gives a simplified representation of a synovial joint to demonstrate the normal relationship of the synovial membrane to the other important structures such as the articular cartilage, articular capsule, synovial fluid and adjacent bones of a diarthrodial joint.

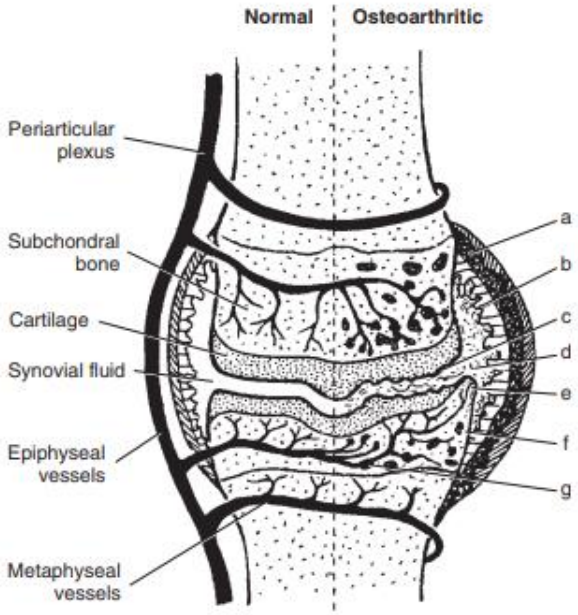

Figure 78-1. A normal synovial joint *(left)*, including articular cartilage, synovial fluid, and synovial membranes, together with changes seen in a joint with osteoarthritis *(right)*. In an osteoarthritic joint, the following abnormalities can be present: *a*, capsular fibrosis; *b*, synovitis; *c*, cartilage failure; *d*, depolymerized hyaluronic acid; *e*, osteophytes; *f*, subchondral cysts; *g*, vascular engorgement. (Modified from March L: Articular Cartilage in Health and Disease. p. 86. In Sambrook P [ed]: The Musculoskeletal System. Churchill Livingstone, New York, 2001.)

Taken from Auer and Stick 2012 Chapter 78 (Frisbie)

Synovial joints are able to articulate smoothly when all of these structures are healthy, and infection of any of these structures can lead to a decreased ability to properly articulate the joint, a reduction in the range of motion, pain in moving the joint, or all of the above.

The synovial membrane, or synovium, is a soft tissue structure that lines some of the space within joints, tendon sheaths, and bursae. It has two layers - the outer intima, which contains fibroblasts and macrophages, and the inner subintima, which is composed of highly vascularized fatty, areolar, and fatty tissues, and is responsible for maintaining

synovial fluid content (Smith 2011, Frisbie 2012). The intima of the synovium is what lines the joint, and the fibroblasts within the intima are responsible for secreting proteins important for proper synovial fluid function. Synovial fluid is formed by ultrafiltration of blood plasma by the capillary network within the subintima of the synovium (Levick 1995). Rate of filtration of blood plasma into synovial fluid is also dependent on mechanical stress, with higher mechanical stress (such as in flexion of a joint) increasing intra-articular fluid pressure, which decreases the rate of filtration of blood plasma into the synovium (Levick 1995). The lubricating capacity of synovial fluid is integral to the normal function of synovial joints, and a key contributor to the lubricating properties of synovial fluid is the protein lubricin. Lubricin is produced by type B synoviocytes in the intimal layer of the synovium and functions by coating the inside of the subintima, and its biochemical properties allow it to prevent cohesion and adhesion of surfaces within the synovium (Frisbie 2012, Flowers et al. 2020). Lubricin is by no means the only protein necessary for proper synovial fluid function. Other important components of synovial fluid include collagen, hyaluronan, and pro-Matrix Metalloproteinases (pro-MMPS) (Frisbie 2012). Maintenance of the synovial fluid is an active process, with synovial fluid volume and concentrations of certain components such as hyaluronan varying based on mechanical stress on the joint (Smith 2011).

Synovial fluid is vital for healthy joint function. If synovial fluid isn't the correct volume or lacks the correct concentrations of important elements like hyaluronan or lubricin, joint degradation will quickly ensue. This is demonstrated in individuals with camptodactyly-arthropathy-coxa vara-pericarditis (CACP) syndrome, a condition in which

the gene that encodes the lubricin protein (PRG4), is mutated, resulting in rapid joint degradation (Marcinelo et al. 1999). However, lubricin and hyaluronan aren't the only important elements of synovial fluid. There are also many biomarkers within synovial fluid that can indicate joint disease, with the most commonly used in veterinary medicine being total protein (TP) and white blood count (WBC) and distribution. The normal TP count in equine synovial fluid is <2g/dl (van Weeren 2016). A normal WBC count in synovial fluid is <500 cells/µl, and a normal WBC composition is 50-500 leukocytes/µl, <10% neutrophils, and >90% mononuclear cells (Frisbie 2012, van Weeren 2016). Even just the color and texture of synovial fluid can indicate whether or not a joint is healthy or infected. Normal synovial fluid is usually "a slightly yellowish, clear, and very viscous fluid"; in contrast, synovial fluid in infected joints is cloudy, and can sometimes adopt a reddish-orange color (van Weeren 2016).

Parameter	Normal	Mild Synovitis (e.g. OCD)	Septic Arthritis
Total Leukocytes (/µl)	50-500	20-250	20-200x10^3
Neutrophils (%)	<10	<10	>90 (variable toxic changes)
Mononuclear cells (%)	>90	>90	<10
Total proteins (g/dL)	0.8-2.5	0.8-3	4.0-8+

Abridged Table, taken from Frisbie and Johnson 2019, Synovial Joint Biology and Pathobiology, in Equine Surgery, Auer et al.

The structure and function of the synovium is very important to understanding the pathophysiology of synovial sepsis. The synovial membrane is the site of entry for synovial infections - this is especially relevant for hematogenous synovial infection, in which microorganisms enter a synovial structure through the bloodstream, but infections can also be spread from neighboring joint structures or through a direct breach in the membrane from an injection or external wound (van Weeren 2016). In synovial infections, a large amount of inflammatory mediators are released including interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNFα), similar to what happens in osteoarthritis, but in much larger amounts (van Weeren 2016). Depending on the causative agent, microorganisms can produce toxins and enzymes, virulence factors, staphylococcal protein A (Palmqvist et al. 2005) and microbial DNA (Deng and Tarkowski 2000) that can directly damage the joint. One of the reasons why the synovium is so readily affected by infection with microorganisms is the large amount of fibrin that is found within an infected joint, providing a scaffold for these organisms to occupy and on which they reproduce. The presence of microorganisms alone can also impede the flow of synovial fluid into the joint cavity, which further compounds the problems associated with synovial sepsis (van Weeren 2016).

Physical damage to the synovial membrane is common in sepsis, with a decrease in extracellular proteoglycan and damage to the collagen network of the synovium being observed (Richardson and Stewart 2019). If left untreated, damage to the associated articular cartilage can become so severe that it can even be observed with the naked eye (van Weeren 2016). In foals, if the infection extends through the subchondral bone and

into the physis, this can have consequences for future limb growth and racing performance (Smith et al. 2004, Hepworth-Warren et al. 2015). Further complications of joint sepsis can include subchondral osteolysis and cyst formation, which in severe cases can carry a poor prognosis for a return to athletic function and in extreme cases for survival.

Overview of Literature on Synovial Sepsis in Horses

Synovial sepsis can be a particularly impactful condition in equines due to the extremely important role their limbs play in normal life, and how reliant they are on pain free locomotion for athletic performance. There are differences between age groups regarding the way in which synovial structures become infected, the specific structures that are typically infected, the types of microorganisms involved, and the possible consequences of the condition. For example, foals are more prone to contracting synovial sepsis as a result of hematogenous spread of microorganisms. The reason for this is foals have a less developed immune system when compared to adults, and if a newborn receives insufficient colostral immunoglobulin from the dam, a condition known as failure of passive transfer of immunity (FPT), the foal will be much more susceptible to infections of any kind (Tyler-McGowan et al. 1997). The greater likelihood of bacterial septicemia in foals compared to adults provides an overall explanation for the increased likelihood of synovial sepsis in this age group compared to adults but there are important features of the vascular anatomy of the physeal area that also make septic arthritis more likely in foals compared to infection of other synovial structures (van Weeren 2016, Wright et al. 2017). Young foals have a transphyseal blood supply that allows bacteria to localize in

the synovial membrane and subchondral bone (van Weeren 2016), as well as highly vascularized epiphyseal vessels towards the articular surface compared to adults (Annear et al. 2011) . As a result, foals are much more likely to contract septic arthritis than either septic tenosynovitis or septic bursitis (Annear et al. 2011, Hepworth-Warren 2015, Glass and Watts 2017).

There are four different types of synovial infection in foals: S, E, P, and T type (Annear et al. 2011). S-type infections are infections limited to the synovium, causing swelling of the joint and surrounding tissue, and are usually seen in foals less than 2 weeks of age. E-type infections affect the joint and the epiphyses of adjacent bones - as a result these more commonly affect joints of long bones, and are frequently seen in 3 to 4 week old foals. P-type infections are infections of the physis, or the growth plate, which have the potential to extend beyond the physis into the joint. Lastly, T-type infections affect the cuboidal bones of the carpus and tarsus, which can then spread to the associated joints. Overall, S- and E-type infections are most common in foals, but more than one type can be seen in the same foal simultaneously (Annear et al. 2011).

In adult horses, synovial sepsis can be caused by three possible routes; following a wound or injury that extends into the joint (Madison 1991, Schneider et al. 1992, Honnas et al. 1992, Meijer et al. 2000, Tremaine 2000, Booth et al. 2001, Frees et al. 2002, Smith et al. 2006), after injection or surgery (defined as “iatrogenically”) (Lapointe et al. 1992, Schneider et al. 1992, Honnas et al. 1992, Hawthorn et al. 2005, Borg et al. 2013, Brunsting et al. 2018), or rarely, from hematogenous spread from somewhere else in the

body (Schneider et al. 1992, Meijer et al. 2000, Byrne et al. 2020). Occasionally the source of the infection is not identified and the cause is referred to as idiopathic (Woodford et al. 2017). While septic tenosynovitis or bursitis is reported in adults more commonly than in foals, septic arthritis is still the most common synovial infection observed in adults. The digital tendon sheath is the most common synovial sheath affected (Honnas et al. 1992, Frees et al. 2000, Smith et al. 2006). Infections of other synovial sheaths such as the tarsal (Santschi et al. 1997, Cauvin et al. 1999), carpal (Hawthorn et al. 2015) and extensor tendon sheaths (Platt and Wright 1997) have also been reported. Reports of septic bursae include involvement of the navicular, bicipital, calcaneal, atlantal, supraspinous and olecranon bursae (Schneider et al. 1992, Vatistas et al. 1995, Honnas et al. 1995, Forrescu et al. 2006, Whitcomb et al. 2006).

Species of Microorganisms Involved in Synovial Sepsis

A wide variety of microorganisms have been found in synovial infections in adult horses and foals. In a retrospective study of 192 horses across all ages, data showed that the most common kinds of Gram positive bacteria found in equine synovial sepsis were hemolytic and non-hemolytic *Staphylococcus* (33 and 18 positive cultures respectively) and *Streptococcus* (22 positive cultures), while the most common types of Gram negative bacteria were enterobacteriaceae (41 positive cultures), *E. coli* (18 positive cultures), and *Pseudomonas* (12 positive cultures) (Schneider et al. 1992). It is also important to note that some cases of sepsis don't yield a positive microbial culture - in the aforementioned study, a total of 43 out of 192 horses (27%) did not yield a positive bacterial culture, but were diagnosed with synovial sepsis using other criteria. Another

study by Frees et al. reported that 35% of cases of synovial sepsis did not yield a positive bacterial culture (Frees et al. 2002). In foals with septic arthritis due to hematogenous infections, the most common group of microorganisms isolated are typically Gram negative bacteria such as *Escherichia coli, Actinobacillus spp., Salmonella spp.,* and *Klebsiella spp*. (Schenider et al. 1992, Annear et al. 2011, Hepworth-Warren et al. 2015). However, one study in 81 foals up to 7 months of age reported that Gram positive infections with *Staphylococcus aureus* and *Streptococcus spp*., were more common – identified in 76% of synovial fluid samples from which positive cultures were obtained (Vos and Ducharme 2008). It is thought that age can be a factor that influences infection type in foals, with foals younger than a month old being much more susceptible to Gram negative infections (Hepworth-Warren et al. 2015). In a study by Hepworth-Warren et al. (2015), 62.5% of 70 synovial fluid samples from foals were Gram negative. Similarly, in a large retrospective of horses of all ages by Schneider et al. (1992) 66% of 52 culture positive synovial fluid samples from foals were Gram negative. *Escherichia coli* is consistently the most common Gram negative species isolated in foals (Schneider et al. 1992, Vos and Ducharme 2008, Annear et al. 2011, Hepworth-Warren et al. 2015). However, there is less consistency between studies as to which is the most common Gram positive organism isolated, two reporting it to be *Staphylococcus aureus* (Schneider et al. 1992, Annear et al. 2011), but another reporting *Staphylococcus epidermidis* (Hepworth-Warren et al. 2015). In foals, *Rhodococcus equi*, a species of Gram positive bacterium, shows a much higher mortality rate compared to other species, due to it being difficult to treat. A retrospective study reported that 10/12 (84%) foals included in the study died as a result of septic arthritis and/or osteomyelitis due to a *Rhodococcus equi*

infection, with 8/10 necropsies reporting severe damage to articular cartilage and surrounding bone (Ruocco et al. 2020).

A retrospective study of 20 adult horses with septic tenosynovitis showed that three had a *Staphylococcus aureus* infection, 2 had *Streptococcus equi*, one had *E. coli*, one had a *Bacillus sp*, one had a *Micrococcus sp*, and seven out of the twenty had no positive culture (Frees et al. 2002). One of the reasons why isolates of *Staphylococcus* are so commonly cultured, especially in cases of adult synovial sepsis, is that many species of *Staphylococcus* are commensal organisms, commonly found on the skin (Van den Eede et al. 2012). Because synovial infections in adults are commonly the result of a communicating wound of some kind, it is logical that these commensal skin organisms can subsequently access a synovial structure to cause sepsis.

Diagnosis of Synovial Sepsis in Horses

Diagnosis of synovial sepsis in equids is commonly achieved using a combination of observations and laboratory tests. Horses with synovial sepsis will commonly show lameness and/or swelling around the affected structure(s), which can be detected by observing the horse. This lameness is generally attributed to joint effusion causing discomfort. Therefore, in horses with a wound allowing egress of synovial fluid, lameness may not always be severe, or even present. As mentioned previously, synovial fluid can be analyzed for biomarkers of synovial sepsis. As previously mentioned, assessment of the color and viscosity of synovial fluid, total protein (TP) count, and white blood cell (WBC) count and distribution is most common (van Weeren 2016).

While there is disagreement in the literature over what values are diagnostic for synovial sepsis in adult horses and foals, the range that commonly qualifies as an elevated TP count is ≥2.5-4 g/dl (Ribera et al. 2011, Wright et al. 2017). Elevated TP count in synovial fluid is supportive of an infection because it means that there is increased blood flow to the damaged synovium (Faryana and Goldenberg 1990). Higher levels of WBCs in the synovial fluid suggests that an immune response is being mounted against an antigen of some kind. Across multiple studies, this elevated WBC count has been defined as being ≥5000-30,000 cells/µl (Smith et al. 2006, Vos and Ducharme 2008, Ribera et al. 2011, Barcelo Oliver et al. 2016, Wright et al. 2017), with one study specifying that in order to be of clinical significance, the relative proportion of neutrophils also had to be elevated to at least $30x10^9$ cells/L (Byrne et al. 2020). Other possible biomarkers of sepsis within synovial fluid can include glucose levels, cartilage oligomeric matrix protein (COMP) and matrix metalloproteinases (MMPs) (Anderson et al. 2018).

Treatment of Synovial Sepsis

Although it can affect a variety of different structures, synovial sepsis is often treated in comparable ways in both adults and foals. Because synovial sepsis is both life threatening and can limit performance, it is important to treat the condition as soon as possible. Antimicrobial therapy is a mainstay of treatment and should ideally be guided by culture and sensitivity testing of synovial samples (Van Weeren 2016, Richardson and Stewart 2019). Empirical antibiotic therapy generally consists of broad spectrum antibiotics (i.e. penicillin, gentamicin, enrofloxacin) given systemically, in addition to local

antibiotic therapy, either by intravenous regional perfusion, or administration directly into the synovial structure. However, with a positive microbial culture, more informed decisions can be made regarding the best antibiotics to use (van Weeren 2016). Systemic administration of antibiotics is especially important in foals because they are far more likely to have microbes circulating in their bloodstream. In addition to antibiotics, aggressive high volume lavage, drainage, and cleaning of the infected synovial structure is another critical component of treatment. This can be achieved by arthrocentesis, arthrotomy or endoscopic arthroscopy (Richardson and Stewart 2019). A common, less invasive technique for removing infected synovial fluid is arthrocentesis, where a needle is inserted into the synovial space to withdraw fluid (Adams et al. 2010). This can be converted to “through and through’ lavage, where two needles are inserted into the synovial space – while sterile isotonic fluid is pushed into one, and the infected synovial fluid is flushed out of the other. One issue with this method is that it can create a “fluid highway” in the synovial space, where some areas have high fluid turnover, and other areas undergo very little flushing of synovial fluid. This can, however, be avoided by massaging the joint to agitate synovial fluid (van Weeren 2016). A more invasive technique for joint lavage is by arthrotomy, whereby the joint space is surgically opened to allow drainage of the synovial fluid (Bertone et al. 1992). Arthroscopy/tenoscopy/bursoscopy are less invasive versions of arthrotomy, where instead of creating a large opening, an endoscopic camera is inserted into the synovial space, allowing the veterinarian to inspect the synovial cavity without needing to open it more extensively. Septic tenosynovitis and bursitis are treated similarly, involving lavage of the synovial structure, debridement of infected tissue, and antibiotics (Platt and Wright

1997, Santschi et al. 1997, Cauvin et al. 1999, Frees et al. 2002, Smith et al. 2006). Indwelling drains may be left in place after surgery for continued treatment post-operatively (Smith et al. 2006).

METHODS

Author disclosure

The authors of this review are English speaking members of a veterinary orthopedics laboratory. All papers that fit the study criteria were included to avoid citation or outcome reporting bias.

Search strategy

Between June 24th and July 3rd, 2021, a systematic literature search was conducted on synovial sepsis in horses. The databases that were searched included PubMed and Web of Science. The search terms were “equine OR horse AND synovial sepsis OR joint sepsis OR tenosynovitis OR bursitis”. No language restrictions were applied in the search strategy, but only articles available in English were considered.

Inclusion criteria

Potential studies were considered eligible for inclusion if the following PICOS criteria were met. **Participants**: foals and adult horses diagnosed with sepsis of any joint, tendon sheath, or bursa. **Interventions**: none required. **Comparisons**: horse age, synovial structure affected, bacteria isolated, antimicrobial resistance. **Outcome**: rates of survival to discharge (long term survival if reported), return to soundness, return to athletic

performance (where available), species of bacteria cultured, and presence of antimicrobial resistant bacteria. **Study Design**: case reports, case series, retrospective studies, and prospective studies published no earlier than 1990.

Exclusion criteria

Potential studies were excluded if sepsis was experimentally or artificially induced, if the study was a review or meta-analysis, if the study was conducted in ponies or draft horses, or if the study was not written in English.

Study selection

One reviewer (MP) screened the title and abstracts of all search results, eliminating obviously non-compatible articles. Three reviewers (MP, HR, GP) independently screened the remaining articles with one reviewer (MP) screening all of the articles, and the other two (HR, GP) screening 108 and 88 papers respectively. Conflicts between reviewers were resolved by discussion amongst all three reviewers.

