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Steroids for symptom control in infectious mononucleosis (Review)

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[Intervention Review]

Steroids for symptom control in infectious mononucleosis

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ABSTRACT

Background

Infectious mononucleosis, also known as glandular fever or the kissing disease, is a benign lymphoproliferative disorder. It is a viral infection caused by the Epstein-Barr virus (EBV), a ubiquitous herpes virus that is found in all human societies and cultures. Epidemiological studies show that over 95% of adults worldwide have been infected with EBV. Most cases of symptomatic infectious mononucleosis occur between the ages of 15 and 24 years. It is transmitted through close contact with an EBV shedder, contact with infected saliva or, less commonly, through sexual contact, blood transfusions or by sharing utensils; however, transmission actually occurs less than 10% of the time. Precautions are not needed to prevent transmission because of the high percentage of seropositivity for EBV. Infectious mononucleosis is self-limiting and typically lasts for two to three weeks. Nevertheless, symptoms can last for weeks and occasionally months.

Symptoms include fever, lymphadenopathy, pharyngitis, hepatosplenomegaly and fatigue. Symptom relief and rest are commonly recommended treatments. Steroids have been used for their anti-inflammatory effects, but there are no universal criteria for their use.

Objectives

The objectives of the review were to determine the efficacy and safety of steroid therapy versus placebo, usual care or different drug therapies for symptom control in infectious mononucleosis.

Search methods

For this 2015 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 7), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (January 1966 to August 2015) and EMBASE (January 1974 to August 2015). We also searched trials registries, however we did not identify any new relevant completed or ongoing trials for inclusion. We combined the MEDLINE search with the Cochrane search strategy for identifying randomised controlled trials (RCTs). We adapted the search terms when searching EMBASE.

Selection criteria

RCTs comparing the effectiveness of steroids with placebo, usual care**,** or other interventions for symptom control for people with documented infectious mononucleosis.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane.

Main results

For this 2015 update, we did not identify any new RCTs for inclusion. The previous version of the review included seven trials with a total of 362 participants. Four trials compared the effectiveness of a steroid to placebo for short-term symptom control in glandular fever, one to aspirin, and two trials explored the effects of steroids in conjunction with an antiviral. Heterogeneity between trials prevented a combined analysis.

Trials under-reported methodological design features. Three trials did not adequately describe sequence generation for randomisation. Four trials provided adequate details of allocation concealment. All trials were double-blind but four were not specific as to who was blinded. Loss to follow-up was under-reported in four trials, making it difficult to exclude attrition bias. The risk of selective reporting in the included trials was unclear.

Across the trials, no benefit was found in 8/10 assessments of health improvement. Two trials found benefit of steroid therapy over placebo in reducing sore throat at 12 hours (eight-day course odds ratio (OR) 21.00, 95% confidence interval (CI) 1.94 to 227.20; one-dose OR 4.20, 95% CI 1.08 to 16.32), but the benefit was not maintained.

In combination with an antiviral drug, participants in the steroid group had less pharyngeal discomfort between days two to four (OR 0.31, 95% CI 0.09 to 1.08) compared to placebo. Across the trials the effects on other common symptoms were less clear. Two trials set out to measure safety; they documented no major adverse effects. In two other trials adverse events were reported, including respiratory distress and acute onset of diabetes. However, the association of the events with the steroid is not definite.

Authors' conclusions

There is insufficient evidence to the efficacy of steroids for symptom control in infectious mononucleosis. There is a lack of research on the side effects and long-term complications.

PLAIN LANGUAGE SUMMARY

Steroids for short-term symptom control in infectious mononucleosis (glandular fever)

Review question

We reviewed evidence about the effect of steroids on symptom control in people with glandular fever (infectious mononucleosis) when compared to placebo or different medications.

Background

Glandular fever is caused by a virus. It spreads in saliva through kissing, coughing and sneezing. Symptoms vary in terms of how severe they are and for how long they persist. While young adults commonly suffer from severe symptoms, some people may have mild symptoms or none. Common symptoms include fever, sore throat, swollen lymph nodes and feeling tired.These symptoms usually last for two to three weeks, but can last for months. Symptom relief and rest are common treatments. Doctors commonly use prednisone, a steroid, to reduce the symptoms of sore throat or enlarged tonsils. However, there is no agreement on its use due to the possibility of little benefit and the chance of side effects.

Study characteristics

Our evidence is current to August 2015. We did not identify any new trials for the update of this review. The previous publication of this review included seven trials with 362 participants. Four trials compared the effect of a steroid to a placebo, one to aspirin, and two trials explored the effects of steroids in conjunction with an antiviral.

The length of treatment varied between a single dose and a 12-day course. The doses used also varied. The length of follow-up varied from short periods (i.e. days or weeks) to longer periods (i.e. six months and 12 months).

Key results

Steroid treatment relieved sore throat in the short term (at 12 hours). The researchers noticed a benefit at two to four days when steroids were used in combination with an antiviral medication, but these findings are limited since researchers assessed them in one or two trials only. The findings on the effect of steroids alone or when used with an antiviral medication for other symptoms were less clear. We are unsure about adverse effects from using steroids. With the exception of two trials, most studies did not set out a prior plan to evaluate the occurrence of side effects, or other adverse events. None of the trials explored adverse effects in the longer term (over years).

Quality of the evidence

The quality of the included trials was generally poor. We cannot know the exact effect of using steroids for glandular fever.

BACKGROUND

Description of the condition

Infectious mononucleosis is also known as glandular fever, mono or the kissing disease. Pathophysiologically, infectious mononucleosis is considered to be a lymphoproliferative disorder that is caused by a virus. It is mostly asymptomatic, but symptoms typically include low-grade fever (although chills are uncommon), nausea and anorexia (without vomiting), lymphadenopathy, pharyngitis, hepatosplenomegaly and fatigue (Cunha 2014; Hellwig 2013).

In terms of aetiology, infectious mononucleosis is most commonly caused by the Epstein-Barr virus (EBV), which is one of the herpes viruses and also known as human herpes virus 4 (HHV-4). EBV occurs worldwide (Hellwig 2013; Luzuriaga 2010). Also, there is a significant genetic factor in the aetiology of infectious mononucleosis supported by the 'circumstantial evidence' from family studies of various Epstein-Barr virus-associated diseases and genome-wide association (GWA). Moreover, evidence of familial aggregation of infectious mononucleosis was found in a recent study (Rostgaard 2014).

Over 95% of adults worldwide have been infected with EBV (Hellwig 2013; Luzuriaga 2010). While the infection in early childhood is often asymptomatic, adolescents or adults usually develop symptoms (Hellwig 2013; Luzuriaga 2010; Maki 1982). In low-income countries or lower socioeconomic status (SES) populations, 80% to 100% of children test positive in serological EBV testing, when they reach the age of six years. Therefore, they generally do not develop symptomatic infectious mononucleosis when they are older. In high-income countries or higher SES populations, only half of children aged between one and five years test serologically positive for EBV; hence a larger number of these people present with symptomatic infectious mononucleosis around the ages of 10 to 30 years (Hellwig 2013; Luzuriaga 2010).

The overall incidence in the United States has been reported to be around 500 cases per 100,000 persons per year (Hellwig 2013). Symptomatic infectious mononucleosis infection has also been reported to be about 30 times higher in white people than in black people in the US (Aronson 2014; Hellwig 2013). However, there are no predisposing differences in terms of gender. There is no evidence that seasonal changes affect its incidence (Hellwig 2013; Luzuriaga 2010). Young adults, for example, college students living in crowded surroundings, have the highest rates of infectious mononucleosis (Aronson 2014; Hellwig 2013; Maki 1982). “Most symptomatic cases occur between the ages of 15 and 24 years” (Walther 2005).

It is transmitted when there is contact with saliva (e.g. kissing), or by sexual intercourse, blood transfusion or infected equipment, however, transmission actually occurs in less than 10% of cases (Aronson 2014; Hellwig 2013). As a large proportion of the population is already seropositive for EBV precautions are not needed to prevent transmission, as it is not a particularly infectious disease (Hellwig 2013).

EBV infection results in a chronic, usually lifelong infection, as the virus resides in cells known as memory B cells, where it may later reactivate and spread through oropharyngeal secretions (Hellwig 2013; Luzuriaga 2010; Souza 2005). "Infectious mononucleosis is self-limiting and typically lasts for two to three weeks" (Berger 2003). Nevertheless, symptoms can last for weeks and occasionally months, leading to discomfort and affecting the educational and professional life aspects of the patients (Candy 2002). "Fatigue is the most common prolonged symptom" (Candy 2002), and “infectious mononucleosis is a risk factor for chronic fatigue syndrome" (White 1995).

Young children infected with EBV commonly have no or only mild symptoms, which may remain undiagnosed. However, older children, teens and young adults commonly exhibit signs and symptoms. The disease begins with a prodromal period of symptoms such as headache, anorexia and fatigue for one to two weeks before the classical symptoms of the disease manifest (Aronson 2014; Hellwig 2013).

Although "EBV remains latent within cells” (Papesch 2001), infectious mononucleosis is considered an acute and transient disease; however, the severity and duration of symptoms vary widely. Some symptoms such as difficulty in breathing due to severe pharyngeal enlargement may require hospitalisation. In recent decades, the number of patients with infectious mononucleosis who require hospitalisation, especially adolescents and young adults, has increased in England and the US, even though there is no evidence of changes in its virulence (Tattevin 2006).

Description of the intervention

Symptom relief and rest are commonly recommended treatments for infectious mononucleosis (AAFP 2000; Brown 2001; Candy 2005; Cohen 2001). Steroids have been used for their anti-inflammatory effects. Prescribing high-dose, short-term steroid therapy (that is, oral prednisolone 40 mg to 60 mg/day, tapered over a three- to 14-day period) for infectious mononucleosis can be traced back to the 1950s. At that time, a number of reports based on single cases or small series of people noted the favourable effect that steroids had on acute symptoms, such as sore throat (Bender 1953; Creditor 1959; Doran 1953; Fiese 1953; Frenkel 1956; Mandel 1955; Mason 1958). Steroids were also reported to be effective in treating complications or accompanying conditions, such as thrombocytopenia (Doran 1953), hepatitis (Bender 1953), pericarditis (Bender 1953), myocarditis (Bender 1953), and encephalitis (Fiese 1953). More recently, steroid treatment has been combined with antivirals, such as acyclovir, with the aim of enhancing their effect (Tynell 1996).

How the intervention might work

The potential long duration of infectious mononucleosis and the age group most likely to be symptomatic is perhaps key in the prescription of steroids for symptom control. As it can affect adolescents and young adults at a time in their school or academic careers when they are expected to be continually productive, there is often a distinct personal need to resume normal life as soon as possible. In addition, it is a time in life where sports and social activities can be a major aspect of everyday life (Candy 2011).

The anti-inflammatory and immunosuppressive properties of glucocorticoids are due to three main molecular mechanisms: the direct genetic expression modifying effects by first binding to glucocorticoids receptors then the binding of the previous combination to the GREs (glucocorticoid-responsive elements), the indirect genetic effects by the interactions of glucocorticoid

receptors with other transcription factors, and lastly, the effects on second-messenger cascades. However, because these effects are not exclusive to inflammation signalling and affect physiological signalling as well, one should bear in mind that using glucocorticoids in treatment often accompanied with adverse effects (Rhen 2005).

However, since the 1960s, when formal trials of their effects began, the use of steroids for infectious mononucleosis has been considered controversial. Much of this controversy is due to the potential for adverse events and long-term effects in a disease that is largely self-limiting (Candy 2011). In particular:

1. there are anecdotal reports of other adverse events associated with steroid use, such as myocarditis and encephalitis (Andersson 1988a); given that these are also rare complications of EBV itself, the risks and benefits of steroids need to be determined accurately;
2. steroids suppress the normal immune response, which may predispose the person to a secondary infection, such as peritonsillar abscess (Handler 1979; Johnsen 1981; Portman 1984);
3. there are unknown long-term effects of using an immunomodulator for a virus that establishes intracellular latency; one possible effect is to contribute to the subsequent development of EBV-associated malignancies, such as Burkitt and Hodgkin lymphomas (Jenson 2000).

In addition, the effectiveness of steroids for symptom control is unclear for some indications, including fever, sore throat and swollen lymph glands. Trial results for these symptoms are conflicting while for other indications (enlarged liver and fatigue) data are scant. There is also the cost of drug therapy to be considered, in particular if the steroids are used in combination with antiviral drugs (Candy 2011).

Why it is important to do this review

This is an update of a Cochrane review first published in 2006 (Candy 2006), updated in 2009 (Candy 2009), and updated again in 2011 (Candy 2011).

There are no universal criteria for the use of steroids in infectious mononucleosis. They are generally used for severe complications, particularly compromised airways (Auwaerter 1999; Ganzel 1996; McGowan 1992; Tsikoudas 2006), but there are reports of practitioners treating all symptomatic patients with steroids (Auwaerter 1999; Burton 2000; Straus 1993; Thompson 2005).

OBJECTIVES

The objectives of the review were to determine the efficacy and safety of steroid therapy versus placebo, usual care or different drug therapies for symptom control in infectious mononucleosis.

