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Corticosteroids for septic arthritis in children (Review)

Delgado-Noguera MF, Forero Delgadillo JM, Franco AA, Vazquez JC, Calvache JA

Delgado-Noguera MF, Forero Delgadillo JM, Franco AA, Vazquez JC, Calvache JA.
Corticosteroids for septic arthritis in children.
Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD012125.
DOI: 10.1002/14651858.CD012125.pub2.

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[Intervention Review]

Corticosteroids for septic arthritis in children

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Editorial group: Cochrane Musculoskeletal Group.
Publication status and date: New, published in Issue 11, 2018.

Citation: Delgado-Noguera MF, Forero Delgadillo JM, Franco AA, Vazquez JC, Calvache JA. Corticosteroids for septic arthritis in children. *Cochrane Database of Systematic Reviews* 2018, Issue 11. Art. No.: CD012125. DOI: 10.1002/14651858.CD012125.pub2.

ABSTRACT

Background

Septic arthritis is an acute infection of the joints characterised by erosive disruption of the articular space. It is the most common non-degenerative articular disease in developing countries. The most vulnerable population for septic arthritis includes infants and preschoolers, especially boys. Septic arthritis disproportionately affects populations of low socioeconomic status. Systemic corticosteroids and antibiotic therapy may be beneficial for treatment of septic arthritis. Even if the joint infection is eradicated by antibiotic treatment, the inflammatory process may produce residual joint damage and sequelae.

Objectives

To determine the benefits and harms of corticosteroids as adjunctive therapy in children with a diagnosis of septic arthritis.

Search methods

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, Latin American Caribbean Health Sciences Literature (LILACS), the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/), ClinicalTrials.gov (www.ClinicalTrials.gov), and Google Scholar. We searched all databases from their inception to 17 April 2018, with no restrictions on language of publication.

Selection criteria

We included randomised controlled trials (RCTs) with patients from two months to 18 years of age with a diagnosis of septic arthritis who were receiving corticosteroids in addition to antibiotic therapy or as an adjuvant to other therapies such as surgical drainage, intra-articular puncture, arthroscopic irrigation, or debridement.

Data collection and analysis

Two review authors independently assessed eligibility, data extraction, and evaluation of risk of bias. We considered as major outcomes the presence of pain, activities of daily living, normal physical joint function, days of antibiotic treatment, length of hospital stay, and numbers of total and serious adverse events. We used standard methodological procedures expected by Cochrane. We assessed the evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation) and created a 'Summary of findings' table.

Main results

We included two RCTs involving a total of 149 children between three months and 18 years of age who were receiving antibiotics for septic arthritis. The most commonly affected joints were hips and knees. These studies were performed in Costa Rica and Israel. In both studies, dexamethasone administered intravenously (ranging from 0.15 to 0.2 mg/kg/dose every six to eight hours) during four days was the corticosteroid, and the comparator was placebo. Trials excluded patients with any degree of immunodeficiency or immunosuppression. The longest follow-up was one year. Trials did not report activities of daily living nor length of hospital stay. Both studies used adequate processes for randomisation, allocation concealment, and blinding, and review authors judged them to have low risk of selection and performance bias. Losses to follow-up were substantive in both studies, and we judged them to have high risk of attrition bias and of selective outcome reporting. We graded all outcomes as low quality due to concerns about study limitations and imprecision.

The risk ratio (RR) for absence of pain at 12 months of follow-up was 1.33, favouring corticosteroids (95% confidence interval (CI) 1.03 to 1.72; P = 0.03; number needed to treat for an additional beneficial outcome (NNTB) = 13, 95% CI 6 to 139; absolute risk difference 24%, 95% CI 5% to 43%).

The RR for normal function of the affected joint at 12 months of follow-up was 1.32, favouring corticosteroids (95% CI 1.12 to 1.57; P = 0.001; NNTB = 13, 95% CI 7 to 33; absolute risk difference 24%, 95% CI 11% to 37%).

We found a reduction in the number of days of intravenous antibiotic treatment favouring corticosteroids (mean difference (MD) -2.77, 95% CI -4.16 to -1.39) based on two trials with 149 participants.

Researchers did not report length of hospital stay. One trial (49 participants) reported that treatment with dexamethasone was associated with a shorter duration of IV antibiotic treatment, leading to a shorter hospital stay, and although duration of hospitalisation was a primary outcome of the study, study authors did not provide data on the duration of hospitalisation. We downgraded the quality by one level for concerns about study limitations (high risk of attrition bias and selective reporting), and by another level for imprecision.

In one trial of 49 participants, researchers followed 29 children for 12 months, and parents reported that no children demonstrated adverse effects of the intervention.

Authors' conclusions

Evidence for corticosteroids as adjunctive therapy in children with a diagnosis of septic arthritis is of low quality and is derived from the findings of two trials (N = 149). Corticosteroids may increase the proportion of patients without pain and the proportion of patients with normal function of the affected joint at 12 months, and may also reduce the number of days of antibiotic treatment. However, we cannot draw strong conclusions based upon these trial results. Additional randomised clinical trials in children with relevant outcomes are needed.

PLAIN LANGUAGE SUMMARY

Corticosteroids for children with septic arthritis

Researchers conducted a review of the effects of corticosteroids given in addition to antibiotics to children with septic arthritis. Evidence was sought until April 2018. After searching for all relevant studies, reviewers found two studies with 149 children. These studies were conducted in hospitalised children with a normal immune system between the ages of three months and 18 years living in Costa Rica and Israel. The longest follow-up was one year. Reviewer findings are summarised below.

What is septic arthritis and what are corticosteroids?

Septic arthritis, which is more frequent in children, is a serious disease caused by bacteria that infect the joints. Patients are usually treated with antibiotics, but secondary inflammation can destroy the joint and can reduce the ability of the joint to function normally. Corticosteroids are a group of medications with anti-inflammatory properties. Corticosteroids may reduce the consequences of inflammation in the joints.

For children with septic arthritis who are taking antibiotics compared to placebo (fake medication)

1. Corticosteroids may reduce pain in affected joints at one year of follow-up

2. Corticosteroids may improve normal function of affected joints at one year of follow-up

3. Corticosteroids may reduce days of intravenous antibiotic treatment needed

4. Corticosteroids may have little or no effect on total or serious adverse effects

We do not have information about the effects of corticosteroids on activities of daily living.

What happens to children with septic arthritis who take corticosteroids in addition to antibiotics?

Absence of pain

1. 24 more of 100 children experienced absence of pain after 12 months with corticosteroids (24% absolute improvement)

2. 96 of 100 children experienced absence of pain compared to 72 of 100 children who took a placebo

Activities of daily living

Included studies did not report this outcome.

Normal physical joint function

1. 24 more of 100 children who received corticosteroids had normal function of the joint after 12 months (24% absolute improvement)

2. 98 of 100 children experienced absence of pain compared to 74 of 100 children who received a placebo

Number of days of intravenous antibiotic treatment

1. Children who received corticosteroids compared with placebo had 2.77 fewer days of intravenous antibiotic treatment

2. Children who received corticosteroids had 8.09 days of intravenous antibiotic treatment

3. Children who received placebo had 10.86 days of intravenous antibiotic treatment

Length of hospital stay

1. We are uncertain whether corticosteroids had an effect on the length of hospital stay because the evidence was of very low quality

Total or serious adverse events

1. None of the patients treated with corticosteroids reported adverse effects at 12 months

Quality of the evidence

Overall, these studies provided low-quality evidence due to small numbers of study participants and concerns about study design. Evidence on length of hospital stay was of very low quality, as this was not clearly reported.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Corticosteroids compared to placebo for septic arthritis in children

Patient or population: septic arthritis in children taking antibiotics
Setting: hospitals in Costa Rica and Israel
Intervention: corticosteroids (dexamethasone)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with corticosteroids				
Pain - absence of pain at 12 months	72 per 100	96 per 100 (74 to 100)	RR 1.33 (1.03 to 1.72)	49 (1 RCT)	⊕⊕◯◯ LOW[a]	Absolute risk difference 24% (95% CI 5% to 43%) NNTB = 13 (95% CI 6 to 139)
Activities of daily living	See comments		-	(0 RCTs)	-	This outcome was not reported in any of the included trials
Number of participants with normal physical joint function - normal function at 12 months of follow-up (long term)	74 per 100	98 per 100 (83 to 100)	RR 1.32 (1.12 to 1.57)	100 (1 RCT)	⊕⊕◯◯ LOW[b]	Absolute risk difference 24% (95% CI 11% to 37%) NNTB = 13 (95% CI 7 to 33)
Number of days of antibiotic treatment - number of days of intravenous antibiotic treatment	Number of days of intravenous antibiotic treatment with placebo was 10.86	Number of days of intravenous antibiotic treatment with corticosteroids was 8.09	MD 2.77 lower (4.16 lower to 1.39 lower)	149 (2 RCTs)	⊕⊕◯◯ LOW[c]	Almost 3 days lower (95% CI 4 days to 1.5 days lower)

Length of hospital stay	See comments	-	(0 RCTs)	-	This outcome was not reported in any of the included trials. Study authors report that treatment with dexamethasone was associated with a shorter duration of IV antibiotic treatment, leading to a shorter hospital stay
Total adverse events at 12 months	See comments	-	49 (1 RCT)	⊕⊕◯◯ LOW[a]	Trial reported that none of the participants showed adverse effects
Serious adverse events at 12 months	See comments	-	49 (1 RCT)	⊕⊕◯◯ LOW[a]	Trial reported that none of the participants showed serious adverse effects

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; NNTB: number needed to treat for an additional beneficial outcome; RCT: randomised controlled trial; RR: risk ratio

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]We downgraded by one level for concerns about study limitations (high risk of attrition bias and selective reporting). We downgraded by another level for imprecision.
[b]We downgraded by one level for concerns about study limitations (unclear risk of detection and reporting bias and high risk of attrition bias). We downgraded by another level for imprecision.

[c]We downgraded by one level for concerns about study limitations (detection, reporting, and attrition bias). We downgraded by another level for imprecision.

BACKGROUND

Description of the condition

Septic arthritis is an acute infection of the joints characterised by erosive disruption of the articular space. It is the most common non-degenerative articular disease in developing countries. Although septic arthritis can be diagnosed at any age, children are most often affected. The incidence of septic arthritis in children from developed countries ranges from five to 12 cases for every 100,000 persons per year (Forero 2013; García-Arias 2011). Infants and preschoolers, especially boys, are most vulnerable to septic arthritis. Septic arthritis disproportionately affects populations of low socioeconomic status (García-Arias 2011).