Statistical analysis

All statistical analyses were performed using Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA) and GraphPad Prism 9 (GraphPad Software Inc., San Diego, CA).

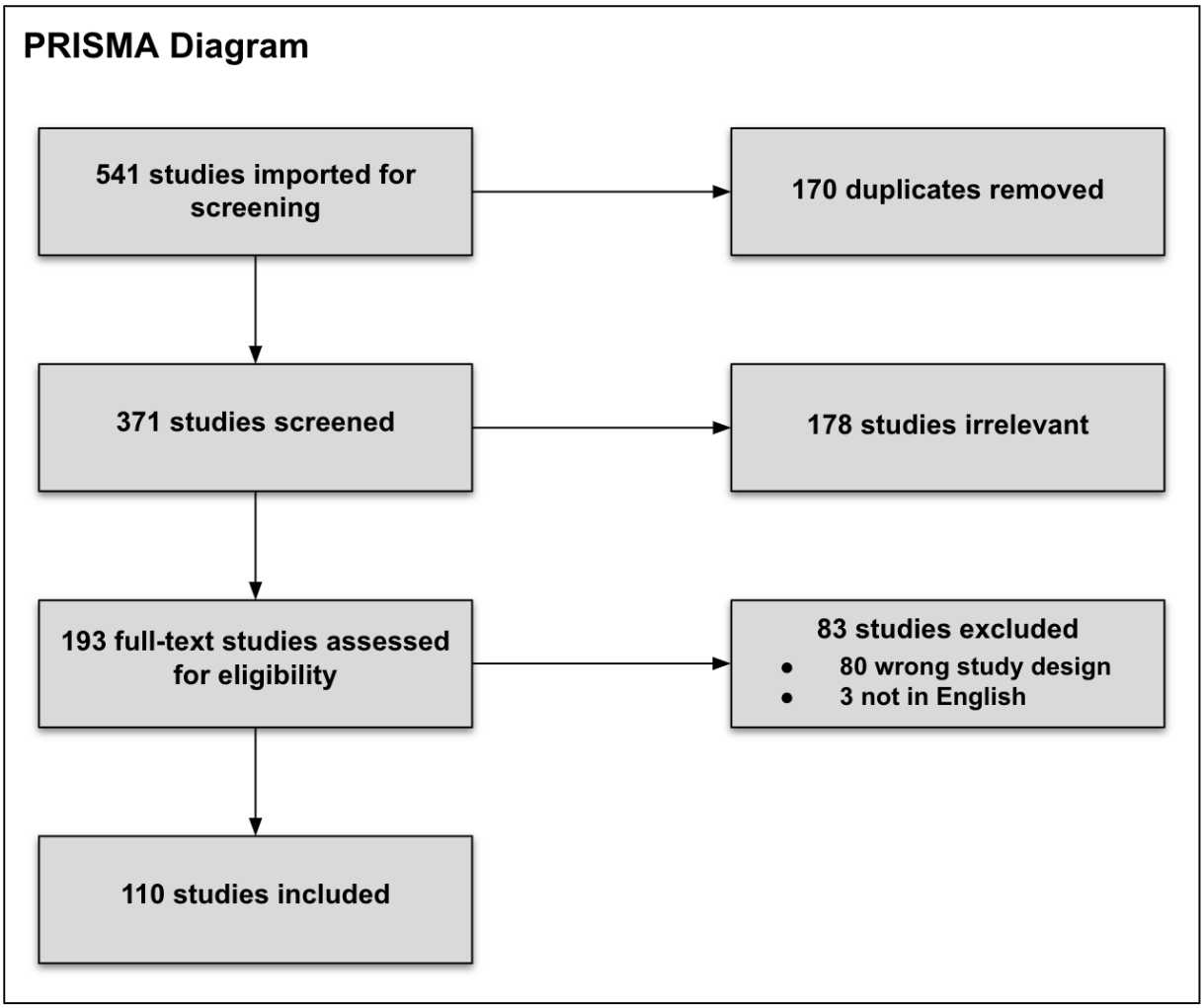

Figure 1. PRISMA Diagram. The search terms yielded a total of 541 results, which were all screened using Covidence v2765 (Veritas Health Innovation Ltd., Melbourne, Australia). There were 170 duplicates, leaving 371 unique studies whose titles and abstracts were screened. Of these, 178 were deemed irrelevant based on title and abstract review, with 193 studies progressing to the full-text screening process. From the 193 studies, 83 studies were excluded in the full-text review: 3 were not available in English; 36 evaluated non-septic structures; 33 used a wrong study design; 8 evaluated sepsis in structures other than joints, tendon sheaths, or bursae; 2 evaluated the wrong

species, and 1 study included experimentally-induced sepsis. In total, 110 studies met the inclusion criteria for this review.

Chapter 1; Etiology and Outcome

Data retrieval and analysis for chapter 1 focused on the etiology, structures affected and outcomes for cases of synovial sepsis in adult horses and foals.

Etiology: For etiology of sepsis, data was analyzed by looking as to how sepsis occurred. Sepsis occurred via one of four possible routes:

i) Traumatic injury to a synovial structure

ii) Introduction of microbes to a synovial structure as a result of a medical intervention (also defined as iatrogenically)

iii) Hematogenous spread of bacteria from the bloodstream to a synovial structure

iv) Cause of sepsis was unknown (also defined as idiopathic)

The frequency with which cases of each of the four routes occurred was obtained and used for data analysis This data was collected for cases of sepsis in adult horses and foals, and for reasons of presentation and analysis both aggregated based on etiology, and separated by age of the horse (adult versus foal). It was hypothesized that the most common etiology of sepsis in adults would be traumatic injury, and in foals, it would be hematogenous spread of bacteria.

Structures Affected: Manuscripts were reviewed and data retrieved regarding which synovial structures were involved in the septic process. Broadly, synovial structures were initially divided into joints, tendon sheaths and synovial bursae. In adults data was collected from all studies that identified cases of synovial sepsis and specified which

synovial structure was involved. If papers reported sepsis of multiple structures from various horses, but did not specify how many cases were of each specific synovial structure affected, they were not included in the construction of data in this category. Within each broad synovial group (joints, tendon sheaths and bursae) the frequency with which a specific anatomic structure was involved was recorded and used for comparative purposes. This data was aggregated to determine which synovial structures were most commonly affected by sepsis. For adults, it was hypothesized that joints would be most commonly affected by sepsis, and that the fetlock would be the most commonly affected joint.

For determining which synovial structures were most frequently affected by sepsis in foals, data was collected from all studies that identified cases of synovial sepsis in foals, and specified which synovial structure was affected. This data was then aggregated to determine which synovial structure; joints, tendon sheaths, or bursae, were most frequently involved. It was hypothesized that foals would be almost exclusively affected by septic arthritis, with very few cases of septic tenosynovitis or bursitis.

Outcome: Survival to discharge was the outcome variable examined in this section and defined in several different ways as follows:

i) Overall rate of survival to discharge from hospital by half-decade (all studies, adults and foals combined). For this category papers were split by year of publication into 7 half-decade groups: 1990-94, 1995-99, 2000-04, 2005-09, 2010-14, 2015-19, and 2020-21.

ii) Overall survival rate to discharge from hospital (all studies, adults and foals) for entire duration of study period (1990-2021)

iii) Overall rate of survival to discharge from hospital , return to soundness, and return to athletic performance (adults only)

iv) Overall survival rate to discharge from hospital by synovial structure (adults only)

Survival rates to discharge from the hospital were expressed as a percentage. Horses that did not survive were euthanized.

Statistical Analyses for Chapter 1

Papers that included fewer than 10 cases were excluded to prevent small sample sizes from disproportionately influencing statistical findings. Normality of data distribution was first determined using a Shapiro-Wilk's test and descriptive statistics using means and standard deviations were calculated where appropriate.

For survival rates over the duration of the study a Welch's One-Way ANOVA was used to determine if there was a difference between groups. It was hypothesized that survival rate would increase over the duration of the study (1990-2021). For comparison of survival rates between adults and foals, a Shapiro-Wilk's test was performed to confirm that the data was normally distributed and a Welch's t test used to determine if there was

a difference between survival rates. It was hypothesized that adults would have a higher rate of survival to discharge than foals.

For determining rates of survival to discharge, return to soundness, and return to athletic performance by category of synovial structure involved (joint, tendon sheath, bursa), papers were also excluded if they reported fewer than 10 cases. Normality of data distribution was determined using a Shapiro-Wilk test. Differences between rates of survival to discharge for cases of septic joints, tendon sheaths, and bursae was compared using a Kruskal-Wallis ANOVA, as data was not normally distributed. Differences between rates of return to athletic performance between cases of septic tendon sheaths and bursae was determined using a Welch's t test as data for this category was normally distributed as appreciated by Shapiro-Wilk's test. There was insufficient data to include the rate of return to athletic performance for cases of septic arthritis in the statistical analysis. It was hypothesized that cases of septic bursitis would have the best outcomes in all 3 categories.

For determining rates of survival to discharge from hospital according to synovial structure involved in adults, papers that included fewer than 10 cases were first excluded to prevent small sample sizes from disproportionately influencing statistical findings. Normality of data distribution was again determined using a Shapiro-Wilk's test and the mean survival rate across all manuscripts for each synovial structure determined. Differences in rates of survival to discharge were determined using Welch's ANOVA.

Chapter 2; Microbiological Isolates

All manuscripts were reviewed for microbiological data and all positive cultures were recorded by genus. For comparative purposes, in adults manuscripts were divided into 3 time periods: 1990-99, 2000-09, and 2010-21 and positive culture results were aggregated by genera for each time period. For foals positive cultures were aggregated over the entire time period of the study. The percentage attributed to each genus was determined for both age groups.

Positive microbiological cultures were further divided into 3 categories for each of the three time periods and aggregated for adults and foals: Gram positive bacteria, Gram negative bacteria, and fungi. Bacterial isolates were further defined morphologically as being Gram positive cocci, rods, and coccobacilli, and Gram negative rods and coccobacilli. The percentages attributed to each group, during each time period were also determined.

Chapter 3; Antimicrobial Resistance Data

Because it was hypothesized that increasing antimicrobial resistance might be a developing problem over the duration of the study the data set was investigated for this issue. Unfortunately, only 2 manuscripts provided sufficient information to make useful comparisons regarding antimicrobial resistance in the treatment of equine sepsis. These papers had 3 categories of bacteria that they both tested for antimicrobial resistance: coagulase positive *Staphylococci*, coagulase negative *Staphylococci*, and beta hemolytic

Streptococci. Bacteria were compared based on which antimicrobial agents were tested. Only data for antimicrobials that both papers tested were included.

RESULTS

Chapter 1

Etiology:

The breakdown by etiology of synovial sepsis in adult horses is depicted in Figure 2. Of the 755 eligible cases from the literature review, trauma was the most common (525/755 or 69.5%), followed by iatrogenic (18.9%, 143/755), idiopathic (9.4%, 71/755) and hematogenous (2.1%, 16/755) causes. By far the most commonly reported cause of synovial sepsis in foals was the hematogenous route (96.4%, 241/250), followed by very small numbers of trauma (2.8%, 7/250) and iatrogenic cases (0.8%, 2/250) (Figure 3).

Structures Affected:

Of the 3 types of synovial structure (joint, tendon sheath, and bursa), joints were the most commonly affected by synovial sepsis in adults, accounting for a total of 57% (1581/2786) of the total cases of synovial sepsis reviewed in the study (Figure 4). However, the most common individual structure to be involved in an adult horse was the digital flexor tendon sheath (DFTS) accounting for 28% (573/2786) of all reports (Figure 4). The joint most commonly affected by sepsis in adults was the tarsus, with 28% (444/1581) of all cases of septic arthritis involving this joint (Figure 5). Following the tarsus, in descending order, the fetlock (21%, 337/1581), carpus (241,1581, 15%), coffin, stifle, pastern, elbow, hip, shoulder and temporomandibular joints were also reported as

being involved in joint sepsis in adult horses (Figure 5). There were 735 cases of septic tenosynovitis identified within the study with sepsis of the DFTS accounting for 78% (573/735) of these reports (Figure 6). Far less commonly involved were the tarsal sheath (9.1%, 67/735) and the carpal extensor sheath (2.6%, 19/735). The bursal structure most commonly affected by sepsis was the navicular bursa, accounting for 46% (217/470) of all reported cases of septic bursitis (Figure 7), although there were almost identical numbers of published reports of septic calcaneal bursitis (46%, 215/470). Much lower numbers of septic bicipital bursitis (4.1%, 19/470) and only occasional reports of sepsis of the infraspinatus, precarpal, intertendinous calcaneal and olecranon bursae were also retrieved (Figure 7).

There were a total of 217 cases of synovial sepsis in foals identified in the study with septic arthritis being by far the most common (94%, 205/217) (Figure 8). Only 4% (9/217) of all cases of synovial sepsis in foals were septic tenosynovitis cases and even less (1%, 3/217) involved septic bursae (Figure 8).

Outcome:

A total of 41 reports were eligible to be used for the comparison of survival rates (for adults and foals combined) in 5 year periods, as shown in Figure 9. Although the lowest survival rate to discharge was documented in the first 5 year period covered by the study (70%, 1990-1994), there was not a statistically significant difference in survival rate over the course of the study ($p=0.17$) (Figure 9). Survival rates for each 5 year time

period were as follows; 1990-94: 71±13%, 1995-99: 93±7%, 2000-04: 83±12%, 2005-09: 86±9%, 2010-14: 79±13%, 2015-19: 85±11%, 2020-21: 88±10%.

The comparison of mean survival rates to discharge between adult horses and foals over the duration of the entire study demonstrated a significantly lower overall survival rate for all cases of synovial sepsis in foals (63%) compared to adults (83%) (p=0.03) (Figure 10).

Overall, high mean survival rates to discharge, return to soundness and athletic performance were documented for each of the 3 types of synovial sepsis in adult horses (Figure 11). Survival rates to discharge for adults (mean, ± s.d) were very similar for each synovial structure; joints (86±14%), tendon sheaths (92±9%) and bursae (85±10%). Very similar results were obtained for return to soundness in adults for each synovial structure; joints (95±8%), tendon sheaths (90±18%) and bursae (89±10%). The mean rates of return to athletic performance were lowest of all the outcome categories, not surprisingly, with 55±40% of adults with a septic joint, 76±23% of adults with septic tenosynovitis and 82±15% of adults with a septic bursa returning to athletic performance. There was no difference between mean rates of survival to discharge (p=0.34), or return to soundness (p=0.67) according to whether a septic joint, tendon sheath, or bursa was involved. Similarly, the return to athletic performance did not differ for adult horses with septic tenosynovitis and bursitis (p=0.40) (Figure 11).

There were 22 reports available to examine survival rates by synovial structure involved in adults (Figure 12). However, these papers only provided sufficient data to

make comparisons in mean survival rates to discharge from hospital for sepsis of the DFTS (87±9%), calcaneal bursa (79±7%), tarsus (78±18%), and coffin (65±10%) in adult horses, and there was no difference in rate of survival between any group (p=0.19) (Figure 12). The groups with insufficient data for statistical analysis were the carpal extensor sheath (100%), navicular bursa (94±9%), fetlock (93±9%), tarsal sheath (92%), and hip (75%).

Chapter 2 – Microbiological Isolates:

Microbiological culture data from the literature was divided into 3 time periods - 1990-99, 2000-09, and 2010-21. For adults with synovial sepsis these results are represented in Figure 13 (1990-1999), Figure 14 (2000-09) and Figure 15 (2010-21). From 1990-99, there were a total of 661 isolates from 16 qualifying studies, with the most commonly isolated genus of microorganism being *Staphylococcus*, comprising 24% (159/661). *Streptococcus* (15%, 99/661) and *E.coli* (10%, 67/661) were the next most common organisms isolated. During the time period 2000-09, there were 146 isolates from 15 studies with *Streptococcus* being the most common genus, accounting for 20% (29/146) of all microbes from 15 reports (Figure 14). *Staphylococcus* (28/146;19%) and *E. coli* (21/146;14%) were the next most common during this time period. For the most recent time period, 2010-21, *Staphylococcus* was again the most common genus, comprising 27% (213/777) of all isolates from 28 reports (Figure 15). *Streptococcus* (143/777;18%) and *Escherichia* (85/777;11%) were again the second and third most common genera isolated during this period.

The most commonly isolated bacterial species in foals was *E. coli,* comprising 26% (27/102) of all isolates across 15 reports for the entire duration of the study (Figure 16). Also of note was that the second and third most common isolates from foals were *Rhodococcus equi* (15%, 15/102) and *Actinobacillus* (13%, 13/102) rather than *Staphylococcus* and *Streptococcus* which were the fourth and fifth most common respectively in this age group.

When the microbiological culture results from all synovial samples were combined for both adults and foals, Gram positive bacteria were the most common type of microorganism, making up 50%, 52%, and 65% of all microbial isolates in each of the 3 time periods respectively (Figure 17). The majority of other microorganisms identified were Gram negative bacteria (42%, 40% and 28% in the 3 time periods respectively) with occasional reports of fungi (1% or less), and approximately 5-10% of all organisms being classified as “unknown”, having provided insufficient information to determine both Gram stain and morphology (Figure 17).

When the bacterial culture results were broken down by morphology for each time period

Gram positive cocci were consistently the most commonly isolated group, comprising 46%, 45%, and 54% of total reports, respectively (Figure 18). Gram negative rods were the second most commonly isolated, comprising 41%, 38%, and 26% of total reports respectively, followed by Gram positive rods (3%, 7%, and 10% of total reports,

respectively), Gram negative coccobacilli (0.61%, 1.5%, and 0.64% of all reports, respectively), and Gram positive coccobacilli (0.64% of all reports from 2010-21).

Chapter 3 - Antimicrobial Resistance:

Unfortunately, data was very limited for antimicrobial resistance, with only 2 studies reporting useful data that permitted comparisons regarding antimicrobial susceptibility testing (Moore et al. 1992 and Gilbertie et al. 2018). Between the publications by Moore et al. 1992 and Gilbertie et al. 2018, which covered the approximate time period of the study, there was an increase in the prevalence of coagulase-positive *Staphylococci* demonstrating resistance to amikacin (0% vs. 46% of isolates reported as resistant), ampicillin (71% vs. 73%), chloramphenicol (4% vs. 19%), erythromycin (5% vs. 35%), gentamicin (29% vs. 54%), penicillin (69% vs. 73%), tetracycline (26% vs. 42%), and trimethoprim-sulfa (21% vs. 35%) (Figure 19). There were no reports of rifampin-resistant coagulase-positive *Staphylococci* in isolates from either study.

With respect to coagulase-negative *Staphylococci* the results were more varied in terms of the development of antimicrobial resistance over the time course of the study (Figure 20). Between the papers by Moore et al. 1992 and Gilbertie et al. 2018, there was an increase in the prevalence of antimicrobial resistant coagulase-negative *Staphylococci* for tetracycline, but a decrease in resistance to ampicillin, erythromycin, gentamicin, penicillin, and trimethoprim-sulfa. There was no change in prevalence of resistance to amikacin (Figure 20). Analysis of the papers by Moore et al. 1992 and Gilbertie et al. 2018, also revealed that there was an increase in the prevalence of antimicrobial resistant

beta hemolytic *Streptococci* with respect to ampicillin, penicillin, and trimethoprim-sulfa, and a decrease in prevalence of resistance amongst this group to amikacin, erythromycin, gentamicin, and tetracycline (Figure 21). There were no reports of any beta hemolytic *Streptococci* resistant to chloramphenicol, although both studies tested for sensitivity to chloramphenicol.

