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EVIDENCE REVIEW

A scoping review of the current evidence on treatment and outcomes following synovial sepsis

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Summary

Background: Synovial sepsis is a frequent cause of morbidity and mortality in horses. Despite advances in diagnostics and treatments, persistent infection or chronic lameness can occur.

Objectives: To perform a scoping review to identify and evaluate the current evidence on the factors implicated in the success of treatment for synovial sepsis.

Study design: Joanna Briggs Institute scoping review.

Methods: A protocol was registered, and a systematic literature search was performed on CAB abstracts, Medline, Scopus and Embase. Inclusion and exclusion criteria were developed and studies systematically reviewed against this. Studies relating to factors affecting treatment success following synovial sepsis were retained and data was extracted on study method, population characteristics and factors significantly associated with treatment outcome.

Results: In total, 2338 studies were identified, and 61 were included to full paper analysis. Eight papers reported significant factors, identifying 15 risk factors associated with two measurements of outcome, either survival and/or return to athletic function. The 15 factors were identified and categorised into pre-, intra- and post-operative factors. Risk factors that were identified included the number or type of synovial structures involved, the presence of pannus, tendon and bone pathology, and the use of systemic antimicrobials. There were many discrepancies in inclusion criteria of cases of synovial sepsis as well as measurement and description of outcome variables.

Main limitations: Non–English language studies or conference proceedings were not included. Only small numbers of papers had similar findings.

Conclusions: Standardisation of inclusion criteria is essential to enable comparisons and analysis between studies on synovial sepsis. Future studies should use methodologies to reduce bias including multicentre and multinational studies, prospective study design and robust statistical modelling.

KEYWORDS

horse, outcome, prognosis, return to athletic function, scoping review, survival, synovial sepsis

The abstract is available in Portuguese in the Supporting Information section of the online version of this article.

1 | INTRODUCTION

Synovial sepsis is an important condition affecting the welfare of horses and can result in mortality or loss of athletic performance. In a clinical setting, gold standard treatment aims for the rapid elimination of infection within the synovial structure by early identification, large volume lavage, debridement and systemic and regional antimicrobial use. Previously, studies investigating survival to discharge after synovial sepsis have reported wide ranges of outcomes (56%-100%).[1-11] There is similar variation for reported rates of horses returning to athletic function (36%-94%).[1,4,7,9-13] These findings highlight that horses can have a successful outcome, but despite gold standard treatment, there are cases where synovial sepsis leads to death or ongoing lameness, and significant financial implications for owners.

Anecdotally, there appears to be a lack of consensus on how different aspects of synovial sepsis treatment affect outcome. For example, some studies have reported that the duration of clinical signs, prior to referral, significantly affected outcome[1,3,6] where others found no significant association.[2,4,7,10,13,14] Similarly, the findings regarding the use of regional antimicrobials are inconclusive with a positive association between use of regional limb perfusion and survival reported in some studies[14] and a negative association reported elsewhere.[10] In addition, different inclusion criteria for synovial sepsis cases and for measurements of treatment outcome are used between research groups.[1,2,9-11,15] Variation in inclusion criteria results in different subsets of horses being given a diagnosis of synovial sepsis and being subsequently investigated making comparisons between study results challenging. This perceived lack of clarity over key definitions and outcome variables, as well as the broad distribution of publications lends this body of literature to a scoping review.

There are many different types of evidence synthesis reviews that can be used to search, appraise and present the literature including but not limited to systematic reviews, meta-analysis, rapid reviews and scoping reviews.[16] There are currently no structured peer-reviewed articles, which describe a systematic search and collation of current evidence investigating synovial sepsis, with only traditional subjective narrative reviews within the literature.[17-19] Systematic reviews are the most commonly used evidence synthesis technique and are widely used within a human healthcare setting.[20] Through structured and transparent searching and analysis of the literature they minimise bias and can provide conclusions, which can influence practice and policy[20,21]; however, systematic reviews are targeted towards answering a specific question. Where discrepancies in studied populations exist within the literature, or when the number and type of relevant studies is unknown, the usefulness of this evidence synthesis technique is reduced.

A scoping review provides an alternative but similarly objective methodology as well as a broad overview of a specific topic.[22] Scoping reviews do not perform any critical analysis of the studies identified, instead through methodological and rigorous peer-reviewed database searching they produce a map of the literature and can identify and clarify key concepts and definitions through extensive charting. In addition, they can investigate research conduct and can recognise knowledge gaps in a body of literature.[21,22] A scoping review can be performed to assess feasibility and, if then appropriate, to identify specific questions prior to performing a detailed systematic review.[23-25] For these reasons, scoping reviews are gaining popularity as an evidence synthesis tool within equine veterinary research.[25-27]

This scoping review aimed to identify and evaluate the current literature available on treatment for synovial sepsis in the horse, including outcomes following different treatment options, and factors associated with the success and failure to respond to treatment. In addition, this scoping review aimed to identify the feasibility and areas appropriate for a future systematic review.

The objectives of this scoping review were as follows:

- To identify the published peer-reviewed literature on the treatment for synovial sepsis in the horse through a systematic search of the databases.
- To extract and chart key data on study characteristics and results for outcome of synovial sepsis in the horse, including survival and return to work.
- To identify any gaps in knowledge in relation to the treatment and outcomes of synovial sepsis.
- To categorise and summarise factors that affect the treatment success in terms of survival and return to work.

2 | MATERIALS AND METHODS

The Preferred Reporting Items for systemic reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) framework was used for this scoping review.[28] This review was registered to an existing protocol (https://osf.io/5sbfk/?view_only=586e7b672deb4342b48da842c9dcb721). All authors and a university librarian provided input and review of the database search strategy. The review was conducted in duplicate by two researchers, one of whom has completed the Joanna Briggs Institute accredited training programme. Any disagreements between the two researchers were decided by a third independent reviewer.

