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Title of Knowledge Summary (maximum 25 words)

In horses, does treatment with intra-articular antimicrobials concurrently with intra-articular corticosteroids reduce the risk of iatrogenic synovial sepsis compared to intra-articular corticosteroids alone?

Author(s) Name, Postnominals, Institution

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KNOWLEDGE SUMMARY

PICO Question:

In horses, does treatment with intra-articular antimicrobials concurrently with intra-articular corticosteroids reduce the risk of iatrogenic synovial sepsis compared to intra-articular corticosteroids alone?

Clinical bottom line:

From the current literature, there is no evidence showing that intra-articular injection of antibiotics in conjunction with corticosteroids reduces the risk of synovial sepsis. However, the intra-articular injection of polysulphated glycosaminoglycans (PSGAGs) in combination with corticosteroids was noted as a risk factor for developing iatrogenic synovial sepsis and therefore concurrent antibiotic injection when administering PSGAGs may be warranted. The reported frequency of infection following intra-articular injection was very low (0.02-0.075%). The overall prevalence of iatrogenic synovial sepsis following all intra-articular injections based on data from all included studies was calculated as 0.03% (CI 0.02-0.04%). However, due to the paucity of literature on the topic, further studies are required in this field to determine more accurate clinical recommendations.

PICO Question

In horses, does the treatment with intra-articular antimicrobials concurrently with intra-articular corticosteroids reduce the risk of iatrogenic synovial sepsis compared to intra-articular corticosteroids alone?

Clinical scenario

Antimicrobials such as amikacin sulphate or gentamicin sulphate are often added to corticosteroid preparations when performing intra-articular injections in horses. This summary aimed to determine whether the risk of iatrogenic synovial sepsis increases in the absence of these antimicrobials and to consider whether injecting them concurrently with intra-articular corticosteroids is necessary.

The evidence

Of the four studies examined, only two studies directly evaluated the prevalence of iatrogenic synovial sepsis following intra-articular injection. Three out of the four studies were retrospective analyses of medical records (Bohlin et al., 2014, Smith et al., 2018, Steel et al., 2013) and one was a survey-based study with retrospective analyses of medical records submitted by questionnaire respondents (Gillespie et al., 2016). One study was a published abstract within non-peer-reviewed conference proceedings. The searches also revealed an abstract by Smith et al. (2013) which was later published as a full study (Smith et al., 2018) and for the purposes of avoiding data replication, only the full study was included.

The scientific literature surrounding this topic was sparse and of inconsistent quality. There were no randomised controlled trials evaluating the risk of iatrogenic synovial sepsis following corticosteroid administration. Most studies comprised retrospective analyses of medical records, which are considered mid-level in the hierarchy of evidence based medicine (Murad et al., 2016). The number of cases of iatrogenic synovial sepsis was very low in all included studies, therefore evaluating risk factors using multivariable models may have been biased by a low number of events per variable. All included studies were likely to have insufficient statistical power to identify a true difference in incidence between different treatments (Pezuzzi et al., 1996).

Summary of the evidence:

Where prevalence and 95% confidence intervals (CI) were not provided in the publication, the author performed calculations where published data permitted using EpiTools epidemiological calculators (Ausvet Pty Ltd, 2019). (*Italics denotes author calculations*).

Steel, C. M., Pannirselvam, R. R., & Anderson, G. A. (2013)	
Population:	16,624 intra-articular injections performed in 1103 Thoroughbred racehorses.
Sample size:	16624 injections in 1103 horses.
Intervention details:	<ul style="list-style-type: none"> • Cases included 16,624 joints injected in 1,103 horses over a 45-month period from 31st March 2002 to 31st December 2005. • Standardised aseptic preparation procedure was used. Hair was not clipped and was scrubbed with 4% chlorhexidine for a minimum of 2 minutes, then 70% alcohol wipes. • Various medications were injected, doses were not recorded. • Non-sterile dressing applied to all except stifle and shoulder joints, where no dressing was applied. • Control group included all horses given intra-articular medication (IAM) on the same day, day before or the day after septic cases (224 controls for 13 cases).
Study design:	Retrospective and prospective descriptive study, with nested matched case-control.
Outcome studied:	<p>Diagnosis of septic arthritis within 1-19 days following intra-articular injection.</p> <p>Septic arthritis was diagnosed if synovial fluid bacterial culture was positive or if synovial fluid analysis revealed elevated total leucocyte count ($>5.0 \times 10^9/L$) with a predominance of neutrophils ($>80\%$) and increased total protein ($>25g/L$).</p>
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> • Of 16,624 joints injected in 1,103 horses, septic arthritis occurred in only 13 joints (13 horses). • The risk of septic arthritis following intra-articular injection was 1 case per 1279 injections or 7.8 per 10,000 joints (<i>prevalence 0.08% [CI 0.05-0.13%]</i>). • Of the 13 septic cases, 12 horses were injected with corticosteroid plus or minus sodium hyaluronate (individual case details unspecified) and one was injected with a homeopathic anti-inflammatory product. • Risk factors identified were veterinary surgeon and type of corticosteroid. • Betamethasone had a lower risk of septic arthritis than dexamethasone. • When data for each joint location were compared there was