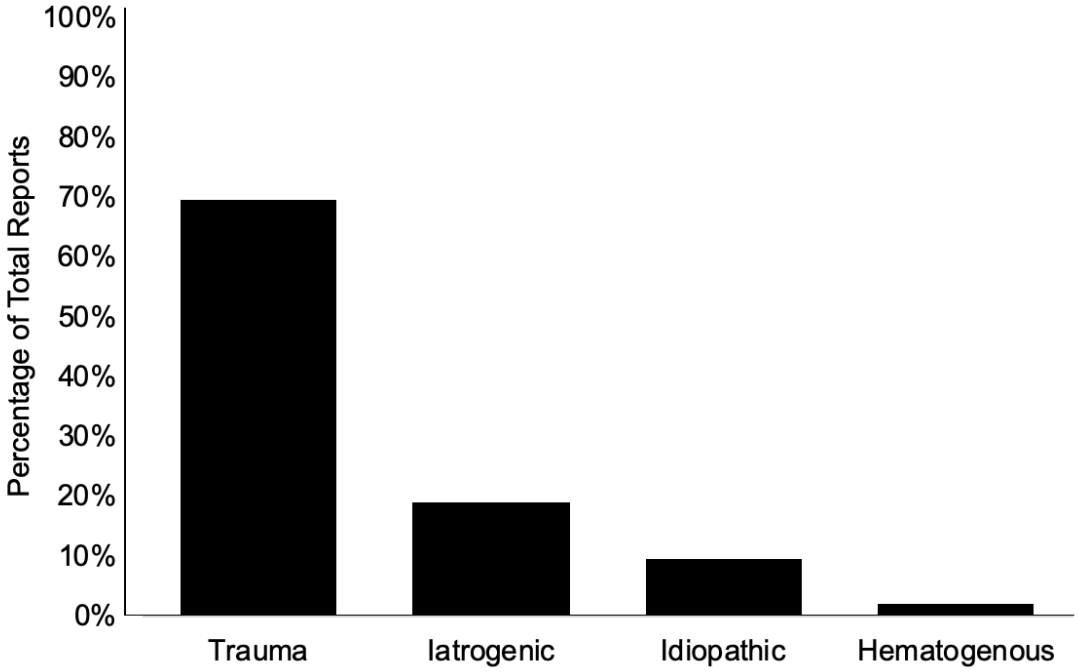

Figure 2. Traumatic Injury was the Most Common Etiology of Synovial Sepsis in Adult Horses. Proportion of Total Cases (n=755) Out of 52 Total Reports. A total of 52 reports provided data on the etiology for 755 cases of adults with synovial sepsis. The most common cause of sepsis in adults was trauma (69.5%, 525/755 cases), followed by iatrogenic (18.9%, 143/755 cases), idiopathic infection (9.4%, 71/755), and hematogenous spread of bacteria (2.1%, 16/755).

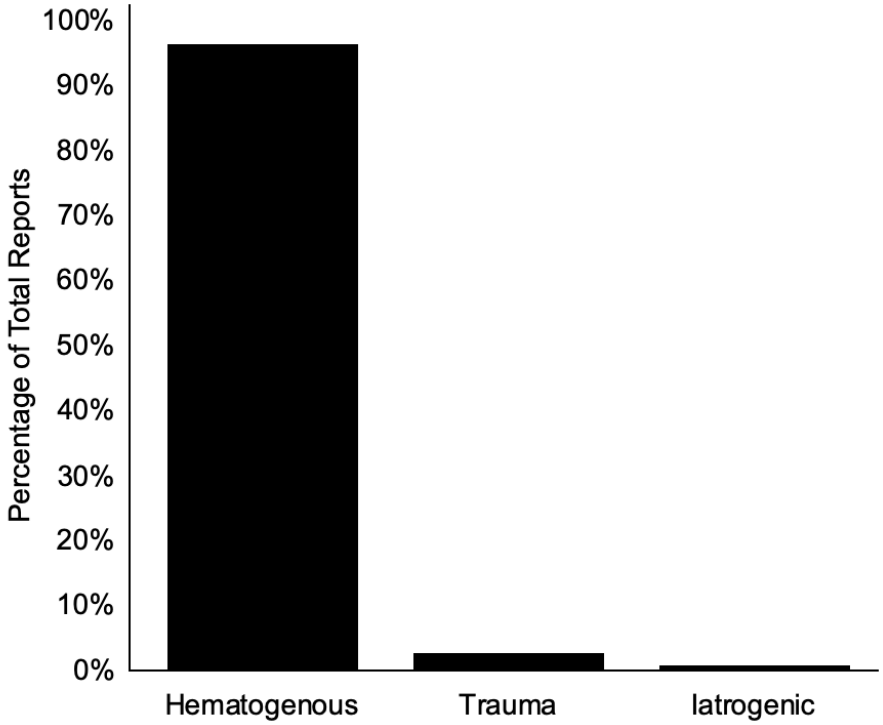

Figure 3. Hematogenous Infection was the Most Common Etiology of Sepsis in Foals. Proportion of Total Cases (n=250) Out of 18 Total Reports. A total of 250 cases from 18 reports provided data on the etiology of synovial sepsis in foals. The most common cause of sepsis was hematogenous spread of bacteria (96.4%, 241/250 cases), followed by traumatic injury (2.8%, 7/250 cases), and lastly by iatrogenic infection (0.8%, 2/250).

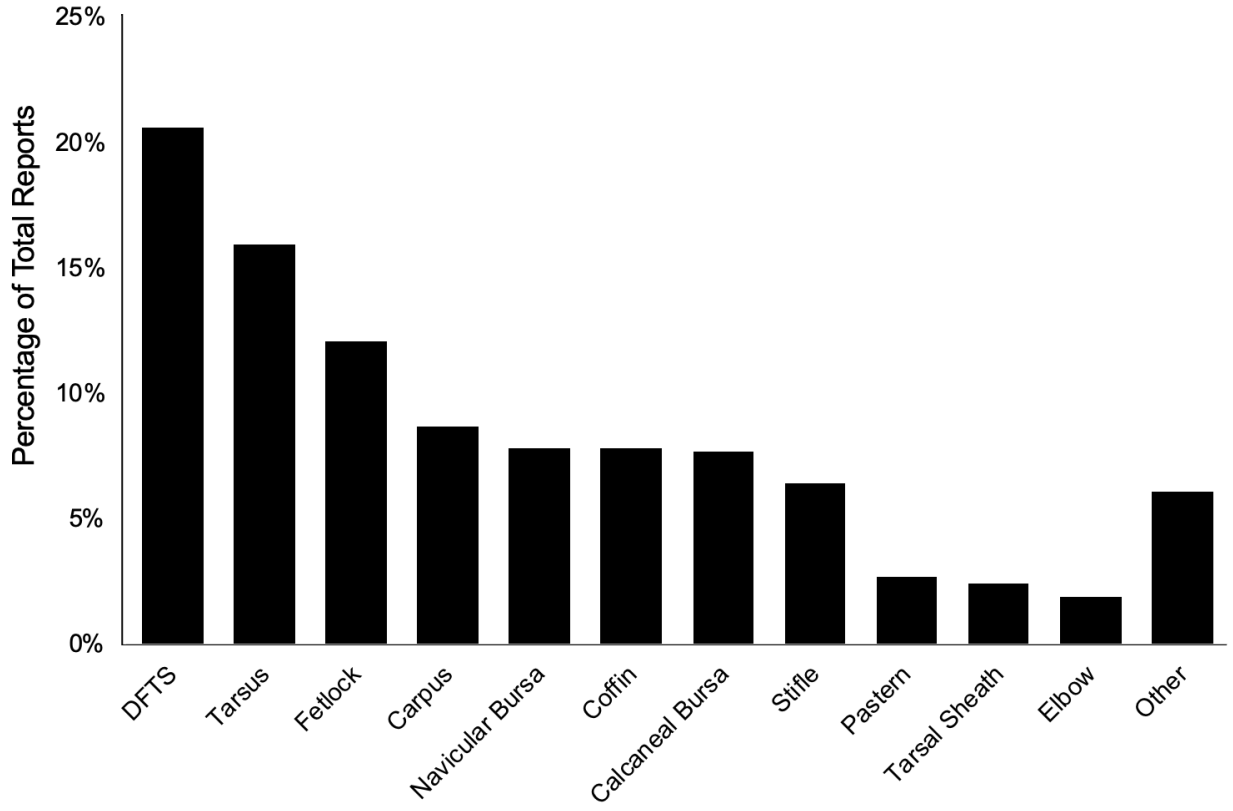

Figure 4. The DFTS was the Most Commonly Reported Septic Synovial Structure. Proportion of Total Cases (n=2,786) Out of 94 Reports. Out of a total of 94 studies that evaluated septic synovial structures, 2,786 septic synovial structures were diagnosed. The structure most commonly affected by sepsis was the digital flexor tendon sheath (20%, 573/2,786), followed by the tarsus (16%, 444/2,786). The most common septic bursa reported was the navicular bursa (7.8%, 217/2,786). Overall, joints were the most commonly affected class of synovial structure with synovial sepsis (1,581), followed by tendon sheaths (735) and bursae (470). Structures were placed in the "Other" category if there were fewer than 20 reports of sepsis across all studies; this group included the bicipital bursa, carpal extensor sheath, hip, shoulder, infraspinatus bursa, and 20 more joints, tendon sheaths, and bursae.

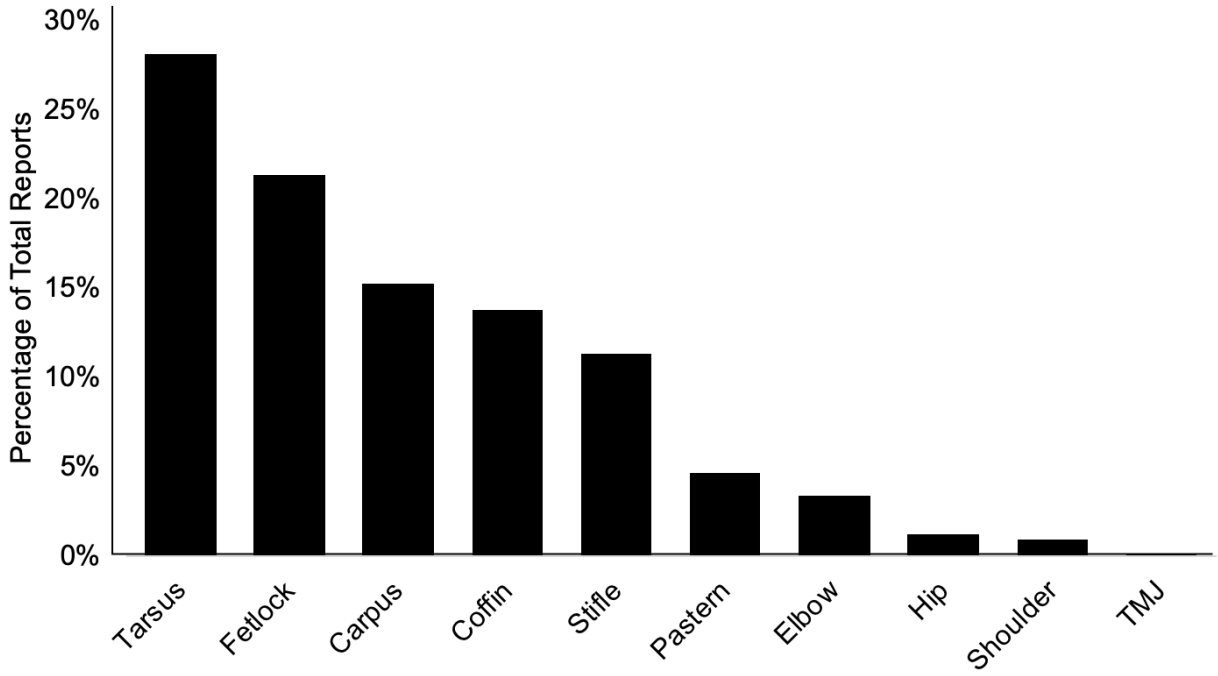

Figure 5. The Tarsus was the Joint Most Commonly Affected by Sepsis. Proportion of Total Cases (n=1,581). A total of 1581 septic joints were reported, with the most commonly affected being those of the tarsus (28%, 444/1,581), fetlock (21%, 337/1,581), and carpus (15%, 241/1,581). Other commonly affected joints were the coffin (13%, 218/1581), stifle, (11%, 179/1581), pastern (4.7%, 74/1581), and elbow (3.4%, 53/1581)

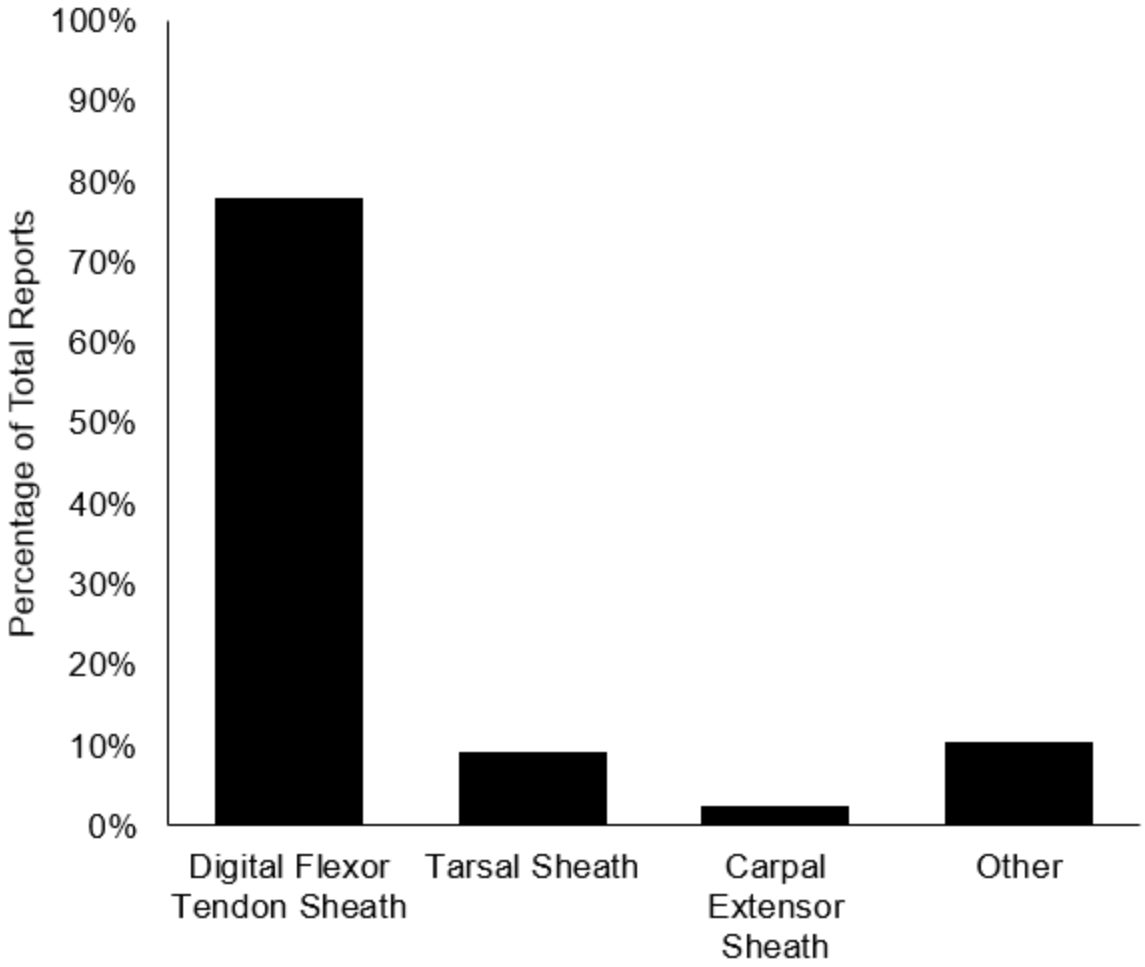

Figure 6. The DFTS was the Tendon Sheath Most Commonly Affected by Sepsis. Proportion of Total Cases (n=735). A total of 735 septic tendon sheaths were reported, with the most commonly affected being the DFTS (78%, 573/735), the tarsal sheath (9.1%, 67/735), and the carpal extensor sheath (2.6%, 19/735). Others included the extensor carpi radialis tendon sheath, extensor tendon sheath, digital extensor tendon sheath, carpal flexor sheath, and the extensor carpi obliquus tendon sheath.

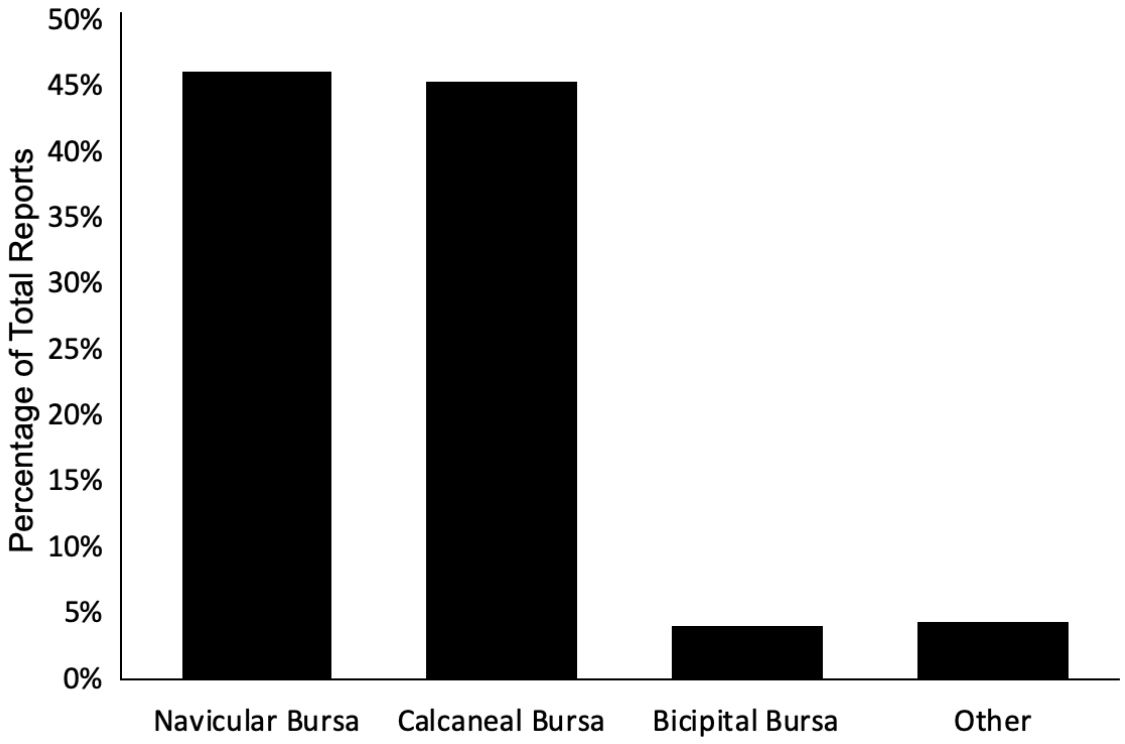

Figure 7. The Navicular Bursa was the Bursa Most Commonly Affected By Sepsis. Proportion of Total Cases (n=470). A total of 470 septic bursae were reported. The most common septic bursae were the navicular bursa (46%, 217/470), calcaneal bursa (46%, 215/470), and the bicipital bursa (4.1%, 19/470). Others included the infraspinatus bursa, precarpal bursa, the intertendinous calcaneal bursa, the olecranon bursa, and six others.