2.1 | Eligibility criteria

Inclusion and exclusion criteria were created to facilitate assessment and appraisal of the titles, abstracts and studies identified and are described in Table 1. Broad inclusion criteria to capture appropriate literature were used. Horses were included if they were greater than 6 months old.

2.2 | Information sources and search strategy

The initial search strategy was performed on 19 May 2020 and updated on 22 September 2020 using Medline In-Process & Non-Indexed

TABLE 1 Inclusion and exclusion criteria for a scoping review of the literature on synovial sepsis in the horse

Criteria	Inclusion	Exclusion
Case	Domesticated adult equids (Horses and ponies)	Donkeys and zebra Foals <6 months and neonates
Exposures	Synovial sepsis of a bursa, tendon sheath or joint	
Intervention	Either medical or surgical treatment[a] for synovial sepsis including lavage, systemic or regional antimicrobials, drainage, use of an implant, specific surgical technique	Papers not relating to treatment
Outcome	Success of treatment – with a focus of either survival[b] and/or return to work[c]	
Language	English or papers with translation available	Translation not available
Study design	Case series, cohort, case control and cross-sectional studies	Narrative, text book chapters, individual case reports
Publication type	Peer reviewed journals Conference proceedings	Unable to obtain full study details Non-peer-reviewed journals Papers published before 1980

[a]Treatment definitions: Lavage – the washing out of a synovial structure with a fluid. Systemic antimicrobials – the administration of antimicrobials via intramuscular, intravenous, oral or subcutaneous routes. Regional antimicrobials – the administration of antimicrobials to a local regional or specific synovial cavity (eg intravenous limb perfusion, intrasynovial injection, intraosseous injection etc). Drainage – systematic withdrawal of fluids and discharges from a synovial cavity. Implant – a material surgically inserted into a tissue for a specific function. Specific surgical technique – details of a novel or specific treatment technique provided.

[b]Survival – included the horse survival to discharge and to other post-operative time points.

[c]Return to work was used as an umbrella term, as decided by the researchers, to include studies relating to any of the following subjective measurements of acceptable function: return to athletic function, return to previous athletic function, return to work.

Citations and Ovid MEDLINE (1946 – present), CAB Abstracts (1973 – present), Scopus Abstract and citation search (1966 – present) and Embase (1974 – present), which include those that are recommended for searching veterinary literature.[29] No date restriction was applied to the search. All references were downloaded and managed in Endnote reference manager (Endnote X9.3.2, Clarivate Analytics).

Search combinations were constructed from the following components using a PICO search strategy:

A exp horses/
B (horse* or pony or ponies or equine or equidae).mp.
C exp sepsis/
D (sepsis or septic).mp
E exp synovial sheaths/
F exp synovial fluid/
G exp tenosynovitis/
H exp tendon/
I exp infection/
J infection*.mp
K ("synovial sepsis" OR "synovial septic" OR "septic arthrit*" OR synovitis).mp
L ((infection* or sepsis or septic) adj3 (synovial or tenosynovitis or bursa* or bursitis or tendon* or joint* or synovium or arthritis)).mp

2.3 | Selection of sources of evidence

The studies were systematically appraised in several steps. Duplicate studies were removed by the primary researcher and titles were assessed by two researchers. Studies were retained if they contained terms relating to outcomes following synovial sepsis, and if this was ambiguous or unclear, the titles were retained to the next stage (abstract review). The abstracts were then independently appraised based on the inclusion and exclusion criteria outlined in Table 1 by two researchers; these were then discussed, with any ambiguous studies taken forward to full text assessment. The studies taken forward to full text assessment were appraised by one researcher based on the inclusion and exclusion criteria, and this was validated by a second researcher to result in a final list of full text studies.

2.4 | Data charting

The full text studies were analysed and relevant data extracted into charts by the primary researcher. Chart headings, publication categorisation and classification was decided and a consensus reached after discussion with all researchers. Study characteristic data were extracted under the following headings: author, year, geographical location, aims, sample size, treatment investigated, outcomes measured and significant outcomes. Treatment data were charted into categories if studies described techniques including: lavage, systemic antimicrobials, regional antimicrobials, drainage, use of an implant, specific surgical technique or treatment not specified. Outcomes measured were classified into either survival and/or return to work; if this was not clearly specified within the publication, then it was discussed between the researchers and a category assigned. Those studies with multivariable statistical analysis of outcome variables were grouped and categorised. Following study characteristic analysis, the studies were charted to include synovial

structure, inclusion criteria, variable investigated, author and measure of association. Inclusion criteria were charted to include the number of diagnostic criteria specified, synovial fluid parameters, direct communication with a synovial structure, subjective assessment of cases and any other details. Case series with no statistical analysis were also categorised dependent on synovial structure and charted to include synovial structure, author, aims and key findings. No additional methodological quality or risk of bias assessment was performed in line with scoping review protocol.[28]

3 | RESULTS

3.1 | Selection of sources

A total of 2338 studies were identified on the initial database searches. Figure 1 highlights the flow diagram of publication handling and assessment as outlined in the selection of sources of evidence. There were 111 studies, which met inclusion criteria for full text assessment; full text scripts were not available for 15 studies with 12 being abstracts from conference proceedings with no corresponding full text, and three were not available. After full text assessment of the remaining studies, nine experimental studies were identified,[30-38] which induced synovial sepsis and investigated specific treatment techniques or changes in diagnostic parameters over a short period (less than 21 days or not specified). These were excluded from further analysis. Other studies were excluded due to language (10), outcome (4), exposure (3) and intervention (2). There were 61 studies that met the final inclusion criteria and data are presented in Table S1 comparing study characteristics, population characteristics as well as significant risk factors identified.

3.2 | Characteristics of sources of evidence

From the 61 included studies, there were 23 studies based in the USA, 18 studies based in the UK, four studies based in Australia, three studies based in Belgium and Canada, and two studies based in Egypt. One study was conducted in each of the following countries: Austria, Germany, Israel, Netherlands, Spain, New Zealand and Ireland. Figure 2 demonstrates the case number of the studies, showing that 49/61 (80.3%) studies had between 1-60 subjects with 12/61 (19.7%) studies having more than 61 subjects. Most studies were based at one equine hospital (42/61, 68.9%), or two hospitals (9/61, 14.8%), and the remaining studies being based at more than two hospitals (7/61, 11.5%) or not specified (3/61, 4.9%).