Specifically, whether steroid therapy

1. reduces the severity and duration of ill health (measured by level of functional disability, time in hospital, inability to work);
2. reduces the severity and duration of common symptoms, including fever, sore throat, swollen lymph glands, enlarged liver and spleen, and fatigue;
3. is an acceptable treatment, measured by the number of side effects/adverse events, trial drop-out rates and patient satisfaction.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) examining the effects of steroids in infectious mononucleosis.

Types of participants

Participants of any age with documented symptomatic infectious mononucleosis; that is, clinical and laboratory diagnoses. We gave priority to trials using virological testing for EBV-specific immunoglobulin M (IgM), but we also included studies using monospot or Paul-Bunnell tests for heterophil antibodies. We included all healthcare settings. We noted the severity of symptoms.

Types of interventions

RCTs that evaluated the effects of a steroid therapy of any dosage, duration or route of administration. We included placebo-controlled trials and trials that compared steroids with usual care (that is to say, those allocated to the control condition did not receive placebo) or other active treatments.

Types of outcome measures

Primary outcomes

1. Overall improvement in health, measured by physical and psychological functional ability, time in hospital, time taken to return to normal activities, patient self report of health and relapse rates.
2. Duration and severity of common symptoms, including fever, sore throat, swollen lymph glands, hepatic and splenic involvement, and fatigue, measured by subjective reports, validated scales, clinical findings and/or laboratory parameters.

Secondary outcomes

1. Side effects, mortality and adverse events, measured by subjective reports, clinical findings and laboratory parameters.
2. The presence or absence of severe complications of glandular fever (that is to say, respiratory obstruction, autoimmune cytopenias, severe cholestasis and chronic fatigue).
3. Patient acceptability of therapy, measured by drop-out rate, patient reports and satisfaction measures.

Search methods for identification of studies

Electronic searches

For this 2015 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 7), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (2011 to August 2015) and EMBASE (2011 to August 2015).

B Candy and M Hotopf ran the previous update search in March 2011. The search covered the Cochrane Central Register of Controlled Trials (CENTRAL 2011, Issue 1), MEDLINE (March 2008 to

February week 3, 2011) and EMBASE (March 2008 to February 2011). For details of earlier searches see Appendix 1.

We used the following search strategy to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE: sensitivity- and precision-maximising version (2008 revision), Ovid format (Lefebvre 2011). We adapted the search terms for searching EMBASE (Appendix 2).

MEDLINE (Ovid)

1 Infectious Mononucleosis/
2 infectious mononucleosis.tw.
3 glandular fever.tw.
4 Epstein-Barr Virus Infections/
5 Herpesvirus 4, Human/
6 (epstein barr or epstein-barr or ebv).tw.
7 or/1-6
8 exp Steroids/
9 steroid*.tw.
10 exp Adrenal Cortex Hormones/
11 corticosteroid*.tw.
12 glucocorticoid*.tw.
13 adrenocorticosteroid*.tw.
14 exp Anti-Inflammatory Agents/
15 (anti-inflammator* or antiinflammator*).tw.
16 Adrenocorticotropic Hormone/
17 (corticotropin* or prednisone* or prednisolone* or cortisone* or hydrocortisone* or dexamethasone* or dexamethasone* or betamethasone* or betametasone* or paramethasone*).tw,nm.
18 or/8-17
19 7 and 18

Searching other resources

For this 2015 update we searched the following trials registries for completed and ongoing trials: the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) and ClinicalTrials.gov (https://clinicaltrials.gov/), but we did not find any completed or ongoing trials that met the inclusion criteria for the review.

Data collection and analysis

Selection of studies

For this 2015 update, three review authors (AH, MFA, YN) independently evaluated citation titles and abstracts identified from the electronic databases using the inclusion criteria. We obtained and assessed the full text of all potentially relevant studies. We resolved differences over study selection by discussion.

For the initial version of this review, study selection was performed by two review authors who independently evaluated citation titles and abstracts identified from the electronic databases using the inclusion criteria (Candy 2011). One of the review authors (BC) obtained the full text of all potentially relevant studies for assessment, with a sub-sample checked by the second review author (MH). Differences over study selection were resolved by discussion.

Data extraction and management

For this 2015 update, we did not find any additional/new studies to include. We had planned that two review authors (AH, MAA) would extract data from all included studies. In addition, to ensure reliability, three review authors (MFA, MFAH and YN) would independently extract data from a random sample of these studies, comprising 10% of the total. Again, we planned to discuss any disagreement, to document decisions and, if necessary, to contact the trial authors for clarification. We planned to extract data presented only in graphs and figures whenever possible, but we would only include the data if two review authors independently had the same result. We planned to contact trial authors through an open-ended request in order to obtain missing information or for clarification, whenever necessary.

The review authors for the initial version of this review extracted data from included studies using a standardised form. They captured:

1. methods: design, randomisation, blinding, inclusion and exclusion criteria, duration of follow-up;
2. sample: population size and characteristics (age, gender and duration of infectious mononucleosis), recruitment and drop-out rates;
3. intervention and control: name of drug(s), route of administration and dose, agent and dose of co-interventions/control(s) and time and duration of therapy; and
4. outcome measures: duration of illness, hospital stay, time to return to usual activities, functional status and severity and duration of symptoms. For dichotomous data, they extracted the number of participants who experienced the outcome in each group and the total number in each group. For continuous data, they extracted the number of participants, the mean value and standard deviation for the outcome in each group.

Assessment of risk of bias in included studies

For this 2015 update, we did not find any additional/new studies to include. We planned that the review authors would independently assess the quality of included trials according to criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to assess the quality of included trials using the Cochrane Collaboration's 'Risk of bias' tool. The instrument assesses six domains:

1. randomisation allocation sequence generation;
2. concealment of allocation sequence;
3. blinding of participants, personnel and outcome assessors;
4. level of completeness of outcome data;
5. freedom from selective reporting; and
6. freedom from other bias.

We planned to assess each domain according to whether the criteria for that domain were met (i.e. low risk of bias), not met (i.e. high risk of bias) or if we were not certain because of insufficient reporting (i.e. unclear bias).

Based on the quality criteria, we planned for subgroup meta-analysis where we would divide trials into the following three categories:

1. all quality criteria were met: low risk of bias;

2. one or more of the quality criteria were only partly met: moderate risk of bias; and
3. one or more criteria were not met: high risk of bias.

Measures of treatment effect

We planned to measure treatment effect on symptoms by using either dichotomous data or an ordinal rating scale. If dichotomous data had been reported, we planned to generate odds ratios (ORs) and their 95% confidence intervals (CI). We planned to assess effects measures for ordinal data as continuous data. We planned to generate the mean difference (MD) for ordinal data if the data were provided as a mean and standard deviation. If different scales were used to measure the same outcome, we planned to use the standardised mean difference (SMD), together with 95% CIs, to pool data.

Unit of analysis issues

For non-standard design RCTs, such as cross-over trials and cluster-RCTs, we planned to follow the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For example, with cluster-RCTs we planned to check for unit of analysis errors and sufficient data being available to recalculate the results using the appropriate unit of analysis (Higgins 2011).

Dealing with missing data

When the standard deviation (SD) for continuous outcomes was missing, we planned to contact the trial authors. When contact with the trial author was not possible, we planned to calculate or impute it using relevant data, only when a minority of the trials (to be combined in a meta-analysis) had a missing SD (Higgins 2011). When we undertook such imputation, we planned to perform sensitivity analyses to assess its impact on combined analyses.

Missing studies can result from an inadequate search for data or from publication bias in that papers with negative findings are less likely to be published. How we planned to deal with this is detailed in the Assessment of reporting biases and Search methods for identification of studies sections.

We planned to report attrition rates, per trial, in the 'Risk of bias' tables. This included, if available, per trial arm reasons for attrition and whether the trial stated any re-inclusions performed in analyses. We did not plan to undertake any imputation for missing participant data.

When the standard deviation (SD) for continuous outcomes was missing, we planned to contact the trial authors. When contact with the trial author was not possible, we planned to calculate or impute it using relevant data, only when a minority of the trials (to be combined in a meta-analysis) had a missing SD (Higgins 2011). When we undertook such imputation, we planned to perform sensitivity analyses to assess its impact on combined analyses.

Assessment of heterogeneity

We planned to assess the included studies for clinical homogeneity. We did not plan to pool data across trials when we found diversity in diagnostic criteria, exposure (treatment), outcomes and length of follow-up.

Assessment of reporting biases

For this 2015 update, we planned to assess the potential for publication bias in funnel plot analysis when we had sufficient and appropriate trial data to combine.

Data synthesis

For this 2015 update, we planned to complete a meta-analysis when possible. When meta-analysis was not possible because of heterogeneity between trials, we planned to use systematic approaches to synthesising the findings of multiple studies. We planned to present the findings by outcome from within these groups.

Subgroup analysis and investigation of heterogeneity

For this 2015 update, we planned to assess statistical heterogeneity between trials using the Chi^2 test and I^2 statistic (we considered a Chi^2 P value of less than 0.05 or an I^2 statistic value equal to or more than 50% to indicate substantial heterogeneity) when meta-analysis was possible. We planned to undertake subgroup analyses to investigate its possible sources when substantial heterogeneity was identified. We planned to undertake subgroup and sensitivity analysis to explore whether the overall effect varied with different trial populations and in the nature and content of the interventions, when meta-analysis was possible.

Sensitivity analysis

We planned to perform sensitivity analysis on the outcome results following the guidance in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). However, the sensitivity analysis could not be performed because there was only one study in every outcome reported.

RESULTS

Description of studies

For this 2015 update, we found no new trials that met the inclusion or exclusion criteria.

Results of the search

In our 2015 update we obtained a total of 186 search results from the electronic searches. We found all of these citations to be irrelevant and none of them were eligible for inclusion.

In the previous 2011 update, the authors obtained a total of 36 search results from the electronic searches. None of these citations were eligible for inclusion.

For the initial version of this review, the authors obtained a total of 1613 abstracts and citations from earlier electronic searches. From the screening of titles and abstracts, they found 16 studies to be potentially relevant. On retrieval of the full text nine studies were not RCTs.

Included studies

We included no additional studies in this 2015 update. Seven RCTs were included in the initial version of this review (Bolden 1972; Collins 1984; Klein 1969; Prout 1966; Roy 2004; Simon 2003; Tynell 1996). See Characteristics of included studies table.

Setting

Four trials were conducted in the USA, two in Europe and one in Canada. Five trials report on single-centre evaluations; two were two-centred evaluations (Prout 1966; Tynell 1996). Four trials were conducted within university/college health services; two within general hospital services, one in a paediatric emergency department (Roy 2004), and one in an infectious diseases department (Tynell 1996). In the other three trials, the sample participants were hospitalised (Bolden 1972; Prout 1966; Tynell 1996). One trial did not report the healthcare location (Simon 2003). All trials were undertaken by researchers either located at universities or in hospitals. In one trial, two of the authors were from a drug company (GlaxoSmithKline) (Simon 2003).

Participants

Diagnosis of infectious mononucleosis was based on various laboratory parameters, clinical expression and symptoms. The laboratory tests used included the monospot test (Collins 1984; Roy 2004), the heterophil test (Bolden 1972; Klein 1969; Prout 1966), the reversal of the ratio between lymphocytes and polymorphonuclear cells in the blood smear (Prout 1966), EBV titre (Bolden 1972; Collins 1984; Roy 2004; Simon 2003), and white blood cell and differential count (Bolden 1972; Collins 1984; Klein 1969). It should be noted that the earlier studies identified were undertaken before the highly specific EBV titre test was available.

The average time from onset of symptoms to initiation of trial treatment was not reported in most trials. In one trial participants were excluded if they had been ill for more than seven days (Tynell 1996). Time from study baseline assessment to initiation of trial treatment was reported in three trials; one treatment was given immediately (Roy 2004), and in two the average was around three days (Klein 1969; Prout 1966).

Age in three trials ranged from adolescents (aged from 14 or 18 years) to young adults (up to 30 years of age) (Collins 1984; Prout 1966; Tynell 1996). Two trials did not report the participants' ages. However, they were likely to be mostly young adults, as the participants were recruited from student university health services (Bolden 1972; Klein 1969). Two trials explored the effects in younger samples, aged two to 18 years (Simon 2003), and eight to 18 years (Roy 2004). Three trials did not report the gender of the participants. In the trials that reported gender, there were consistently more males than females.

Intervention

Two trials explored the effects of steroids in conjunction with an antiviral: these were acyclovir (Tynell 1996), and valacyclovir (Simon 2003). The steroids evaluated were prednisone (Bolden 1972; Collins 1984), prednisolone (Simon 2003; Tynell 1996), paramethasone (Klein 1969; Prout 1966), and dexamethasone (Roy 2004).

The duration of treatment varied. In four trials the tapered schedules were for more than five days. One trial involved one dose (Roy 2004), and another used a schedule that was adjusted to the individual participant's responsiveness to treatment (Prout 1966). In Bolden's study there were two intervention arms: one a six-day and one a 12-day schedule. Dosages varied from a starting dose of 5 mg prednisone (or equivalent to) to 25 mg prednisone (or equivalent to). The dexamethasone trial used a dose of 0.3 mg per kg. Six trials were placebo-controlled, the other used aspirin as the comparative treatment (Bolden 1972). Six trials used oral treatments. In one trial intravenous treatment was used if participants had difficulty swallowing (Tynell 1996). The seventh trial did not specify how the treatment was administered (Simon 2003).