Septic arthritis often affects the hip, knee, elbow, and ankle joints (Young 2011). Signs and symptoms include pain, oedema, erythema, and functional limitation, as well as shivering, sickness, emesis, and fever. Symptoms may vary in very young or breastfeeding children (Harel 2011; Odio 2003).

The bacteria responsible for septic arthritis generally vary with age, comorbid conditions, socioeconomic status, and immunogenic and vaccination status of the patient (Dodwell 2013). *Staphylococcus aureus* is isolated in 37% to 56% of all cases (García-Arias 2011). Studies have shown that gram-negative bacteria such as *Escherichia coli, Proteus mirabilis, Klebsiella* spp, and Enterobacteriaceae are also responsible for septic arthritis, specifically among children younger than four years. Septic arthritis due to *Streptococcus* has decreased as a result of mass vaccination (Mathews 2008a). Recent studies have found that emerging bacteria play a critical role in septic arthritis. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been found to be responsible for 30% to 40% of osteoarticular infections in the United States (Dodwell 2013). *Kingella kingae,* which causes unusual clinical symptoms, has also been isolated. Other pathogens such as *Haemophilus influenzae* type B,*Neisseria gonorrhoeae,* and*Candida albicans* have been involved in development of the disease (Dodwell 2013).

Bacterial colonisation in septic arthritis most frequently occurs via the hematogenous route. Researchers have also described direct inoculation through an injury or infection in surrounding tissue (Mathews 2008a). The risk of complications is higher among children under two years of age because the epiphysis is permeated by blood vessels, and this facilitates bacterial colonisation through the growth plates (Kang 2009; Mathews 2008b).

Characteristics of the synovial membrane foster bacterial reproduction 24 to 48 hours after infection. The synovial membrane reacts with hyperplasia, and neutrophils and monocytes release cytokines and proteases, producing exudation (Kang 2009). Consequently, neutrophils inhibit synthesis of the cartilage, causing destruction of the articulation in approximately seven days. Infiltration of neutrophils can damage adjacent bone and metaphyseal growth cartilage, producing osteoarthritis (Mathews 2010).

Clinicians evaluate C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and blood cultures (Choe 2013; Harel 2011; Odio 2003), as well as synovial liquid (Al Saadi 2009), in diagnosing septic arthritis. They also perform other examinations such as X-ray, echography, magnetic resonance imaging, gammagraphy, and evaluation of the synovial liquid (Al Saadi 2009). Accuracy of the diagnosis depends on bacterial isolation from the articular exudate or the blood culture (Harel 2011).

Description of the intervention

Staphylococus aureus hampers the autoimmune response via factors related to virulence, as this organism triggers numerous signals that exacerbate the humoral immune response. *Staphylococus aureus* suppresses the innate immune system, increasing humoral immune answer and facilitating the development of septic arthritis. This in turn promotes progressive destruction of the cartilage and of the chondral bone, generating the clinical manifestations associated with septic arthritis (Bremell 1992).

Systemic corticosteroids and antibiotics may be beneficial for treatment of septic arthritis (Al Saadi 2009). In septic arthritis, even if the joint infection is eradicated by antibiotic treatment, the inflammatory process produces residual joint damage and sequelae. Corticosteroids are thought to have a therapeutic role in attenuating the inflammatory response mediated by cytokines and interleukins, and in avoiding sequelae or complications (i.e. restricted articulation movements, articular dysfunction) (Baghdadi 2012; Brouwer 2015).

How the intervention might work

During acute joint infection, Toll-like receptors are activated, with substantial release of pro-inflammatory cytokines such as Interleukin (IL)-1-beta, IL-17, IL-6, and tumour necrosis factor (TNF)-alpha (Colavite 2014; Farrow 2015). This inflammatory process promotes osteoclast differentiation, bone reabsorption, and matrix metalloproteinase (MMP) release, leading to bone and cartilage destruction (Farrow 2015; Kwan 2004). Intra-articular pressure is increased (secondary to joint effusion), which mechanically reduces blood/nutrient supply to the joint and increases cellular damage (Farrow 2015; Shirtliff 2002).

Pharmacodynamic effects of corticosteroids are mediated through binding to glucocorticoid receptors. Phospholipase A2 (a potent intracellular producer of prostaglandins, free radicals, and leukotrienes) is inhibited, and deleterious effects on several pro-inflammatory cytokines such as IL-1, interferon (IFN)-γ, and TNF-alpha, are evident. As a result, corticosteroids could attenuate the destruction of cartilage and of the synovial membrane and capsule.

Why it is important to do this review

Septic arthritis is a limiting and relatively common condition, especially in children. Corticosteroid therapy may have potential benefits for septic arthritis, as well as a positive impact on the patient's quality of life. Therefore, it is important to conduct a systematic review to determine the benefits and harms of such treatment, to guide clinicians when treating paediatric patients with this diagnosis.

We conducted this review according to guidelines provided by the Cochrane Musculoskeletal Group Editorial Board (Ghogomu 2014).

OBJECTIVES

To determine the benefits and harms of corticosteroids as adjunctive therapy in children with a diagnosis of septic arthritis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) reported as full text, those published as abstract only, and unpublished data. We applied no language restrictions.

Types of participants

We included patients from two months to 18 years of age with the diagnosis of septic arthritis, as defined by the authors of each study, who were receiving corticosteroids in addition to antibiotic therapy or as adjuvant to other therapies.

The diagnosis of septic arthritis is based mainly on the presence of clinical symptoms, a detailed history, and a careful examination (acute onset of swelling pain, local warmth, and severe limitation of motion in any joint), along with findings of laboratory tests (elevated levels of acute phase reactants, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), and/or increase in white blood cell (WBC) count). A definitive diagnosis of septic arthritis is made by direct demonstration of bacteria from synovial fluid or blood (gram-stained smear or direct cultures).

Types of interventions

We included trials in which researchers treated participants with antibiotics and/or other co-interventions plus corticosteroids administered by any route (oral, intramuscular, intravenous, or intra-articular), at any dose. As controls, we considered patients treated only with antibiotics and/or any therapy other than corticosteroids, such as surgical drainage, intra-articular puncture (using a needle to release articular pressure or to extract intra-articular fluid), arthroscopic irrigation, or debridement.

We allowed the following co-interventions, provided they were not part of the randomised treatment and were given to participants in all treatment arms of the trial: drainage: intra-articular puncture, arthroscopic irrigation, and debridement.

Types of outcome measures

Major outcomes

1. Pain measured by different scales (visual analogue scales, numerical rating scales, or facial drawings scales)
2. Activities of daily living (measured by parent report, self-report, or any assessment instrument appropriate to participant age (e.g. Activities of Daily Living (ADL) Scale, Klein-Bell Activities of Daily Living Scale (KB ADL))
3. Number of participants with normal physical joint function (normal angle of joint movement according to age and sex, measured with a goniometer/other instrument and/or compared with that of the contralateral healthy joint)
4. Number of days of antibiotic treatment
5. Length of hospital stay
6. Total number of adverse events
7. Number of serious adverse events

Outcomes were measured at short term (one day to one month), medium term (one month to six months), and long term (beyond six months).

Scales used to measure paediatric pain are subjective; therefore, numerical scales and scales of facial drawings are used more frequently.

We created a 'Summary of findings' table using the same outcomes as above to report long-term measurements (beyond six months).

Search methods for identification of studies

Electronic searches

We searched the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, Latin American Caribbean Health Sciences Literature (LILACS), the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/), ClinicalTrials.gov (www.ClinicalTrials.gov), and Google Schoolar. We searched all databases from their inception to 17 April 2018, with no restrictions on language of publication.

See Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6, and Appendix 7, for details of each search strategy.

Searching other resources

We checked the reference lists of all primary studies and reviewed articles for additional references. We searched relevant manufacturers' websites for trial information.

We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and reported within the review the date this was done.

We sent emails to the authors of included clinical trials to ask if they were aware of other similar clinical trials.

Data collection and analysis

Selection of studies

Two review authors (AF, JF) independently screened titles and abstracts for inclusion of all potentially relevant studies identified as a result of the search, and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publications, and two review authors independently screened these and identified studies for inclusion, then identified and recorded the reasons for exclusion of ineligible studies. We resolved disagreements through discussion or, if required, by consultation with a third review author (MD, JMC). We identified and excluded duplicates and collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and a Characteristics of excluded studies table.

Data extraction and management

We used a data collection form that had been piloted on at least one study in the review when extracting study characteristics and outcome data. One review author (AF or JF) extracted study characteristics from included studies. A second review author (JAC) spot-checked study characteristics for accuracy against the trial report. We extracted the following study characteristics.

1. Methods: study design, total duration of study, number of study centres and locations, study setting, withdrawals, and date of study.
2. Participants: N, age mean and range, sex, disease duration, severity of condition, diagnostic criteria, important baseline data; inclusion criteria, and exclusion criteria.
3. Interventions: intervention of interest, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Characteristics of the design of the trial, as outlined below in the Assessment of risk of bias in included studies section.
6. Notes: funding for trial and declarations of interest of all trial authors.

Two review authors (AF, JF) independently extracted outcome data from included studies. We extracted numbers of events and numbers of participants per treatment group for dichotomous outcomes, and means and standard deviations and numbers of participants per treatment group for continuous outcomes. We noted in the Characteristics of included studies table if outcome data were not reported in a usable way, and if data had been transformed or estimated from a graph. We resolved disagreements by consensus or by consultation with a third person (JAC or MD). One review author transferred data into the Review Manager file (RevMan 2014).

We double-checked that data had been entered correctly by comparing data presented in the systematic review against the study reports.

For data extraction, we analysed data as presented by study authors for each outcome considered. Regarding outcomes, we extracted final values data, adjusted values if reported, intention-to-treat (ITT) data, and the final time point if available.

Assessment of risk of bias in included studies

Two review authors (AF, JF) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion or by consultation with another review author (MD, JAC). We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as having high, low, or unclear risk, and we provided a quote from the study report, as well as a justification for our judgement, in the 'Risk of bias' table. We summarised 'Risk of bias' judgements across different studies for each of the domains listed. We considered the impact of missing data for key outcomes.

When information on risk of bias relates to unpublished data or corresponds to a trial list, we noted this in the 'Risk of bias' table. When considering treatment effects, we took into account the risk of bias for studies contributing to that outcome.

We have presented the figures generated by the 'Risk of bias' tool to provide summary assessments of risk of bias.