	<p>no significant difference in the number of cases.</p> <ul style="list-style-type: none"> • None of the 824 joints injected with amikacin developed septic arthritis. Of the 15,800 joints injected without amikacin, 13 developed iatrogenic synovial sepsis. There was no statistically significant association between the absence of amikacin and development of synovial sepsis (Fisher's exact test $P > 0.99$).
Limitations:	<ul style="list-style-type: none"> • The effect of the individual performing skin preparation was not studied because information was unavailable for 7 of the 13 septic cases and for 50% of the non-septic cases. • Study did not clarify whether veterinary surgeon or assistant performed skin preparation. Due to certain veterinary surgeons having an apparently higher rate of septic cases than others, this would have been useful information in order to determine if there were differences in aseptic technique despite a standardised procedure being in place. • Non-sterile dressing applied to all except stifle and shoulder joints, where no dressing was applied. • Medication doses were not recorded so association between corticosteroid dose and septic cases could not be evaluated. • Statistical validity of results is limited by a large number of injections with relatively low number of septic cases for comparison (resulting in a low number of events per variable for analysis of risk factors).

Gillespie, C. C., Adams, S. B., & Moore, G. E. (2016)	
Population:	Equine veterinarians who were members of the American Association of Equine Practitioners (AAEP) in 2014.
Sample size:	241 surveys were returned containing details of 319,760 intra-articular injections.
Intervention details:	<ul style="list-style-type: none"> • A link to an online survey was distributed to all members of the AAEP via email a total of 3 times between 17th March and 9th May 2014. • The survey consisted primarily of multiple choice questions about intra-articular injection site preparation methods, injection methods, types of medication used and aftercare. • Several open questions and written responses were also included. • Guidelines were provided for determining joint sepsis. Medical records for septic cases were requested and analysed.
Study design:	Retrospective survey-based cross-sectional study.
Outcome studied:	Reported rate of joint sepsis following intra-articular injection. Guidelines for diagnosing sepsis included one or more of: increased

	<p>lameness score attributed to the injected joint, peri-articular swelling, joint effusion, cloudy or turbid synovial fluid, elevated total protein of the synovial fluid and elevated nucleated cell count of synovial fluid.</p>
<p>Main findings: (relevant to PICO question):</p>	<p>Only 27% of respondents provided data regarding joint sepsis. 67 out of 319,760 injected joints became septic following injection; 2.10 septic joints per 10,000 intra-articular injections (<i>prevalence 0.02% [CI 0.02-0.03%]</i>)</p> <p>Infection rates were significantly lower when:</p> <ul style="list-style-type: none"> • Veterinary surgeons prepared their own injection sites. • Veterinary surgeons had fewer than 20 years of practice experience. • <p>Infection rates were significantly higher when:</p> <ul style="list-style-type: none"> • Hair was removed at the injection site. <p>Some findings were significant on the univariable analysis but were not retained in the final multivariable model and these included:</p> <ul style="list-style-type: none"> • Lower infection rates when the intra-articular injection site was prepared for longer than 7 minutes • Lower infection rates when surgeons wore sterile or non-sterile gloves when performing the injection • Higher infection rates when veterinary surgeons used the same needle to draw up medications and perform the injection. <p>No significant reduction in joint sepsis was noted with the concurrent intra-articular injection of antimicrobials.</p>
<p>Limitations:</p>	<ul style="list-style-type: none"> • Horses with septic joints diagnosed by one veterinary surgeon but injected by another (i.e., second opinions) were not included in the study. This could have falsely lowered the apparent infection rate as approximately 60% of respondents reported treating infections in horses that were injected by other veterinary surgeons. • Risk of misclassification bias – the method of diagnosing synovial sepsis was recommended in the study though the true method of diagnosis may have varied between veterinary respondents. • Study was questionnaire-based and thus open to non-response, response and recall bias. • Response rate was low with only 241 respondents, which equates to a response rate of around 2.5%, with only 26.6% of respondents providing data on joint infections. • Statistical validity of results is limited by a large number of injections with relatively low number of septic cases for comparison (resulting in a low number of events per variable for analysis of risk factors). • Exact numbers of corticosteroid injections and how many of these were septic are not provided, limiting the reliability of interpretation of these results in direct relevance to the