Three trials reported additional treatments provided to all participants (Bolden 1972; Klein 1969; Roy 2004). In one trial, all participants had a 12-day course of phenoxymethyl penicillin and partial bed rest until apyrexial, with an emphasis placed on early mobilisation (Bolden 1972). Another provided a penicillin course, aspirin and throat gargles to all participants (Klein 1969). In another, participants were encouraged to use paracetamol for co-analgesia (Roy 2004).

Outcomes and follow-up assessment

The effectiveness of steroids was evaluated on a range of symptoms and outcomes. The most evaluated outcome was sore throat (Collins 1984; Klein 1969; Prout 1966; Roy 2004; Tynell 1996). Other outcomes that were reported by more than one trial were duration of fever (Bolden 1972; Prout 1966; Roy 2004), fatigue (Collins 1984; Simon 2003), duration of absence from work because of sickness (Collins 1984; Tynell 1996), psychological morbidity (Bolden 1972; Collins 1984), and the rate of return to normal activities (Collins 1984; Roy 2004).

One trial set out a priori to evaluate adverse effects or complications relating to steroids (Collins 1984). Adverse effects occurring were reported in one trial (Roy 2004).

The length of follow-up varied from shorter-term: three days (Klein 1969), seven days (Roy 2004), 20 days (Simon 2003), and four weeks (Collins 1984), to longer-term: six months (Tynell 1996), and 12 months (Bolden 1972). One trial did not specify the actual length of follow-up but reported follow-up for more than 30 days (Prout 1966).

Excluded studies

There were no additional excluded studies in this 2015 update. The previous publication of this review excluded nine studies, all of which were not RCTs. See Characteristics of excluded studies table.

Risk of bias in included studies

The risk of bias of the previously included studies is summarised in Figure 1, and Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

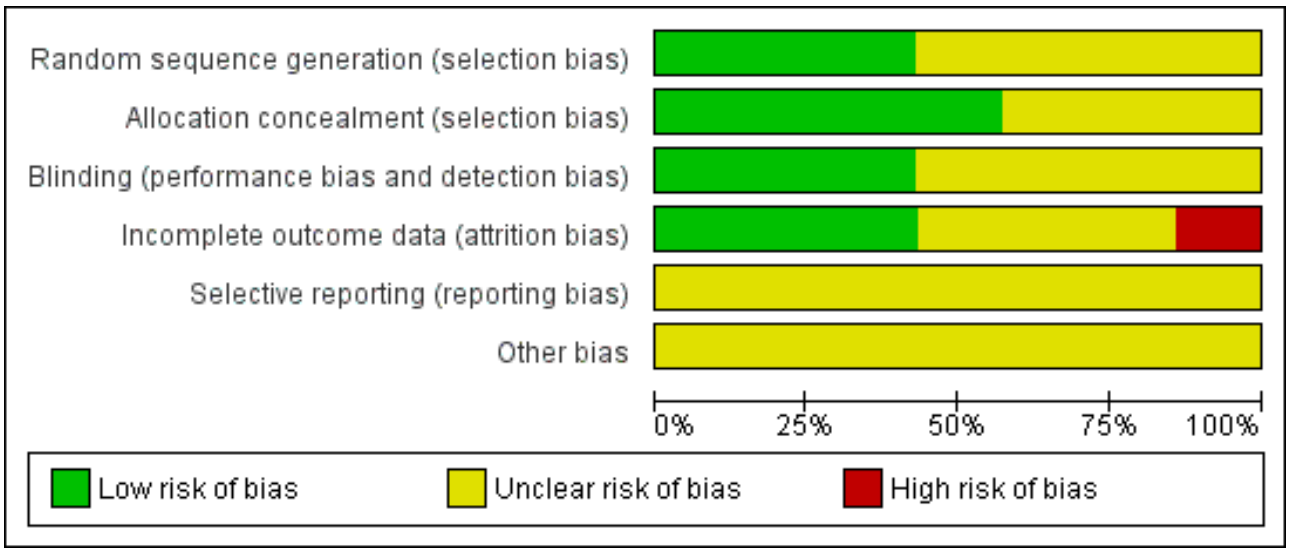
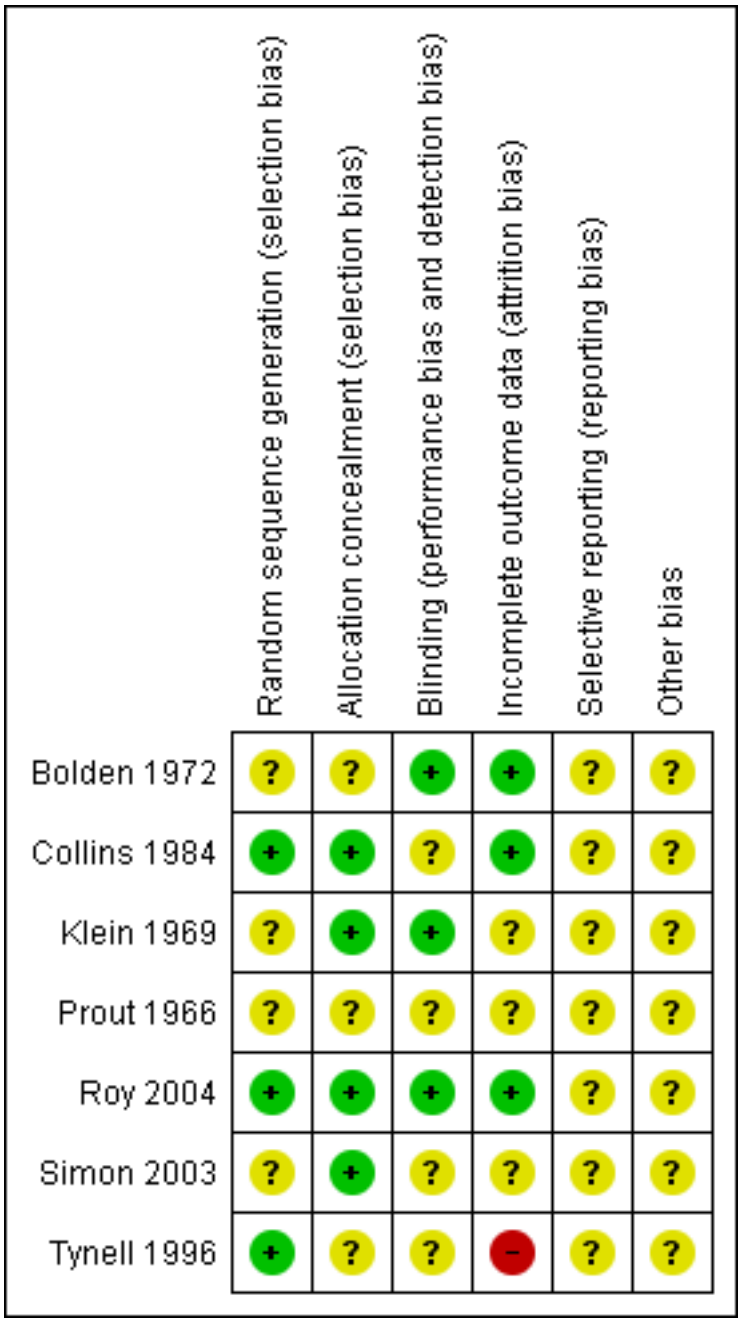


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Three trials did not adequately describe the sequence generation for randomisation (Bolden 1972; Simon 2003; Tynell 1996). Four trials provided adequate details on allocation concealment (Collins 1984; Klein 1969; Roy 2004; Simon 2003).

Blinding

All trials were double-blinded but four were not specific as to who was blinded (that is to say, participant, clinician or/and outcome assessor) (Collins 1984; Prout 1966; Simon 2003; Tynell 1996).

Incomplete outcome data

Loss to follow-up was under-reported in four trials, making it difficult to exclude attrition bias (Klein 1969; Prout 1966; Simon 2003; Tynell 1996).

Selective reporting

The risk of selective reporting in the included trials was unclear.

Other potential sources of bias

There is no clear evidence of any other potential risk of bias in the included studies.

Effects of interventions

The initial version of this review included seven trials; the most recent trial was published in 2003. Across the seven trials there was little overlap in steroid treatment schedules, diagnostic criteria or outcomes assessed and some data were inadequately reported. In other words, the trials were heterogeneous in their outcome assessment and how this was reported, therefore we did not combine the results of the trials.

Steroid as a monotherapy

Five trials assessed the effectiveness of a steroid as a monotherapy (Bolden 1972; Collins 1984; Klein 1969; Prout 1966; Roy 2004).

Primary outcomes

1. Overall improvement in health

Physical and psychological functional ability

Three trials reported assessments relating to overall improvement; none fully reported the data (Bolden 1972; Collins 1984; Prout 1966). In two trials there was no significant difference in psychological morbidity between the steroid group and the comparison group (Bolden 1972; Collins 1984).

Time in hospital

One trial reported a reduced hospital stay in the steroid group (three days versus six days in the comparison group) (Prout 1966).

Return to normal activities

Two trials assessed the rate of return to normal activities (Collins 1984; Roy 2004); we did not combine the findings from the trials as one was a one-dose trial (Roy 2004), and the other a week's treatment (Collins 1984). In three of four assessments there was no significant difference found between those in the intervention group and the comparison group.

In one trial more participants in the steroid group than the control group had returned to normal activities at one week (odds ratio (OR) 5.13, 95% confidence interval (CI) 1.23 to 21.36) (Analysis 1.1), but at four weeks return to normal activities was not significantly different (OR 0.92, 95% CI 0.17 to 4.89) (Collins 1984) (Analysis 1.2). The other trial found at one week that the rates were not significantly different between the steroid and placebo group (OR 2.14, 95% CI 0.52 to 8.81) (Roy 2004) (Analysis 1.3). One of the trials also explored sickness absence from school (Collins 1984). It found that for participants who were absent at the start of the trial (n = 21) the number of participants returning at one week was not significantly different between those in the steroid group and those in the comparison group (OR 3.33, 95% CI 0.47 to 23.47) (Analysis 1.4).

Relapse

One trial reported that one participant in the comparison group and one in the active treatment group relapsed (Bolden 1972). In another trial, four participants in the active drug group relapsed after treatment (Prout 1966).

2. Duration and severity of common symptoms

Fever

Two trials assessed duration of fever (Bolden 1972; Prout 1966). In two assessments out of four, steroids reduced fever.

In one trial, steroids in comparison with aspirin did not reduce the number of days with a fever in participants on a six-day course, but did on the 12-day course (mean difference (MD) -2.69, 95% CI -8.72 to 3.34 (Analysis 3.1); MD -3.89, 95% CI -7.05 to -0.73 (Analysis 3.2). In the other trial, for fever duration between those in the active group compared to the comparison group, the results were different between the two research centres (12.8 versus 8.2 days; 1.99 versus 3.7 days) (Prout 1966).

Sore throat

Four trials evaluated the effectiveness of steroids in the treatment of sore throat (Collins 1984; Klein 1969; Prout 1966; Roy 2004). We did not combine the findings from the trials because of heterogeneity in outcome assessment and in dose schedules.

At 12 hours two trials found that steroids significantly relieved sore throat discomfort compared to placebo (one-dose OR 4.20, 95% CI 1.08 to 16.32; eight-day course OR 21.00, 95% CI 1.94 to 227.20, respectively) (Analysis 1.5; Analysis 1.6).

At subsequent follow-ups there was no significant difference between placebo and steroid therapy: at 24, 36, 48, 60 and 72 hours (OR 2.85, 95% CI 0.78 to 10.47 (Analysis 1.7); OR 6.00, 95% CI 1.02 to 35.37 (Analysis 1.8); OR 1.00, 95% CI 0.29 to 3.48 (Analysis 1.9); OR 0.53, 95% CI 0.10 to 2.84 (Analysis 1.10); OR 0.80, 95% CI 0.18 to 3.57 (Analysis 1.11), respectively); at one, two and four weeks (OR 0.95, 95% CI 0.06 to 16.31 (Analysis 1.12); OR 1.50, 95% CI 0.34 to 6.56 (Analysis 1.13); OR 1.42, 95% CI 0.24 to 8.26 (Analysis 1.14), respectively).

Other symptoms: fatigue, anorexia, swallowing, pharyngeal secretions and ability to concentrate

One trial assessed other symptoms (Collins 1984). At one and four weeks there was no significant difference in improvement in fatigue (OR 0.40, 95% CI 0.12 to 1.35) (Analysis 1.15); OR 0.79, 95% CI 0.19 to 3.24 (Analysis 1.16), respectively). There were also no statistically significant differences between those in the actively treated group and those in the control group at one and four weeks following treatment in: anorexia (OR 0.67, 95% CI 0.14 to 3.35) (Analysis 1.17); (OR 2.86, 95% CI 0.28 to 29.56) (Analysis 1.18); swallowing (OR 2.00, 95% CI 0.31 to 12.89) (Analysis 1.19); (OR 0.59, 95% CI 0.11 to 3.20) (Analysis 1.20); pharyngeal secretions (OR 0.30, 95% CI 0.07 to 1.32) (Analysis 1.21); (OR 0.74, 95% CI 0.09 to 5.89) (Analysis 1.22); and ability to concentrate (OR 0.48, 95% CI 0.11 to 2.07) (Analysis 1.23); (OR 0.98, 95% CI 0.18 to 5.28) (Analysis 1.24).