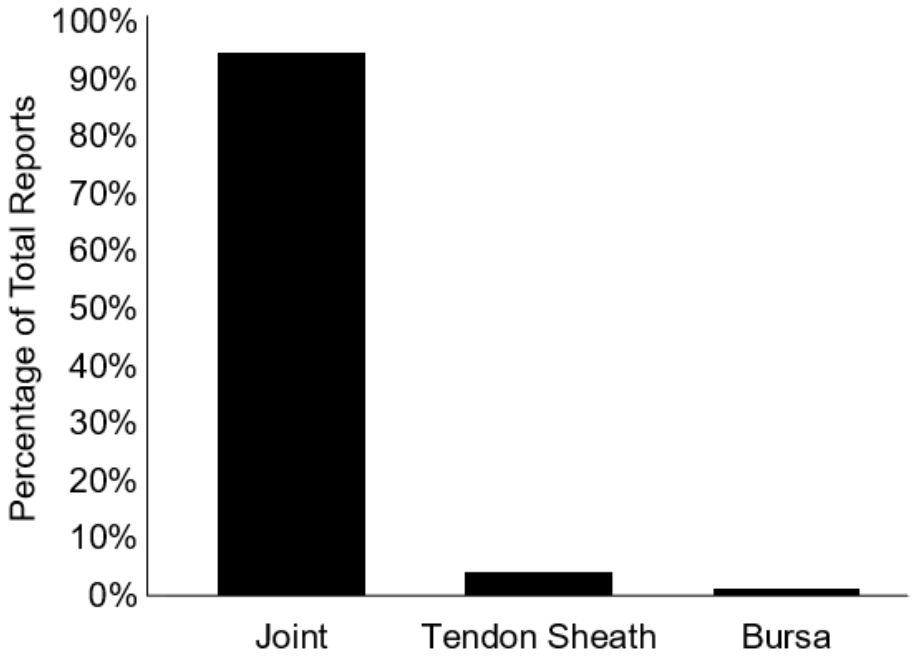

Figure 8. In Foals, Joints were the Most Commonly Affected Synovial Structure. Percentage of Total Cases (n=217). 16 Reports. A total of 217 synovial structures were reported as being affected by sepsis in foals. The most common class of synovial structure affected by sepsis were joints, with 94% (205/217) of all cases being septic arthritis. Tendon sheaths comprised 4% (9/217) of all cases, and bursae comprised 1% (3/217).

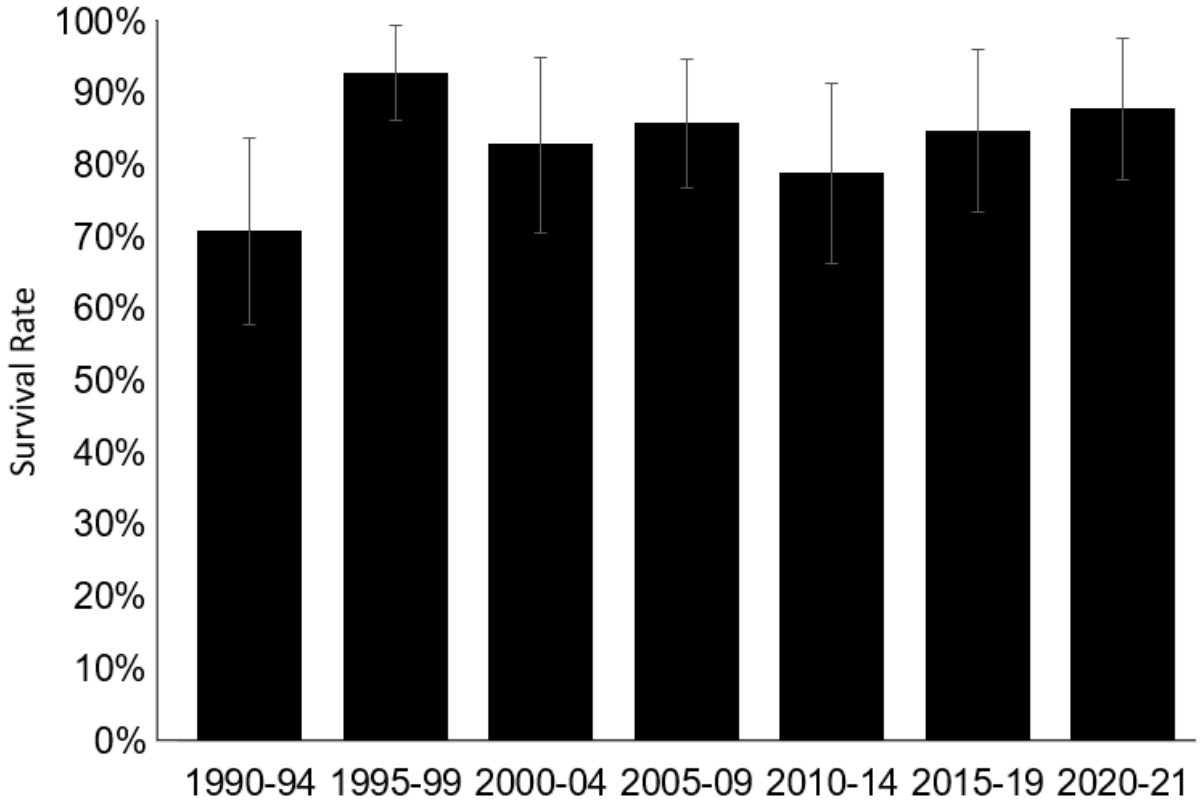

Figure 9. Rate of Survival to Discharge Did Not Vary Between Half-Decades (p=0.17). Mean and Standard Deviation (41 reports). This figure shows survival rates for every paper published within set 5-year intervals. To avoid having smaller studies dominate the statistical findings, only studies that reported at least 10 cases were included. Included were 6 studies in the 1990-94 period, 3 studies in the 1995-99 period, 6 studies in the 2000-04 period, 6 studies in the 2005-09 period, 7 studies in the 2010-14 period, 7 studies in the 2015-19 period, and 6 studies in the 2020-21 period. The bars show the mean survival rate and the error bars show standard deviations. Survival rates for each 5 year time period were as follows; 1990-94: 71±13%, 1995-99: 93±7%, 2000-04: 83±12%, 2005-09: 86±9%, 2010-14: 79±13%, 2015-19: 85±11%, 2020-21: 88±10%. There were no differences in reported survival rates between any time period (p=0.17, Welch's one-way ANOVA test).

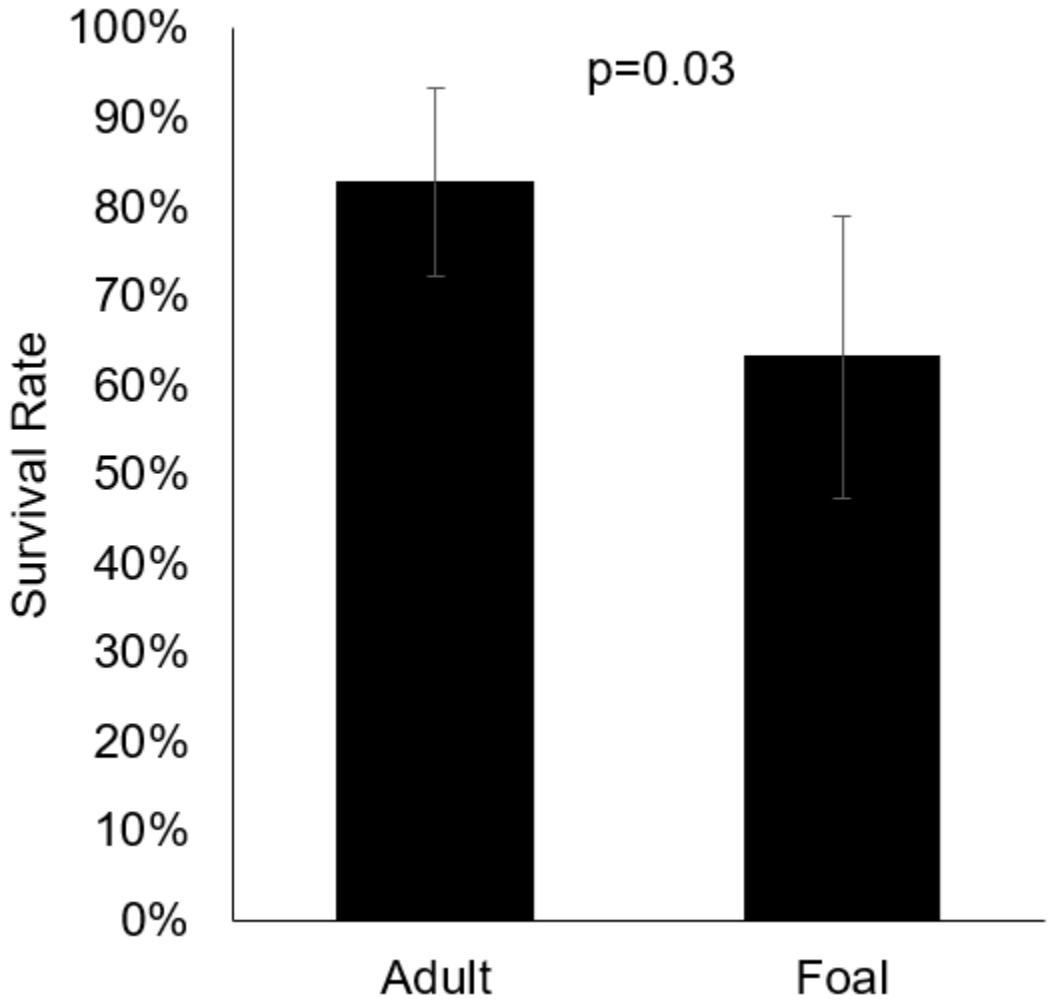

Figure 10. Adults Had Higher Reported Survival Rates Than Foals (p=0.03). Mean reported survival rates to hospital discharge for foals and adult horses. Only studies that reported >=10 foals or adults were included. The bars show the mean survival rate and the error bars show standard deviation. Adult horses had significantly higher survival rates than foals (mean of 83% as compared to 63%) (p=0.03, Welch's one-way ANOVA).

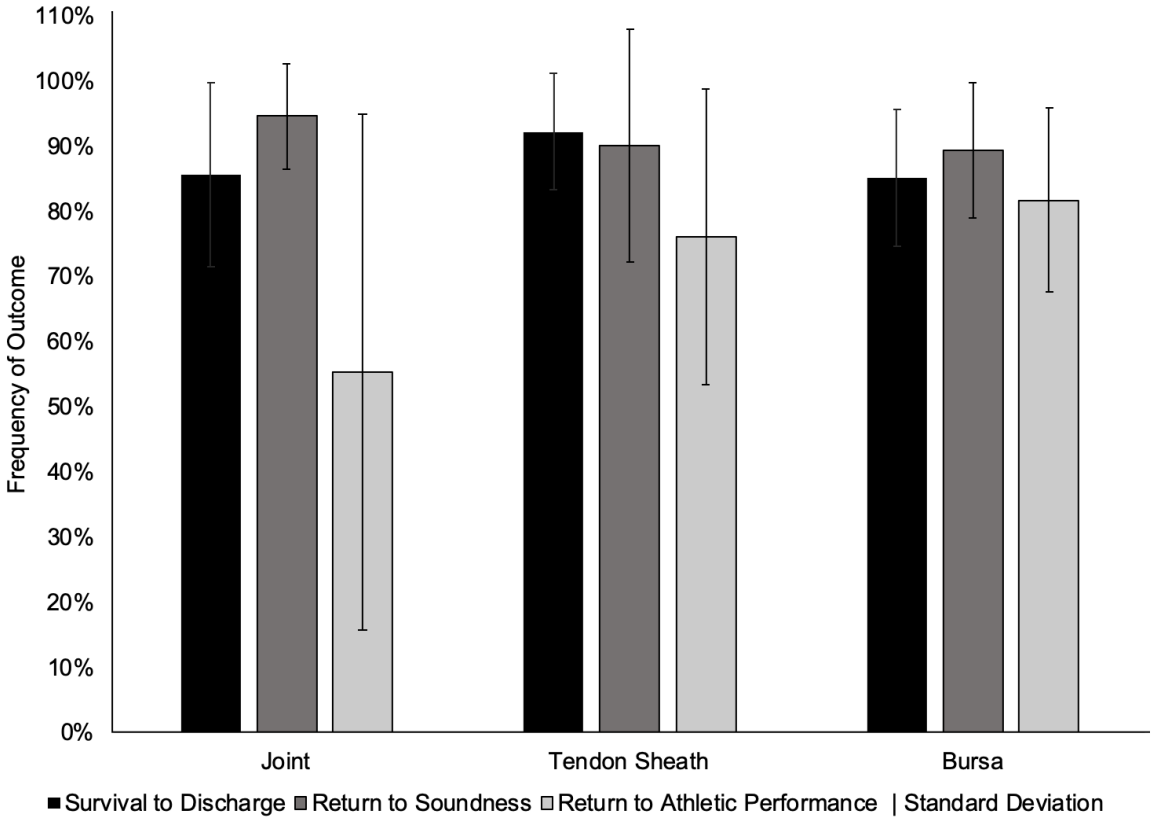

Figure 11. Rates of Survival to Discharge (p=0.34), Return to Soundness (p=0.67), and Return to Athletic Performance (p=0.40) Did Not Vary Between Cases of Septic Joints, Tendon Sheaths, and Bursae in Adult Horses. Mean and Standard Deviation. This figure reports all 3 outcomes of interest regarding synovial sepsis in adult horses: survival to discharge, return to soundness, and return to previous level of athletic performance by structure affected (joints, tendon sheaths, and bursae). To avoid bias towards smaller studies, studies were excluded if they did not have at least 10 subjects in a particular category. There was no difference between the rates of survival to discharge from hospital for horses with septic joints (86±14%), tendon sheaths (92±9%), or bursae (85±10%) (p=0.34, Kruskal-Wallis ANOVA). There was no difference between the rates of return to soundness for horses with septic joints (95±8%), tendon sheaths (90±18%), and bursae (89±10%) (p=0.67). There was insufficient data to analyze the rate

of return to athletic performance for horses with septic joints, but a Welch's t test determined that there was no difference between the rates of return to athletic performance for horses with septic tendon sheaths (76±23%) and septic bursae (82±14%) (p=0.40). Rate of return to athletic performance for cases of septic arthritis was 55±40%.

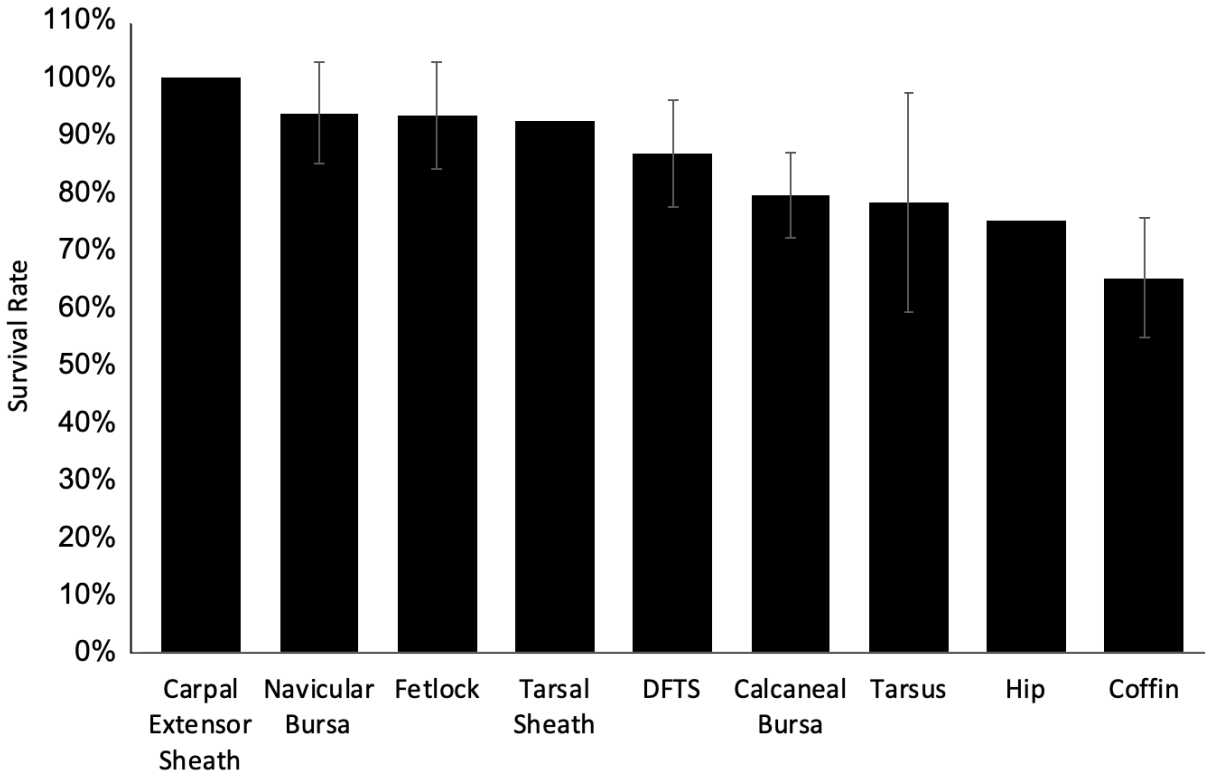

Figure 12. Site of Infection Does Not Affect Rate of Survival to Discharge (p=0.19). Mean and Standard Deviation. 22 Reports. Manuscripts were only included if they reported ≥10 outcomes for cases with synovial sepsis affecting at least one of these structures. Bars and error bars represent mean survival rate and standard deviation, respectively. Bars without error lines only had one study with a sufficient number of subjects for inclusion. The carpal extensor sheath, fetlock, hip, navicular bursa, and tarsal

sheath groups had insufficient data for statistical analysis. A Welch's ANOVA test showed no difference in survival rates between the DFTS (87±9%), calcaneal bursa (79±7%), tarsus (78±19%), and coffin (65±10%) groups (p=0.19). For groups with insufficient data for statistical analysis, survival rates were as follows: carpal extensor sheath: 100%, navicular bursa: 94±9%, fetlock: 93±9%, tarsal sheath: 92%, hip: 75%.

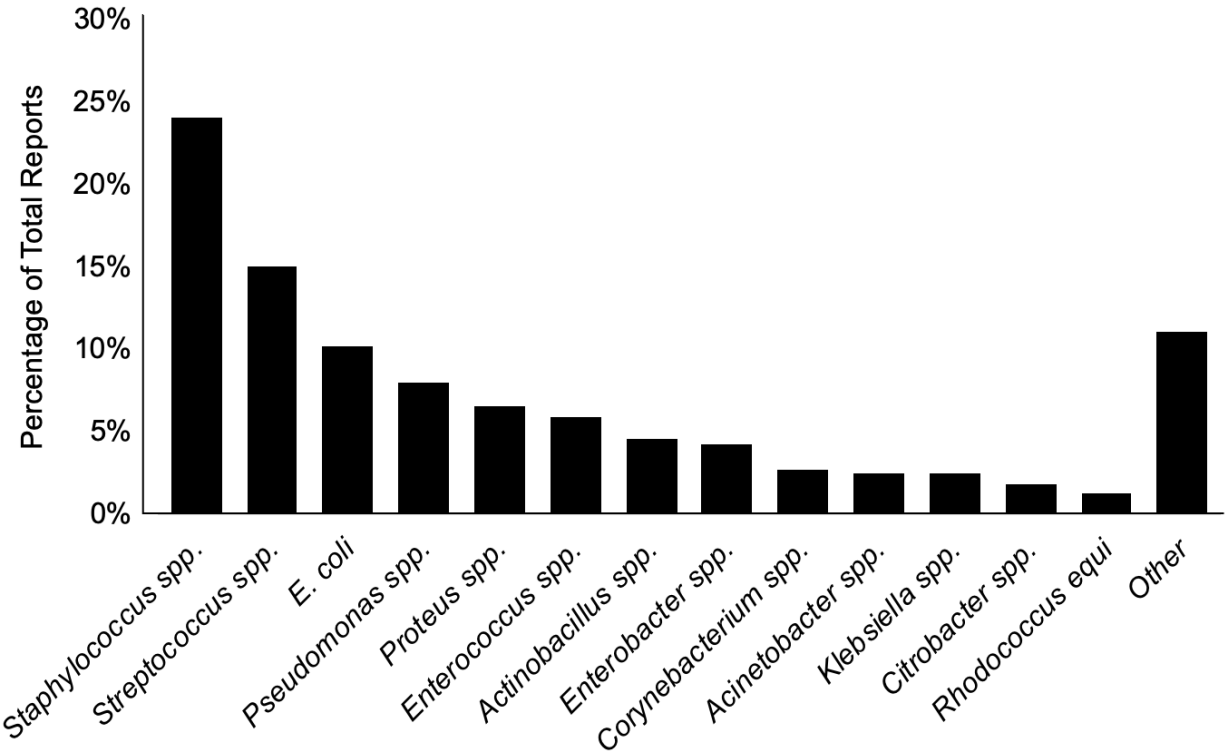

Figure 13. *Staphylococcus* was the Most Common Microbial Culture from 1990-99. Percentage of Total Reports (n=661). Out of 16 studies published between 1990 and 1999, 661 positive bacterial isolates were obtained. Cultures were included in the "Other" category if they comprised less than 1% of all total reports or if the genus of bacteria was not reported. *Staphylococcus* spp. were the most common isolates (24%, 159/661), followed by *Streptococcus* spp. (15%, 99/661), and *E. coli* (10%, 67/661).