	PICO question.
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Bohlin, A. M., Kristoffersen, M., & Toft, N. (2014)	
Population:	Medical records of 2,833 horses from one private equine hospital
Sample size:	2,833 horses, 14,124 intra-articular injections.
Intervention details:	<ul style="list-style-type: none"> Medical records of 2,833 horses and 14,124 intra-articular injections were identified and analysed.
Study design:	Retrospective analysis of medical records.
Outcome studied:	Prevalence of septic arthritis following intra-articular injection.
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> No horses undergoing intra-articular diagnostic anaesthesia alone experienced infectious arthritis. No specific joint had increased risk of infection. Infectious arthritis was rare following intra-articular injection. (Overall treatment 17.0/10,000 [0.17%], Corticosteroids 16.1/10,000 [0.161%], hyaluronate 15.9/10,000 [0.159%], and PSGAG 39.4/10,000 [0.394%]). Treating veterinary surgeon was identified as a risk factor. Combined polysulphated glycosaminoglycan (PSGAG) and corticosteroid treatment was identified as a risk compared with corticosteroid treatment alone.
Limitations:	<ul style="list-style-type: none"> Only the extended abstract of this study was available published in the scientific proceedings from the AAEP annual convention (not peer reviewed). The abstract does not contain enough information to accurately interpret the findings of the study. No data regarding study duration are provided. The method of diagnosing septic arthritis was not specified. The authors state that approximately 1,000 horses treated with prophylactic antibiotics would prevent one infection following intra-articular injection, though data on the use of antibiotics in the study population were not obtained.

Smith, L., Wylie, C.E., Palmer, L. & Ramzan, P.H.L. (2018)	
Population:	Case records for every horse that received intra-synovial medications performed by ten ambulatory clinicians in one UK equine hospital between 1 st January 2006 and 31 st December 2011.
Sample size:	9,456 intra-synovial injections in 1,732 horses over 4,331 sessions.
Intervention details:	<ul style="list-style-type: none"> 1,732 horses receiving therapeutic intra-synovial injections using standardised aseptic technique.

	<ul style="list-style-type: none"> Records were cross-referenced against admissions of synovial sepsis cases to the hospital and against cytology submissions. Post-medication sepsis was considered if the horse developed two or more of four signs of synovial sepsis within 8 weeks of medication (listed below) and failed to respond to conservative therapy.
Study design:	Retrospective analysis of medical records.
Outcome studied:	<p>Prevalence of iatrogenic synovial sepsis following intra-articular injections.</p> <p>Synovial sepsis was defined as any horse developing two or more of four signs, including lameness, joint distension, synovial white blood cell count $>10 \times 10^9/L$, or synovial total protein $>25g/L$ within 8 weeks of intra-articular medication of the same joint. Cases that resolved with conservative therapy (short-courses of non-steroidal anti-inflammatory drugs and antimicrobials) were not diagnosed as septic.</p>
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> Frequency of iatrogenic synovial sepsis was very low (0.04%). 89.3% of injections included corticosteroids, 93.4% included amikacin. 4 horses developed iatrogenic synovial sepsis – two following injection of PSGAGs, one following triamcinolone acetonide combined with amikacin sulphate and one following triamcinolone acetonide alone. Administration of intra-synovial PSGAGs was associated with an increased risk of iatrogenic synovial sepsis, though the 95% confidence intervals cross 0, therefore this finding was not statistically significant. Concurrent injection of amikacin sulphate with any other intra-synovial medication was associated with a low risk of developing iatrogenic synovial sepsis (attributable risk - 1.02%, [CI -2.21 – 0.16]), though the confidence interval crosses 0, therefore this finding was not statistically significant.
Limitations:	<ul style="list-style-type: none"> 93.4% of injections included a prophylactic antibiotic (amikacin sulphate) so true risk of sepsis without concurrent antimicrobial administration is difficult to quantify. High proportion of racehorses within study population may limit external validity. Case definition of synovial sepsis in relation to descriptive clinical parameters (lameness, joint swelling) was open to interpretation and may vary between veterinary surgeons. Data analysed in sessions rather than per individual injection; there were 9,456 injections performed in total though data is analysed over 4,331 sessions. Statistical validity of results is limited by a large number of injections with relatively low number of septic cases for

	comparison (resulting in a low number of events per variable for analysis of risk factors).
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Appraisal, application and reflection