Secondary outcomes

1. Side effects, mortality and adverse events

None of the trials planned a priori to assess adverse events. One trial reported possible complications relating to the steroid treatment, with one participant developing an acute onset of diabetes mellitus with acidosis. Another participant (who initially improved) developed a peritonsillar cellulitis, requiring hospitalisation and active treatment (Collins 1984).

2. The presence or absence of severe complications of glandular fever

One trial set out a priori to explore whether steroids decrease or increase the incidence of complications of infectious mononucleosis, although it did not report evidence either way in the results (Prout 1966). In one trial, four ambulant participants were admitted to hospital: three were in the control group

(Roy 2004). The fourth participant in the steroid-treated group was admitted for severe pharyngitis and dehydration. She later developed respiratory distress and was found to have a pleural effusion and empyema and was admitted to a paediatric intensive care unit for two weeks. Empyema is a rare complication, therefore the association of steroids with this complication is unclear.

3. Patient acceptability of therapy, measured by drop-out rate, patient reports and satisfaction measures

Patient acceptability of treatment was not evaluated in any of the trials.

Steroid as an adjunct therapy

Two trials assessed the effectiveness of steroids as an adjunct to an antiviral drug (Simon 2003; Tynell 1996).

Primary outcomes

1. Overall improvement in health

Physical and psychological functional ability

In one trial the median duration of sickness absence was similar in both groups (treated 13 days (range two to 42 days) versus 11 days (range one to 98 days) in the placebo group (Tynell 1996)).

2. Duration and severity of common symptoms

Fever

One trial assessed duration of fever (Simon 2003). It found at 20 days a non-significant improvement in the duration of fever in the treated group (OR 3.00, 95% CI 0.68 to 13.31) (Analysis 2.1).

Sore throat

One trial assessed sore throat (Tynell 1996). It found that between two and four days fewer participants in the actively treated group reported a sore throat (OR 0.31, 95% CI 0.09 to 1.08) (Analysis 2.2).

Fatigue

One trial assessed fatigue (Simon 2003). It found that at 20 days steroids improved resolution of fatigue (OR 8.00, 95% CI 1.52 to 42.04) (Analysis 2.3).

Weight loss

In the trial that assessed weight loss there was no significant difference between the intervention and comparison group (at day 14, OR 0.66, 95% CI 0.26 to 1.66) (Tynell 1996) (Analysis 2.4).

Combined symptom assessment scores

In combined symptom assessment scores the trial found no significant differences between those in the treatment group and those in the comparison group.

Combined score for symptoms of sore throat, fatigue, swollen glands, nausea and chills (OR 9.33, 95% CI 0.96 to 90.94) (Simon 2003) (Analysis 2.5) .

Combined score for symptoms of sore throat, stomach ache, fatigue, swollen glands, headache, vomiting, rash, nausea, chills, swollen eyes, runny nose, cough and sweats (OR 2.00, 95% CI 0.38 to 10.51) (Simon 2003) (Analysis 2.6).

Secondary outcomes

1. Side effects, mortality and adverse events

One trial set out to measure safety; it documented no major adverse events occurring in either trial arm (Tynell 1996).

2. The presence or absence of severe complications of glandular fever

The occurrence of severe complications of infectious mononucleosis was not reported in either of the trials.

3. Patient acceptability of therapy, measured by drop-out rate, patient reports and satisfaction measures

Patient acceptability of treatment was not evaluated in either of the trials.

DISCUSSION

Summary of main results

For this 2015 update, we did not identify any new randomised controlled trials (RCTs) on the effect of steroid treatment on infectious mononucleosis.

The initial version of this review sought to determine the evidence for the efficacy of steroid treatment for symptom relief in infectious mononucleosis. Seven trials were identified, with the most recent being published in 2003. Across the seven trials there was little overlap in steroidal treatment schedules, diagnostic criteria or outcomes assessed and some data were inadequately reported.

The initial version of this review found evidence from two trials that steroids as a monotherapy are effective in reducing the symptoms of sore throat initially but not after 12 hours of treatment. Evidence on other symptoms was more limited. In two trials, three participants in the steroidal group developed severe complications that may have been related to steroidal therapy: specifically, in one participant empyema, in another peritonsillar cellulitis and in the third acute onset diabetes mellitus with acidosis.

Overall completeness and applicability of evidence

This 2015 update has not provided additional information. Results of the initial version of this review must be interpreted in light of the limitations of this review. In particular, the small number of studies and participants (especially as few studies included children in the early teenage years and younger, where infectious mononucleosis is not uncommon). Also, many of the results resulted in wide confidence intervals, probably due to small sample sizes, making it difficult to be sure that the sample sizes studied were adequate to exclude confidently the possibility of false positive results or negative results. Moreover, the reported differences in findings between trials post 12 hours may be related to lack of power, or also to differences in the population studied, diagnostic criteria and steroid treatment. For instance, the study that found no effects after 12 hours used a lower dose of steroids. Evidence from another study suggests that steroids are effective in combination with acyclovir at two to four days (Tynell 1996).

Quality of the evidence

Various methodological limitations to the evidence provided in the included trials were noted in the initial version of this review. Not all trials fully reported key methodological characteristics, including randomisation sequence generation and allocation concealment,

who was blinded and loss to follow-up. The two studies that explored the earlier effects of steroids on relief from sore throat were the only studies that presented positive findings to state a primary outcome. The other three trials that reported positive findings did not specify a primary outcome or which specific symptoms they were evaluating. This suggests that a multiple hypothesis analysis was undertaken.

Where outcomes overlapped, we did not pool trial results as the trials were heterogeneous in key characteristics. One reason for such heterogeneity is that these studies span nearly half a century, during which time diagnostic tests improved, leading some trials to include participants who, based on current virological tests, would not have been diagnosed with glandular fever. In addition to variable definitions of infectious mononucleosis, symptom severity at entry (although it was not always specified) is likely to have differed, as some trials only used hospitalised, as opposed to ambulatory, participants. In some trials, a participant's symptoms may have been less severe as the trial waited for a laboratory diagnosis before active treatment was started.

Studies were also heterogeneous in treatment: steroid therapy varied in dosage and type.

Another important limitation is that, apart from two trials, most studies did not set out a priori to evaluate the incidence of side effects, complications relating to infectious mononucleosis or other adverse events. None of the trials explored adverse effects in the longer term (over years).

Potential biases in the review process

We did not have previous knowledge of the past work in this area so any new RCTs found after the initial version of this review could not be biased in terms of how we managed or reported data. We do not feel that we have excluded any data that others would have used.

Agreements and disagreements with other studies or reviews

This updated version of the review essentially agrees with the previous publication of this review (Candy 2011).

Authors' conclusions

AUTHORS' CONCLUSIONS

Implications for practice

There is not enough evidence to the efficacy of corticosteroid treatment for symptom control in people with otherwise uncomplicated glandular fever. Furthermore, there is no compelling reason to select corticosteroids over other effective therapeutic agents for short-term relief of sore throat.

Implications for research

The initial version of this review did not provide a clear impetus for further primary research studies to measure overall improvement effects or common symptoms, in particular fever (Candy 2011). The value of further research is clearer for relief of sore throat, if short-term benefit is felt to be clinically important. Any further evaluations of the effectiveness of steroids for symptom control in people with infectious mononucleosis need to evaluate what would be clinically significant effects, and to record adverse effects and complications in the short and long term.

For this 2015 update we agree with the authors of the initial version of this review.

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CHARACTERISTICS OF STUDIES

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

Bolden 1972

Methods	Double-blind randomised controlled trial
Participants	38 participants Eligibility criteria: the laboratory findings were reviewed 3 months after clinical diagnosis and the diagnosis was only confirmed if 2 of the following were/had been present: (1) The participant needed to be clinically suffering from generalised swollen lymph glands, general malaise a sore throat or swollen spleen (2) The heterophil antibody test became positive within 3 weeks (3) The differential white count and abnormal mononuclear cells were suggestive of glandular fever
Interventions	Intervention 1: oral prednisone tapered 6-day course Intervention 2: oral prednisone tapered 12-day course Control: aspirin
Outcomes	Duration of fever, psychiatric score, rate of relapse
Notes	—
Risk of bias	

Bolden 1972 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Does not state how they generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Clinician and participant blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	26/38 completed trial. 7 of the 12 participants that were withdrawn from the trial had been misdiagnosed. Another 3 were withdrawn as no diagnosis was reached for their symptoms. The other 2 participants were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	—
Other bias	Unclear risk	—

Collins 1984

Methods	Double-blind, randomised, placebo-controlled trial
Participants	47 participants Eligibility criteria: by attending physician and confirmed by a positive monospot test
Interventions	Intervention: oral prednisolone 60 mg tapered over 6 days Control: placebo
Outcomes	Resolution of symptoms of fatigue and sore throat. Time of absence from work/school, rate of return to social activity, level of pharyngeal secretions and ability to concentrate
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	States "predetermined randomisation schedule"
Allocation concealment (selection bias)	Low risk	Schedule held by pharmacy
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Does not state who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	44/47 completed the trial

Collins 1984 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	—
Other bias	Unclear risk	—

Klein 1969

Methods	Double-blind, randomised, placebo-controlled trial
Participants	24 participants Eligibility criteria: at initial interview symptoms and physical findings of glandular fever (does not specific what these are) plus laboratory findings of white cell differential count showing the lymphocytes to compromise 50% of more of the total count with atypical lymphocytes being noted. In addition a repeat blood test 72 to 96 hours later having similar results or a heterophil titre in excess of a 1:56 dilution. The authors state that as the study progressed the 'mono test' (not clear what this refers to) became available and was also performed at the initial visit
Interventions	Intervention: oral corticosteroids, either prednisolone, prednisolone or cortisone. The intake equalled 10 mg starting dose of steroid tapered over 8 days Control: placebo
Outcomes	Duration of sore throat
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomisation code"
Allocation concealment (selection bias)	Low risk	Randomisation code held by pharmaceutical company
Blinding (performance bias and detection bias) All outcomes	Low risk	Physician and participant
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	—
Selective reporting (reporting bias)	Unclear risk	—
Other bias	Unclear risk	—

Prout 1966

Methods	Double-blind, randomised, placebo-controlled trial
Participants	82 participants

Prout 1966 *(Continued)*

	Eligibility criteria: clinical features of fever, sore throat, enlargement of cervical lymph nodes and laboratory parameters of reversal of the ratio between lymphocytes and polymorphonuclear cells in the blood smear, presence of 'atypical' cells in over 5% of the blood smear and positive agglutination in dilutions of 1:64 or greater
Interventions	Intervention: oral paramethasone acetate 2 mg (states equivalent to 5 mg prednisone). The initial dose was 8 tablets decreasing by 1 tablet a day so long as improvement continued Control: placebo
Outcomes	Duration of fever, hospital stay and sore throat
Notes	Allocation concealment: adequate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States "used random numbers"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported who was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	—
Selective reporting (reporting bias)	Unclear risk	—
Other bias	Unclear risk	—

Roy 2004

Methods	Double-blind, randomised, placebo-controlled trial
Participants	40 participants Eligibility criteria: presence and duration of sore throat, odynophagia, respiratory distress, fatigue and fever. A bacterial throat culture, monotest and Epstein-Barr virus were performed to reach final diagnosis of infectious mononucleosis-induced acute sore throat
Interventions	Intervention: one dose of dexamethasone oral 0.3 mg/kg Control: placebo
Outcomes	Duration of sore throat, fever and rate of return to social activities
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement

Roy 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Allocation sequence held remotely
Blinding (performance bias and detection bias) All outcomes	Low risk	All personnel and participants blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	—
Selective reporting (reporting bias)	Unclear risk	—
Other bias	Unclear risk	—

Simon 2003

Methods	Double-blind, placebo-controlled trial 2 active treatment groups (1) valacyclovir and a steroid, (2) valacyclovir plus placebo
Participants	45 participants Eligibility criteria: fever, sore throat, swollen lymph glands, exudative pharyngitis and EBV illness confirmed by positive EBV antibody profile showing acute illness
Interventions	Intervention 1: valacyclovir 20 mg/kg/dose with 3 doses per day for 14 days plus prednisolone 1 mg/kg/day for 5 days Intervention 2: valacyclovir 20 mg/kg/dose with 3 doses per day for 14 days plus placebo A once per day for 5 days Control: placebo B 3 times per day for 14 days plus placebo A once per day for 5 days
Outcomes	(1) combined score of sore throat, stomach ache, fatigue, swollen glands, headache, vomiting, rash, nausea, sweats, chills, swollen eyes, runny nose and cough (2) selected score for sore throat, swollen glands, fatigue, nausea and chills (3) feeling bad (4) fatigue
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Does not state
Allocation concealment (selection bias)	Low risk	Allocation handled remotely
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Does not state who was blinded

Simon 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Does not state how many participants were lost to follow-up. Patients that did not complete the study or had a missing result had their last observation carried forward
Selective reporting (reporting bias)	Unclear risk	—
Other bias	Unclear risk	—