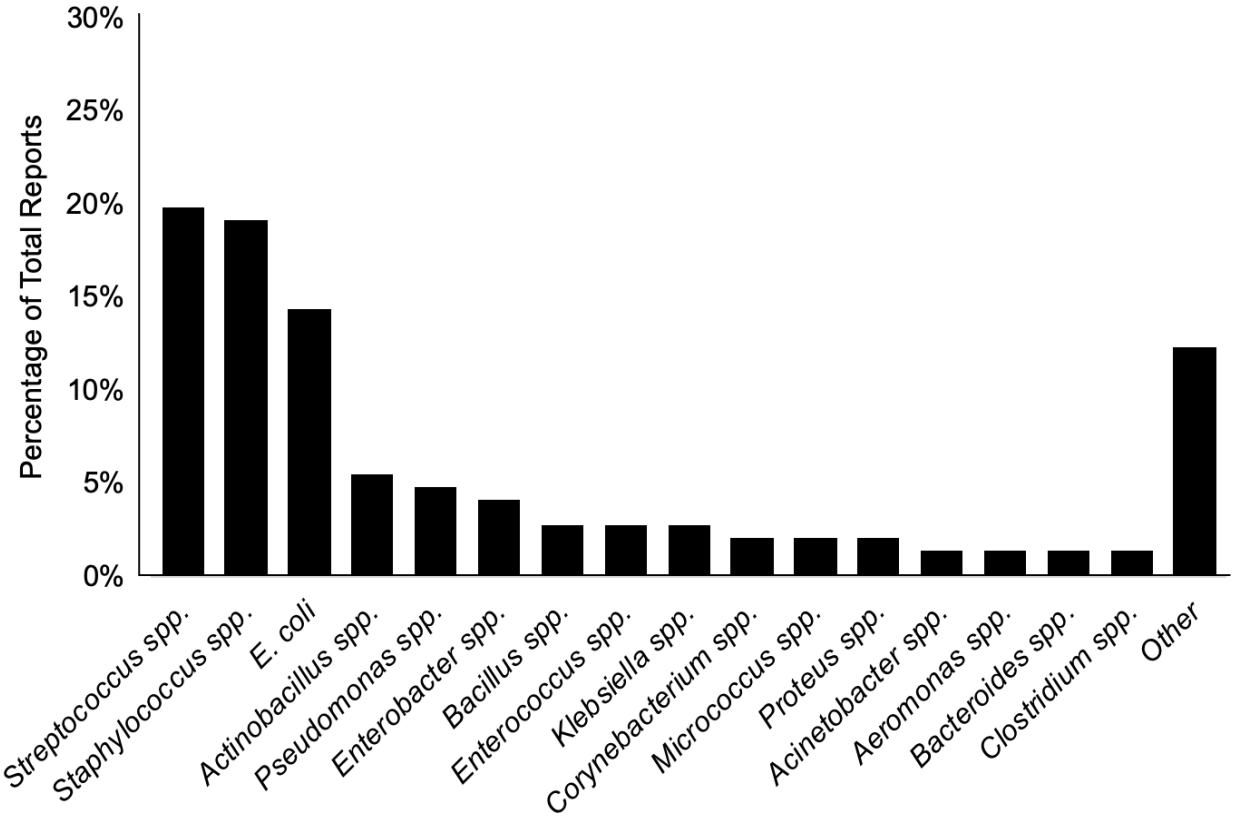

Figure 14. *Streptococcus* was the Most Common Microbial Culture from 2000-09, Percentage of Total Reports (n=146). Out of 15 studies published between 2000 and 2009, 146 positive bacterial isolates were obtained. Cultures were included in the "Other" category if they comprised less than 1% of all total reports or if the genus of bacteria was not reported. *Streptococcus* spp. were the most common isolates (20%, 29/146), followed by *Staphylococcus* spp. (19%, 28/146), and *E. coli* (14%, 21/146).

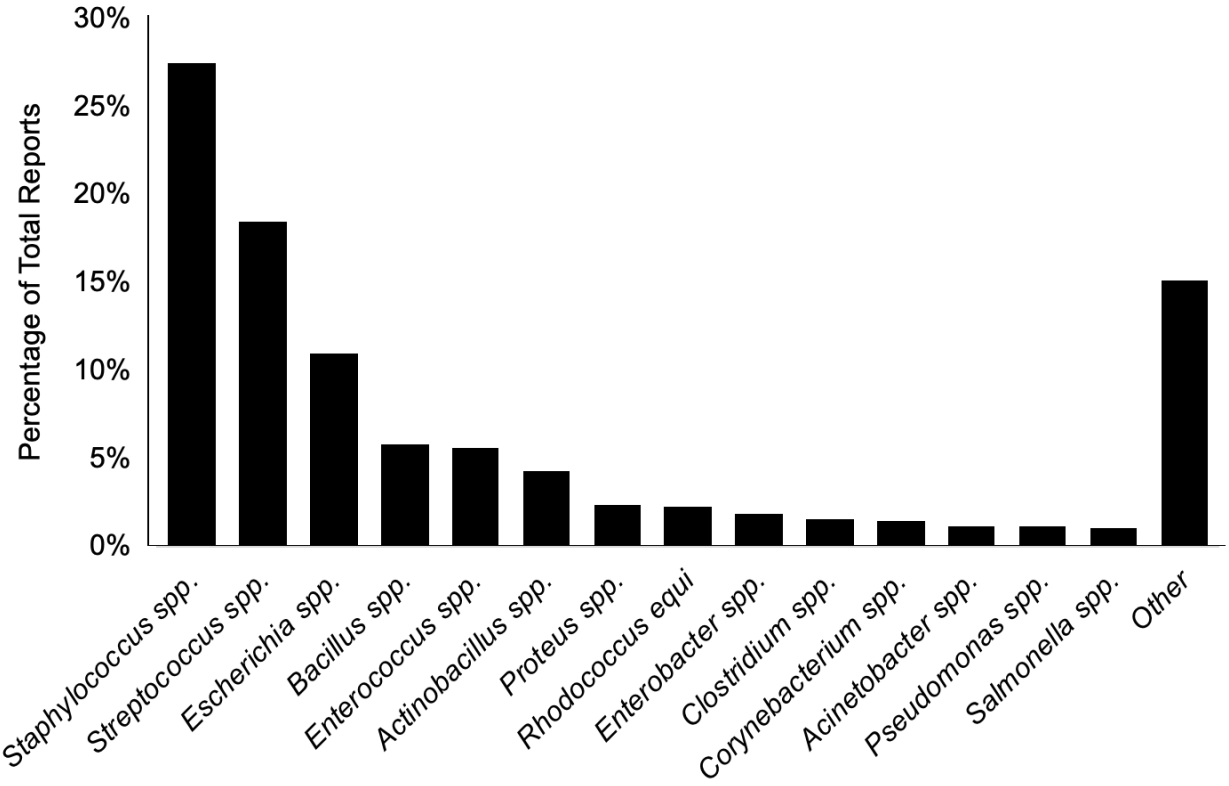

Figure 15. *Staphylococcus* was the Most Common Microbial Culture from 2010-21, Percentage of Total Reports (n=777). Out of 28 studies published between 2010 and 2021, 777 positive bacterial isolates were obtained. Cultures were included in the "Other" category if they represented less than 1% of all total reports or if the genus of bacteria was not reported. *Staphylococcus* spp. were the most common isolates (27%, 213/777), followed by *Streptococcus* spp. (18%, 143/777), and *Escherichia* spp (11%, 85/777).

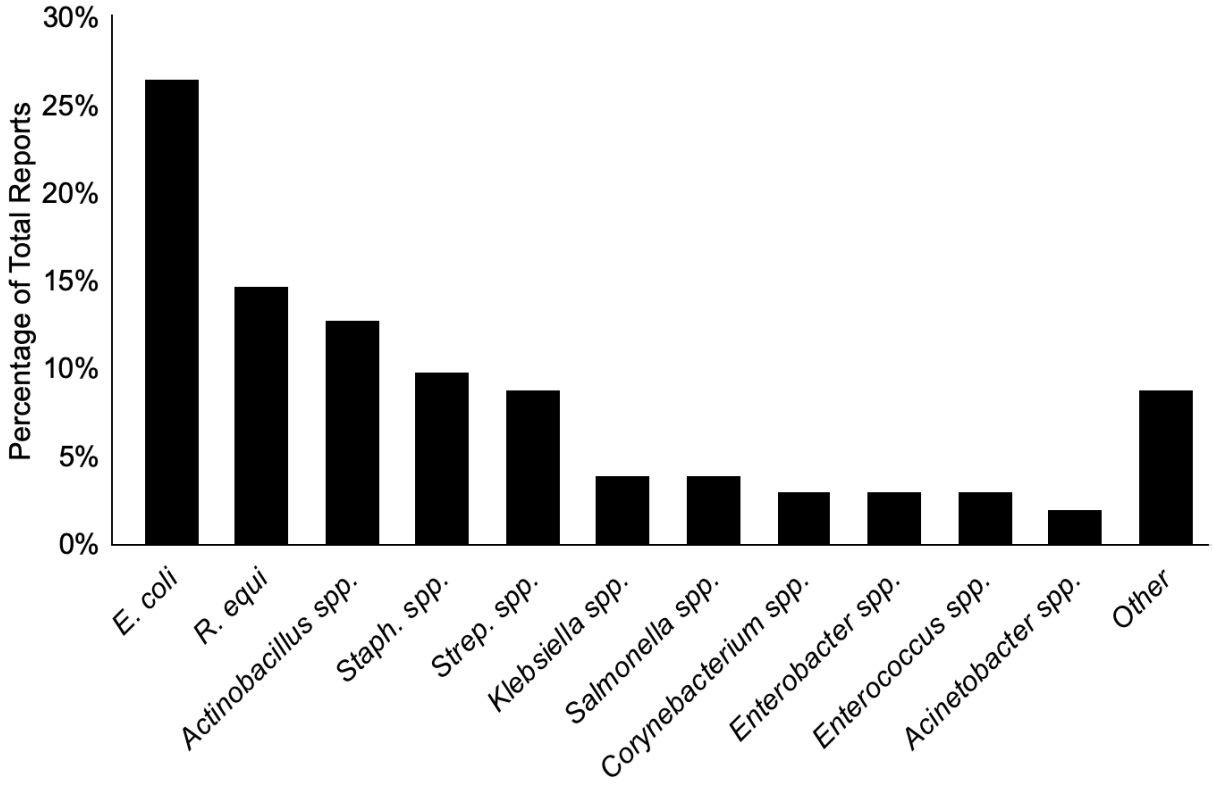

Figure 16. *E. coli* was the Most Common Microbial Isolate in Foals. Percentage of Total Reports (n=102). Out of 15 studies published between 1991 and 2020, 102 positive bacterial cultures were obtained from cases of synovial sepsis in foals. Cultures were placed in the "Other" category if they comprised less than 1% of all reports, or if they did not provide genus of bacteria. The most commonly isolated bacterium in foals was *E. coli* (26%, 27/102), followed by *Rhodococcus equi* (15%, 15/102), and *Actinobacillus* spp. (13%, 13/102).

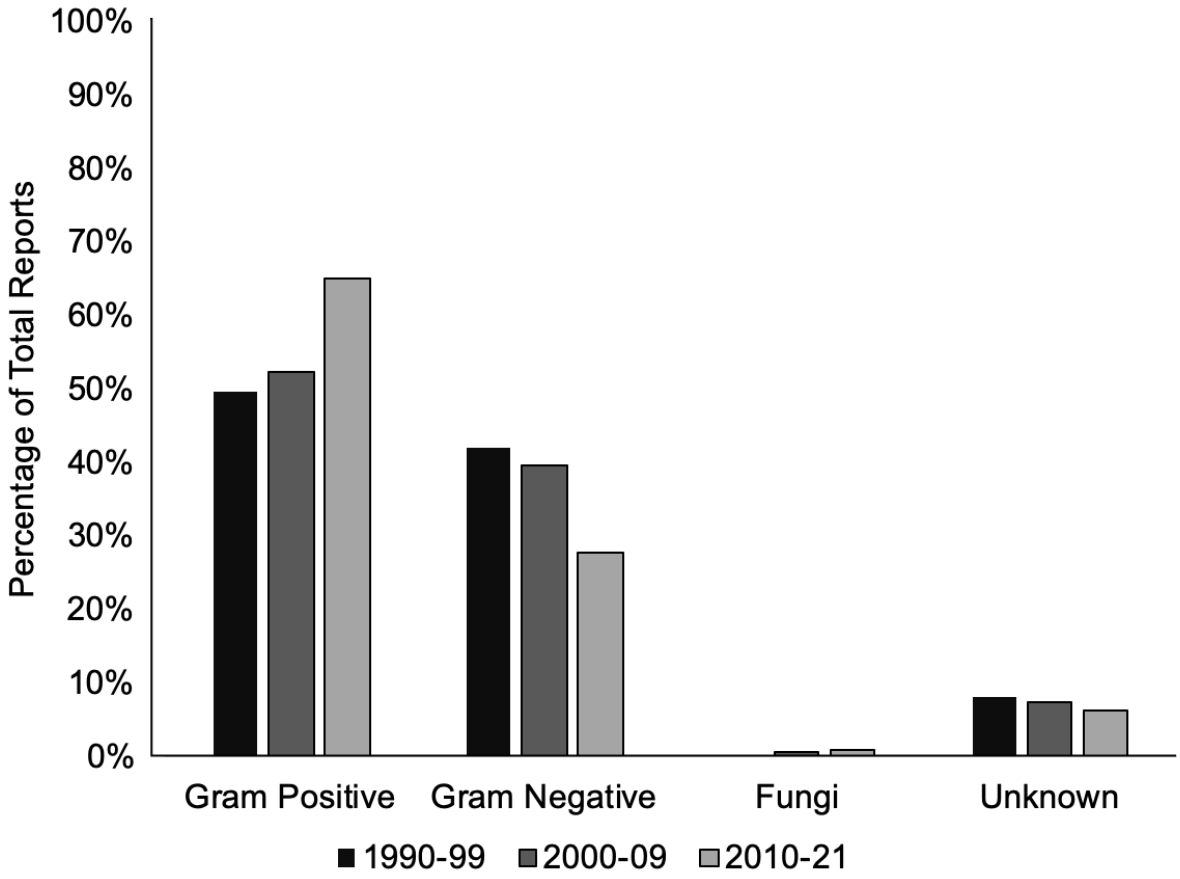

Figure 17. Gram-Positive Bacteria were the Most Common Microbial Isolates from Synovial Fluid. Percentage of Total Isolates (n=1,584). This figure demonstrates the distribution of microorganisms that were isolated from septic synovial fluid samples (adults and foals) across 3 time periods: 1990-99 (n=661), 2000-2009 (n=146), and 2010-21 (n=777). Gram positive bacteria were the most common isolates for all 3 time periods at 50%, 52%, and 65% of total reports, respectively, followed closely by gram negative bacteria at 42%, 40%, and 28%, respectively. Fungi were the least commonly isolated microbes, comprising 0.74% of all reports from 2000-09, and 1% of all reports from 2010-21. From 2000-09, there was a report of the fungus *Candida utilis*, and from 2010-21, there were reports of *Candida albicans*, *Fusarium*, and *Scedosporium*, as well as yeast.

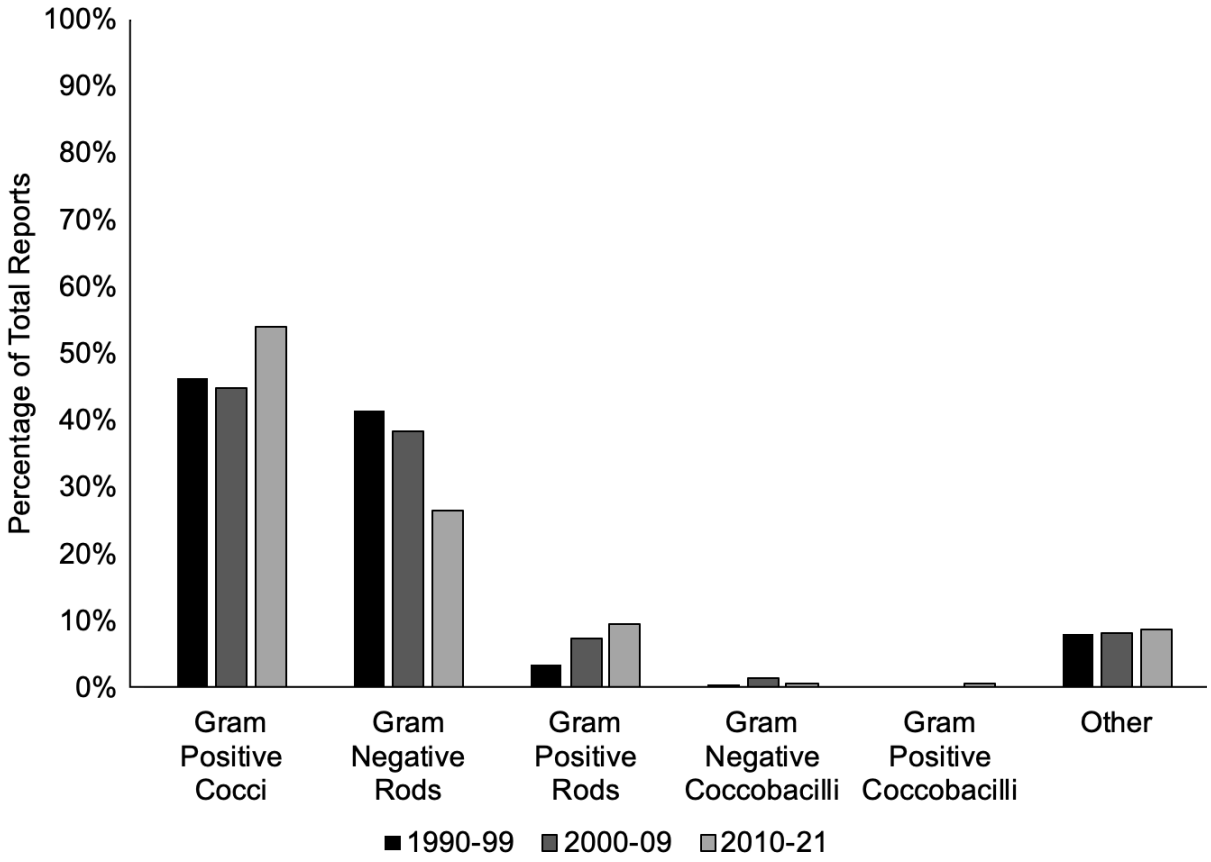

Figure 18. The Most Common Morphology of Bacterial Isolates Was Gram-Positive Cocci. Percentage of Total Isolates (n=1,575). This figure shows the Gram stain results and morphology of all bacterial isolates across 3 time periods: 1990-99, 2000-09, and 2010-21. Across all 3 time periods, Gram positive cocci were the most common bacterial isolates (46%, 45%, and 54%, respectively), followed by Gram negative rods (41%, 38%, and 26%, respectively). Gram positive rods comprised 3%, 7%, and 10% of all reports, respectively, and Gram negative coccobacilli comprised 0.61%, 1.5%, and 0.64% of all reports, respectively. The least common isolates were Gram positive coccobacilli, found only in the 2010-21 time period, and comprising only 0.64% of all reports from that period. These bacteria were *Trueperella pyogenes*, *Brevibacterium epidermidis*, and *Weissella*

confusa. Bacteria were placed in the “Other” category if there was insufficient information provided to determine both Gram stain and morphology.