The current literature suggests that the frequency of infection following all intra-articular injections is very low and equates to roughly one case per 1,000, 1,279 or 2,364 injections according to Steel et al., 2013, Bohlin et al., 2014 and Lewis et al., 2018 respectively. These figures equate to a prevalence of iatrogenic sepsis of 0.02-0.08%. The overall prevalence of synovial sepsis following all intra-articular injections based on data from all included studies was calculated as 0.03% [CI 0.02-0.04%]. The prevalence of synovial sepsis following corticosteroid injections across three studies which provided the necessary data (Bohlin et al., 2016, Smith et al., 2018 and Steel et al., 2013) was 0.1% [CI 0.07-0.014%].

Table 1: Prevalence estimates for synovial sepsis for all intra-articular injections across all studies (as calculated by author).

Study	Injections	Septic cases	Prevalence (%)	CI (%)
Steel et al. (2013)	16,624	13	0.08	0.05-0.13
Bohlin et al. (2014)	14,124	24	0.16	0.10-0.26
Gillespie et al. (2016)	319,760	67	0.02	0.02-0.03
Smith et al. (2018)	9,456	4	0.04	0.02-0.11
ALL	359,964	108	0.03	0.02-0.04

Table 2: Prevalence estimates for iatrogenic synovial sepsis following corticosteroid injections in the three studies which provided the necessary data (as calculated by author).

Study	Corticosteroid Injections	Septic cases	Prevalence (%)	CI (%)
Steel et al. (2013)	15,934	12	0.08	0.04-0.13
Bohlin et al. (2014)	10,000	16	0.16	0.1-0.26
Smith et al. (2018)	3,871	2	0.05	0.01-0.19
ALL	29,805	30	0.1	0.07-0.14

From the studies examined, there is no evidence that injecting antibiotics in conjunction with corticosteroids reduces the frequency of synovial sepsis following intra-articular injection.

There is some evidence indicating that the risk of iatrogenic synovial sepsis following intra-articular medication may be increased by a number of factors, including:

- The veterinary surgeon not performing the skin preparation herself/himself
- The veterinary surgeon being over 20 years qualified
- Clipping the injection site
- Skin preparation with chlorhexidine for fewer than 7 minutes *
- Not wearing gloves *
- Using the same needle to draw up medications and to inject the joint *

(where * denotes factors that were statistically significant on univariable analysis though not on multivariable analysis (Gillespie et al., 2016))

Two of the included studies provided weak evidence of an increased risk of synovial sepsis following the injection of PSGAGs. Smith et al. (2018) reported that injection of PSGAGs was positively associated with iatrogenic synovial sepsis, though this finding was not statistically significant. Bohlin et al., 2014, also reported that injection of PSGAGs in combination with corticosteroids appeared to increase the risk of infection. Although not included in the summarised evidence due to it not meeting the inclusion criteria, a paper by Gustafson et al. (1989) reported that PSGAGs potentiate the risk of iatrogenic infection. Gustafson found that intra-articular injection of 125mg amikacin immediately after inoculating the joint with *Staphylococcus aureus* significantly decreased the potentiation of infection by the PSGAG. From these data, it can be concluded that concurrent injection of antimicrobials when injecting PSGAGs may be warranted. Further studies with larger sample sizes would be required to confirm whether concurrent antibiotic administration when injecting PSGAGs is necessary.

Responsible use of antimicrobials is of paramount importance across all health sectors and making appropriate, evidence based choices is crucial to prevent the development of antimicrobial resistance. Therefore, the following recommendations can be made:

- Sterile skin preparation should be performed for a minimum of 7 minutes when using chlorhexidine, ideally by the veterinary surgeon performing the intra-articular injection.
- Gloves should be worn for skin preparation as well as for intra-articular injection.
- Needles should be changed after drawing up medications and before intra-articular injection.
- Veterinary surgeons should consider not clipping the injection site, though this will depend on the length of hair, visibility of landmarks and gross contamination of the surrounding hair and skin.
- Intra-articular injection of antimicrobials is unlikely to be necessary, though may be warranted if PSGAGs are being injected.

Although some of the above factors were only statistically significant on univariable analysis rather than multivariable, they have been included in the clinical recommendations for performing intra-articular injections as they are factors that may be implemented with ease in a clinical setting. A systematic review of aseptic skin preparation procedures for intra-articular injections in horses would be of benefit to equine practitioners, with particular attention to clipping and the substance used for disinfection (e.g., chlorhexidine or iodine). An investigation of skin preparation protocols in relation to septic arthritis rates would also be of great benefit to equine practitioners.