Tynell 1996

Methods	Double-blind, placebo-controlled trial. 2 centres Active treatment acyclovir and a steroid
Participants	86 participants Eligibility criteria: clinical feature of sore throat, swollen lymph glands, general malaise and that symptoms had been present for more than 7 days, had a baseline oral temperature of over 37.5 ◦C, had atypical mononuclear cells in peripheral blood and a positive heterophil antibody test
Interventions	Intervention: acyclovir 800 mg orally 5 times a day or 5 mg per kg as a 1-hour IVI every 8 hours until oral could be taken. Both with prednisolone, dosage dependent on participant's weight at entry: initially at 0.7 mg kg daily tapered over 10 days Control: placebo
Outcomes	Duration of general illness, sore throat, weight loss or absence from school or work
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation codes
Allocation concealment (selection bias)	Unclear risk	The randomisation codes were open to the chief pharmacist but blinded to the investigators
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Does not state who was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	At end of follow-up 49/86 remained in trial. Does not address incomplete data
Selective reporting (reporting bias)	Unclear risk	—
Other bias	Unclear risk	—

EBV: Epstein-Barr virus
IVI: intravenous infusion

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

Study	Reason for exclusion
Andersson 1988a	Non-randomised controlled trial
Antila 1962	Non-randomised controlled trial
Bender 1967	Non-randomised controlled trial
Brandfonbrener 1986	Non-randomised and outcome not symptom control
Breen 1965	Retrospective non-randomised
Evans 1960	Non-randomised controlled trial
Gordon 1968	Non-randomised controlled trial
Schumacher 1963	Non-randomised controlled trial
Simonsen 1996	Non-randomised controlled trial

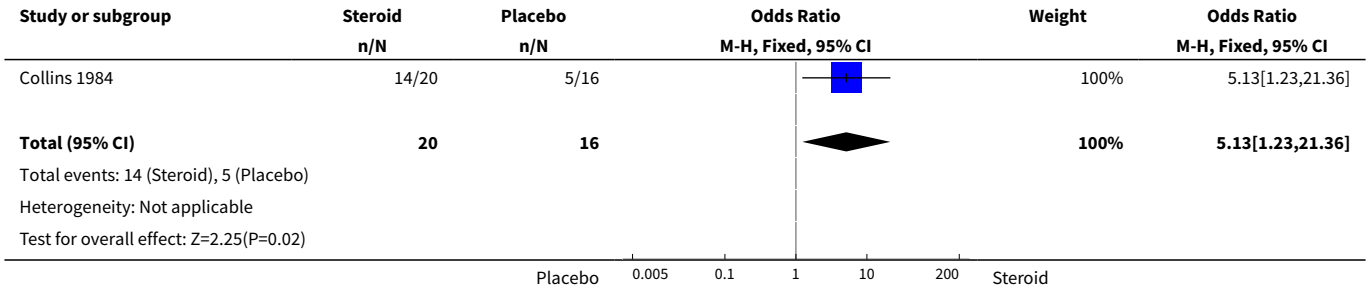
DATA AND ANALYSES

Comparison 1. Steroid versus placebo

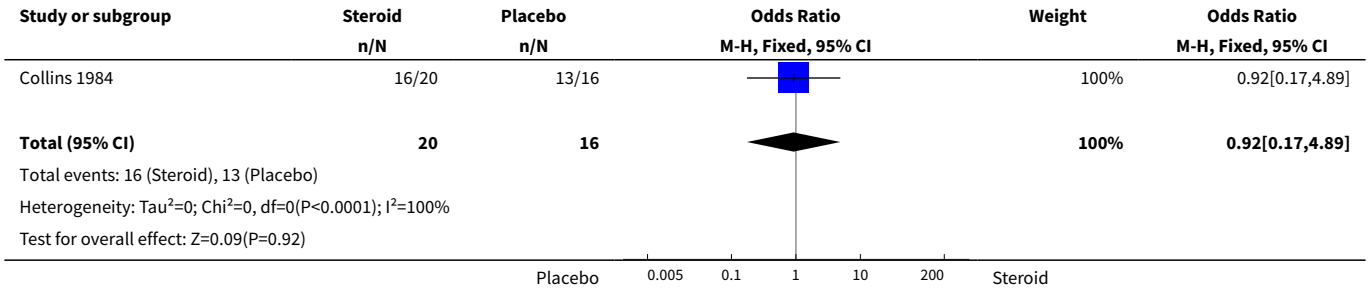
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Return to normal activities at 1 week	1	36	Odds Ratio (M-H, Fixed, 95% CI)	5.13 [1.23, 21.36]
2 Return to normal activities at 4 weeks	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.17, 4.89]
3 Return to normal activities at 1 week	1	32	Odds Ratio (M-H, Fixed, 95% CI)	2.14 [0.52, 8.81]
4 Sickness absence at 1 week	1	21	Odds Ratio (M-H, Fixed, 95% CI)	3.33 [0.47, 23.47]
5 Relief of sore throat at 12 hours: 1 dose	1	39	Odds Ratio (M-H, Fixed, 95% CI)	4.2 [1.08, 16.32]
6 Relief of sore throat at 12 hours: 8-day course	1	24	Odds Ratio (M-H, Fixed, 95% CI)	21.0 [1.94, 227.20]
7 Relief of sore throat at 24 hours	1	40	Odds Ratio (M-H, Fixed, 95% CI)	2.85 [0.78, 10.47]
8 Relief of sore throat at 36 hours	1	24	Odds Ratio (M-H, Fixed, 95% CI)	6.0 [1.02, 35.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Relief of sore throat at 48 hours	1	40	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.29, 3.48]
10 Relief of sore throat at 60 hours	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.10, 2.84]
11 Relief of sore throat at 70 hours	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.8 [0.18, 3.57]
12 Relief of sore throat at 1 week	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.06, 16.31]
13 Relief of sore throat at 2 weeks	1	35	Odds Ratio (M-H, Fixed, 95% CI)	1.5 [0.34, 6.56]
14 Relief of sore throat at 4 weeks	1	35	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.24, 8.26]
15 Fatigue at 1 week	1	44	Odds Ratio (M-H, Fixed, 95% CI)	0.4 [0.12, 1.35]
16 Fatigue at 4 weeks	1	44	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.19, 3.24]
17 Anorexia at 1 week	1	29	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.14, 3.35]
18 Anorexia at 4 weeks	1	29	Odds Ratio (M-H, Fixed, 95% CI)	2.86 [0.28, 29.56]
19 Swallowing at 1 week	1	32	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.31, 12.89]
20 Swallowing at 4 weeks	1	32	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.11, 3.20]
21 Pharyngeal secretions at 1 week	1	37	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.07, 1.32]
22 Pharyngeal secretions at 4 weeks	1	37	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.09, 5.89]
23 Inability to concentrate at 1 week	1	33	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.11, 2.07]
24 Inability to concentrate at 4 weeks	1	33	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.18, 5.28]

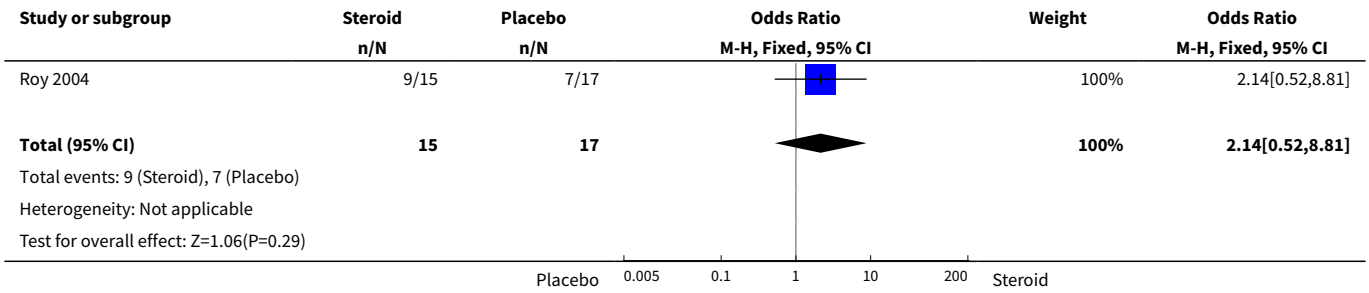
Analysis 1.1. Comparison 1 Steroid versus placebo, Outcome 1 Return to normal activities at 1 week.



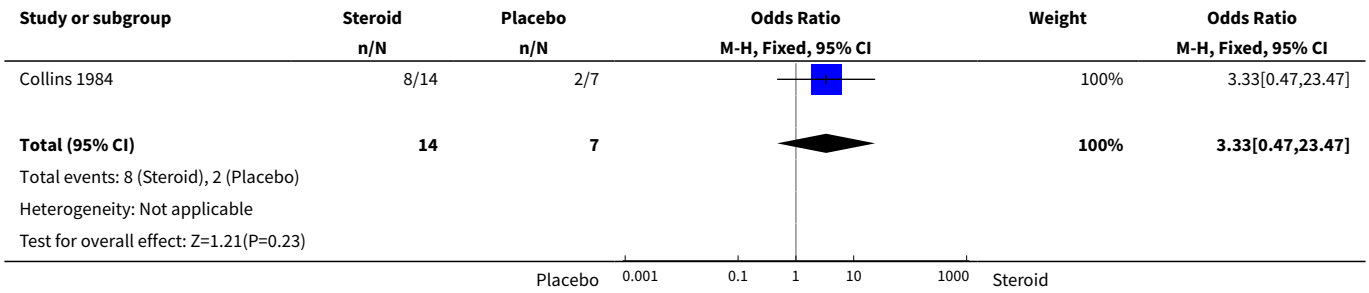
Analysis 1.2. Comparison 1 Steroid versus placebo, Outcome 2 Return to normal activities at 4 weeks.



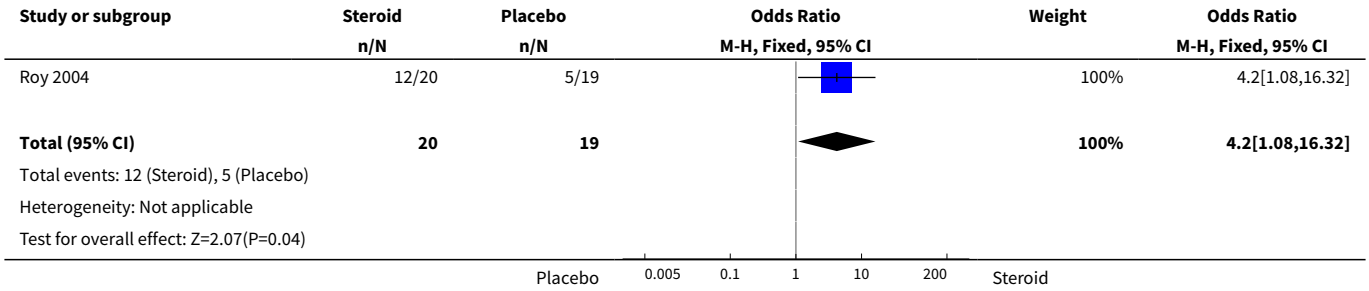
Analysis 1.3. Comparison 1 Steroid versus placebo, Outcome 3 Return to normal activities at 1 week.



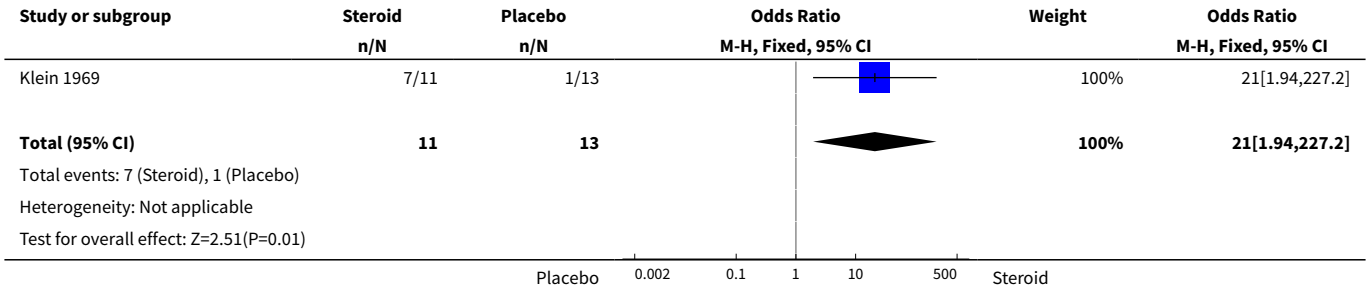
Analysis 1.4. Comparison 1 Steroid versus placebo, Outcome 4 Sickness absence at 1 week.