Assessment of bias in conducting the systematic review

We conducted this review according to the published protocol and reported any deviations from it in the Differences between protocol and review section.

Measures of treatment effect

We analysed dichotomous data as risk ratios (RRs) or Peto odds ratios when the outcome was a rare event (approximately < 10%), along with 95% confidence intervals (CIs).

We analysed continuous data (i.e. continuous pain scales, visual analogue scales, numerical rating scales, or facial drawings scales) as mean differences (MDs) or standardised mean differences (SMDs) (depending on whether the same scale was used to measure an outcome), along with 95% CIs. We transformed outcome data to a continuous scale depending on each situation (e.g. facial drawings scales 0 to 6). We entered data presented as a scale with a consistent direction of effect across studies.

When researchers used different scales to measure the same conceptual outcome (e.g. disability), we calculated SMDs with corresponding 95% CIs. We back-translated the SMD to a typical scale (i.e. 0 to 10 for pain) by multiplying the SMD by a typical among-person standard deviation (e.g. the standard deviation of the control group at baseline from the most representative trial).

In the Effects of interventions results section and in the 'Comments' column of the 'Summary of findings' table, we provided the absolute per cent difference, the relative per cent change from baseline, and the number needed to treat for an additional beneficial outcome (NNTB) (we provided the NNTB only when the outcome showed a statistically significant difference).

For dichotomous outcomes, such as serious adverse events, we calculated NNTB from the control group event rate and the RR using the Visual Rx NNTB calculator (Cates 2008). We calculated the NNTB for continuous measures using the Wells calculator.

For dichotomous outcomes, we calculated the absolute risk difference using the risk difference statistic in RevMan and expressed this result as a percentage. For continuous outcomes, we calculated the absolute benefit as improvement in the intervention group minus improvement in the control group, expressed in original units.

Unit of analysis issues

When a single trial reported multiple trial arms, we included only the relevant arms. If two comparisons (e.g. drug A vs placebo and drug B vs placebo) were combined in the same meta-analysis, we halved the control group to avoid double-counting.

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as abstract only, when data are not available for all participants). When it was not possible, and when missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by performing a sensitivity analysis. We clearly described assumptions and imputations applied to handle missing data, and we explored the effect of imputation by performing sensitivity analyses.

For dichotomous outcomes (e.g. number of withdrawals due to adverse events), we calculated the withdrawal rate by using the number of randomised participants in the group as the denominator.

For continuous outcomes (e.g. mean change in pain score), we calculated the MD or the SMD based on the number of participants analysed at a given time point. If researchers did not present the number of participants analysed for each time point, we used the number of randomised participants in each group at baseline.

When possible, we computed missing standard deviations from other statistics such as standard errors, CIs, or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If we could not calculate standard deviations, we imputed them (e.g. from other studies in the meta-analysis).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity for the included studies in terms of participants, interventions, outcomes, and study characteristics to determine whether a meta-analysis was appropriate. We did this by observing data included in the data extraction tables. We assessed statistical heterogeneity by visually inspecting the forest plot to assess obvious differences in results between studies, and by using I^2 and Chi^2 statistical testing.

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), an I^2 value of 0% to 40% might 'not be important'; 30% to 60% may represent 'moderate' heterogeneity; 50% to 90% may represent 'substantial' heterogeneity; and 75% to 100% represents 'considerable' heterogeneity. As noted in the *Cochrane Handbook for Systematic Reviews of Interventions*, we kept in mind that the importance of I^2 depends on (1) magnitude and direction of effects and (2) strength of evidence for heterogeneity.

For the Chi^2 test, a P value ≤ 0.10 indicated evidence of statistical heterogeneity.

When we identified substantial heterogeneity, we reported it and investigated possible causes by following the recommendations provided in Section 9.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of reporting biases

If we needed to evaluate reporting bias, we created and examined a funnel plot to explore a possible small-study bias. To interpret funnel plots appropriately, we looked at different possible reasons for funnel plot asymmetry, as outlined in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and we related this to review results (Sterne 2011).

To assess outcome reporting bias, we checked the trial protocols against published reports. For studies published after 1 July 2005, we screened the Clinical Trials Register at the International Clinical Trials Registry Platform of the World Health Organization

(http://apps.who.int/trialssearch) for the a priori trial protocol. We evaluated whether selective reporting of outcomes was present.

Data synthesis

We conducted meta-analyses only when this was meaningful (i.e. if treatments, participants, and the underlying clinical question were similar enough for pooling). We used a random-effects model.
If pooling was not possible, we summarised results of the included trials by using a descriptive approach. We made a summary table under each study to report participants, interventions, controls, and outcomes. Then, we discussed study findings, strengths, and weaknesses from a clinical perspective.

'Summary of findings' table

We created a 'Summary of findings' table using the outcomes listed at Types of outcome measures.
Two review authors(AF, JF) independently assessed evidence quality. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to studies that contributed data to the meta-analyses for prespecified outcomes. We used methods and recommendations described in Sections 8.5 and 8.7, and in Chapters 11 and 13, Section 13.5, of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Schünemann 2011), as well as GRADEpro 2015. We justified all decisions to downgrade or upgrade the quality of studies by using footnotes, and we made comments when necessary to aid the reader in understanding the review.
In the Comments column of the 'Summary of findings' table, we provided the absolute per cent difference, the relative per cent change from baseline, and the number needed to treat for an additional beneficial outcome (NNTB) (we provided the NNTB only when the outcome showed a statistically significant difference).

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

1. Age (infants (up to two years), preschoolers (two to five years), and school children (older than six years)).
2. Route of administration (intra-articular vs intramuscular vs oral vs intravenous).·
3. Co-intervention type: drainage, intra-articular puncture, arthroscopic irrigation, or debridement.

We planned to use the formal test for subgroup interactions in Review Manager (RevMan 2014), and we intended to apply caution in interpreting subgroup analyses, as advised in Section 9.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Sensitivity analysis

We planned to carry out the following sensitivity analyses.

1. By risk of bias of included studies: we will classify a study as having high risk of bias when one or more domains of the 'Risk of bias' assessment tool is classified as being at high risk of bias.
2. By diagnosis: we will classify a study based on clinical criteria without bacterial isolation.

Interpreting results and reaching conclusions

We followed the guidelines for interpreting results as provided in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions*, and we were aware of distinguishing lack of evidence of effect from lack of effect (Higgins 2011). We based our conclusions only on findings from the quantitative or narrative synthesis of included studies prepared for this review. We avoided making recommendations for practice, and our implications for research suggest priorities for future research and outline remaining uncertainties in the area.

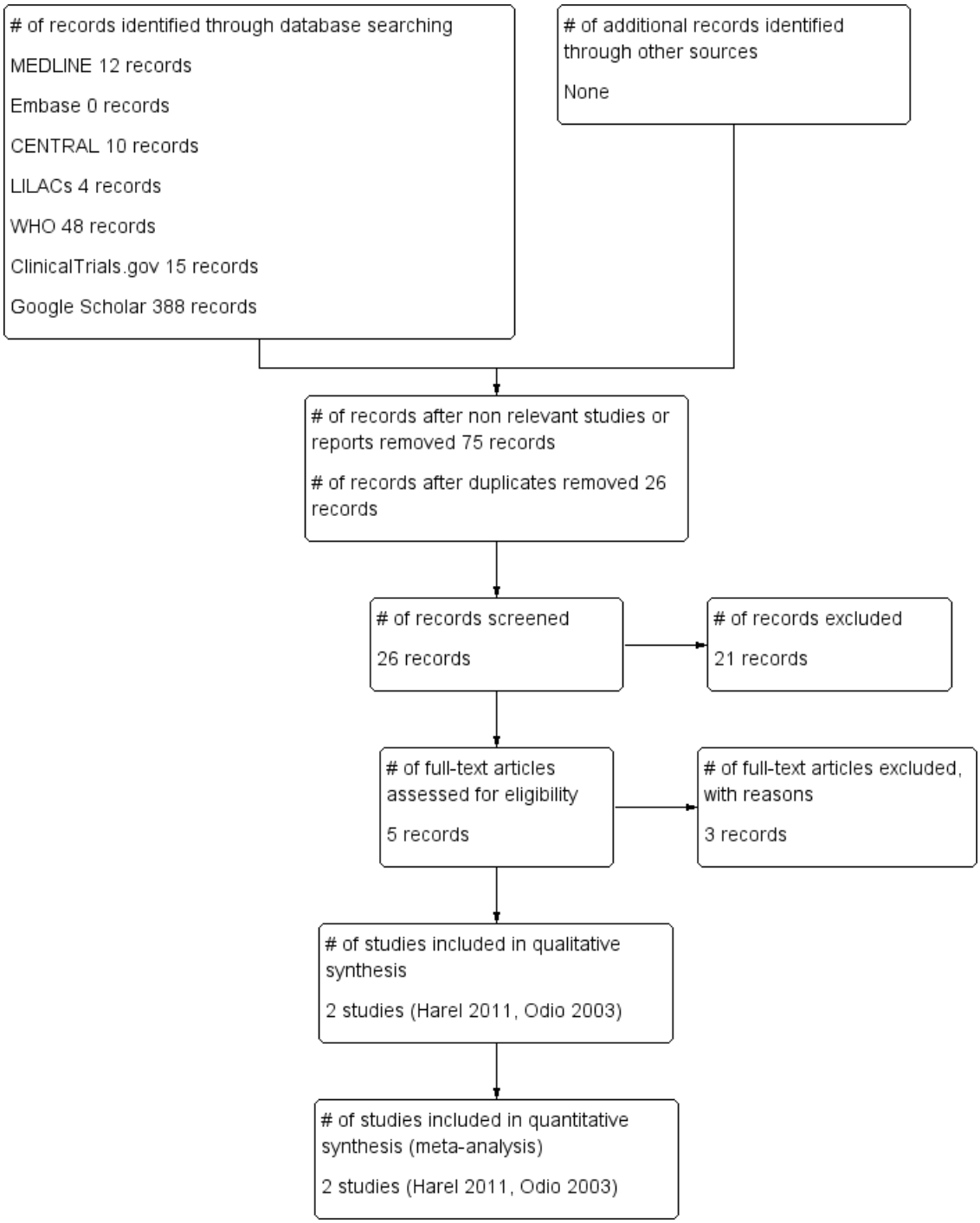
RESULTS

Description of studies

Results of the search

Through our search strategy, we identified the following numbers of studies until 13 April 2018: MEDLINE 12, Embase 0, CENTRAL 10, LILACS 4, WHO 48, ClinicalTrials.gov 15, and Google Scholar 388, for a total of 477 records. We have presented the search process in a flow chart (Figure 1).