The most frequent type of study designs were retrospective case series (26/61) and retrospective cross-sectional studies (26/61)

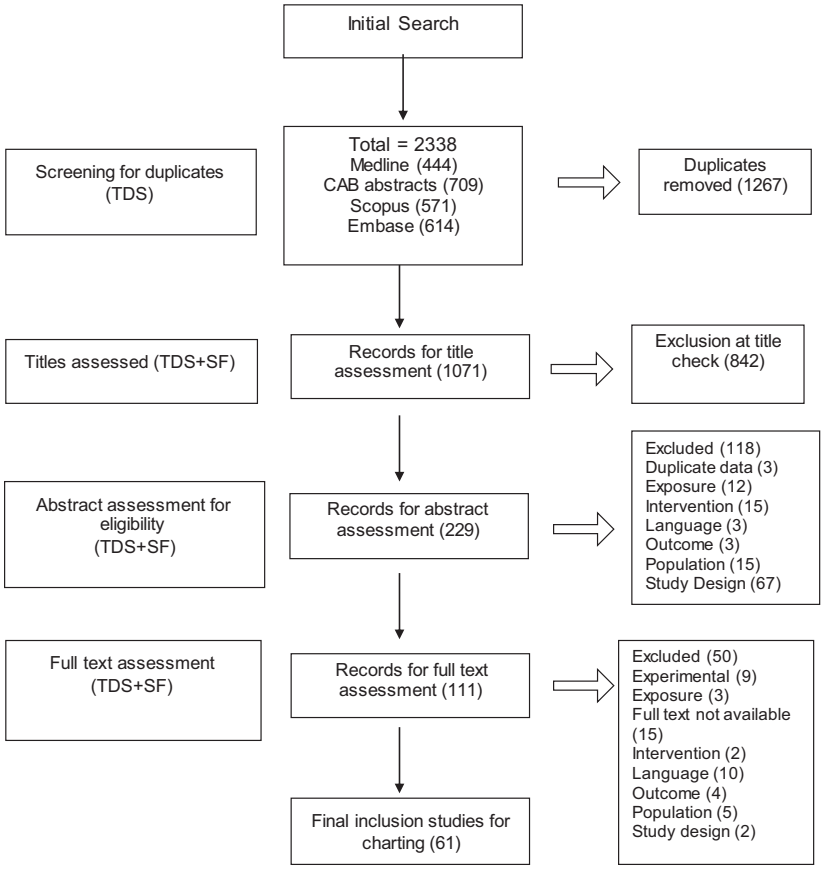

FIGURE 1 Flow diagram outlining the process used to identify studies on outcomes after synovial sepsis following systematic review of the available literature. Initials relate to authors: TDS, Therese de Souza; SF, Sarah Freeman

followed by retrospective cohort (4/61), prospective case series (3/61), prospective observational (1/61) and retrospective case-controlled studies (1/61). Figure 3 demonstrates the different study types plotted dependent on publication date in 5-year ranges.

Of the treatments techniques described within the studies, a combination of lavage, systemic and regional antimicrobials was described in 54/61 studies, and drainage was described in 20/54 of these studies. A specific surgical technique or surgical implant was described in 21/61 and 13/61 studies.

Within these 61 studies, eight investigated outcomes following synovial sepsis using multivariable analysis. The inclusion criteria of these eight studies and the reported results are presented in Table 2 and 3, respectively. Eighteen studies did not use a multivariable analytical approach but used different statistical analysis (15/18) to investigate outcome and the results are presented in Table S2. Three studies (3/18) found no statistically significant data on outcome and were not included.[7,39,40] Descriptive case series that reported outcomes on specific causes, treatment techniques or specific synovial structures are presented in Table S3.

Other small groups and themes of studies were identified. There were six studies that investigated the prevalence of synovial sepsis after iatrogenic intervention and reported the outcome of these horses.[41-46] All six studies had small numbers of horses (range 3-16), and no statistical analysis was performed on outcome for any of the studies. One study specifically described treatment for horses with blackthorn synovitis,[47] and one study identified outcomes in working equids.[48]

3.3 | Results of individual sources

Eight studies investigated outcome following synovial sepsis using multivariable analysis, and Table 2 presents the inclusion criteria specified within the eight studies. One study included descriptive details of the diagnosis of synovial sepsis.[10] Seven studies specified different values of synoviocentesis parameters for the diagnosis of cases of synovial sepsis including the white blood cell count (range 5-30 × 10^9 cells/L), with five of these studies further specifying a percentage of polymorphonuclear cells (80%-90%)[2,9,11,14,49] and six studies identified different total protein concentrations (range 20-40 g/L).[1,2,9,11,14,49] Five studies identified a positive bacterial culture, and[2,9,11,14,49] two identified cytological features of

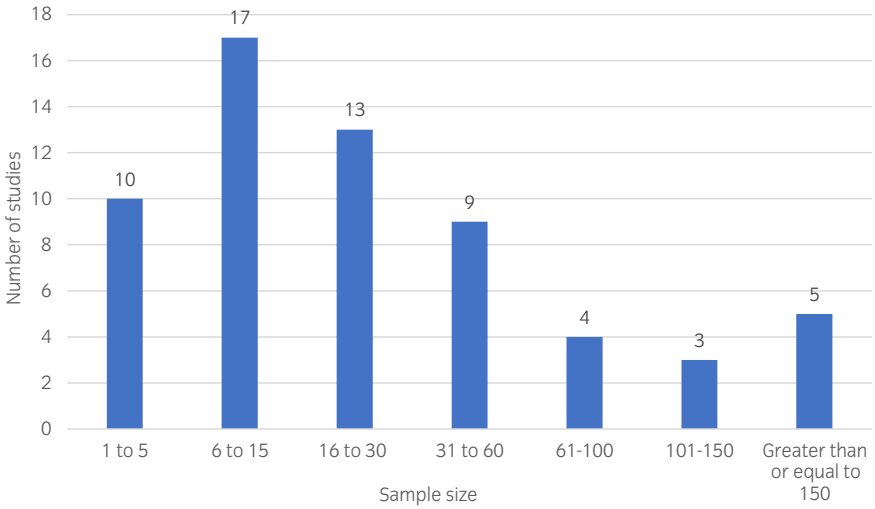

FIGURE 2 Chart to show the number of studies with different sample sizes identified for a scoping review of outcomes after synovial sepsis