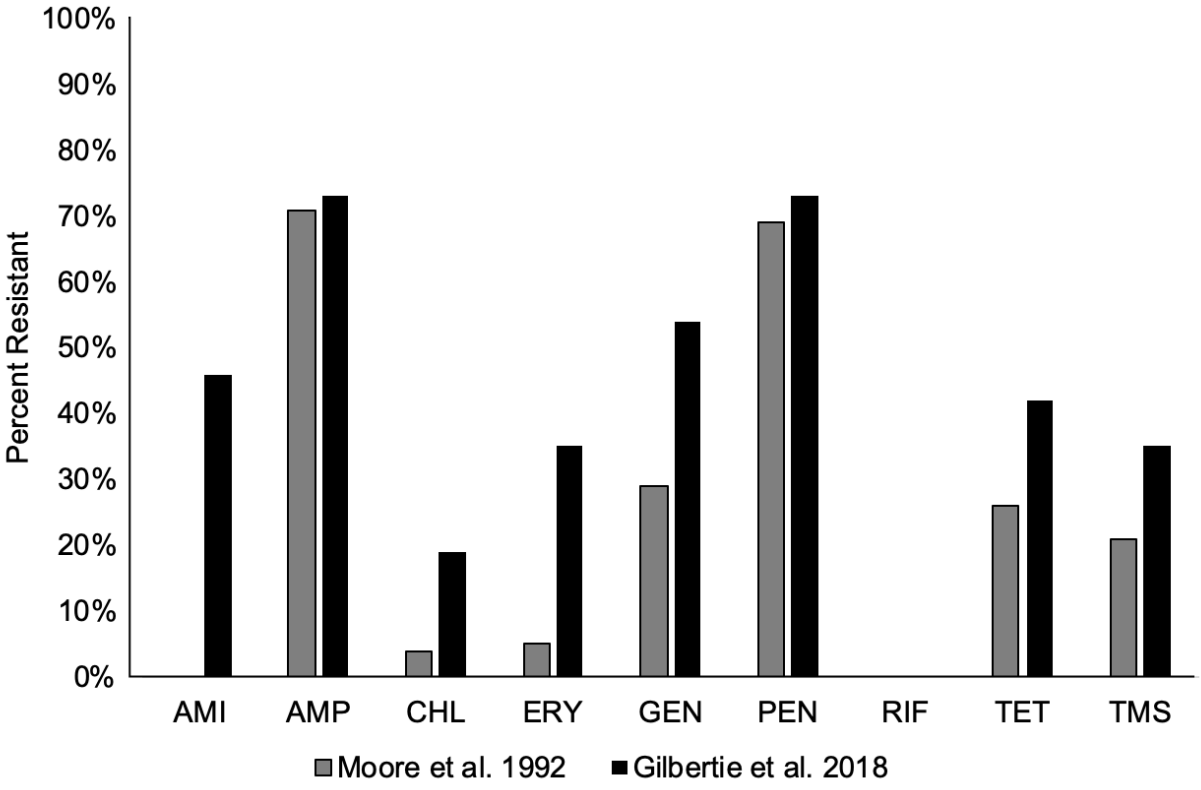

Figure 19. Comparison of Antimicrobial Resistance Patterns From 1992 to 2018 in Coagulase-Positive *Staphylococcus* spp, Proportion of Total Reports (n=76). This figure compares the percentage of samples of coagulase-positive *Staph*. spp reported as antimicrobial-resistant by Moore et al. 1992 (n=50) and Gilbertie et al. 2018 (n=26). Data for antimicrobials only tested in one of the two papers were not included. An increase in antimicrobial-resistant coagulase-positive *Staphylococci* was observed for every antimicrobial tested except rifampin. Moore *et al.* 1992 reported that 0/30 samples tested were resistant to amikacin, whereas Gilbertie *et al.* 2018 reported that 46% (12/28) of all samples were resistant to amikacin. Percentage of isolates resistant to ampicillin increased from 71% to 73%, chloramphenicol increased from 4% to 19%, erythromycin

increased from 5% to 35%, gentamicin increased from 29% to 54%, penicillin increased from 69% to 73%, tetracycline increased from 26% to 42%, and trimethoprim-sulfa increased from 21% to 35%. Rifampin was the only antimicrobial that didn't report an increase in susceptibility over time, with both studies reporting that all samples were susceptible to rifampin. AMI: amikacin, AMP: ampicillin, CHL: chloramphenicol, ERY: erythromycin, GEN: gentamicin, PEN: penicillin, RIF: rifampin, TET: tetracycline, TMS: trimethoprim-sulfa.

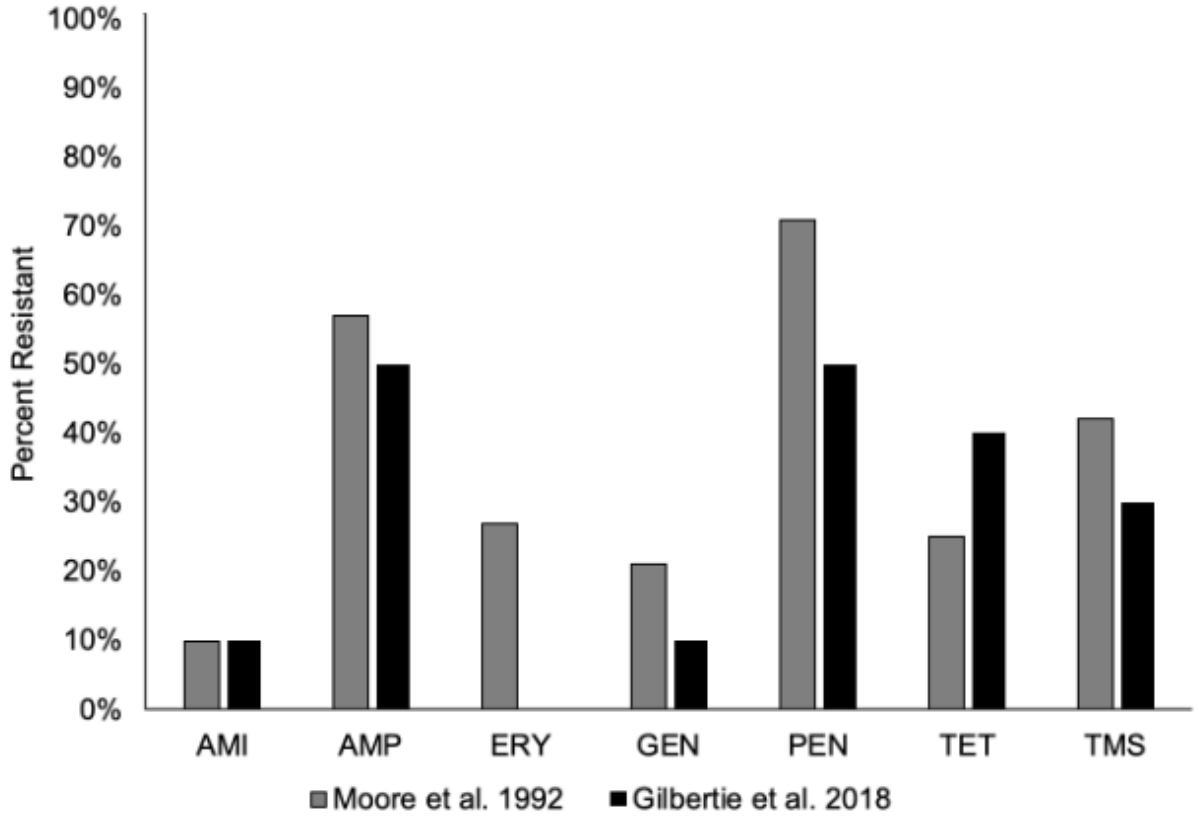

Figure 20. Comparison of Antimicrobial Resistance Patterns From 1992 to 2018 in Coagulase-Negative *Staphylococcus* spp, Proportion of Total Reports (n=41). This figure compares the percentage of samples of coagulase-negative *Staph*. spp. reported as antimicrobial-resistant by Moore et al. 1992 (n=31) and Gilbertie et al. 2018 (n=10).

Data for antimicrobials only tested in one of the two papers were not included. A decrease in antimicrobial-resistant coagulase-negative *Staphylococci* was observed for every antimicrobial tested except amikacin and tetracycline. Both Moore *et al.* 1992 and Gilbertie *et al.* 2018 reported that 1/10 samples of coagulase-negative *Staph* spp. were resistant to amikacin. Moore *et al.* 1992 reported that 3/12 samples were resistant to tetracycline, whereas Gilbertie *et al.* 2018 reported that 4/10 samples were resistant to tetracycline. AMI: amikacin, AMP: ampicillin, ERY: erythromycin, GEN: gentamicin, PEN: penicillin, TET: tetracycline, TMS: trimethoprim-sulfa.

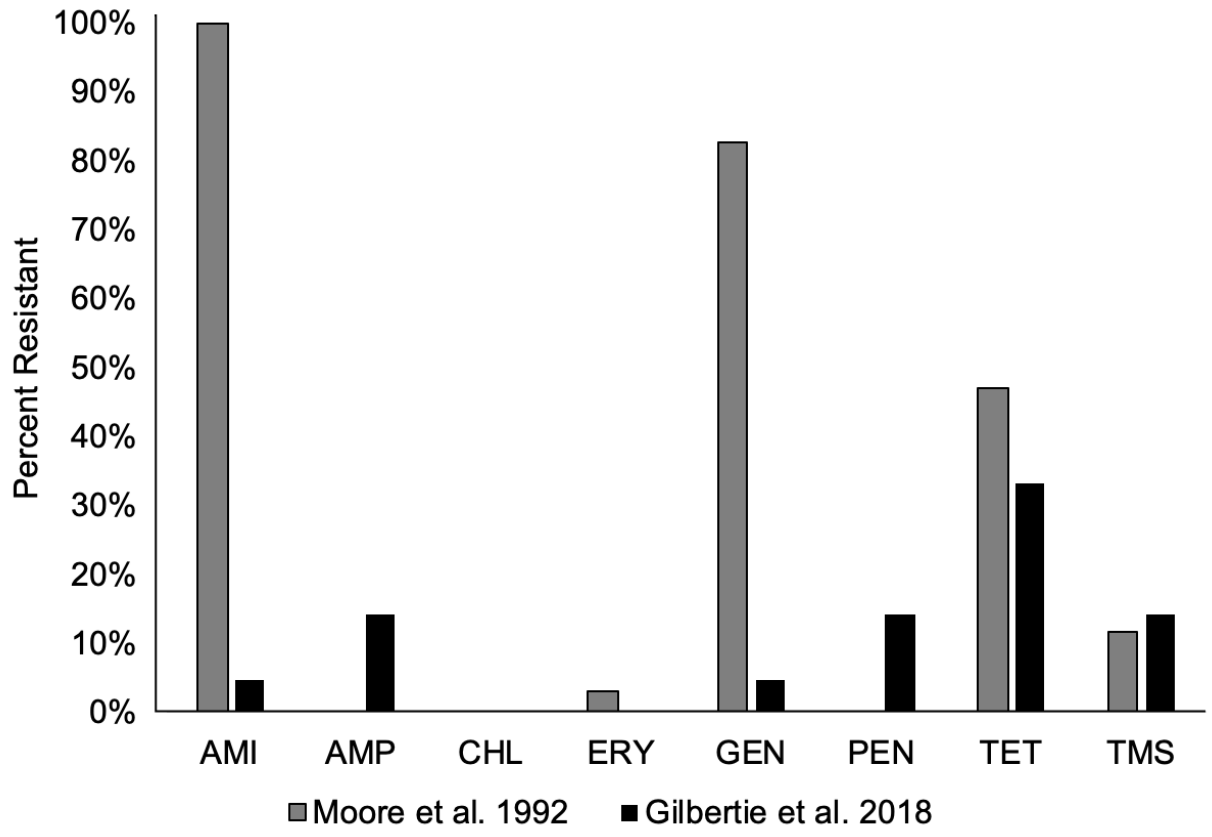

Figure 21. Comparison of Antimicrobial Resistance Patterns From 1992 to 2018 in Beta Hemolytic *Streptococcus* spp, Proportion of Total Reports (n=61). This figure compares the percentage of samples of beta-hemolytic *Strep*. spp. reported as antimicrobial-resistant by Moore et al. 1992 (n=40) and Gilbertie et al. 2018 (n=21). Data for antimicrobials only tested in one of the two papers were not included. An increase in antimicrobial resistant *Streptococcus* was observed for ampicillin, penicillin, and trimethoprim-sulfa. A decrease in antimicrobial resistant *Streptococcus* was observed for amikacin, erythromycin, gentamicin, and tetracycline. There was no observed change in prevalence of chloramphenicol-resistant beta-hemolytic *Streptococcus*. Moore *et al.* 1992 reported that 0/34 samples were resistant to chloramphenicol, and Gilbertie *et al.* 2018 reported that 0/21 samples were resistant to chloramphenicol. AMI: amikacin, AMP: ampicillin, CHL: chloramphenicol, ERY: erythromycin, GEN: gentamicin, PEN: penicillin, TET: tetracycline, TMS: trimethoprim-sulfa.

DISCUSSION:

Chapter 1 -

The most common cause of synovial sepsis in adult horses was direct contamination of synovial structures, with trauma comprising 70% of cases, and iatrogenic infection 19% (Figure 2). Because of the environment in which they live and the athletic use to which they are put adult horses are prone to traumatic injuries of their distal limbs. These can include getting kicked by other horses, running into fences, or being injured while exercising, which are all possible means by which the skin over synovial structures, especially those of the limbs can be breached allowing

microorganisms to gain entry to a synovial structure. Unfortunately, the second most common cause in adults was iatrogenic, accounting for 19% of all cases, a complication that can occur when equine athletes receive intra-articular medications such as corticosteroids, hyaluronic acid and glycosaminoglycans (Lapointe et al. 1992), or following arthroscopic surgery (Weese 2008, Borg et al. 2013, Brunsting et al. 2017). Infection of the skin over a surgical site within 30 days of an orthopedic procedure with skin organisms such as Staphylococci or Staphylococci (Weese 2008) or contamination of an area of lacerated skin over a distal limb joint or tendon sheath is more likely in horses than humans because of the environment in which horses live.

In contrast, the most common route by which synovial sepsis occurred in foals was hematogenous, accounting for 96% of all cases, although it was the least common in adults in whom it accounted for less than 1% of cases. This difference relates to the propensity of foals to systemic sepsis when they suffer from failure of passive transfer (FPT). This occurs in foals who have received insufficient colostrum from their dam. FPT causes a deficiency in immunoglobulins that increases the risk of bacterial septicemia in the first few weeks of life (Annear et al. 2011, Hepworth-Warren et al. 2015). Bacteria can gain access to the foal's bloodstream through the umbilicus, or the respiratory or alimentary tract and spread to multiple synovial joints and organs (Hepworth-Warren et al. 2015, Glass and Watts 2017). In neonatal foals, septic arthritis is much less likely to be associated with a skin wound or occur due to iatrogenic means as was shown by the very low prevalence for these etiologies in this study (2.8% and 0.8% respectively).

Overall, of the three categories of synovial structures across all publications examined in this study (joints, tendon sheaths, and bursae), joints were most commonly affected by sepsis when data from foals and adults were combined. However, of all synovial structures, the one most commonly affected by sepsis was the DFTS. This is likely due to the fact that all four limbs have a DFTS, and being located distally on each limb it is prone to trauma from lacerations due to kicks and other injuries. Although there are fetlock, pastern and coffin joints on each limb too, these were less commonly involved in synovial sepsis than the joints of the tarsus. The DFTS is also possibly more susceptible to sepsis than other synovial structures because of its anatomical location as a very superficial structure, located just underneath the skin, just above the fetlock and covering several centimeters. Thus, it is very prone to punctures and lacerations to the distal aspect of each limb, unlike the coffin joint for example which is more protected by the hoof.

As mentioned, the joint most commonly affected by septic arthritis was the tarsus. For the purposes of data analysis in this systematic review all of the joints of the tarsus (tibiotarsal, tarsometatarsal. Intertarsal, and tarsocrural) were grouped together into one category. This was done mainly to avoid having to exclude too many papers from the review and data analysis because not all papers reported results on the separate tarsal joints consistently and individually. However, there are considerable differences in volume and the degree of motion in the respective joints. For example, the tibiotarsal joint is susceptible to be iatrogenically infected following injection of corticosteroids or joint medications in athletes. As well as infection being introduced iatrogenically, trauma to the

tarsal joints when horses kick with their hindlimbs, or being injured by another kicking horse is more likely in the anatomic region of this joint.

The bursa most commonly affected by sepsis was the navicular bursa, although with only slightly greater frequency than the calcaneal bursa (217/470 total cases versus 215/470). Similar to the DFTS, there are 4 navicular bursae, one in each hoof, making it perhaps more likely that the navicular bursa would be involved numerically. Penetrating wounds to the hoof and heel bulb lacerations can often affect the navicular bursa, as well as the coffin joint, which are located very close to each other within the hoof. The navicular bursae of the front limbs were more frequently involved than those of the hind limbs suggesting that it is not kicking behavior that leads to trauma and infection of the navicular bursae but more often a penetrating wound from the horse stepping on something like a thorny bush (Wright et al. 1999, Suarez-Fuentes et al. 2018). The calcaneal bursa was the second most commonly affected bursa, which is likely due to its proximity to the tarsus. Given that the tarsus was the most common septic joint, it makes sense that the calcaneal bursa, located dorsal to the tarsus, would also be commonly affected by trauma, leading to a septic infection.

The results demonstrated that survival rate did not change significantly over the course of this study, which was something of a surprise. Over a 30-year period it might be expected that diagnosis and treatment approaches would have advanced and led to better outcomes. In fact the highest survival rate to discharge was identified for the time period 1995-1999 (>90%), with the other time periods during the study varying between

80 and 90%. However, there do not seem to have been many changes in the therapies described in the papers reviewed over the time period; joint lavage, arthroscopy, tenoscopy, surgical drainage and systemic antibiotics were all approaches in use in the 1990s and still in use today. It is also possible that improvements have been made, or even that cases are being diagnosed more quickly, but at the same time, cases are getting more difficult to treat. This is reflected in Figure 19, which suggests that there is an increased prevalence of antimicrobial resistant coagulase-positive *Staph*. spp. This would make cases harder to treat, with antimicrobials being less effective against increasingly resistant bacteria.

The overall average survival rate to discharge for adults was significantly higher ($p=0.03$) for adults (83%) than foals (63%) (Figure 10). Since neonatal foals are much more susceptible to hematogenous infection with bacteria than adults, foals with septic arthritis often have other complications such as pneumonia and numerous joints infected rather than just a single structure (Annear et al. 2011, Glass and Watts 2017). Foals may also have extension into a physis and osteomyelitis making their prognosis even worse (Glass and Watts 2017). Another factor worth considering is the willingness of a client to pursue treatment. Some clients may elect to euthanize a septic foal without attempting treatment due to decreased prognosis of athleticism as a result of joint or lung damage, among other possible complications. On the other hand, an adult who has shown promise can still return to full athletic performance, or if they cannot return to athletic performance, can be a productive breeding stud or broodmare, so the client may be more likely to pursue treatment.