Figure 1. Study flow diagram.



Included studies

We included two studies - Odio 2003 and Harel 2011 (total 149 children) - conducted to evaluate the clinical effects of corticosteroids as adjunctive therapy for children with septic arthritis. Both studies were randomised controlled trials, and both used placebo in the control group. Study authors stated no funding sources. We recorded details of these papers under Included studies and in the Characteristics of included studies tables. We found no other references to these studies.

The author of one of the included studies was a co-author of a cohort study that we excluded (Fogel 2015).

We sent emails to the authors of included clinical trials to ask if they were aware of other similar clinical trials, but we received no response.

Participants

Odio 2003 was a clinical trial conducted in Costa Rica in 123 children, and Harel 2011 was conducted in Israel in 46 patients. Children in Odio 2003 were between three months and 13 years of age. In Harel 2011, the age of participants was between six months and 18 years. The most commonly affected joints were lower limbs, hips, and knees in both trials. Trials excluded patients with any degree of immunodeficiency or immunosuppression.

Interventions

Both trials used dexamethasone as the experimental intervention. In Odio 2003, investigators administered treatment by the intravenous route, at 0.2 mg/kg/dose IV every eight hours for 12 consecutive doses. In Harel 2011, study authors provided 0.15 mg/kg/dose every six hours for 16 consecutive doses.

Outcomes

The main outcome in Odio 2003 was the normal function of the affected joint at the end of therapy (short term), at six months (medium term), and at 12 months (long term). Trialists measured outcomes as dichotomous variables. Secondary endpoints included time to clinical and laboratory normalisation in terms of the following: days of resolution of symptoms, absence of fever, absence of spontaneous pain or pain to passive or active movement, absence of warmth and oedema, normal range of movement of the joint, and days of normalisation of serum C-reactive protein. Another outcome was duration (number of days) of intravenous and oral antibiotics.

The main outcome in Harel 2011 was the number of days to clinical and laboratory normalisation (number of days until no fever, number of days until no local heat, number of days until no redness of the joint, number of days until pain free, number of days until full range of movement of the joint, number of days until normal function of the joint, last day ESR +25 mm/h, last day WBC +15.000, and last day CRP +0.5 mg/dL). Additionally, study authors reported duration (number of days) of intravenous and oral administration of antibiotics. They reported the presence of pain as dichotomous data over the long term and as assessed by phone call at 12 months. Finally, they reported numbers of total and serious adverse events as assessed by parental reporting at 12 months.

Excluded studies

We excluded three studies: van Oosterhout 2006, Arti 2014, and Fogel 2015. Reasons for exclusion included type of intervention and type of study design. We have provided specific reasons for exclusion in the Excluded studies table.

Risk of bias in included studies

We assessed the risk of bias in included studies using details provided in Chapter 8.7a of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We have included a summary for 'Risk of bias' in the Characteristics of included studies table, in the methodological quality graph (Figure 2), and in the methodological quality summary (Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

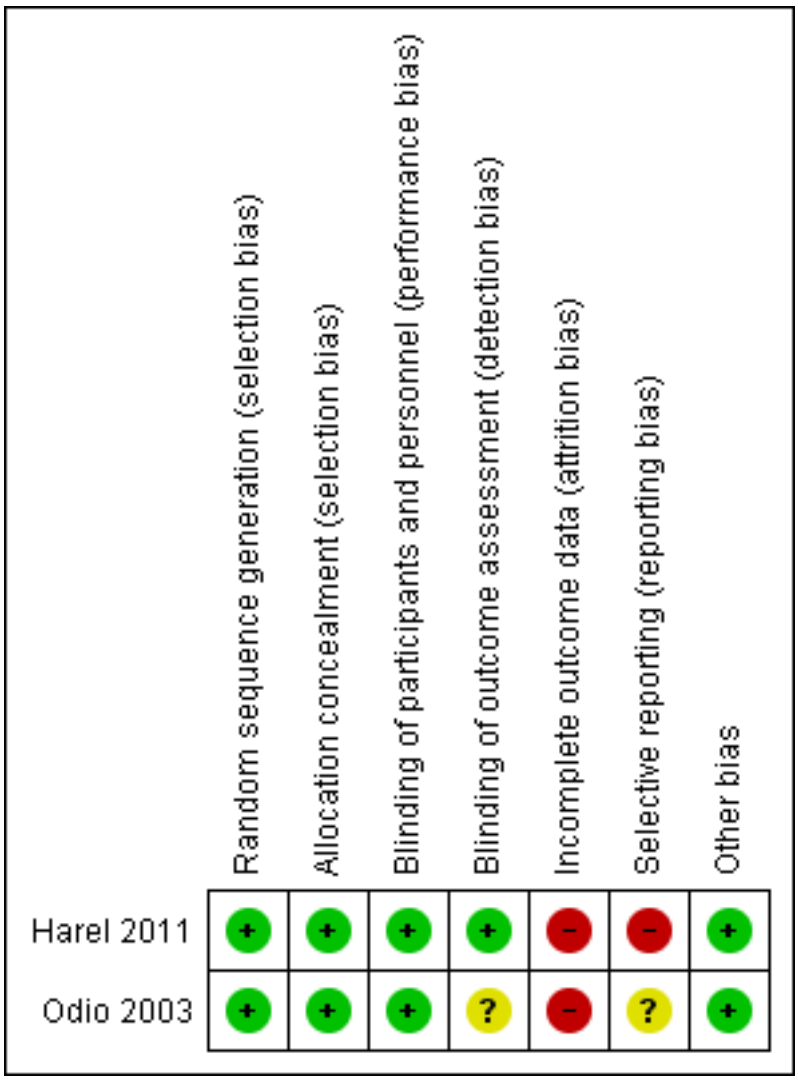
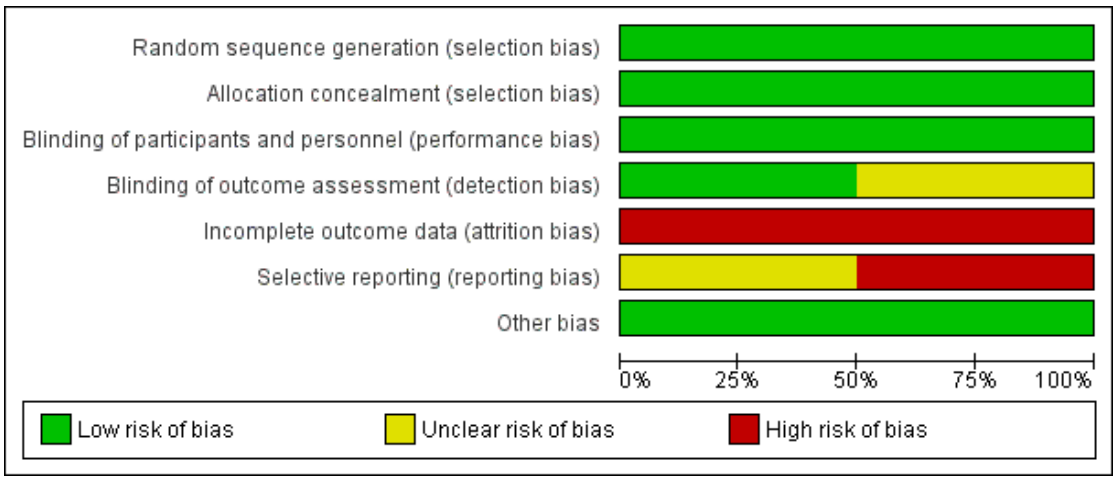


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Random sequence generation

We judged both Odio 2003 and Harel 2011 as having low risk of bias. These studies explicitly reported the randomisation process. Odio 2003 explicitly reported the randomisation sequence assignment.

Allocation

We judged both Odio 2003 and Harel 2011 as having low risk of bias, as they explicitly reported the allocation concealment process.

Blinding

The two included clinical trials reported an appropriate blinding procedure for both participants and study personnel; thus, we judged them as having low risk of bias (Harel 2011; Odio 2003).

Blinding of outcome assessment

When we assessed blinding of outcome assessment, we judged Odio 2003 as having unclear risk of detection bias because study authors did not mention how they assessed outcomes. We judged Harel 2011 as having low risk of detection bias.

Incomplete outcome data

Both studies reported losses to follow-up (Harel 2011; Odio 2003). Odio 2003 described loss to follow-up of 18.7%, with similar data for experimental and control groups. Harel 2011 indicated that loss to follow-up was 40.9%, and that this finding was not similar between groups (intervention 30%, placebo 52%). We judged both studies as having high risk of bias for incomplete outcome data.

Selective reporting

Harel 2011 did not clearly describe how study authors measured sequelae as a long-term outcome. In addition, study authors did not report the primary prespecified outcome of the trial, as mentioned in the Methods section of the trial report (length of hospital stay). Therefore, we judged this study as having high risk of bias for selective reporting. Odio 2003 did not present in a clear way data for the outcome of range of movement of the joint.

Effects of interventions

See: **Summary of findings for the main comparison** Corticosteroids (dexamethasone) compared to placebo for septic arthritis in children

1. Pain

1.1. Absence of pain

Only Harel 2011 with 49 participants considered this outcome at long term (12 months). Researchers reported data as a categorical outcome (presence or absence of pain). The risk ratio (RR) for absence of pain at 12 months of follow-up (long-term) was 1.33 (95% confidence interval (CI) 1.03 to 1.72; P = 0.03; number needed to treat for an additional beneficial outcome (NNTB) = 13, 95% CI 6 to 139)). We downgraded quality by one level for

concerns about study limitations (high risk of bias for attrition and selective reporting). We downgraded by another level for imprecision due to small sample size, which resulted in a large confidence interval.

1.2. Number of days until pain free

Only Harel 2011 with 49 participants considered this outcome. Compared with placebo, the number of days until pain free was 3.58 days lower with corticosteroids (mean difference (MD) -3.58, 95% CI -7.41 to 0.25). Data show no statistically significant differences (P = 0.07). The quality of the evidence was low due to concerns about attrition bias, selective reporting, and imprecision (due to a large confidence interval and the small number of study participants).

2. Activities of daily living

We found no studies reporting this outcome.

3. Number of participants with normal physical joint function

3.1. Number of days until normal function of the joint

Harel 2011 with 49 participants considered this outcome. Compared with placebo, the number of days until normal function of the joint was 2.07 days lower with corticosteroids (MD -2.07, 95% CI -5.47 to 1.33). Data show no statistically significant differences (P = 0.23). The quality of the evidence was low due to concerns about attrition bias, selective reporting, and imprecision.