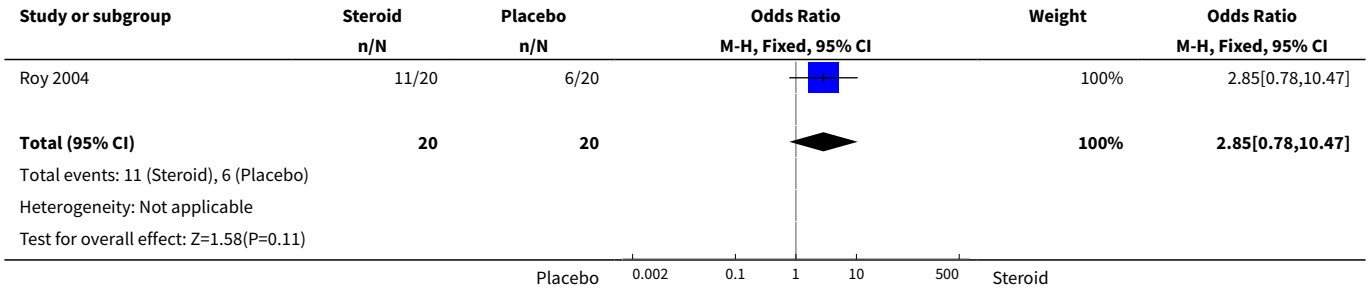
Analysis 1.5. Comparison 1 Steroid versus placebo, Outcome 5 Relief of sore throat at 12 hours: 1 dose.



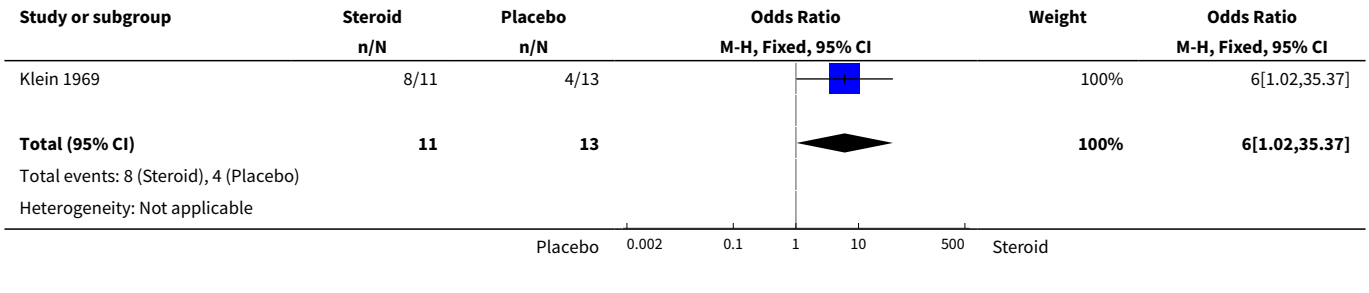
Analysis 1.6. Comparison 1 Steroid versus placebo, Outcome 6 Relief of sore throat at 12 hours: 8-day course.

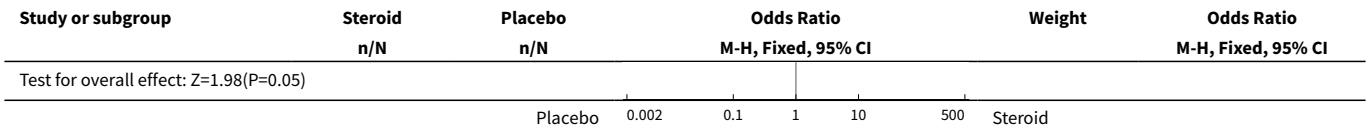


Analysis 1.7. Comparison 1 Steroid versus placebo, Outcome 7 Relief of sore throat at 24 hours.

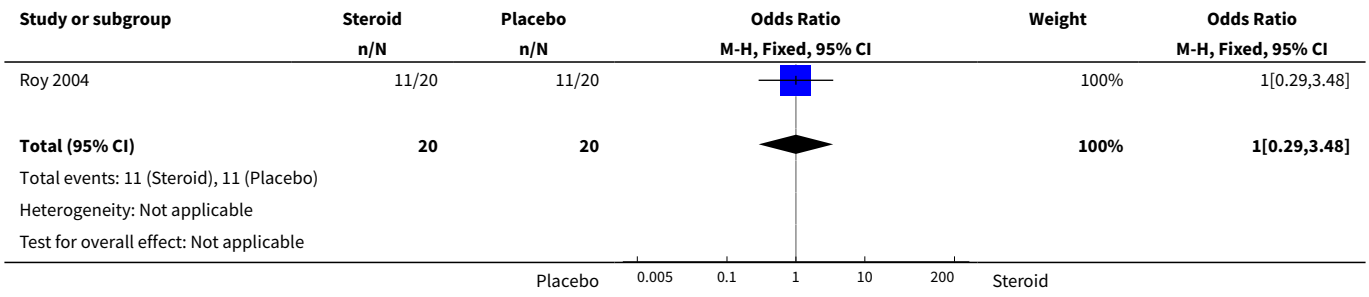


Analysis 1.8. Comparison 1 Steroid versus placebo, Outcome 8 Relief of sore throat at 36 hours.

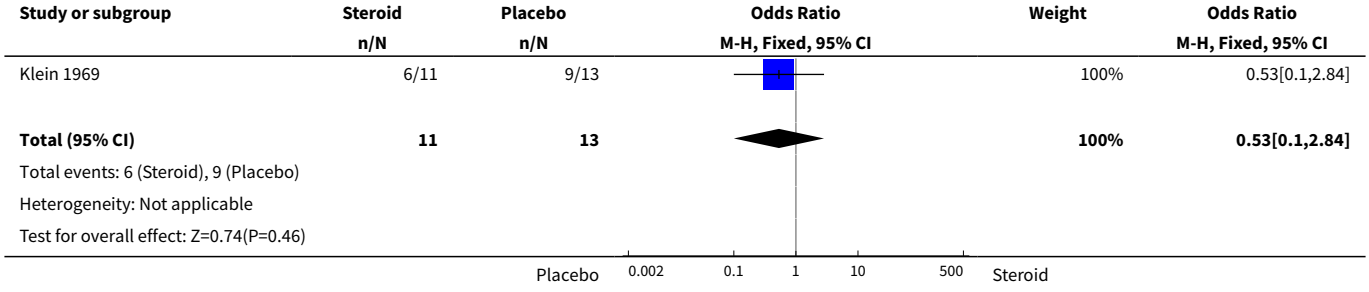




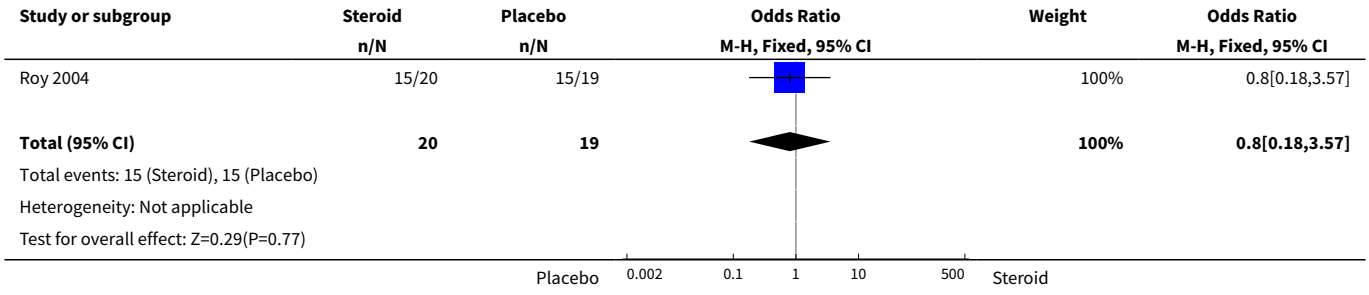
Analysis 1.9. Comparison 1 Steroid versus placebo, Outcome 9 Relief of sore throat at 48 hours.



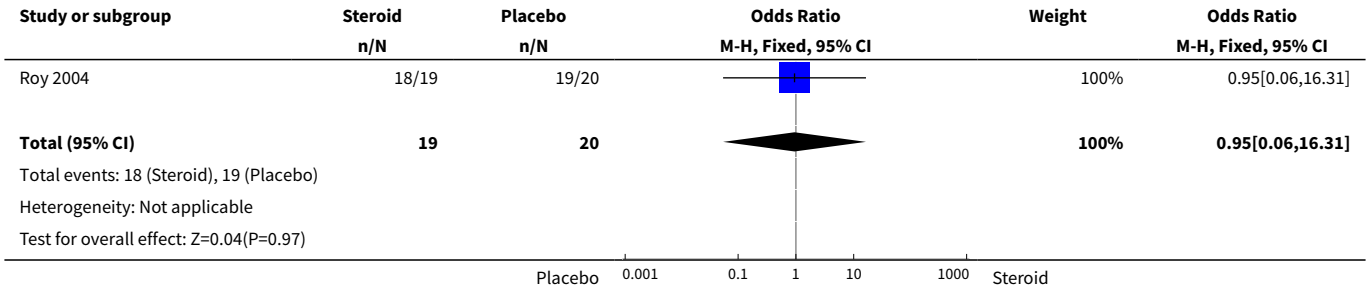
Analysis 1.10. Comparison 1 Steroid versus placebo, Outcome 10 Relief of sore throat at 60 hours.



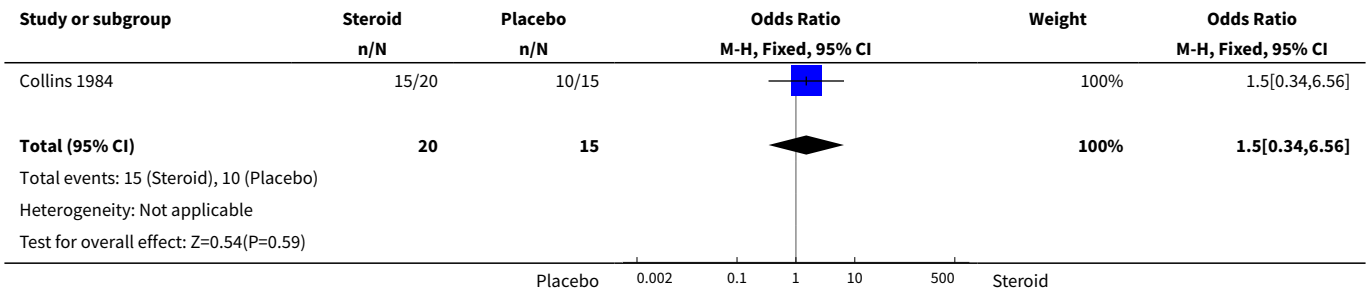
Analysis 1.11. Comparison 1 Steroid versus placebo, Outcome 11 Relief of sore throat at 70 hours.



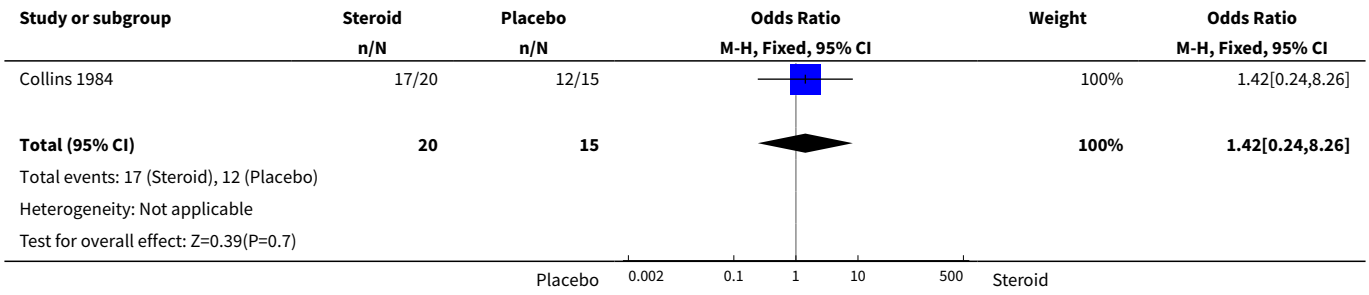
Analysis 1.12. Comparison 1 Steroid versus placebo, Outcome 12 Relief of sore throat at 1 week.



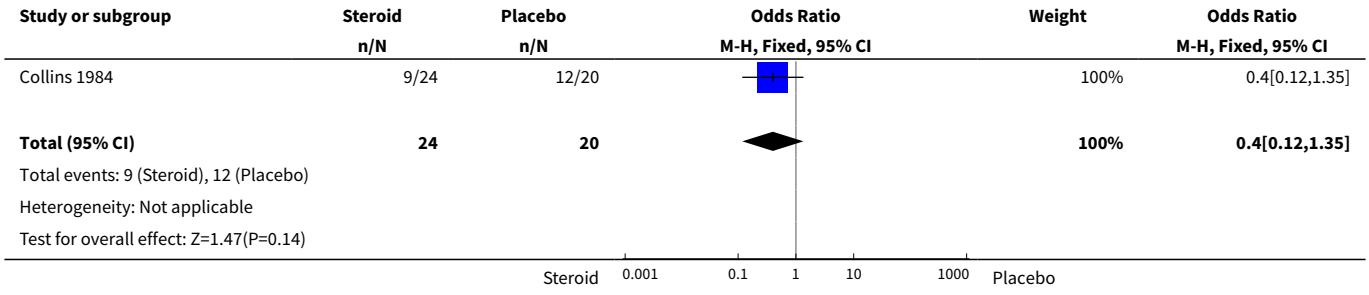
Analysis 1.13. Comparison 1 Steroid versus placebo, Outcome 13 Relief of sore throat at 2 weeks.