Rates of survival to discharge, return to soundness, and return to athletic performance did not vary significantly based on the class of synovial structure affected by sepsis. For each synovial structure mean survival rates to discharge from the hospital were high (86%, 92% and 85% for joints, tendon sheaths and bursae respectively), and very high proportions of these survivors went on to return to soundness (95%, 90% and 89%) and athletic performance (54%, 76% and 82%) respectively. It is worth pointing out that all of the studies involved in this systematic review were retrospective clinical papers and not every study provided follow-up data on horses after discharge, so data regarding return to soundness and/or athletic performance was often unavailable. These types of papers also make comparisons difficult because they take place at different institutions with different types of horse populations and owners and the decisions to euthanize the patient may be sometimes financial, or sometimes more emotional. There was also inconsistency between papers as to what defined a return to athletic performance; in some it was performing at a comparable competitive level to before sepsis (Smith et al. 2006), compared to others where it was just making a race start (Lapointe et al. 1992). More studies are indicated to corroborate these findings, to allow for more robust comparisons to be made regarding the outcome and post-treatment performance of horses with cases of septic arthritis, tenosynovitis and bursitis.

When rate of survival to discharge from hospital was examined by individual synovial structure, the highest survival rates were identified for the carpal extensor sheath (100%), navicular bursa (94%) and the fetlock joint (93%). The lowest survival rate was

documented for cases of sepsis of the coffin joint (65%) implying that this is the hardest joint to treat. Statistically there was no difference in survival to discharge for any structure but due to low numbers only comparisons between cases of sepsis of the calcaneal bursa, coffin, DFTS, and tarsus could be made.

Chapter 2 -

The 2 most commonly isolated genera of bacteria in adult horses across all 3 decades covered by this review were *Staphylococcus* spp. (1990-99 and 2010-21) and *Streptococcus* spp. (2000-09). These bacteria are commonly found on the surface of the skin so that following trauma that causes a laceration or a penetrating wound into a synovial structure they can easily be introduced into an area that would normally be sterile. Once these bacteria gain access to the synovium, infection results that causes damage via the proteolytic enzymes and inflammatory mediators they incite (van Weeren 2016). The third most commonly isolated organism across the study was the Gram-negative bacterium, *E. coli*, which can also be found on the skin, but is also a gut organism that is present in feces. Horses do not live in “clean” environments and their skin can be contaminated by fecal microorganisms very easily when they lie down in stalls or fields, or come into contact with their own or other horses’ fecal material. This connection to fecal microorganisms may also explain some of the less common isolates such as *Enterobacter and Enterococcus* obtained in studies such as those by Moore et al. (1992) and Robinson et al. (2016). Another study of chronic wounds in horses found that *E. coli* was isolated in 14% (7/51) of skin samples and 8% of chronic wounds (4/51) confirming the relevance of this organism as a contaminant of skin wounds (Westgate et al. 2011).

These findings suggest that the skin microbiota might be the strongest indicator of what bacterial species will be encountered in cases of synovial sepsis in adults because of the strong association with trauma as the most common etiology in this age of animal. Fecal organisms and the gut microbiome are also relevant because of the issue of environmental contamination in stalls and fields; the transfer of fecal organisms to the hooves can lead to introduction of these following kicks, or lying down in a contaminated area. *E. coli* can be found in the intestines of both healthy horses and horses with enteritis (van Duijkeren et al. 2000), and it is therefore possible that a hindlimb wound over the tarsus, hindlimb DFTS, fetlock or pastern will become contaminated with this organism. Unfortunately, many microbiological studies in the literature do not correlate bacterial species with synovial structure infected, which would be an interesting further study. Gut microbes can also be introduced into open wounds by flies. Flies are very attracted to horse feces, with enteric parasitic species such as *Habronema muscae* spending their larval stages in horse feces (Schuster and Sivakumar 2017, Salant et al. 2021). *Habronema* and many other species of flies that feed on, or live part of their life cycle in, feces are attracted to open wounds and may be responsible for the introduction of fecal bacteria into open wounds that track to synovial structures.

Unfortunately, many of the larger retrospectives did not report which species of bacteria were most commonly isolated in cases of iatrogenic sepsis, the second most common cause of synovial sepsis in adults after trauma. However, one study reported that out of 5 cases of iatrogenic sepsis that yielded a positive bacterial culture, there were 2 cultures of *Staphylococcus aureus*, 1 *Streptococcus* spp., 1 *Pasteurella* spp., and 1

coliform species (Hawthorn et al. 2016). Another study by Brunsting et al. (2016) identified *Staphylococcus* and *Streptococcus* species in 9 of 19 septic arthritis cases that developed postoperatively following elective arthroscopy. Thus, although data are very limited, it can be reasonably proposed that cases of iatrogenic synovial sepsis are also likely to be associated with bacteria commonly found on the skin. The study by Brunsting et al. (2016) highlights that the incidence of surgical site infection following arthroscopy is very rare as the 19 infected joints in that study were from a total of 1741 procedures in 1079 horses.

There were some important differences in the most commonly isolated bacteria in foals with synovial sepsis versus adults, and these can be best explained by understanding how sepsis differs in adults and foals. The three most common organisms in foals were *Escherichia coli* (26%)*, Rhodococcus equi* (15%) and *Actinobacillus* spp.(13%) (Figure 16). *E.coli* and *Actinobacillus* are common causes of septicemia in neonatal foals (Annear et al. 2011, Hepworth-Warren et al. 2015), consistent with the most common etiology of synovial sepsis being hematogenous (Figure 3). It is most common for septic foals to have received insufficient colostrum from their mother, resulting in failure of passive transfer of immunity (FPT). A study demonstrated that when 8 foals were deprived of colostrum and provided with an alternative source of milk for the first 24 hours of life, 7 showed clinical signs of sepsis, with 4 of 7 subjects necessitating euthanasia; in contrast, none of the 6 control foals given colostrum became septicemic (Robinson et al. 1993). This highlights the importance of receiving sufficient colostrum from the mare, as well as a key difference between synovial sepsis in foals and adults. Immunocompromised foals with FPT may then be exposed to microbes by inhalation,

ingestion or via an infected umbilicus (Glass and Watts 2017) rather than through contaminated skin wounds or iatrogenically. Thus, it stands to reason that the microbes most commonly isolated from septic joint samples taken from foals should be similar to those most commonly isolated from systemic sepsis in foals. The findings of this systematic review (Figure 16) are corroborated by a large retrospective study of 562 septic foals, which also found that the most commonly isolated microbe from the blood was *E. coli*, comprising 17% of all total isolates (Furr et al. 2020). Figure 16 also shows that *Staphylococcus* and *Streptococcus* spp. were isolated as the fourth and fifth most common species from foals with synovial sepsis. Interestingly, the study by Furr et al. also stated that *Staphylococcus* and *Streptococcus* comprised 17% and 13% of all blood cultures, respectively, demonstrating that there is notable overlap between microbes found in synovial and systemic sepsis in foals. It is probable that contamination of the umbilicus from the surrounding skin might lead to infection and hematogenous spread of these two types of bacteria rather than by ingestion or inhalation.

The second most frequently identified bacterial species in foals was *Rhodococcus equi* (Figure 16). This is a Gram-positive bacterium found in the environment that is likely to be introduced to the foal via the respiratory tract. It is an especially common infection in dry and dusty areas such as Texas where the organism is likely to be aerosolized from the soil (Giguere et al. 2011). Once introduced to the lungs, *R. equi* can cause pneumonia, and can spread hematogenously to synovial structures, causing synovial sepsis. It tends to affect older foals (1-6 months of age) and has a grave prognosis when septic arthritis and osteomyelitis occur (Ruocco et al. 2020). A major issue with treating *R. equi* is that

antimicrobials that are effective against *R. equi* in vitro, such as penicillin and gentamicin, are not as effective in vivo (Giguere et al. 2011). This can be seen in the study focusing on *R. equi* infections in foals included in this thesis by Ruocco et al. (2020) in which 10/12 foals with *R. equi* sepsis or osteomyelitis died or were euthanized. Eight of the euthanized foals had septic arthritis, and 2 had osteomyelitis. On necropsy, a common finding was severe joint and/or bone degeneration as a result of synovial sepsis or osteomyelitis. An additional problem with treating *R. equi* is that the commonly used combination of erythromycin and rifampin can cause diarrhea in foals, which can lead to antibiotic-induced colitis (Giguere et al. 2011). The combination of the difficulty in treating *R. equi* combined with the risk of adverse consequences of antibiotics used in *R. equi* treatment and the severity of symptoms caused by synovial sepsis makes *R. equi* infection a very challenging problem.

Chapter 3 -

Although there were very few studies examining antimicrobial susceptibility patterns in microbial isolates obtained from cases of synovial sepsis in adult horses and foals over the course of the whole systematic review, the publication of the two large studies by Moore et al. in 1992 and Gilbertie et al. in 2018 allowed for direct comparisons at the beginning and towards the end of the entire study period. This was particularly fortunate because many other clinical studies within this review that included culture results either did not report any sensitivity testing at all, or had different antibiotic testing profiles to those in the papers by Moore et al. (1992), and Gilbertie et al. (2018). An additional problem that hindered comparisons concerning antimicrobial resistance in the

review was the nomenclature used by authors to describe the different isolates obtained; very often authors stopped at the genus level for example, or categorized *Staphylococci* or *Streptococci* in ways that made direct comparisons impossible. For example, some papers chose to categorize *Staphylococci* as coagulase-positive or negative in microbiology results, while others chose to categorize them as hemolytic or non-hemolytic. Additionally, there are different methods of evaluating antimicrobial susceptibility, which creates an additional challenge in evaluating change in AMR over time. Moore et al. used the Kirby-Bauer method, which measures zones of inhibition, whereas Gilbertie et al. 2018 used the Sensititre system, which measures minimum inhibitory concentration (MIC). Therefore, it is possible that the observed differences in resistance patterns between Moore et al. (1992) and Gilbertie et al. (2018) were due to the use of two different methods of assessing resistance patterns. Perhaps the value of future studies would be helped by standardizing how bacterial isolates are reported. Antimicrobial data reporting could also be standardized.

These two studies were conducted 26 years apart and were conducted at Ohio State University (Moore et al. 1992) and the University of Pennsylvania (Gilbertie et al. 2018). Although these two Universities are not very far apart geographically there are a number of factors that might have influenced the accuracy of comparing antimicrobial susceptibility patterns between the studies. Ideally, direct comparison would have been made across an extended time period in a population from just one area that had been consistently exposed to the same antibiotic prescribing practices. If types of antibiotic use varied considerably between veterinarians in Ohio and Pennsylvania, or even in the

horses and foals from which the samples in these studies were obtained then that would have influenced results. Both of the veterinary schools at Ohio State and the University of Pennsylvania operate referral hospitals, so cases that these hospitals see are referrals from other practices more local to the clients. The practices that refer patients to the University hospitals have their own approach for prescribing antimicrobials, which likely differ from one practice to another. This could account for some of the observed differences in antimicrobial resistance and certainly would likely have been different over 26 years. Furthermore, antimicrobials are widely used in agriculture, which has frequently led to the development of antimicrobial-resistant bacteria, so prevalence of antimicrobial resistant strains could vary depending on the usage of antimicrobials in local agriculture, and the degree of interaction between equines and local livestock (Landers et al. 2012).

While antimicrobial sensitivity testing is commonplace clinically in the diagnosis and treatment of synovial sepsis, very few papers included in this study reported the results of their sensitivity tests. As both Moore et al. 1992 and Gilbertie et al. 2018 demonstrated, the acquisition of antimicrobial resistance is not an all or nothing trait, with some isolates showing increased resistance to certain antimicrobials, but less resistance to others. For example, Moore et al. (1992) reported that 21/21 samples of beta-hemolytic *Streptococcus* spp. were resistant to amikacin, whereas out of 32 samples tested, only 1 was resistant to erythromycin. Perhaps the adoption of centralized databases that allow veterinarians access to up to date diagnostic laboratory sample results might increase both the reporting and awareness of antimicrobial resistance amongst bacterial isolates. This type of effort is already being attempted in the United Kingdom with a surveillance

project funded by the Horse Trust for the identification of AMR in samples submitted to diagnostic laboratories across the country (Isgren 2021).

There are a variety of factors that can account for the general trend for increased antimicrobial resistance. These can include natural competency, the ability to participate in horizontal gene transfer, and the ability of bacteria to modify metabolic pathways to inhibit antimicrobial activity, which makes comparing trends between different classes of antimicrobials difficult. For example, penicillin and ampicillin are beta lactams, a class of antibiotic which targets bacterial cell wall synthesis (Pandey and Cascella 2002). Erythromycin is a macrolide and gentamicin an aminoglycoside, both of which inhibit bacterial growth by binding to ribosomal subunits to inhibit protein synthesis (Arenz and Wilson 2016). Because different classes of antimicrobials target different pathways within bacteria, resistance to one class of antimicrobials does not guarantee that a microbe will be resistant to other classes of antimicrobials. Of particular concern in horses, and other species, is the development of multidrug resistance by *Staphylococcus aureus*, a common coagulase positive *Staphylococcus* isolated from a large number of cases of synovial sepsis in this review. Methicillin-resistant *Staphylococcus aureus* (MRSA) have been identified in incisional, wound and septic conditions in horses and are of great concern because they are both hard to treat and can be transmitted to humans working with equine patients (Weese et al. 2006, Knych and Magdesian 2021). MRSA has been documented in association with septic arthritis in horses (Weese et al. 2006), although none of the papers eligible for this systematic review described a case of synovial sepsis due to this particular strain. As well as MRSA strains, increasing antimicrobial resistance

in other equine isolates such as those from enteric infections are of growing concern, especially for pathogens that are zoonotic like *Salmonella* (Knych and Magdesian 2021).

While these papers do not shed much light on the change in AMR in equine synovial sepsis, they do highlight the importance of antimicrobial selection in the treatment of synovial sepsis. Moore et al. discuss the importance of reserving certain antimicrobials for use only when appropriate. For example, they state that while trimethoprim-sulphonamides are cheap and easy to administer, they should only be used when culture and susceptibility results are known. Additionally, Moore highlights that certain combinations of drugs, while highly effective, should be reserved for certain severe orthopedic conditions, such as in horses undergoing surgical repair of long bone fractures, where infection can prevent proper union of the bone. Gilbertie et al. discuss the dangers of increased resistance to fluoroquinolones such as enrofloxacin, and how resistance to fluoroquinolones has increased rapidly in recent years. The authors state that the effectiveness of fluoroquinolones against biofilms means that increased resistance has dire consequences for synovial infections with biofilm-forming bacteria.

Knowing the prevalence of antimicrobial-resistant bacterial isolates is important for the safety of equine patients worldwide, as well as the safety of companion and food animals and humans. Therefore it is important that data regarding antimicrobial resistance are collected and made more accessible to practitioners and academics. This could integrate with patient health records so that veterinarians could know in an up to date way which species of bacteria are being reported as being resistant to antimicrobials, both

nationally and locally. Having this information more widely available would make it possible to observe and follow trends on a wider scale, and adapt treatments. A recent study conducted by Schnepf et al. (2020) found that use of electronic practice management software (EPMS) generated “large scale data” on antimicrobial usage in horses, and that this did not require additional work from the practitioner (Schnepf et al. 2020). Usage of EPMS might allow for greater integration of health records for patients, which, in turn, could allow for greater generation of data regarding trends in antimicrobial resistance. The United States has a system of monitoring antimicrobial resistance in humans and food animals, called the National Antimicrobial Resistance Monitoring System (NARMS) (Karp et al. 2017). Perhaps by adding horses to the list of species covered by this monitoring system there would be benefits for both equines and humans. Internationally, regulatory authorities within the United Kingdom have stated in their most recent 5 year national action plan regarding antimicrobial resistance that they are going to finance activities to “collect and share data… with relevant decision makers globally”. Additionally this funding will help develop systems in developing countries across Sub-Saharan Africa, as well as South and South-East Asia to develop sustainable surveillance programs to monitor antimicrobial resistance (Gove and Hancock 2019). The United States could create a similar program that encourages sharing of information between North, Central, and South American countries, as well as those in the Caribbean, to help control the prevalence of antimicrobial resistance throughout the Americas. Cooperation between practitioners and government agencies, as well as cooperation across borders to control the prevalence of antimicrobial-resistant pathogens is important for the safety

of equine patients, as well as for the safety of all humans, food animals, and companion animals.

CONCLUSION:

Synovial sepsis is an important orthopedic disease in equids that can affect both foals and adults. Due to the high likelihood of irreversible joint, tendon sheath, or bursa damage, synovial sepsis is a particularly devastating condition in equine athletes and so it is important that improvements in diagnosis and treatment continue to be made in order to improve outcomes. The systematic review of the literature performed for this thesis covered a 31 year time period from 1990 to 2021 and was designed to examine a number of factors in foals and adults within its three chapters. Firstly, the causes, structures involved, and importantly, information about survival rates to discharge, return to soundness, and athletic performance and how those might have changed over the duration of the study. The findings that foals almost always developed septic arthritis due to hematogenous infections but adults were more often commonly infected via traumatic wounds or due to iatrogenic causes was not surprising and consistent with what had been written in the literature. Similarly, the fact that survival rates were discovered to be lower in foals compared to adults makes sense because the underlying reason for synovial sepsis in foals is septicemia due to FPT. This typically involves multiple joints and other body systems rather than a single synovial structure such as more often occurs in an adult horse. A more surprising finding perhaps was that mean survival rates, as well as rates of return to soundness and athletic performance did not change significantly over the study period. One might have expected improvements over a 30 year time period.

However, reviewing the literature demonstrated a number of things that might have influenced this. Firstly, only 2 studies, Lapointe et al. (1992) and Wright et al. (2003) reported rates of return to athletic performance for 10 or more cases of septic arthritis in equine athletes. Similarly, only 4 studies were available to examine this information for cases of septic bursitis in equine athletes. If numbers are low, although an effort was made to exclude papers with low case numbers to keep statistical accuracy, then it is unlikely that moderate improvements will be identified. This might be especially true in adults because survival to discharge and returns to soundness and athletic performance were already in the 80-90% range. Another issue was the variation in how and over what time frame authors defined return to soundness and return to athletic performance; this makes consistent comparisons difficult. In the future, perhaps co-ordinated multi-center studies that use consistent definitions for return to soundness and athletic performance might help identify subtle improvements.

In the second and third chapters microbiological culture and antimicrobial susceptibility data were reviewed, and again, there were some anticipated findings and some more surprising ones. The most common genera of microbes did not change in adults over the course of the study with the 3 most commonly isolated microbes across all time periods (*Staphylococcus, Streptococcus* and *E. coli*) being skin and environmental contaminants that would be expected to infect traumatic wounds of the limbs and to be introduced iatrogenically. In foals the most common bacteria identified were *E.coli, Rhodococcus equi*, and *Actinobacillus* spp., organisms that are often associated with hematogenous bacterial infections of neonatal foals. Although many

papers reported the genus of bacteria isolated, reporting of species was inconsistent; future studies could benefit from species in addition to genera. There was not a great deal of antimicrobial resistance data available for review and this is definitely an area to expand upon with future studies. Several papers mentioned that sensitivity testing was performed but did not report the results; greater consistency with reporting this information would be valuable. There is obvious equine and human health impact from the development of antimicrobial resistance, and although there were reports of high resistance to certain antimicrobials from both Moore et al. and Gilbertie et al., there are a multitude of factors that make direct comparisons between these two papers inadvisable. Given that increasing antimicrobial resistance, including MRSA infections, are of concern in equine medicine it will be important to closely monitor the prevalence of emerging antimicrobial resistance. This could be achieved by establishing national and/or international databases that improve access for equine veterinarians to antimicrobial sensitivity and resistance data. In the United Kingdom a quarterly disease surveillance report is published by the British Equine Veterinary Association that provides information on several bacteria of importance in horses, including MRSA (Isgren 2021). Avoiding further increases in antimicrobial resistance necessitates a combined effort involving antimicrobial stewardship and greater reporting and standardization of culture and susceptibility testing, but there is no current national monitoring system for antimicrobial resistance in horses in the US as there is for humans and food producing animals (NARMS).