3.2. Number of days until full range of movement

Harel 2011 with 49 participants considered this outcome. Compared with placebo, the number of days until full range of movement was 5.24 days lower with corticosteroids (MD -5.24, 95% CI -10.37 to -0.11). Data show statistically significant differences (P = 0.05). The quality of the evidence was low due to concerns about attrition bias, selective reporting, and imprecision, because the confidence interval was very large for number of days until full range of movement.

3.3. Normal function at the end of treatment (short term)

Odio 2003 with 100 participants considered this outcome in the short term at the end of treatment. Study authors reported data as categorical outcomes. The risk ratio for normal function at the end of treatment (short term) was 1.41 (95% CI 1.16 to 1.72; P = 0.0007; NNTB = 8, 95% CI 5 to 20). We downgraded quality by one level for concerns about study limitations (unclear risk of detection and reporting bias and high risk of attrition bias). We downgraded by another level for imprecision (due to few participants and a wide confidence interval).

3.4. Normal function at six months of follow-up (medium term)

Odio 2003 with 100 participants considered this outcome in the medium term. Researchers reported data as categorical outcomes. The estimated risk ratio for normal function at six months of follow-up (medium term) was 1.58 (95% CI 1.27 to 1.97; P < 0.0001; NNTB = 5, 95% CI 3 to 11). We downgraded quality by one level for concerns about study limitations (unclear risk of detection and reporting bias and high risk of attrition bias). We downgraded by another level for imprecision (due to few participants and a wide confidence interval).

3.5. Normal function at 12 months of follow-up (long term)

Odio 2003 with 100 participants considered this outcome in the long term. Investigators reported data as categorical outcomes. The risk ratio for normal function at 12 months of follow-up (long term) was 1.32 (95% CI 1.12 to 1.57; P = 0.001; NNTB = 13, 95% CI 7 to 33). We downgraded quality by one level for concerns about study limitations (unclear risk of detection and reporting bias and high risk of attrition bias). We downgraded by another level for imprecision (due to few participants and a wide confidence interval).

3.6. Number of days until resolution of symptoms

Only Odio 2003 with 100 participants considered this outcome. Compared with placebo, the number of days until resolution of symptoms was 5.47 days lower with corticosteroids (MD -5.47, 95% CI -6.98 to -3.96). Data show statistically significant differences (P < 0.00001). We downgraded the quality of the evidence because of unclear risk of detection bias and selective reporting and high risk of attrition bias. This result may be clinically relevant from the patient perspective.

4. Number of days of antibiotic treatment

4.1. Number of days of intravenous antibiotic treatment

Two studies with a total of 149 participants measured this outcome (Harel 2011; Odio 2003). Study authors reported this as a continuous variable. Compared with placebo, the number of days of intravenous antibiotic treatment was 2.77 days lower with corticosteroids (MD -2.77, 95% CI -4.16 to -1.39). Data show statistically significant differences (P < 0.0001), and heterogeneity between studies was 0%. We downgraded quality by one level for

concerns about study limitations (detection, reporting, and attrition bias). We downgraded by another level for imprecision (due to few participants and a wide confidence interval).

4.2. Number of total days of antibiotic treatment

Two studies with a total of 149 participants measured this outcome and reported it as a continuous variable (Harel 2011; Odio 2003). Compared with placebo, the total number of days of antibiotic treatment was 3.11 days lower with corticosteroids (MD -3.11, 95% CI -6.94 to 0.73). Data show no statistically significant differences (P = 0.11), and heterogeneity between studies was 60%. We downgraded quality by one level for concerns about study limitations (detection, reporting, and attrition bias). We downgraded by another level for imprecision (due to few participants and a wide confidence interval).

5. Length of hospital stay

We found no studies reporting this outcome.

Harel 2011 with 49 participants indirectly reported this outcome. Researchers found that treatment with dexamethasone was associated with a shorter duration of IV antibiotic treatment, leading to a shorter hospital stay. They did not provide numerical data and did not clearly report the outcome. We downgraded quality by one level for concerns about study limitations (high risk of bias of attrition and selective reporting). We downgraded by another level for imprecision due to small sample size.

6. Total adverse events

Harel 2011 with 49 participants reported this outcome. At long term, investigators followed up with 29 children, and none demonstrated adverse effects of the intervention. We downgraded quality by one level for concerns about study limitations (high risk of attrition bias and selective reporting). We downgraded by another level for imprecision due to small sample size, which resulted in a large confidence interval.

7. Serious adverse events

Harel 2011 with 49 participants reported this outcome as presented above. No other studies reported additional serious adverse events.

We conducted no planned subgroup or sensitivity analyses due to lack of data.

DISCUSSION

Summary of main results

For septic arthritis in children, even though bacterial infection is eradicated by antibiotic treatment, the inflammatory process continues, generating residual articular damage with irreversible loss of joint function. The inflammatory process is characterised by rapid arrival of polymorphonuclear cells, activated macrophages, and T cells, as well as by the production of cytokines, which destroy the articular cartilage (Colavite 2014). It is thought that corticosteroids could have a therapeutic role in reducing the inflammatory response as mediated by cytokines and interleukins, thus avoiding residual sequelae or improving function with septic arthritis (Kang 2009; Kwan 2004).

In our review, we aimed to determine the effect of corticosteroids as adjunctive therapy for children with septic arthritis and found that findings of our comprehensive literature search were scarce. Only two randomised clinical trials conducted in Costa Rica and Israel, respectively, met our inclusion criteria (Harel 2011; Odio 2003); thus, researchers have tested very few interventions with corticosteroids for this condition during childhood. Outcomes reported in those trials, such as pain, symptom resolution, joint function, joint range of movement, and the presence of sequelae, are clinically important. None of the included studies followed up with children beyond 12 months. Trials did not report activities of daily living nor length of hospital stay.

Regarding measured outcomes, the risk ratio (RR) for absence of pain at 12 months of follow-up was 1.33, favouring corticosteroids, with the number needed to treat for an additional beneficial outcome (NNTB) of 13. The RR for normal function of the affected joint at 12 months of follow-up was 1.32, favouring corticosteroids, with an NNTB of 13. We conducted a meta-analysis including the two studies and found a reduction in the number of days of intravenous antibiotic treatment favouring corticosteroids, with a mean difference (MD) of -2.77 days (Harel 2011; Odio 2003). In one trial of 49 participants followed to 12 months (Harel 2011), parents reported that no children demonstrated adverse effects of the intervention (Summary of findings for the main comparison).

Both studies described an adequate randomisation process and adequate allocation concealment and blinding, and we judged them to have low risk of selection and performance bias. The number of losses to follow-up was substantive in both studies, and we judged these studies as having high risk of attrition bias and selective outcome reporting. We graded all outcomes as low quality due to concerns about study limitations and imprecision (Summary of findings for the main comparison).

Both studies assessed outcomes not prespecified in our protocol, such as return to normal values of parameters used during clinical follow-up of infectious processes (e.g. C-reactive protein). Both studies reported a shorter time to reaching normal values.

Overall completeness and applicability of evidence

Because of the potential benefit of an inexpensive adjuvant corticosteroid therapy, our review question remains important. Additional studies including larger numbers of participants would increase our confidence in these results. Lack of studies was a major limitation of this review. Participants and interventions included in these trials are representative of usual clinical practice. Included studies were published in Costa Rica and Israel and included children between three months and 18 years of age, with lower limbs reported as the most commonly affected joints.

Both trials used dexamethasone as the experimental intervention. Dexamethasone led to a reduction in pain at 12 months, an increase in the number of participants with normal function of the joint at 12 months, and a reduced number of days of IV antibiotic treatment. However, the included studies did not assess important outcomes from the patient perspective, such as activities of daily living. Current data are limited to 12 months of follow-up. We conducted no planned subgroup or sensitivity analyses due to lack of data.

We classified quality of the evidence as low due to limitations in risk of bias and to the number of studies with imprecision. Nevertheless, results have led us to believe that this is an acceptable intervention for children with septic arthritis. Corticosteroids are an accessible, available, and inexpensive intervention.

Quality of the evidence

Studies identified for this review remain insufficient to provide robust support for use of this intervention. We identified two trials for inclusion in this review, and both used dexamethasone as the corticosteroid and placebo as the comparative intervention (Harel 2011; Odio 2003). Investigators studied a total of 149 children with a follow-up period of one year. Both studies described adequate processes for randomisation, allocation concealment, and blinding, and we judged them as having low risk of selection and performance bias. However, the number of losses to follow-up was substantive in both studies, and we judged them as having high risk of attrition bias. In addition, we judged Harel 2011 as having high risk of selective outcome reporting. One trial described serious adverse events and length of hospital stay as narrative statements without providing additional data.

We used the GRADE approach to evaluate the body of evidence, and we prepared Summary of findings for the main comparison. In general, we assessed the quality of evidence for the most important outcomes as low. We downgraded quality of the evidence for outcomes because of concerns about attrition bias, selective reporting, and imprecision.

Potential biases in the review process

The possibility that some studies may not have been identified during the search conducted for this review is small. We sent emails to the authors of included clinical trials to ask if they were aware of other similar clinical trials, but we received no response.

The small number of trials included in analyses reduced the robustness of these findings, introducing imprecision to the estimates. In our review process, we attempted to control for bias by strictly adhering to Cochrane methods (Higgins 2011). We applied no language restrictions, and we updated searches several times using multiple databases and handsearching. By searching clinical trial registries (e.g. clinicaltrials.gov), we enhanced the opportunity to identify unpublished trials as well as selective reporting of outcomes.

We used a standardised procedure to determine selection and inclusion of studies in this review, and review authors were trained in data extraction.

Agreements and disagreements with other studies or reviews

Some studies support a potentially harmful effect when corticosteroids are used to treat infectious disease (Aljeab 2016). However, some systematic reviews of interventions show a beneficial effect of corticosteroids in such conditions. Results obtained with these interventions include a reduction in sequelae and mortality when used for child meningitis (Brouwer 2015). Researchers have examined effects of corticosteroids on neonatal meningitis (Ogunlese 2015), on sepsis (Annane 2009), and during acute sinusitis in children (Head 2016; Zalmanovici 2013). However, regarding septic arthritis in children, and even in adults, a small number of clinical trials have published research on this topic. Therefore, the main limitation of this systematic review is the lack of clinical trials; this insufficient evidence makes difficult the routine use of corticosteroids for treating children with septic arthritis.