The quality of the evidence included in this summary is mixed. One study (Bohlin et al., 2014) was only available as an abstract within non-peer reviewed conference proceedings and did not contain enough information to reliably interpret the results of the study. One further study did not provide enough information regarding exact medications injected (corticosteroids vs others) to accurately interpret the results with direct relevance to the PICO question (Gillespie et al., 2016). None of the studies ranks highly in the hierarchy of research and evidence based medicine (Arlt & Heuwieser, 2016, Murad et al., 2016). The poor quality and heterogeneity of the studies precluded meta-analysis of their results.

In answer to the PICO question, it can be concluded that injecting antibiotics in conjunction with corticosteroids is likely to be unnecessary. However, there is a paucity of strong, evidence-based research on

the subject. Although the available studies provide useful data, they have limited external validity and insufficient statistical power. Further studies are required in this area to reach a definitive conclusion for this particular PICO question. Given the very low frequency of iatrogenic synovial sepsis following intra-articular injection reported in the included studies, a randomised controlled trial is unlikely to be feasible and a multicenter case control study would likely be required in order to recruit an adequate number of cases to achieve sufficient statistical power.

Methodology Section

Search Strategy	
Databases searched and dates covered:	<p>CAB Abstracts – 1973 to 26th February 2019.</p> <p>Pubmed via the NCBI website; 1910 to 26th February 2019</p> <p>ScienceDirect – Elsevier – unknown to 26th February 2019</p> <p>Scopus – unknown to 26th February 2019</p> <p>Wiley Online Library – unknown to 26th February 2019</p>
Search terms:	<p>The search terms used for CAB Abstracts, Pubmed, Wiley Online Library and Scopus were:</p> <p>Search 1: “(intra-articular OR intraarticular OR intra-synovial OR joint OR synovial OR articular) AND (injection OR medication OR administration) AND (corticosteroid OR cortico-steroid OR steroid OR corticoid OR betamethasone OR triamcinolone OR methylprednisolone OR dexamethasone) AND (risk OR risks OR infection OR sepsis OR complication OR complications) AND (antibiotic OR antimicrobial OR antibacterial OR amikacin OR gentamicin OR antibiosis OR anti-microbial OR antibiotics OR antimicrobials) AND (horse OR horses OR equine)”.</p> <p>Search 2: “(intra-articular OR intraarticular OR joint OR synovial OR articular) AND (injection OR medication) AND (corticosteroid OR cortico-steroid OR steroid OR corticoid OR betamethasone OR triamcinolone OR methylprednisolone OR dexamethasone) AND (risk OR risks OR infection OR sepsis OR complication OR complications) AND (horse OR horses OR equine)”.</p> <p>Search 3: “(intra-articular OR intraarticular OR joint OR synovial OR articular) AND (injection OR medication) AND (antibiotic OR antimicrobial OR antibacterial OR amikacin OR gentamicin OR antibiotics OR anti-microbial) AND (horse OR horses OR equine)”.</p> <p>The search terms for ScienceDirect (which does not support searches of more than 8 Boolean connectors per field), as well as all of the databases mentioned above were:</p> <p>Search 4: “(intra-articular OR intraarticular OR joint OR synovial OR articular) AND (injection OR medication) AND (infection OR sepsis) AND (horse OR horses OR equine)”.</p> <p>Reference lists and bibliographies of discovered articles were also examined to identify other relevant publications, none of which were found.</p>

	The Wiley Online Library search yielded 1,344 results with Search 1, necessitating subject refinement to Veterinary Medicine, Medical Science and Equine Science.
Dates searches performed:	26 th February 2019.

Exclusion / Inclusion Criteria	
Exclusion:	Studies not related to the PICO question Studies performed in other species Non-English language publications Abstract and full text unavailable
Inclusion:	Studies relevant to the PICO question in the English language.

Search Outcome						
Database	Number of results	Excluded – not related to PICO	Excluded – studies in other species	Excluded – Non-English language	Excluded – abstract and full text unavailable	Total relevant papers
CAB Abstracts	129	124	0	1	0	4
Pubmed	115	112	0	0	1	2
Science Direct	275	2	272	1	0	0
Scopus	51	46	1	0	1	3
Wiley Online Library	1,344	209	1,129	1	1	4
Combined total from all databases of relevant papers when duplicates removed						4

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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