The papers reviewed for this thesis were mainly retrospective clinical studies, and often involved small numbers of cases, limiting the ability to demonstrate how one treatment might be better than another. The lack of compatibility between the wide variety of studies also makes comparisons difficult. As new treatments are developed or combined with existing ones perhaps greater communication and standardization of protocols between equine hospitals that see cases of synovial sepsis would allow more impactful conclusions to be drawn.

ACKNOWLEDGEMENTS:

I would like to thank Drs. Heidi Reesink and Garett Pearson for being my mentors throughout the process of writing this thesis. I would also like to thank Dr. McKenna Caspers, Brittany Papa, and the entire Reesink lab for providing me with valuable feedback and ideas for my thesis, as well as helping to foster my academic career. Lastly, I would like to thank Dr. Erin Eldermire from the Flower-Sprecher Veterinary Library at the CVM for helping me with my literature search, especially showing me how to select search terms and how to properly use literature databases.

APPENDIX:

Table 1. Etiology of Synovial Sepsis in Adult Horses, Proportion of Total Cases (n=755) Out of 52 Total Reports.

Paper	Cause	Quantity
1991 Honnas	Trauma	22
	Idiopathic	2
1992 Bohn	Trauma	1
1992 Honnas	Trauma	11
	Iatrogenic	1
1992 Lapointe	Iatrogenic	15
1992 Schneider	Iatrogenic	19
	Wound	2
	Idiopathic	3
1992 Schneider	Iatrogenic	68
	Trauma	46
	Idiopathic	12
1995 Gibson	Wound	3
1996 Dunkerley	Trauma	1
1996 Vatistas	Trauma	2
1997 Chan	Trauma	1
1997 Magee	Trauma	1
1998 Gough	Trauma	1
1998 Tudor	Idiopathic	1

1999 Prendergast	Trauma	6
	Iatrogenic	2
	Idiopathic	2
1999 Wright	Trauma	16
2000 Booth	Trauma	1
2000 Chan	Trauma	12
2000 Groom	Trauma	8
2000 Meijer	Trauma	15
	Hematogenous	6
	Iatrogenic	6
2000 Ramzan	Hematogenous	1
2000 Rhoads	Trauma	1
2000 Summerhays	Trauma	8
2001 Booth	Trauma	6
2002 Fugaro	Trauma	2
2004 Archer	Hematogenous	1
2004 Booth	Trauma	7
2004 Fraser	Trauma	39
2004 Kidd	Trauma	1
2006 Forrescu	Hematogenous	1
2006 Lopes	Trauma	7
	Iatrogenic	5
	Idiopathic	4

2006 Nagy	Idiopathic	1
2006 Whitcomb	Trauma	2
	Idiopathic	1
2008 Cohen	Iatrogenic	1
2009 Pille	Wound	139
	Iatrogenic	13
	Idiopathic	27
2010 Fajt	Trauma	1
2010 Stewart	Trauma	25
	Iatrogenic	9
2011 Marsh	Trauma	4
2012 Herdan	Trauma	2
2013 McNally	Trauma	3
2013 Visser-Meijer	Iatrogenic	1
2014 Stratico	Trauma	3
2015 O'Sullivan	Hematogenous	1
2016 Robinson	Trauma	82
	Hematogenous	5
	Idiopathic	5
	Iatrogenic	3
2016 Walker	Trauma	2
2017 Santinelli	Trauma	1
2017 Woodford	Idiopathic	1

2018 Lores	Hematogenous	1
2020 Ashton	Trauma	35
2020 Byrne	Idiopathic	11
2020 Elce	Trauma	3
2020 Lenoir	Idiopathic	1
2021 Bergstrom	Trauma	3

Table 2. Etiology of Sepsis in Foals, Proportion of Total Cases (n=250) Out of 18 Total Reports.

Paper	Cause	Quantity
1991 Honnas	Hematogenous	1
1992 Honnas	Trauma	1
1992 Schneider	Trauma	2
1992 Schneider	Hematogenous	66
1997 Hawkins	Iatrogenic	2
1998 Hawkins	Hematogenous	1
2000 Meijer	Hematogenous	12
2004 Lescun	Trauma	1
2009 Pille	Hematogenous	35
2010 Stewart	Hematogenous	3
	Trauma	1
2012 Griffin	Trauma	1
2012 Haggett	Hematogenous	1
2012 Herdan	Trauma	1
2014 Lawhon	Hematogenous	2

2017 Barcelo-Oliver	Hematogenous	12
2017 Wright	Hematogenous	60
2018 Rinnovati	Hematogenous	16
2020 Ruocco	Hematogenous	10

Table 3. Synovial Structure Affected By Synovial Sepsis, Proportion of Total Cases (n=2,786) Out of 94 Reports.

Structure	Percentage
DFTS	21%
Tarsus	16%
Fetlock	12%
Carpus	9%
Navicular Bursa	8%
Coffin	8%
Calcaneal Bursa	8%
Stifle	6%
Pastern	3%
Tarsal Sheath	2%
Elbow	2%
Other	6%

Table 4. Joints Affected By Sepsis, Proportion of Total Cases (n=1,581).

Joint	Percentage
Tarsus	28%

Fetlock	21%
Carpus	15%
Coffin	14%
Stifle	11%
Pastern	5%
Elbow	3%
Hip	1%
Shoulder	1%
TMJ	0%

Table 5. Tendon Sheaths Affected By Sepsis, Proportion of Total Cases (n=735).

Tendon Sheath	Percentage
Digital Flexor Tendon Sheath	78.0%
Tarsal Sheath	9.1%
Carpal Extensor Tendon Sheath	2.6%
Unspecified Tendon Sheath	2.2%
Extensor Carpi Radialis Tendon Sheath	1.8%
Extensor Tendon Sheath	1.5%
Carpal Flexor Sheath	1.5%
Common Digital Extensor Tendon Sheath	1.4%
Long Digital Extensor Tendon Sheath	1.2%
Digital Extensor Tendon Sheath	0.5%
Extensor Carpi Obliquus Tendon Sheath	0.1%

Lateral Digital Extensor Tendon Sheath	0.1%

Table 6. Bursae Affected By Sepsis, Proportion of Total Cases (n=470).

Bursa	Percentage
Navicular Bursa	46.2%
Calcaneal Bursa	45.7%
Bicipital Bursa	4.0%
Infraspinatus Bursa	0.9%
Acquired Precarpal Bursa	0.6%
Intertendinous Calcanean Bursa	0.6%
Olecranon Bursa	0.6%
Acquired Dorsal Metatarsophalangeal Bursa	0.2%
Carpal Bursa	0.2%
Cranial Nuchal Bursa	0.2%
Intertubercular Bursa	0.2%
Podotrochlear Bursa	0.2%
Ulnaris Lateralis Bursa	0.2%

Table 7. Class of Synovial Structures Most Commonly Affected By Sepsis in Foals. Percentage of Total Cases (n=217).

Class of Synovial Structure	Percentage
Joint	94%

Tendon Sheath	4%
Bursa	1%

Table 8. Survival Rate By Half Decade (41 reports).

1990-94	Percentage	Fraction
Schneider et al. 1992	92%	24/26
Lapointe et al. 1992	80%	12/15
Honnas et al. 1991	72%	18/25
Schneider et al. 1992	64%	122/192
Pereman et al. 1991	62%	21/34
Honnas et al. 1992	58%	7/12
1995-99		
Platt et al. 1997	100%	15/15
Prendergast et al. 1999	90%	9/10
Wright et al. 1999	88%	14/16
2000-04		
Wright et al. 2003	98%	119/121
Chan et al. 2000	92%	11/12
Frees et al. 2002	90%	18/20
Fraser et al. 2004	77%	30/39
Post et al. 2003	71%	17/24
Meijer et al. 2000	69%	27/39

2005-09		
Meagher et al. 2006	100%	23/23
Lescun et al. 2006	90%	28/31
Smith et al. 2006	88%	79/90
Pille et al. 2009	87%	130/150
Werezka et al. 2007	78%	40/51
Lopes et al. 2006	75%	12/16
2010-14		
Taylor et al. 2010	90%	185/206
Kelmer et al. 2012	87%	39/45
Milner et al. 2014	86%	183/214
Walmsley et al. 2011	84%	63/75
Stewart et al. 2010	81%	30/37
Rubio-Martinez et al. 2012	72%	69/96
Findley et al. 2014	54%	51/95
2015-19		
Suarez-Fuentes et al. 2018	100%	19/19
Butz et al. 2017	95%	21/22
Crosby et al. 2019	90%	145/161
Hawthorn et al. 2016	88%	14/16
Wright et al.2017	80%	48/60
Barcelo-Oliver et al. 2017	75%	9/12
Rinnovati et al. 2018	69%	11/16

2020-21		
Ashton et al. 2020	100%	35/35
Byrne et al. 2020	100%	11/11
Isgren et al. 2020	84%	108/128
Duggan et al. 2021	83%	24/29
Mosichuk et al. 2021	82%	23/28
Sinovich et al. 2020	77%	17/22

Table 9. Survival Rate By Age.

Paper	Age Group	Fraction Survived to Discharge
Honnas et al. 1992	Adult	18/24
Honnas et al. 1992	Adult	7/12
Lapointe et al. 1992	Adult	12/15
Schneider et al. 1992	Adult	92/126
Prendergast et al. 1999	Adult	9/10
Wright et al. 1999	Adult	14/16
Chan et al. 2000	Adult	11/12
Meijer et al. 2000	Adult	22/27
Post et al. 2003	Adult	17/24
Fraser et al. 2004	Adult	30/39
Lescun et al. 2006	Adult	20/22
Lopes et al. 2006	Adult	12/16
Pille et al. 2009	Adult	115/128

Stewart et al. 2010	Adult	28/34
Walmsley et al. 2011	Adult	63/75
Ashton et al. 2020	Adult	35/35
Byrne et al. 2020	Adult	11/11
Duggan et al. 2021	Adult	24/29
Schneider et al. 1992	Foal	30/66
Meijer et al. 2000	Foal	5/12
Pille et al. 2009	Foal	15/22
Barcelo-Oliver et al. 2017	Foal	9/12
Wright et al. 2017	Foal	48/60
Rinnovati et al. 2018	Foal	11/16

Table 10. Percent Survival to Discharge from Hospital by Class of Synovial Structure.

	Percent Survived to Discharge
Joint	
Honnas et al. 1992	58.30%
Lapointe et al. 1992	80%
Meijer et al. 2000	81.50%
Lescun et al. 2006	90.90%
Meagher et al. 2006	100%
Stewart et al. 2010	78.60%
Butz et al. 2017	95.50%
Ashton et al. 2020	100%

Tendon Sheath	
Honnas et al. 1991	75%
Schneider et al. 1992	91.70%
Schneider et al. 1992	100%
Platt et al. 1997	100%
Prendergast et al. 1999	90%
Chan et al. 2000	91.70%
Fraser et al. 2004	76.90%
Lopes et al. 2006	87.50%
Meagher et al. 2006	100%
Stewart et al. 2010	93.80%
Kelmer et al. 2012	100%
Ashton et al. 2020	100%
Bursa	
Wright et al. 1999	87.50%
Post et al. 2004	70.80%
Suarez-Fuentes et al. 2018	100%
Isgren et al. 2020	84.40%
Duggan et al. 2021	82.80%

Table 11. Percent Return to Soundness by Class of Synovial Structure.

	Percent Returned to Soundness
Joint	

Lapointe et al. 1992	91.70%
Lescun et al. 2006	78.60%
Meagher et al. 2006	91.70%
Stewart et al. 2010	100%
Kelmer et al. 2012	100%
Rinnovati et al. 2018	100%
Ashton et al. 2020	100%
Tendon Sheath	
Schneider et al. 1992	70.80%
Platt et al. 1997	100%
Chan et al. 2000	100%
Fraser et al. 2004	90%
Lopes et al. 2006	50%
Meagher et al. 2006	100%
Stewart et al. 2010	100%
Kelmer et al. 2012	100%
Ashton et al. 2020	100%
Bursa	
Wright et al. 1999	76.90%
Post et al. 2003	86.70%
Suarez-Fuentes et al. 2018	100%
Isgren et al. 2020	83.30%
Duggan et al. 2021	100%

Table 12. Percent Return to Athletic Performance by Class of Synovial Structure.

	Percent Returned to Athletic Performance
Joint	
Lapointe et al. 1992	27.30%
Wright et al. 2003	83.30%
Tendon Sheath	
Honnas et al. 1991	60%
Schneider et al. 1992	42.90%
Platt et al. 1997	100%
Frees et al. 2002	100%
Smith et al. 2006	86.70%
Werezka et al. 2007	56.80%
Bursa	
Wright et al. 2003	69.20%
Suarez-Fuentes et al. 2018	70%
Isgren et al. 2020	94.50%
Duggan et al. 2021	93.30%

Table 13. Survival Rate by Structure.

Carpal Extensor Sheath	
Platt et al. 1997	100%
Fetlock	

Kelmer et al. 2012	86.70%
Ashton et al. 2020	100%
Tarsal Sheath	
Schneider et al. 1992	92.30%
DFTS	
Prendergast et al. 1999	90%
Frees et al. 2002	90%
Fraser et al. 2004	76.90%
Lopes et al. 2006	75%
Smith et al. 2006	87.80%
Kelmer et al. 2012	100%
Calcaneal Bursa	
Post et al. 2003	70.80%
Isgren et al. 2020	84.40%
Duggan et al. 2021	82.80%
Tarsus	
Meijer et al. 2000	65.40%
Lescun et al. 2006	100%
Rinnovati et al. 2018	68.80%
Hip	

Barcelo-Oliver et al. 2017	75%
Coffin	
Peremans et al. 1991	60%
Honnas et al. 1992	58.30%
Mosichuk et al. 2021	76.90%
Carpal Extensor Sheath	
Platt et al. 1997	100%
Fetlock	
Kelmer et al. 2012	86.70%

Table 14. Positive Microbial Cultures 1990-99.

Microbe	Percentage
Staphylococcus spp.	24.1%
Streptococcus spp.	15.0%
E. coli	10.1%
Anaerobes	8.2%
Pseudomonas spp.	8.0%
Proteus spp.	6.5%
Enterococcus spp.	5.9%
Actinobacillus spp.	4.5%
Enterobacter spp.	4.2%
Corynebacterium spp.	2.7%

Acinetobacter spp.	2.4%
Klebsiella spp.	2.4%
Citrobacter spp.	1.8%
Rhodococcus equi	1.2%
Salmonella	0.9%
Bacillus	0.8%
Pasteurella	0.5%
Aeromonas	0.2%
Micrococcus	0.2%
Morganella	0.2%
Pasteurella multocida	0.2%
Providencia	0.2%

Table 15. Positive Microbial Cultures 2000-09.

Microbe	Percentage
Streptococcus spp.	19.9%
Staphylococcus spp.	19.2%
E. coli	14.4%
Actinobacillus spp.	5.5%
Pseudomonas spp.	4.8%
Other	4.8%
Enterobacter spp.	4.1%
Bacillus spp.	2.7%
Enterococcus spp.	2.7%

Klebsiella spp.	2.7%
Corynebacterium spp.	2.1%
Micrococcus spp.	2.1%
Proteus spp.	2.1%
Mixed Culture	2.1%
Acinetobacter spp.	1.4%
Aeromonas spp.	1.4%
Bacteroides spp.	1.4%
Clostridium spp.	1.4%
Brucella abortis	0.7%
Candida utilis	0.7%
Fusobacterium	0.7%
Pasteurella	0.7%
Propiobacter	0.7%
Salmonella	0.7%
Serratia marcescens	0.7%
Proteus spp.	0.7%

Table 16. Positive Microbial Cultures 2010-21.

Microbe	Percentage
Staphylococcus spp.	27.4%
Streptococcus spp.	18.4%
Escherichia spp.	10.9%
Bacillus	5.8%

Enterococcus	5.5%
Actinobacillus	4.2%
Proteus	2.3%
Rhodococcus equi	2.2%
Enterobacter	1.8%
Clostridium	1.5%
Corynebacterium	1.4%
Acinetobacter	1.2%
Pseudomonas	1.2%
Salmonella	1.0%
Klebsiella	0.8%
Pasteurella	0.5%
Prevotella	0.5%
Aerococcus viridans	0.4%
Aspergillus	0.4%
Bacteroides	0.4%
Citrobacter freudii	0.4%
Truperella pyogenes	0.4%
Aeromonas	0.3%
Candida albicans	0.3%
Coliform	0.3%
Mycobacterium	0.3%
Pantoea	0.3%

Serratia spp.	0.3%
Sphingomonas	0.3%
Achromobacter	0.1%
Actinomyces	0.1%
Aureobacterium	0.1%
Brevibacterium epidermidis	0.1%
Erwinia	0.1%
Fusarium	0.1%
Listeria monocytogenes	0.1%
Micrococcus	0.1%
Moraxella osloenis	0.1%
Paenibacillus amylolyticus	0.1%
Propionibacterium acnes	0.1%
Scedosporium	0.1%
Sphingobacterium multivarum	0.1%
Weissella confusa	0.1%
Yeast	0.1%

Table 17. Positive Microbial Cultures in Foals.

Microbe	Percentage
E. coli	26.5%
Rhodococcus equi	14.7%
Actinobacillus	12.7%

Staphylococcus	9.8%
Streptococcus	8.8%
Klebsiella	3.9%
Salmonella	3.9%
Corynebacterium	2.9%
Enterobacter	2.9%
Enterococcus	2.9%
Anaerobes	2.9%
Acinetobacter	2.0%
Bacillus	1.0%
Bacteroides	1.0%
Clostridium perfringens	1.0%
Coliform	1.0%
Proteus mirabilis	1.0%
Weissella confusa	1.0%

Table 18. Microorganisms Isolated From Synovial Fluid.

	1990-99	2000-09	2010-21
Gram Positive	50%	52%	65%
Gram Negative	42%	40%	28%
Fungi	0%	1%	1%
Unknown	8%	7%	6%

Table 19. Gram Stain and Morphology of Bacterial Isolates.

	1990-99	2000-09	2010-21
Gram Positive Cocci	46%	45%	54%
Gram Negative Rods	41%	38%	26%
Gram Positive Rods	3%	7%	10%
Gram Negative Coccobacilli	1%	1%	1%
Gram Positive Coccobacilli	0%	0%	1%
Other	8%	8%	9%

Table 20. Change in Antimicrobial Resistance Patterns From 1992 to 2018 in Coagulase-Positive *Staphylococcus* spp.

Paper	Number Tested	AMI	AMP	CHL	ERY	GEN	PEN	RIF	TET	TMS
1992 Moore	50	0/30	34/48	2/47	2/41	14/48	33/48	0/1	12/46	9/43
2018 Gilbertie	26	12/26	19/26	5/26	9/26	14/26	19/26	0/26	11/26	9/26

Table 21. Change in Antimicrobial Resistance Patterns From 1992 to 2018 in Coagulase-Negative *Staphylococcus* spp.

Paper	Number Tested	AMI	AMP	ERY	GEN	PEN	TET	TMS
1992 Moore	31	1/10	8/14	3/11	3/14	10/14	3/12	5/12
2018 Gilbertie	10	1/10	5/10	0/10	1/10	5/10	4/10	3/10

Table 22. Change in Antimicrobial Resistance Patterns From 1992 to 2018 in Beta Hemolytic *Streptococcus* spp.

Paper	Number Tested	AMI	AMP	CHL	ERY	GEN	PEN	TET	TMS
1992 Moore	40	21/21	0/35	0/34	1/32	29/35	0/34	16/34	4/34
2018 Gilbertie	21	1/21	3/21	0/21	0/21	1/21	3/21	7/21	3/21

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