The findings of this systematic review are in accordance with the findings of another recent review (Farrow 2015). The Farrow review identified the same clinical trials included here and also included studies based on different designs and studies conducted in animal models. However, only one author conducted the former systematic review, and that review author limited the search to articles published in the English language.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence for corticosteroids as adjunctive therapy for children with a diagnosis of septic arthritis is of low quality and was derived from two trials (N = 149). Corticosteroids may increase the proportion of patients without pain and the proportion of patients with normal function of the affected joint at 12 months, and may reduce

the number of days of antibiotic treatment. However, we cannot draw strong conclusions based upon the findings of these trials.

Implications for research

We need additional randomised clinical trials to test the benefits and harms of corticosteroids as adjunctive therapy versus placebo in children with septic arthritis. New studies should consider a wide range of childhood ages and should be designed to avoid attrition bias and selective reporting. Investigators must describe administration of corticosteroids very clearly and must account for the type of corticosteroid used, dosage, route of administration, and co-interventions. Researchers should consider outcomes relevant to patients, such as activities of daily living, and should measure, report, and assess these outcomes using a comprehensive and clear approach. Finally, the follow-up period should be long enough to detect any long-term sequelae.

ACKNOWLEDGEMENTS

To Departmento de Pediatría, Facultad Ciencias de la Salud, Universidad del Cauca, Popayán, Colombia, especially to Jaime Bonilla, former professor of the department, who originally developed the idea from a real clinical scenario.

To Marta Roque and Xavier Bonfill from the Iberoamerican Cochrane Center of Barcelona.

To Ivan Solá for his collaboration in conducting the literature search.

To Rodrigo Vásquez-De Kartzow for his collaboration in providing clinical advice during preparation of the protocol.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Harel 2011

Methods	Randomised double-blind placebo-controlled trial
Participants	Children aged 6 months to 18 years with septic arthritis hospitalised at Schneider Children's Medical Center of Israel, and at Sapir Medical Center, from March 1999 to December 2007 Diagnosis: "the diagnosis of septic arthritis was based on 3 criteria: (1) acute onset of swelling, pain, local warmth, and severe limitation of motion in any joint,except for the hip or shoulder, in which severe pain and limitation of motion were sufficient for diagnosis; (2) all involved joints were aspirated on admission. Joint fluid with a turbid purulent appearance and containing 50,000 white blood cells (WBC)/mm³ was considered septic; (3) elevated levels of acute phase reactants:erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or WBC count. In all patients both synovial fluid and blood were cultured before treatment" Exclusion criteria: history of chronic arthritis, autoimmune disease, or immune deficiency; arthritis secondary to a puncture wound Total number randomised: N = 49 (24 assigned to the dexamethasone group and 25 to the placebo group)
Interventions	Dexamethasone IV 0.15 mg/kg/dose every 6 hours for 16 consecutive doses (4 days) ; administered 30 minutes before and up to 2 hours after the first dose of parenteral antibiotics Placebo group received 0.9% saline solution (equivalent to dexamethasone timing and volume) All participants received antibiotic therapy, first parenteral and then oral. Some participants underwent surgical drainage. No participants received anti-inflammatory drugs
Outcomes	1. Pain reported as dichotomous scale (presence/absence) at long-term follow-up (12 months); assessed by phone call 2. Serious adverse events reported at long term as dichotomous scale 3. Outcome not reported; length of hospital stay reported as proxy number of days of IV antibiotic treatment; outcome reported as a narrative statement 4. Duration of intravenous/oral administration of antibiotics 5. Secondary endpoint: presence of late sequelae (follow-up at 2, 5, 12 months) 6. Time to clinical and laboratory normalisation and duration of hospitalisation (first day fever - first day no local heat - first day no redness - first day pain free - first day full range of movement - first day normal function - last day ESR +25 mm/h - last day WBC +15.000 - last day CRP +0.5 mg/dL) 7. Each parameter rated on a scale of 1 (least severe) to 3 (most severe). Scores summed to determine the arthritis index
Comparison	Placebo
Notes	No funding support

Harel 2011 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "After enrolment, patients were allocated 1:1 to receive dexamethasone or placebo according to a list of computer-generated random numbers kept by the pharmacist"
Allocation concealment (selection bias)	Low risk	Randomisation was performed in the pharmacy, and researchers seemed not to be aware of which participants would receive treatment or placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: The bottles were labelled "dexamethasone study" Placebo consisted of saline only, packaged in identical bottles
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers did not know which group participants belonged to at the time of evaluation of the affected joint
Incomplete outcome data (attrition bias) All outcomes	High risk	"The study protocol was offered to the parents of 60 children, of whom 11 refused to participate" 49 children were randomised to intervention (24) and control groups (25). No participants were lost in the short-term follow-up period, but in the long-term follow-up period, 4/49 were lost at 2 months, 10/49 at 6 months, and 20/49 at 12 months
Selective reporting (reporting bias)	High risk	This study did not report its primary outcome details (length of hospital stay). In addition, study authors did not provide clear information on long-term results or measurement of sequelae
Other bias	Low risk	

Odio 2003

Methods	Randomised double-blind placebo-controlled trial
Participants	Children 3 months to 13 years of age with septic arthritis Quote: "Documented septic arthritis was considered when there were bacterial growth and purulence of the synovial fluid (purulence was defined as the presence of 5000 white blood cells/mm³, 60% of segmented forms, lactate dehydrogenase (LDH) 500 IU, glucose 30 mg/dl) or (2) bacteria isolated from blood and presence of a purulent synovial fluid with or without bacteria seen in the Gram-stained smear" Exclusion criteria: previous history of septic arthritis in the same or the contralateral joint; arthritis secondary to a puncture wound; known history of autoimmune disease; had received steroids in the previous 2 months (except for asthma); congenital or acquired osteoarticular anomalies, history of a foreign body in the affected joint, or Gram-negative coliform bacilli isolated from blood, cerebrospinal fluid, articular fluid, or another significant body fluid; underlying disease that would preclude the long-term (12-month) evaluation; had received 48 hours of treatment with an orally or parenterally administered antibiotic Total number randomised: N = 123 children (61 to the dexamethasone group and 62 to the placebo group)
Interventions	IV dexamethasone 0.2 mg/kg/dose IV every 8 hours for 12 consecutive doses. The first dose of dexamethasone was administered 15 to 20 minutes before the first dose of parenteral antibiotics All participants received antibiotic therapy; participants received 7 days of IV therapy followed by 7 or more days of ambulatory oral therapy Placebo group received 0.9% saline solution (equivalent of dexamethasone timing and volume) All participants underwent a diagnostic arthrocentesis performed by one of the orthopaedic surgeons within the first 12 hours of admission
Outcomes	1. Normal function of the affected joint at the end of therapy, at 6 months, and at 12 months - reported as dichotomous result 2. Secondary endpoint: speed of clinical and laboratory normalisation (days to resolution of symptoms, including absence of fever, absence of spontaneous pain or pain to passive or active movement, absence of warmth and oedema, normal range of movement of the joint, and days of normalisation of serum C-reactive protein) 3. Duration of intravenous/oral administration of antibiotics, duration of intravenous/oral administration of antibiotics
Comparison	Placebo
Notes	Parents or legal guardians providing written informed consent were eligible for the study No funding support

Risk of bias

Bias	Authors' judgement	Support for judgement

Odio 2003 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "After enrolment patients were selected from a list of computer-generated random numbers kept by the Pharmacist (GA) to receive in a 1:1 randomisation: dexamethasone 0.2 mg/kg/dose iv every 8 h for 12 consecutive doses; or saline at an equivalent volume of that of the corresponding dexamethasone, given iv at the same intervals and number of doses"
Allocation concealment (selection bias)	Low risk	Quote: "Treatment was allocated by opening of sequential, blinded envelopes containing drug assignments"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Received saline at an equivalent volume of that of the corresponding dexamethasone, given iv at the same intervals and number of doses. Blinded envelopes containing drug assignments"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Overall 123 children who were asked to participate were enrolled in the study" 61 dexamethasone; 62 placebo 23 children were unavailable for various reasons 100 participants were fully evaluated (50 intervention group; 50 control group)
Selective reporting (reporting bias)	Unclear risk	Study authors did not report clearly their prespecified outcome "range of movement of the joint"
Other bias	Low risk	Not detected

CRP: C-reactive protein.
ESR: erythrocyte sedimentation rate.
LDH: lactate dehydrogenase.
WBC: white blood cell.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arti 2014	Excluded by study type - not a randomised controlled trial
Fogel 2015	Excluded by study type - not a randomised controlled trial
van Oosterhout 2006	Excluded by population and Intervention

DATA AND ANALYSES

Comparison 1. Corticosteroids versus placebo

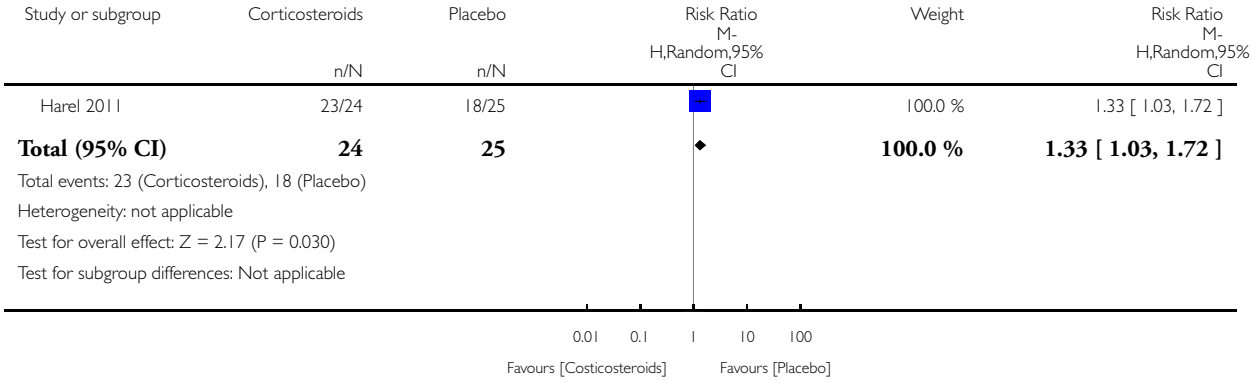
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain - absence of pain	1	49	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.03, 1.72]
2 Pain - number of days until pain free	1	49	Mean Difference (IV, Random, 95% CI)	-3.58 [-7.41, 0.25]
3 Number of participants with normal physical joint function - number of days until normal function of the joint	1	49	Mean Difference (IV, Random, 95% CI)	-2.07 [-5.47, 1.33]
4 Number of participants with normal physical joint function - number of days until full range of movement	1	49	Mean Difference (IV, Random, 95% CI)	-5.24 [-10.37, -0.11]
5 Number of participants with normal physical joint function - normal function at the end of treatment (short term)	1	100	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.16, 1.72]
6 Number of participants with normal physical joint function - normal function at 6 months of follow-up (medium term)	1	100	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.27, 1.97]
7 Number of participants with normal physical joint function - normal function at 12 months of follow-up (long term)	1	100	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.12, 1.57]
8 Number of participants with normal physical joint function - number of days until resolution of symptoms	1	100	Mean Difference (IV, Random, 95% CI)	-5.47 [-6.98, -3.96]
9 Number of days of antibiotic treatment - number of days of intravenous antibiotic treatment	2	149	Mean Difference (IV, Random, 95% CI)	-2.77 [-4.16, -1.39]
10 Number of days of antibiotic treatment - number of total days of antibiotic treatment	2	149	Mean Difference (IV, Random, 95% CI)	-3.11 [-6.94, 0.73]

Analysis 1.1. Comparison 1 Corticosteroids versus placebo, Outcome 1 Pain - absence of pain.