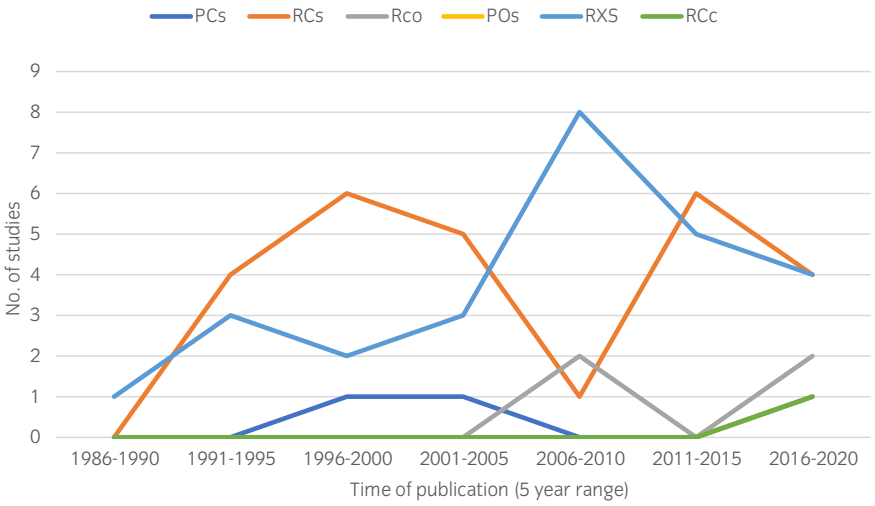

FIGURE 3 Chart to show the trend of different publication types of the studies identified from a scoping review of outcomes after synovial sepsis between the years 1986-2020. Abbreviations: PCs, prospective case series; POs, prospective observational study; RCc, retrospective case-controlled study; Rco, retrospective cohort study; RCs, retrospective case series; RXS, retrospective cross-sectional study

TABLE 2 Inclusion criteria specified by the studies, which reported risk factors affecting outcome after synovial sepsis in the horse

Author	Number of criteria specified	Synovial fluid analysis						Wound/direct communication	Subjective assessment	Other details
		Gross appearance of SF	Nucleated cell count	% of PMN	Total protein concentration	Positive bacterial culture	Cytological examination			
Crosby et al	X	X	≥30 × 10^9 cells/L	>80%	≥30 g/L	√	X	√	X	
Findley et al	X	X	>20 × 10^9 cells/L	X	>20 g/L	X	X	√	X	
Gilbertie et al	X	X	>10,000 cells/μL	X	X	X	X	X	√	Supprative or fibrinous inflammation at PME
Isgren et al	≥1 of the following[a]	X	≥10 × 10^9 cells/L	>80%	>30 g/L	√	Intracellular bacteria	√	X	
Milner et al	X	X	≥5 × 10^9 cells/L	>80%	>30 g/L	√	X	√	X	
Rubio Martinez et al	≥3 of the following	X	>30,000 cells/μL	>90%	>4 g/dL	√	Organisms present, degenerative changes to PMN	X	X	
Wereszka et al	X	X	>30,000 cells/μL	>90%	>4 g/dL	√	X	X	X	Clinical parameters suggestive of synovial sepsis (lameness, heat, effusion of DFTS, surgical findings)
Wright et al	X	√	√	X	√	X	X	√	X	

Abbreviations: √, included inclusion criteria; DFTS, digital flexor tendon sheath; PME, post-mortem examination; PMN, polymorphonuclear leukocytes; SF, synovial fluid; X, not specified.

[a]Needed all SF parameters to be elevated to count as 1 of the criteria.

TABLE 3 Key findings of studies that reported risk factors affecting outcome after synovial sepsis in the horse