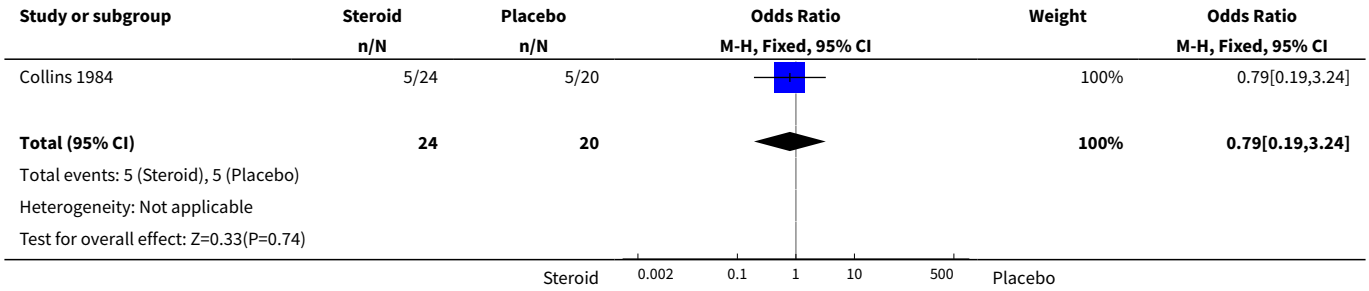
Analysis 1.14. Comparison 1 Steroid versus placebo, Outcome 14 Relief of sore throat at 4 weeks.



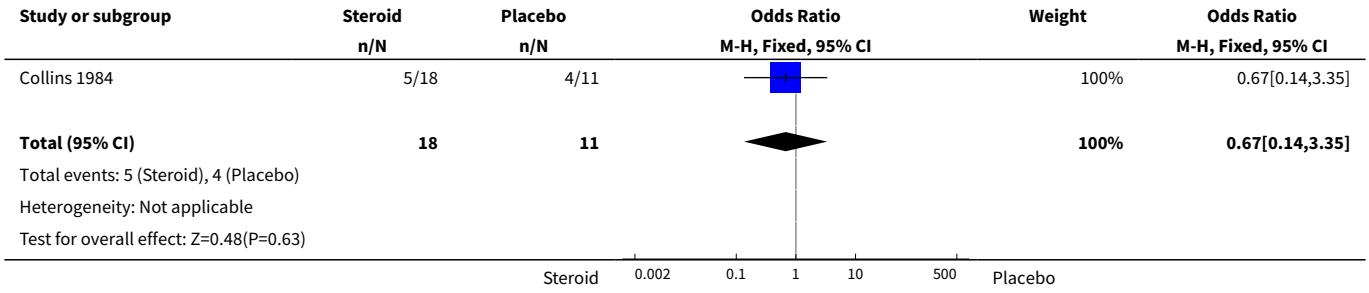
Analysis 1.15. Comparison 1 Steroid versus placebo, Outcome 15 Fatigue at 1 week.



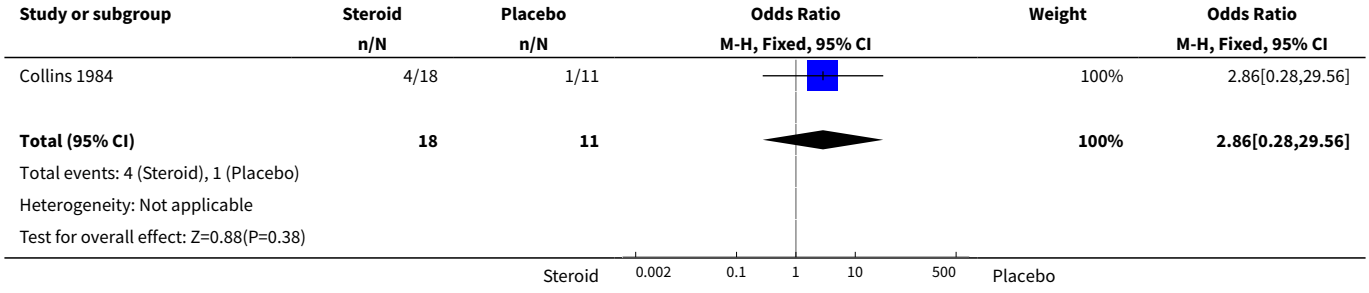
Analysis 1.16. Comparison 1 Steroid versus placebo, Outcome 16 Fatigue at 4 weeks.



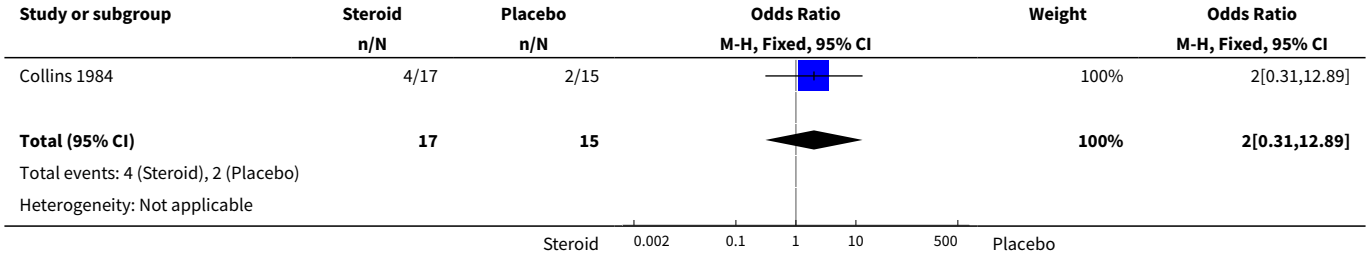
Analysis 1.17. Comparison 1 Steroid versus placebo, Outcome 17 Anorexia at 1 week.

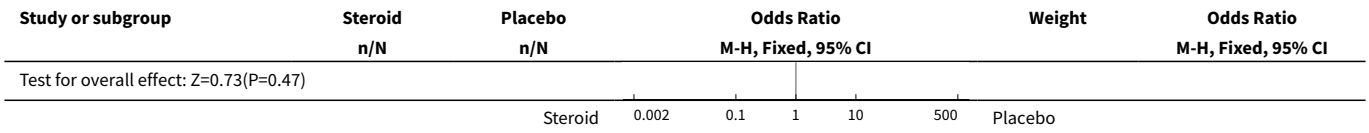


Analysis 1.18. Comparison 1 Steroid versus placebo, Outcome 18 Anorexia at 4 weeks.

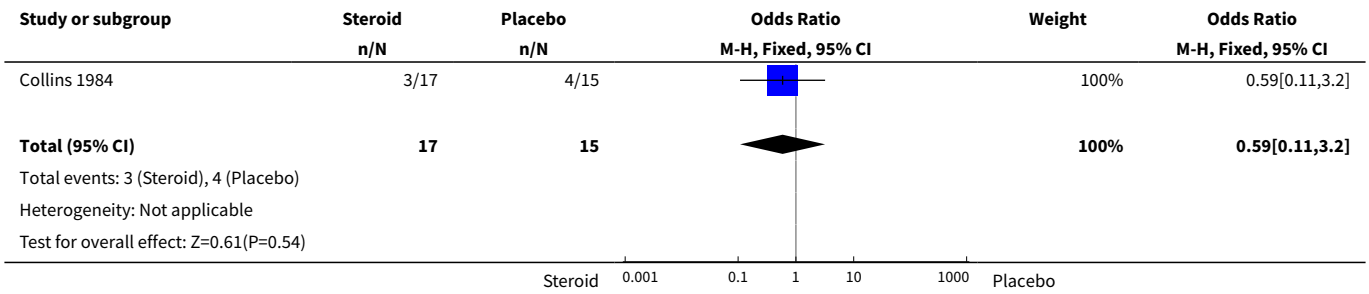


Analysis 1.19. Comparison 1 Steroid versus placebo, Outcome 19 Swallowing at 1 week.

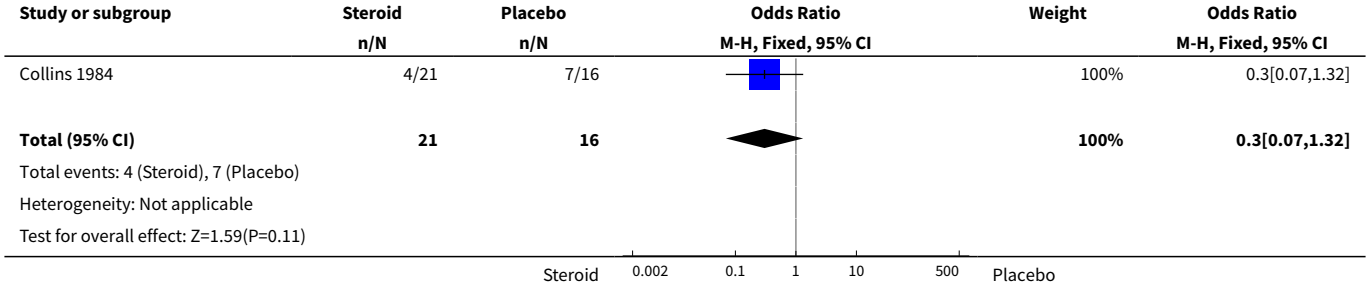




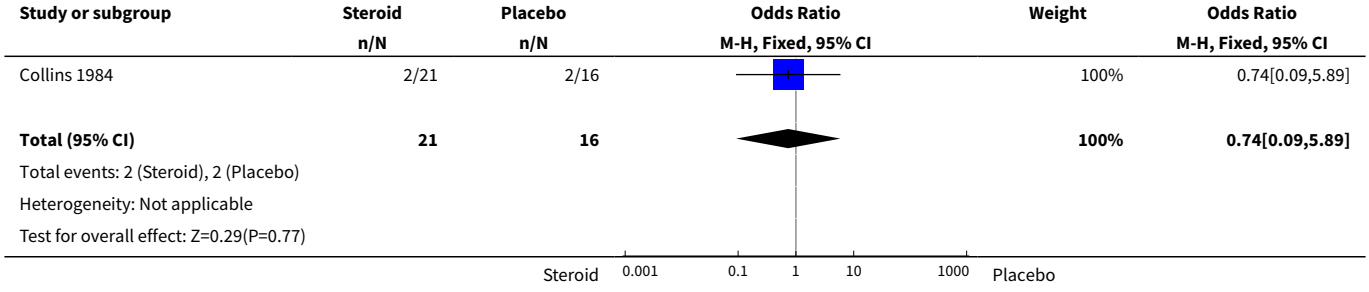
Analysis 1.20. Comparison 1 Steroid versus placebo, Outcome 20 Swallowing at 4 weeks.



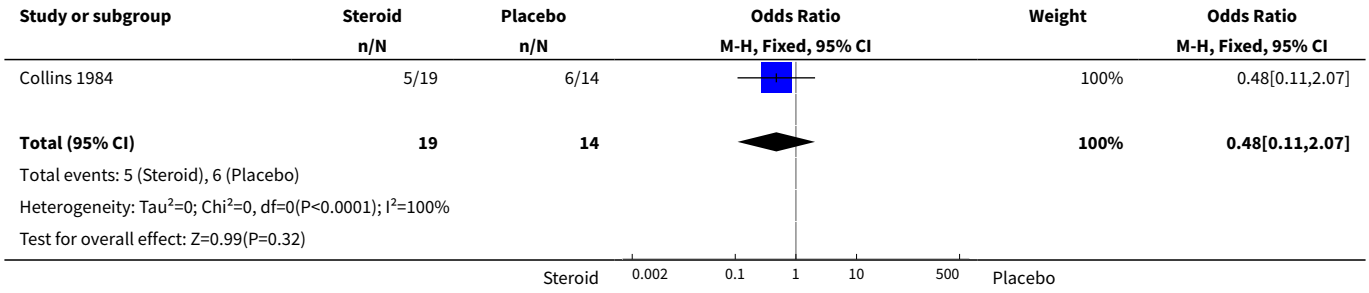
Analysis 1.21. Comparison 1 Steroid versus placebo, Outcome 21 Pharyngeal secretions at 1 week.



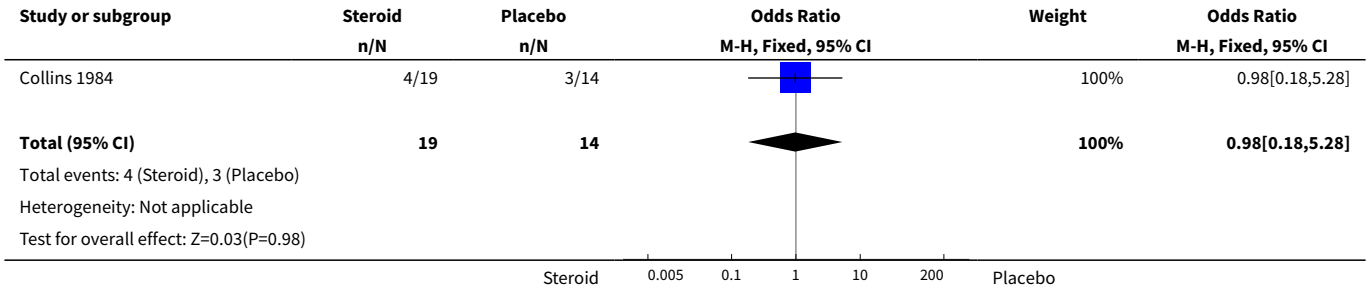
Analysis 1.22. Comparison 1 Steroid versus placebo, Outcome 22 Pharyngeal secretions at 4 weeks.