Review: Corticosteroids for septic arthritis in children

Comparison: 1 Corticosteroids versus placebo

Outcome: 1 Pain - absence of pain

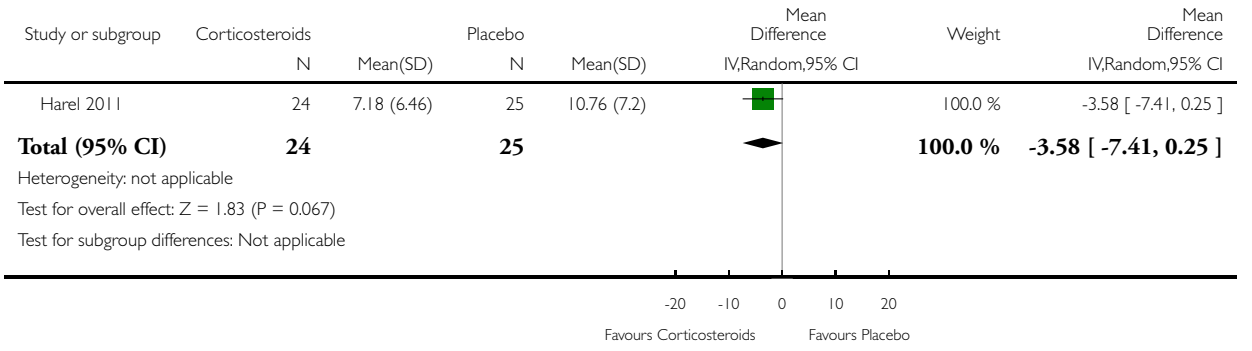


Analysis 1.2. Comparison 1 Corticosteroids versus placebo, Outcome 2 Pain - number of days until pain free.

Review: Corticosteroids for septic arthritis in children

Comparison: 1 Corticosteroids versus placebo

Outcome: 2 Pain - number of days until pain free

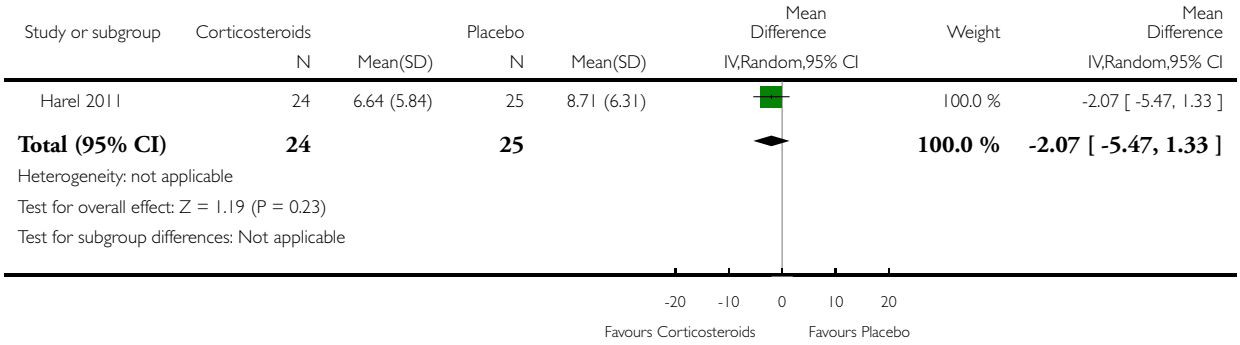


Analysis 1.3. Comparison 1 Corticosteroids versus placebo, Outcome 3 Number of participants with normal physical joint function - number of days until normal function of the joint.

Review: Corticosteroids for septic arthritis in children

Comparison: 1 Corticosteroids versus placebo

Outcome: 3 Number of participants with normal physical joint function - number of days until normal function of the joint

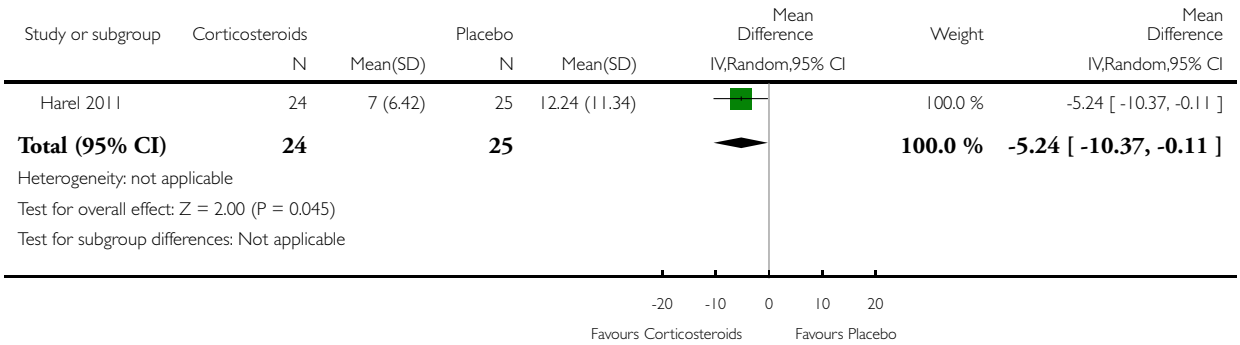


Analysis 1.4. Comparison 1 Corticosteroids versus placebo, Outcome 4 Number of participants with normal physical joint function - number of days until full range of movement.

Review: Corticosteroids for septic arthritis in children

Comparison: 1 Corticosteroids versus placebo

Outcome: 4 Number of participants with normal physical joint function - number of days until full range of movement



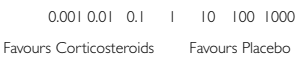
Analysis 1.5. Comparison 1 Corticosteroids versus placebo, Outcome 5 Number of participants with normal physical joint function - normal function at the end of treatment (short term).

Review: Corticosteroids for septic arthritis in children

Comparison: 1 Corticosteroids versus placebo

Outcome: 5 Number of participants with normal physical joint function - normal function at the end of treatment (short term)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Odio 2003	48/50	34/50		100.0 %	1.41 [1.16, 1.72]
Total (95% CI)	**50**	**50**		**100.0 %**	**1.41 [1.16, 1.72]**
Total events: 48 (Corticosteroids), 34 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.41 (P = 0.00066)					
Test for subgroup differences: Not applicable					



Analysis 1.6. Comparison 1 Corticosteroids versus placebo, Outcome 6 Number of participants with normal physical joint function - normal function at 6 months of follow-up (medium term).

Review: Corticosteroids for septic arthritis in children

Comparison: 1 Corticosteroids versus placebo

Outcome: 6 Number of participants with normal physical joint function - normal function at 6 months of follow-up (medium term)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Odio 2003	49/50	31/50		100.0 %	1.58 [1.27, 1.97]
Total (95% CI)	**50**	**50**		**100.0 %**	**1.58 [1.27, 1.97]**
Total events: 49 (Corticosteroids), 31 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.07 (P = 0.000047)					
Test for subgroup differences: Not applicable					

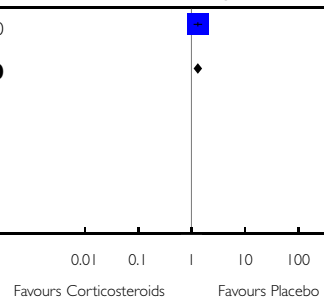
Analysis 1.7. Comparison 1 Corticosteroids versus placebo, Outcome 7 Number of participants with normal physical joint function - normal function at 12 months of follow-up (long term).

Review: Corticosteroids for septic arthritis in children

Comparison: 1 Corticosteroids versus placebo

Outcome: 7 Number of participants with normal physical joint function - normal function at 12 months of follow-up (long term)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Odio 2003	49/50	37/50		100.0 %	1.32 [1.12, 1.57]
Total (95% CI)	**50**	**50**		**100.0 %**	**1.32 [1.12, 1.57]**
Total events: 49 (Corticosteroids), 37 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.26 (P = 0.0011)					
Test for subgroup differences: Not applicable					



Analysis 1.8. Comparison 1 Corticosteroids versus placebo, Outcome 8 Number of participants with normal physical joint function - number of days until resolution of symptoms.

Review: Corticosteroids for septic arthritis in children

Comparison: 1 Corticosteroids versus placebo

Outcome: 8 Number of participants with normal physical joint function - number of days until resolution of symptoms

Study or subgroup	Corticosteroids N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Odio 2003	50	2.34 (5.06)	50	7.81 (2.04)		100.0 %	-5.47 [-6.98, -3.96]
Total (95% CI)	**50**		**50**			**100.0 %**	**-5.47 [-6.98, -3.96]**

Heterogeneity: not applicable

Test for overall effect: Z = 7.09 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Corticosteroids versus placebo, Outcome 9 Number of days of antibiotic treatment - number of days of intravenous antibiotic treatment.

Review: Corticosteroids for septic arthritis in children

Comparison: 1 Corticosteroids versus placebo

Outcome: 9 Number of days of antibiotic treatment - number of days of intravenous antibiotic treatment

Study or subgroup	Corticosteroids N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Harel 2011	24	9.91 (4.84)	25	12.6 (5.2)		24.2 %	-2.69 [-5.50, 0.12]
Odio 2003	50	7.2 (1.2)	50	10 (5.6)		75.8 %	-2.80 [-4.39, -1.21]
Total (95% CI)	**74**		**75**			**100.0 %**	**-2.77 [-4.16, -1.39]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 3.93 (P = 0.000084)

Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Corticosteroids versus placebo, Outcome 10 Number of days of antibiotic treatment - number of total days of antibiotic treatment.