Risk factor	Structure or type of injury if specified[a]	Author	Measures of association (multivariable analysis)
Horse factors	Nail penetration	Findley et al (2014)	Group 2 breeds (Thoroughbred/Thoroughbred crosses, Warmbloods/Warmblood crosses and Arabs) were less likely to return to the pre-injury level of activity than Group 1 breeds (cobs, ponies, draught breeds and draught breed crosses) (OR 32.1, 95% CI 2.2-135.4, $P = .001$)
		Rubio Martinez et al (2012)	Mares were more likely to survive than geldings (OR 9.814, 95% CI, 1.798-53.559, $P = .03$), and intact males were more likely to survive than geldings (OR 5.33, 95% CI, 0.619- 45.9, $P = .03$).
		Wright et al (2003)	In horses that survived, non-Thoroughbred horses had significant associations with reduced post-operative performance compared with Thoroughbreds and Thoroughbred-X (OR 6.256 95% CI 1.248-31.371 $P = .026$)
Synovial structure (s)		Rubio Martinez et al (2012)	The probability to return to performance at a level equal to or higher than before the injury was higher for horses in which the hindlimb was involved, compared with those in which the forelimb was involved (OR 16.44, 95% CI 1.71-110.23, $P = .028$).
		Rubio Martinez et al (2012)	Horses with a single synovial structure involved were more likely to survive long-term than horses with multiple synovial structures (including synovial tendon sheaths, bursae and joints) involved (OR 6.205, 95% CI 1.168-32.952, $P = .032$).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka et al (2007)	Horses with sepsis of an adjacent joint were less likely to survive at least 1 year after surgery, compared with horses without evidence of sepsis of an adjacent joint (OR 0.131, 95% CI 0.015-0.0947, $P < .044$).
		Wright et al (2003)	In horses that survived, a combination of synovial structure involvement had significant associations with reduced post-operative performance compared to single synovial involvement (joint, tendon sheath, bursae) (OR 7.250 95% CI 1.244-42.259, $P = .028$).
Injury	Nail penetration	Findley et al (2014)	Direct penetration of the central sulcus of the frog was associated with euthanasia during hospitalisation (OR 10, 95% CI 1.9-51.8, $P = .002$).
		Milner et al (2014)	Presence of a wound on admission was associated with increased likelihood of survival (OR 4.75, 95% CI 1.21-18.65, $P = .02$).
Duration of clinical signs prior to referral	Nail penetration	Findley et al (2014)	Increasing number of days to presentation was significantly associated with failure to return to pre-injury level of athletic function (OR 1.1, 95% CI 1.1-1.6, $P < .0001$).
	Nail penetration	Findley et al (2014)	Increasing number of days from injury to presentation was associated with euthanasia during hospitalisation (OR 1.2, 95% CI 1.0-1.3, $P = .006$).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka et al (2007)	Horses in which duration of clinical signs was <1 day were significantly more likely to survive at least 1 year after surgery, compared with horses in which duration of clinical signs was >10 days (OR 15.6, 95% CI 1.24-500, $P < .027$).
Treatment prior to referral	Calcaneal bursae	Isgren et al (2020)	The administration of systemic antimicrobials prior to referral was associated with reduced mortality (HR 0.25, 95% CI 0.11-0.60, $P = .002$).
Synovial fluid analysis pre-operatively		Gilbertie et al (2018)	Increased likelihood of euthanasia significantly associated with coagulase positive Staphylococcus spp. (OR 7.66, 5.46-10.74, $P < .0001$), β-haemolytic *Streptococcus* spp. (OR 5.18, 3.56-7.55, $P < .0001$), *Enterococcus* spp. (OR 18.38, 11.45-29.52, $P = .002$), *Enterobacteriaceae* (OR 31.37, 22.28-44.17, $P < .0001$), *Pseudomonas aeruginosa* (OR 9.31, 5.30-16.34, $P = .0004$) or other Gram-negative species (OR 3.51, 2.07-5.94, $P = .001$).
		Gilbertie et al (2018)	Increased likelihood of euthanasia significantly associated with infections by Gram-negative organisms (OR 5.03, 3.77-6.72, $P < .0001$)
		Gilbertie et al (2018)	Increased likelihood of euthanasia significantly associated with multi-drug resistance (MDR) (OR 16.11, 12.09-21.45, $P < .0001$)
		Gilbertie et al (2018)	Increased likelihood of euthanasia for MDR Gram-positive organisms (OR 1.85, 1.21-2.81, $P < .005$) and Gram-negative organisms (OR 119.24, 70.57-201.46, $P < .0001$)
		Milner et al (2014)	Higher synovial fluid TP levels measured on admission were associated with a reduced likelihood of survival (OR 0.88, 95% CI 0.83-0.94, $P < .001$).

(Continues)

TABLE 3 (Continued)

Risk factor	Structure or type of injury if specified[a]	Author	Measures of association (multivariable analysis)
Presence of pannus		Milner et al (2014)	Horses with evidence of moderate/severe synovial inflammation identified during endoscopic examination were around four times less likely to survive to discharge than horses with no synovial inflammation (OR 0.28, 95% CI 0.12-0.67, $P = .004$).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka et al (2007)	Presence of severe pannus was significantly associated with a decreased likelihood of returning to a previous or higher level of performance (OR 0.067, 95% CI 0.010-0.455, $P < .006$).
		Wright et al (2003)	For horses that returned to performance, the presence of pannus had significant associations with reduced post-operative performance and nonsurvival (OR 2.839, 95% CI 1.013-7,995, $P = .047$).
		Wright et al (2003)	Presence of marked pannus was significantly associated with nonsurvival compared with moderate/minor or no pannus (OR 5.487, 95% CI 1.081-27.854, $P = .040$).
Tendon injury	Calcaneal bursae	Isgren et al (2020)	Moderate/severe tendon involvement (≥30% cross sectional area) was associated with increased mortality (HR 7.95, 95% CI 3.33-19.0, $P < .001$).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka et al (2007)	Horses with partial or complete tendon rupture were significantly less likely to survive at least 1 year after surgery, compared with horses without evidence of tendon rupture (OR 0.064, 95% CI 0.003-0.554, $P < .026$).
	Tendon sheaths (DFTS, tarsal sheath, carpal extensor sheath)	Wereszka et al (2007)	The presence of tendon injuries (fraying or tearing of the tendon seen during surgery or tendonitis diagnosed ultrasonographically) (OR 0.094, 95% CI 0.013-0.674, $P <.019$) were significantly associated with a decreased likelihood of returning to a previous or higher level of performance.
Bone pathology	Nail penetration	Findley et al (2014)	Concurrent injury to the pedal bone was associated with euthanasia during hospitalisation (OR 32.1, 95% CI 2.6-101.9, $P = .005$).
		Wright et al (2003)	Presence of osteochondral pathology was significantly associated with nonsurvival (OR 6.38, 95% CI 1.31-31.03, $P = .022$).
		Wright et al (2003)	Presence of osteomyelitis was significantly associated with nonsurvival (OR 6.259, 95% CI 1.651-23.654, $P = .007$).
Number of surgeries	Nail penetration	Findley et al (2014)	More than one surgery was significantly associated with failure to return to pre-injury level of athletic function (OR 5.6, 95% CI 1.0-32.7, $P = .03$).
		Milner et al (2014)	Horses undergoing greater than one endoscopic procedure were around 5 times less likely to survive to hospital discharge (OR 0.19, 95% CI 0.05-0.70, $P = .005$).
Surgical factors	Nail penetration	Findley et al (2014)	The hospital at which the horse was treated was associated with failure to return to the pre-injury level of athletic function (OR 2.9, 95% CI 0.6-14.6, $P < .0001$) (OR 0.5, 95% CI 0.003-0.8, $P < .0001$) (OR 1.4, 95% CI 0.2-9.9, $P < .0001$).
	Nail penetration	Findley et al (2014)	The hospital at which the horse was treated was associated with euthanasia during hospitalisation (OR 0.1, 95% CI 0.3-0.9, $P = .006$) (OR 0.2, 95% CI 0.02-0.8, $P = .006$) (OR 0.01, 95% CI 0.007-0.4, $P = .006$).
		Milner et al (2014)	Anaesthetic induction during normal working hours was associated with increased likelihood of survival (OR 0.36, 95% CI 0.15-0.88 $P = .02$). Horses undergoing anaesthetic induction outside of normal working hours were around three times less likely to survive to hospital discharge.
Lavage technique		Rubio Martinez et al (2012)	Horses that were not treated with intrasynovial continuous lavage with isotonic fluids were more likely to return to the same or higher level compared with those in which ISCL with isotonic fluids was used (OR, 43.99, 95% CI, 1.929 to >999.999; $P = .018$).