Review: Corticosteroids for septic arthritis in children

Comparison: 1 Corticosteroids versus placebo

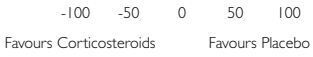
Outcome: 10 Number of days of antibiotic treatment - number of total days of antibiotic treatment

Study or subgroup	Corticosteroids		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Odio 2003	50	14.43 (2.78)	50	19 (6.18)		64.1 %	-4.57 [-6.45, -2.69]
Harel 2011	24	21.91 (8.57)	25	22.4 (8)		35.9 %	-0.49 [-5.14, 4.16]
Total (95% CI)	**74**		**75**			**100.0 %**	**-3.11 [-6.94, 0.73]**

Heterogeneity: $Tau^2 = 5.05$; $Chi^2 = 2.55$, df = 1 (P = 0.11); $I^2 = 61\%$

Test for overall effect: Z = 1.59 (P = 0.11)

Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. MEDLINE strategy

1 exp child/ (1763534)

2 children.ti,ab. (914218)

3 childhood.ti,ab. (208371)

4 preschool.ti,ab. (21229)

5 exp infant/ (1061549)

6 exp adolescent/ (1856011)

7 teenager.ti,ab. (2243)

8 teen.ti,ab. (4821)

9 adolescent.ti,ab. (99455)

10 (septic and arthritis).ti,ab. (5587)

11 (Infectious and Arthriti*).ti,ab. (3014)

12 (Viral and Arthriti*).ti,ab. (1810)

13 (Bacterial and Arthriti*).ti,ab. (2921)

14 (Suppurat* and Arthriti*).ti,ab. (422)

15 exp Arthritis, Infectious/ (13612)

16 exp Bone Diseases, Infectious/ (36471)

17 or/1-9 (3511215)

18 or/10-16 (55623)

19 17 and "14".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (206897)

20 steroid$.ti,ab. (213677)

21 corticosteroidS.ti,ab. (60090)

22 glucocorticoid$.ti,ab. (61322)

23 beclomethasone.ti,ab. (2714)

24 betamethasone.ti,ab. (4454)

25 budesonide.ti,ab. (4736)

26 cortisone.ti,ab. (15137)

27 dexamethasone.ti,ab. (51495)

28 flunisolide.ti,ab. (307)

29 fluticasone.ti,ab. (3496)

30 fludrocortisone.ti,ab. (998)

31 hydrocortisone.ti,ab. (15503)

32 cortisol.ti,ab. (55612)

33 methylprednisolone.ti,ab. (14299)

34 mometasone.ti,ab. (820)

35 prednisolone.ti,ab. (23671)

36 prednisone.ti,ab. (24821)

37 triamcinolone.ti,ab. (6914)

38 or/20-37 (457730)

39 38 and 19 (7297)

40 residual disfunction.ti,ab. (0)

41 residual dysfunction.ti,ab. (50)

42 length of stay.ti,ab. (44159)

43 acute phase reactants.ti,ab. (2005)

44 exp Acute-Phase Proteins/ (131720)

45 or/40-44 (176844)

46 39 and 45 (95)

47 randomised controlled trial.pt. (458773)

48 controlled clinical trial.pt. (92329)

49 randomized.ti,ab. (440255)

50 placebo.ti,ab. (193277)

51 drug therapy.sh. (29520)

52 randomly.ti,ab. (289459)

53 trial.ti,ab. (499045)

54 groups.ti,ab. (1809247)

55 or/47-54 (2672077)

56 exp animals/ not humans.sh. (4446637)

57 55 not 56 (2266689)

58 or/47-57 (6713326)

59 18 and 38 and 58 (179)

60 limit 59 to ed=20161101-20180415 (12)

Appendix 2. Embase strategy

1 exp child/ (2707672)

2 children.ti,ab. (1250996)

3 childhood.ti,ab. (286482)

4 preschool.ti,ab. (25919)

5 exp infant/ (1055881)

6 exp adolescent/ (1485784)

7 teenager.ti,ab. (3377)

8 teen.ti,ab. (6076)

9 adolescent.ti,ab. (131264)

10 (septic and arthritis).ti,ab. (7279)

11 exp Arthritis, Infectious/ (19353)

12 exp Bone Diseases, Infectious/ (10751)

13 or/1-9 (3754338)

14 or/10-12 (30653)

15 13 and 14 (7254)

16 steroid$.ti,ab. (313418)

17 corticosteroid$.ti,ab. (143223)

18 glucocorticoid$.ti,ab. (80955)

19 beclomethasone.ti,ab. (3725)

20 betamethasone.ti,ab. (6558)

21 budesonide.ti,ab. (7400)

22 cortisone.ti,ab. (27919)

23 dexamethasone.ti,ab. (70813)

24 flunisolide.ti,ab. (454)

25 fluticasone.ti,ab. (6075)

26 fludrocortisone.ti,ab. (1640)

27 hydrocortisone.ti,ab. (25065)

28 cortisol.ti,ab. (72653)

29 methylprednisolone.ti,ab. (22112)

30 mometasone.ti,ab. (1428)

31 prednisolone.ti,ab. (36953)

32 prednisone.ti,ab. (44551)

33 triamcinolone.ti,ab. (9548)

34 or/16-33 (699576)

35 34 and 15 (208)

36 residual disfunction.ti,ab. (0)

37 residual dysfunction.ti,ab. (67)

38 length of stay.ti,ab. (80011)

39 acute phase reactants.ti,ab. (3322)

40 exp Acute-Phase Proteins/ (9425)

41 or/36-40 (90820)

42 35 and 41 (6)

43 random$.tw. (1302852)

44 factorial$.tw. (32916)

45 crossover$.tw. (66245)

46 cross over.tw. (29372)

47 cross-over.tw. (29372)

48 placebo$.tw. (276701)

49 (doubl$ adj blind$).tw. (191951)

50 (singl$ adj blind$).tw. (21073)

51 assign$.tw. (338486)

52 allocat$.tw. (127346)

53 volunteer$.tw. (236660)

54 crossover procedure/ (55437)

55 double blind procedure/ (151027)

56 randomised controlled trial/ (498277)

57 single blind procedure/ (31098)

58 or/43-57 (2020259)

59 42 and 58 (3)

60 limit 59 to dd=20161101-20180415 (0)

Appendix 3. CENTRAL strategy

1 exp child/ (49994)

2 exp infant/ (28393)

3 exp adolescent/ (94975)

4 infan*.ti,ab. (26252)

5 baby*.ti,ab. (1812)

6 babies.ti,ab. (2413)

7 toddler*.ti,ab. (896)

8 minor*.ti,ab. (14651)

9 boy*.ti,ab. (5074)

10 girl*.ti,ab. (4908)

11 kid.ti,ab. (34)

12 kid*.ti,ab. (14241)

13 child*.ti,ab. (75127)

14 schoolchild*.ti,ab. (1030)

15 school child*.ti,ab. (1813)

16 adolescen*.ti,ab. (15148)

17 juvenil*.ti,ab. (1302)

18 youth*.ti,ab. (3801)

19 teen*.ti,ab. (1355)

20 pediatric*.ti,ab. (15519)

21 paediatric*.ti,ab. (4095)

22 peadiatric*.ti,ab. (6)

23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (216315)

24 exp Arthritis, Infectious/ (79)

25 exp Bone Diseases, Infectious/ (207)

26 septic arthritis.ti,ab. (68)

27 24 or 25 or 26 (320)

28 23 and 27 (127)

29 exp Steroids/ (42100)

30 steroid*.ti,ab. (15116)

31 corticosteroid*.ti,ab. (12070)

32 glucocorticoid*.ti,ab. (2934)

33 beclomethasone.ti,ab. (1723)

34 betamethasone.ti,ab. (1393)

35 budesonide.ti,ab. (3159)

36 cortisone.ti,ab. (306)

37 dexamethasone.ti,ab. (6101)

38 flunisolide.ti,ab. (189)

39 fluticasone.ti,ab. (3641)

40 fludrocortisone.ti,ab. (121)

41 hydrocortisone.ti,ab. (1669)

42 cortisol.ti,ab. (7695)

43 methylprednisolone.ti,ab. (2359)

44 mometasone.ti,ab. (807)

45 prednisolone.ti,ab. (3395)

46 prednisone.ti,ab. (5086)

47 triamcinolone.ti,ab. (1568)

48 24 or 25 or 26 or 27 or 28 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 (51518)

49 28 and 48 (127)

50 limit 49 to yr=2016-2018 (10)

Appendix 4. LILACS strategy

Artritis séptica AND Esteroides

Appendix 5. WHO strategy

septic arthritis
OR Arthritis, Infectious OR Bone Diseases, Infectious
AND
Steroid* OR corticosteroid* OR glucocorticoid* OR beclomethasone OR betamethasone OR budesonide OR cortisone OR dexamethasone OR flunisolide OR fluticasone
OR fludrocortisone OR hydrocortisone OR cortisol OR methylprednisolone OR mometasone OR prednisolone OR prednisone OR triamcinolone

Appendix 6. Clinical trials strategy

septic arthritis

Appendix 7. Google Scholar strategy

Arthritis septic child children corticoids dexamethasone Glucocorticoids prednisone prednisolone Clinical Trial Randomized Controlled Trials -animals

CONTRIBUTIONS OF AUTHORS

Mario Delgado conceived, designed, and wrote the protocol and review, and provided a methodological, clinical, and policy perspective. Jessica Forero and Alexis Franco wrote the protocol and provided a clinical perspective. Jose Andres Calvache planned search strategies and provided methodological and statistical perspectives. Juan C Vazquez provided a methodological perspective and supported translation to English.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- University of Cauca, Popayan, Colombia, Colombia.

(Academic support)

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We found outcomes that can be informative from clinical and patient perspectives. We added minor outcomes to our prespecified ones. These outcomes include (1) pain measured by different scales - number of days until pain free, (2) number of participants with normal physical joint function - number of days until normal function of the joint, (3) number of participants with normal physical joint function - number of days until full range of movement, and (4) number of participants with normal physical joint function - number of days until resolution of symptoms.

We did not carry out sensitivity and subgroup analyses because included trials did not provide enough data for the prespecified subgroups.

We did not restricted the primary analysis or any result to trials at low risk of detection and selection bias.