(Continues)

TABLE 3 (Continued)

Risk factor	Structure or type of injury if specified[a]	Author	Measures of association (multivariable analysis)
Regional antimicrobials		Wright et al (2003)	For horses that returned to performance, the use of regional IV antimicrobials had significant associations with reduced post-operative performance and nonsurvival (OR 3.192, 95% CI 1.085-9.394, $P = .035$).
		Wright et al (2003)	In horses that survived, use of regional IV antimicrobials had significant associations with reduced post-operative performance compared with not using regional IV antimicrobials (OR 4.256 95% CI 1.056-17.153, $P = .042$).
Systemic antimicrobials		Crosby et al (2019)	For return to function when considering each individual synovial structure, treatment with doxycycline was negatively associated with return to function (OR 0.39, 95% CI 0.19-0.8, $P = .031$).
		Crosby et al (2019)	Increasing number of days of treatment with systemic antimicrobials was associated with increased likelihood of survival for each horse (OR 1.15, 95% CI 1.04-1.27, $P = .025$) and when considering each individual synovial structure (OR 1.11, 95% CI 1.04 − 1.17, $P = .004$).
		Rubio Martinez et al (2012)	Higher long-term survival rates for horses that received systemic antimicrobials prior to admission compared with those that did not receive systemic antimicrobials (OR,11.89, 95% CI 2.017-70.181, $P = .006$).
		Wright et al (2003)	For horses that returned to performance, the duration of systemic antimicrobials >7 days had significant associations with reduced post-operative performance and nonsurvival (OR 13.960, 95% CI 1.786-109.133, $P = .012$).
		Wright et al (2003)	For horses that returned to performance, the use of systemic antimicrobials >12 days had significant associations with reduced post-operative performance and nonsurvival (OR 15.429, 95% CI 1.891-125.862, $P = .011$).
Synovial fluid analysis post-operatively		Milner et al (2014)	Synovial fluid TP value measured post-operatively was significantly associated with survival (likelihood of survival decreasing as TP values increased) (OR 0.94, 95% CI 0.90-0.98, $P = .013$).

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; DFTS, digital flexor tendon sheath; HR, hazards ratio; ISCL, intrasynovial continuous lavage; IV, intravenous; MDR, multidrug resistance; OR, odds ratio; TP, total protein.

[a]If structure or nature of injury not specified it relates to general synovial structures (which can include joints tendon sheaths and bursae) caused by a range of inciting causes.

bacteria colonisation.[14,49] One study separated horses with "fresh intrasynovial lacerations with minimal contamination" from horses with established synovial sepsis,[14] whereas confirmation of synovial involvement was a criterion of inclusion for others.[1,2,11,49]

The treatment techniques involved lavage, systemic and regional antimicrobials in six of eight studies.[1,2,9-11,49] In one study, a specific surgical technique of regional limb perfusion was described.[14] Treatment techniques were not specified in one paper.[15] The outcome measured for all eight studies was survival to hospital discharge with or without including return to athletic function. The timeframe of follow-up differed between the studies; two studies looked at survival without residual lameness,[2,15] whereas six studies had a range of follow-up times between three months and 16 years post-operatively. Three studies used an objective measurement of outcome using race records either solely or in combination with telephone questionnaires[10,11,49] with three other studies using only telephone questionnaires to owners, trainers or referring veterinarians for follow-up.[1,9,14]

Table 3 demonstrates the 15 risk factors that were found to be statistically significant evidence of association including: horse factors, synovial structure, type of injury, duration of clinical signs prior to referral, treatment prior to referral, synovial fluid analysis pre-operatively, presence of pannus, tendon injury, bone pathology, number of surgeries, surgical factors, lavage technique, regional antimicrobials, systemic antimicrobials, synovial fluid analysis post-operatively. Table 4 highlights the number of studies within each category of risk factor divided into pre-operative (n = 6), intraoperative (n = 6) and post-operative factors (n = 3).

4 | DISCUSSION

This scoping review has identified the pertinent and current literature available on treatment for synovial sepsis and found a varied group of 61 studies from fourteen countries. From these sixty-one studies, eight have been identified that report significant risk factors and outcome. Within this body of literature, key issues that have been identified include the lack of consistency in inclusion criteria and follow-up duration and measurement of outcome between studies, and the small number of studies that identify significant risk factors.

TABLE 4 Summary of studies reporting significant risk factors affecting treatment outcome after synovial sepsis

	Risk factor type	Number of studies
Pre-operative	Horse factors	2
	Cause of injury	2
	Synovial structure involved	3
	Synovial fluid analysis	2
	Treatment prior to referral	1
	Duration of clinical signs prior to referral	2
Intraoperative	Bone pathology	2
	Tendon pathology	2
	Presence of pannus	3
	Surgical factors	2
	Lavage	1
	Number of surgeries	2
Post-operative	Systemic antimicrobials	3
	Regional antimicrobials	1
	Post-operative synovial fluid analysis	1

4.1 | Summary of evidence – research conduct

4.1.1 | Definitions

"To advance knowledge of a clinical entity, we must begin with a definition".[50] Refining inclusion criteria for horses with synovial sepsis is a difficult undertaking as it is a broad term used to describe a dynamic pathological process of a vast range of clinical presentations. There are currently no evidence-based recommendations for inclusion criteria or diagnosis for cases of synovial sepsis. Of the eight studies identified within this scoping review that report risk factors affecting outcome after synovial sepsis, there were marked differences in diagnostic criteria for synovial fluid "cut-off" parameters and varied differentiation and separation of contaminated or infected synovial structures. By using different definitions, this resulted in different subsets of horses being included and investigated under an umbrella term of synovial sepsis, making comparisons of results between studies impossible. Previous scoping reviews have identified this issue within different bodies of literature and acknowledge that variability identified in inclusion criteria of study subjects can restrict the ability to conduct systematic reviews.[51] Establishing agreement with inclusion criteria is a common issue within research settings. In human literature, consensus methods are often used to provide guidelines regarding key features of pathology and treatment, as well as creating diagnostic criteria for specific diseases.[52,53] Consensus methods include techniques such as nominal group processes, consensus development panels, and Delphi techniques, and are based on evidence based medicine. If this is not available then recommendations are based on knowledge and expertise of specialists through a set protocol of discussion.[53,54] Their findings should be frequently reviewed in order to adapt with changing evidence and practice.[52] There are several consensus statements within veterinary scientific writing, which provide guidelines and recommendations to other practitioners and researchers for specific diseases.[55] There is currently no consensus statement for synovial sepsis and this could significantly improve future research if clarity and agreement over inclusion criteria could be implemented.

4.1.2 | Measurement of outcome

There were key differences identified in the measurement of outcome variables. The main measurements of outcome after synovial sepsis were survival to hospital discharge and/or return to athletic function (Table S1). Of the studies that looked at return to athletic function, this was defined differently. Some studies looked at survival without residual lameness,[2,15] whereas others tried to quantify the level at which the horse was working either subjectively with telephone questionnaires[1,9,14] or objectively in combination with online race records.[10,11,49] Cook et al, has proposed a set of definitions reporting outcomes for clinical orthopaedic trials and suggests using the terms return to "full function", "acceptable function" and "unacceptable function".[56] This framework, if implemented, could provide guidance for authors as well as consistency between studies. There were also differences in the time frame of "long-term" follow-up and the method of follow-up between studies. There was a large range in the follow-up duration between studies from 3 months to 16 years post-operatively. Defining and stating the duration of follow-up more transparently and implementation of standardised time frames would make interpretation of outcome measurements clearer. Again, the lack of consistency means consolidation of the evidence and interpretation of studies investigating return to athletic function remains challenging and further evidence synthesis, including a systematic review, is not possible.

4.1.3 | Study design and conduct

Study design features that were identified as limiting the quality of evidence included the small number of studies that accounted for confounding variables, the lack of treatment details described within the materials and methods, and the small sample sizes. Within the 61 studies, 18 cross-sectional studies were identified that investigated outcomes following synovial sepsis, which did not account for confounding factors within their statistical analysis (Table S2). Only eight studies were identified to take into consideration confounding factors and used multivariable analysis. Multivariable analysis is an essential statistical tool to enable complex relationships to be established between several variables and should be used in studies where study design is unable to account for confounding bias.[57,58]

In addition, adequate details of treatment techniques were often lacking. Of the eight studies identifying significant factors affecting outcome, six of eight described some form of treatment technique

involving lavage, systemic and regional antimicrobials with one study not specifying any treatment techniques used at all. Significant details of surgical techniques including wound resection and closure, synovial resection, lavage fluid and volume or drainage could be important variables affecting treatment outcome. This can be accounted for if the studied population all receive the same treatment, and this is clearly stated during the study design process; however, if these are not controlled nor described then further details of treatment techniques should be included within the results to allow comparisons and improve the external validity of the research. This is a common finding within the studies identified and may be due to the retrospective nature of the study design, with data being collected from clinical case records. This could be improved in the future by standardised reporting and inclusion of clear descriptions of surgical techniques either within the study design or results. In addition, the use of prospective study designs investigating these factors could be of benefit to assessing confounding variables.

Sample size is a common limitation of veterinary and human research.[59] This scoping review identified that within the 61 studies initially identified, 80% of the studies had less than 60 subject participants. Of the eight studies that identified specific risk factors, one contained less than 60 subjects[9] and seven included more than 61 subjects. The power of a study increases with sample size.[59,60] This is applicable to investigating outcomes after synovial sepsis when differences between outcomes are small. Death after treatment of synovial sepsis is relatively infrequent and the differences between horses reaching a better or worse level of athletic function are likely to be small and multifactorial. Larger sample sizes can improve the ability to detect small differences or investigate multiple variables and can facilitate more robust statistical modelling, thereby improving the quality of the data.[61,62] Most studies investigated data from a single hospital (68.9%), with only seven studies investigating data from three or more hospitals, which likely contributed to the small number of study participants. Multicentre and multinational studies provide both access to a larger sample size increasing the ability to detect small differences as well as providing greater variety of the population studied, enabling the results to be applicable to the general population.[63]

4.2 | Summary of evidence – key findings and factors identified

The findings from the small number of studies with similar risk factors were categorised into three groups, and this identified that there were six pre-operative, six intraoperative and three post-operative risk factors. Within these categories, the most commonly represented risk factors were the number of synovial structures involved,[9,10,14] the presence of pannus,[2,9,10] presence of tendon and bone pathology[1,9,10,49] and the use of systemic antimicrobials.[10,11,14]

Although no risk assessment was performed, this scoping review identified themes within these studies. Interestingly, from those studies that investigated all synovial structures (including tendon sheaths, bursae and joints), no specific synovial structure was reported to have a worse or better prognosis. However, three studies found that horses with injuries involving multiple synovial structures had a reduced likelihood of survival.[9,10,14] In addition, five studies identified that more severe injuries with concurrent tendon injury,[9,49] bone pathology[1,10] or presence of moderate to severe pannus[2,9,10] were significant negative prognostic indicators for both survival and return to work. However, establishing detailed criteria and grades for different tendon, bone and synovial pathology is necessary to further determine the nuances of these associations.

The use of systemic antimicrobials was found by three studies to affect survival and return to work.[10,11,14] Rubio-Martinez et al found horses that received systemic antimicrobials prior to admission had higher survival rates compared to those that did not. This finding has not been previously reported and suggests that early intervention can improve outcomes. Crosby et al found that the use of a specific antimicrobial, doxycycline, was associated with a negative outcome. The authors suggested that typically doxycycline was used for refractory cases in their population. This may have skewed its use towards cases that had not responded to initial broad-spectrum antimicrobials. The presence of a wound communicating with the synovial structure was found to be a factor associated with better survival.[2] One hypothesis from that study was that this was due to earlier identification of wounds by clients compared with more insidious causes of synovial sepsis, which may allow earlier implementation of treatment.[2] All eight of the studies in Table 3 investigated how timing of the injury prior to referral affected outcome. Surprisingly, only two studies found a significant association with duration of injury prior to referral with a poorer prognosis for survival and return to work.[1,9] It is anecdotally believed that there is a "golden" window in which treatment for synovial sepsis carries a greater chance of success; however, there is a lack of robust evidence within this body of literature to support this impression. Early recognition of wounds, increased awareness of synovial structures and implementation of treatment is undeniably desirable and further research into owners' and veterinarians' initial triage of potential synovial sepsis cases is important to further quantify these associations.

This scoping review highlights that only a small number of studies have found associations with similar risk factors, which would make these associations difficult to analyse with a systematic review; however, themes that have been identified and could warrant future investigation include how early recognition influences the early implementation of antimicrobial treatment, bone and tendon involvement and intrasynovial pannus formation.

4.3 | Limitations of the scoping review

There are several inherent limitations to the scoping review process. A scoping review does not provide analytical critique of the literature compared with a systematic review nor does it specifically answer a research question.[21] It can provide an overview without specific details or assessment of risk within the published work and identify bodies of evidence for more detailed analysis through a systematic review.[21] Broad search terms and inclusion criteria were

used to capture as many of the appropriate studies as possible using the key veterinary research databases including Medline, CAB abstracts and Scopus,[29] which were outlined in the a priori protocol; however, this search strategy did not identify some studies, which would have met the inclusion criteria, and had been identified by a hand search of the references of the included studies. An additional search engine, Embase, was included after the initial searches, which allowed further studies to be captured likely due to differences in indexing and inclusion of additional journals.[29] Quality control check points for search strategies should be implemented in scoping reviews, or independent assessment to ensure an appropriate breadth and representative literature is captured.

Conference proceedings and full texts not in English language where no translation was available were excluded. Conference proceedings offer an important source of new data often prior or exclusive to publication elsewhere, with some studies suggesting less than 10% of conference proceedings being subsequently published.[64] In addition, there may be a selection bias for conference proceedings with positive results to be subsequently published and, therefore, the results of conference proceedings may offer a true representation of both positive and negative results.[65] An extensive search strategy was performed to gain access to the full papers; however, 15 studies were not available, 12 of which were abstracts from conference proceedings. It could benefit future work if conference proceedings were more widely accessible with effective dissemination.

Several steps were taken to reduce bias and subjectivity within the methodology. An a priori protocol was developed and inclusion and exclusion criteria developed after collaborative discussion between authors. The search terms used were developed by the authors with consultation from an experienced librarian to help with specific database nuances. Systematic assessment of the studies was performed independently by two authors, with any ambiguous titles or abstracts being taken through to the next round of assessment; however, the charting process was performed by one author and verified by all others, which could have led to selection bias. It has been suggested to use two authors to independently chart all texts and to discuss any discrepancies that could reduce this selection bias in the future.[22,66]

Scoping reviews can act as an evidence synthesis tool, as well as providing an evidence-based precursor to performing a systematic review. At this stage, although no further critical analysis of the relevant risk factors was presented, the limited number and poor compatibility between studies would mean a systematic review would not be possible as an additional evidence synthesis tool. This is a common conclusion of scoping reviews; Tricco et al found only 12% of scoping reviews included a recommendation of a systematic review in their conclusions.[22]

5 | CONCLUSION AND RECOMMENDATIONS

This scoping review has extracted and categorised the current evidence relevant to treatment outcomes after synovial sepsis to aid clinicians, and to inform future research.

Key future research recommendations include the following:

- The development of standardised inclusion criteria for cases of synovial sepsis and more comparable measurements of outcome are essential for more detailed evidence synthesis of this body of literature to occur.
- Use of methodologies to reduce bias including multicentre and multinational studies, prospective study design and robust statistical modelling.
- Standardised reporting of treatment techniques within study design descriptions.

Risk factors that were identified included the number or type of synovial structures involved, the presence of pannus, tendon and bone pathology and the use of systemic antimicrobials. Future areas of research are important to establish criteria and grades for different tendon, bone and synovial pathology and to assess the effect of early recognition of synovial sepsis and implementation of treatment on desirable outcomes.

CONFLICT OF INTERESTS

No competing interests have been declared.

AUTHOR CONTRIBUTIONS

All authors contributed to study design and methodology. T. de Souza and S. Freeman carried out the database searches and exclusion, with consultation of other authors if required. Data extraction and interpretation was performed by all authors. All authors contributed to manuscript preparation and critical review.

ETHICAL ANIMAL RESEARCH

The study was reviewed and approved by the School of Veterinary Medicine and Science Ethics Committee, University of Nottingham.

INFORMED CONSENT

Not applicable.

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SUPPORTING INFORMATION

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