Analysis 1.23. Comparison 1 Steroid versus placebo, Outcome 23 Inability to concentrate at 1 week.



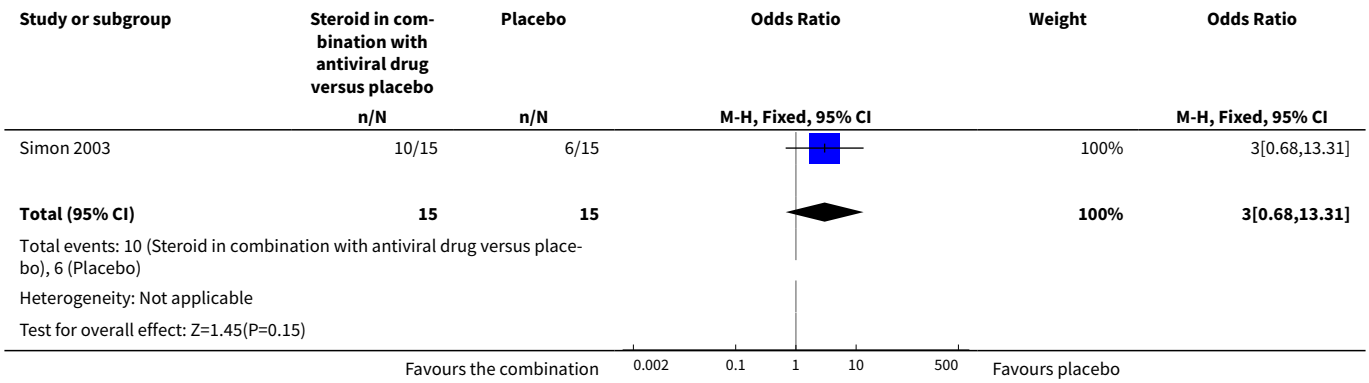
Analysis 1.24. Comparison 1 Steroid versus placebo, Outcome 24 Inability to concentrate at 4 weeks.



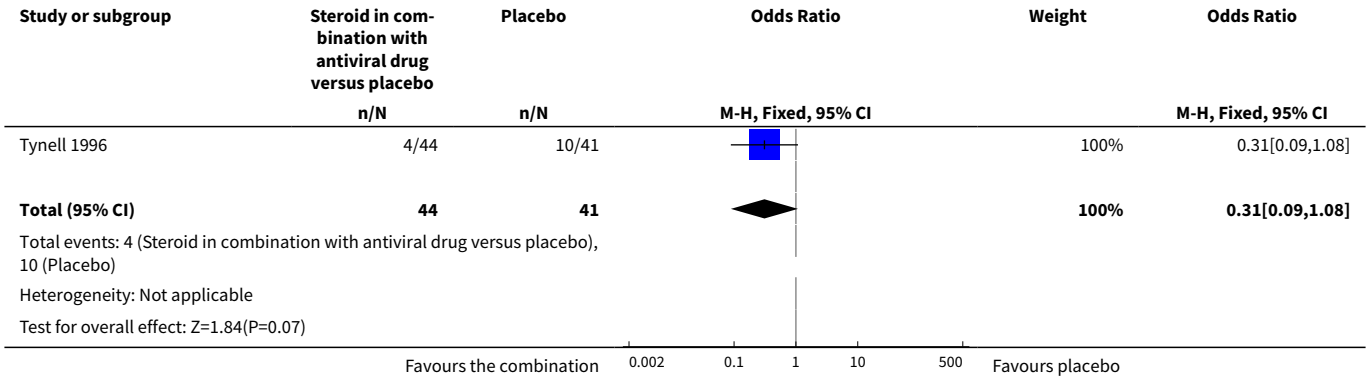
Comparison 2. Steroid in combination with antiviral drug versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of fever. Steroids in combination with acyclovir	1	30	Odds Ratio (M-H, Fixed, 95% CI)	3.0 [0.68, 13.31]
2 Severe pharyngeal discomfort between 2 and 4 days. Steroids in combination with acyclovir	1	85	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.09, 1.08]
3 Resolution of fatigue at 20 days. Steroids in combination with valacyclovir	1	30	Odds Ratio (M-H, Fixed, 95% CI)	8.0 [1.52, 42.04]
4 Regain of weight at 14 days	1	79	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.26, 1.66]
5 Selected symptom score improvement	1	30	Odds Ratio (M-H, Fixed, 95% CI)	9.33 [0.96, 90.94]
6 Total symptom score improvement	1	30	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.38, 10.51]

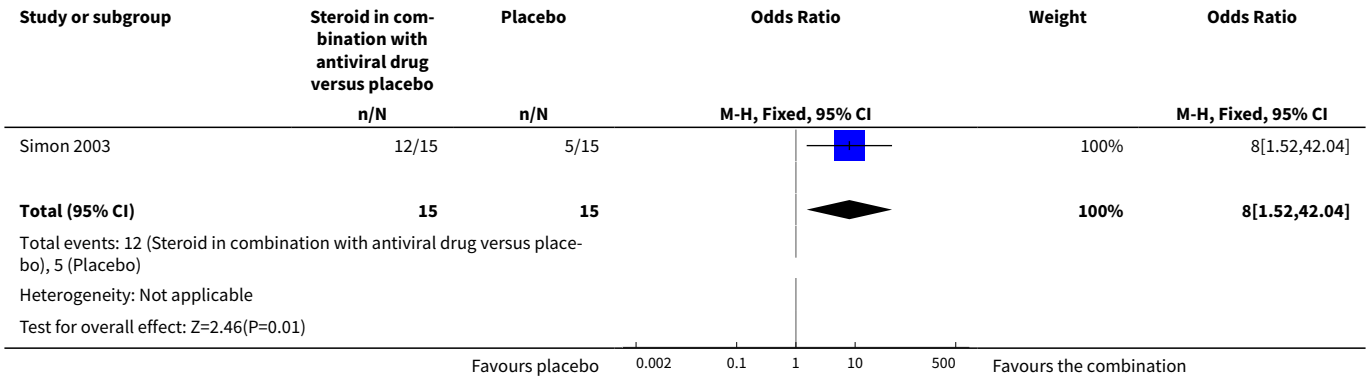
Analysis 2.1. Comparison 2 Steroid in combination with antiviral drug versus placebo, Outcome 1 Duration of fever. Steroids in combination with acyclovir.



Analysis 2.2. Comparison 2 Steroid in combination with antiviral drug versus placebo, Outcome 2 Severe pharyngeal discomfort between 2 and 4 days. Steroids in combination with acyclovir.

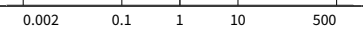


Analysis 2.3. Comparison 2 Steroid in combination with antiviral drug versus placebo, Outcome 3 Resolution of fatigue at 20 days. Steroids in combination with valacyclovir.



Analysis 2.4. Comparison 2 Steroid in combination with antiviral drug versus placebo, Outcome 4 Regain of weight at 14 days.

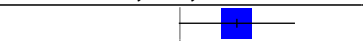
Study or subgroup	Steroid n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Tynell 1996	13/42	15/37		100%	0.66[0.26,1.66]
Total (95% CI)	**42**	**37**		**100%**	**0.66[0.26,1.66]**
Total events: 13 (Steroid), 15 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.89(P=0.38)					



Placebo Steroid

Analysis 2.5. Comparison 2 Steroid in combination with antiviral drug versus placebo, Outcome 5 Selected symptom score improvement.

Study or subgroup	Steroid in combination with antiviral drug versus placebo n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Simon 2003	14/15	9/15		100%	9.33[0.96,90.94]
Total (95% CI)	**15**	**15**		**100%**	**9.33[0.96,90.94]**
Total events: 14 (Steroid in combination with antiviral drug versus placebo), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.92(P=0.05)					



Favours placebo Favours the combination

Analysis 2.6. Comparison 2 Steroid in combination with antiviral drug versus placebo, Outcome 6 Total symptom score improvement.

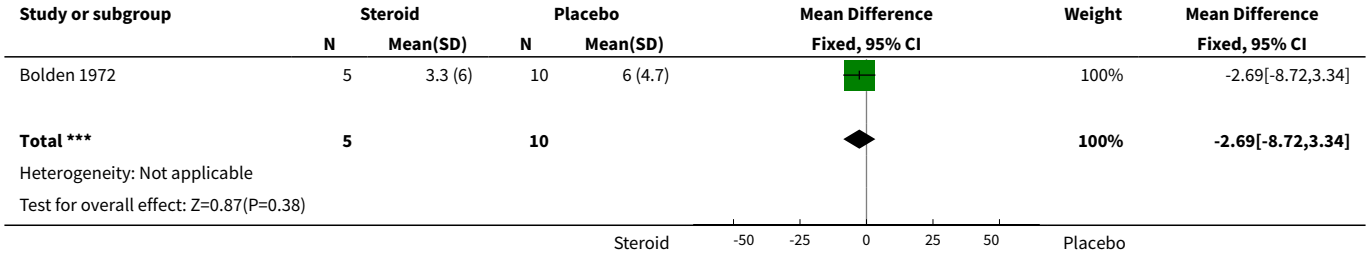
Study or subgroup	Steroid in combination with antiviral drug versus placebo n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Simon 2003	12/15	10/15		100%	2[0.38,10.51]
Total (95% CI)	**15**	**15**		**100%**	**2[0.38,10.51]**
Total events: 12 (Steroid in combination with antiviral drug versus placebo), 10 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					

Favours the combination Favours placebo

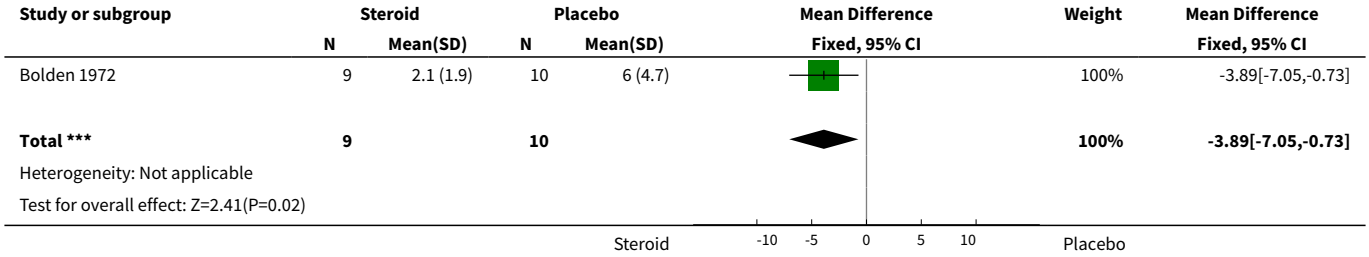
Comparison 3. Steroid versus aspirin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of temperature: 6-day steroid course	1	15	Mean Difference (IV, Fixed, 95% CI)	-2.69 [-8.72, 3.34]
2 Duration of temperature: 12-day steroid course only	1	19	Mean Difference (IV, Fixed, 95% CI)	-3.89 [-7.05, -0.73]

Analysis 3.1. Comparison 3 Steroid versus aspirin, Outcome 1 Duration of temperature: 6-day steroid course.



Analysis 3.2. Comparison 3 Steroid versus aspirin, Outcome 2 Duration of temperature: 12-day steroid course only.



APPENDICES

Appendix 1. Previous searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2008, Issue 2), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (January 1966 to Week 4, April 2008); EMBASE (January 1974 to May 2008) and the UK National Research Register (September 2007).

The following search strategy was used to search MEDLINE and CENTRAL. The MEDLINE search was combined with the Cochrane search strategy for identifying RCTs (Lefebvre 2011). The search terms were adapted when searching EMBASE and the UK National Research Register.

MEDLINE (Ovid)

1 Infectious Mononucleosis/
2 infectious mononucleosis.tw.
3 glandular fever.tw.
4 Epstein-Barr Virus Infections/

5 (Epstein Barr or Epstein-barr or EBV).tw.
6 1 or 2 or 3 or 4 or 5
7 exp Steroids/
8 (steroid not anabolic).tw.
9 exp Adrenal Cortex Hormones/
10 glucocorticoid*.tw.
11 corticosteroid*.tw.
12 adrenocorticosteroid*.tw.
13 exp Anti-Inflammatory Agents/
14 anti-inflammatory agent*.tw.
15 exp Adrenocorticotropic Hormone/
16 (corticotropin or prednisone or prednisolone or cortisone or hydrocortisone or dexamethasone or betamethasone or paramethasone).tw.
17 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18 6 and 17

Appendix 2. Embase.com search strategy

#23	#22 AND [EMBASE]/lim AND [1-3-2008]/sd NOT [27-10-2010]/sd
#22	#18 AND #21
#21	#19 OR #20
#20	random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/2 (blind* OR mask*)):ab,ti
#19	'randomised controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#18	#5 AND #17
#17	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#16	corticotropin*:ab,ti OR prednisone*:ab,ti OR prednisolone*:ab,ti OR cortisone*:ab,ti OR hydrocortisone*:ab,ti OR dexamethasone*:ab,ti OR dexamethasone*:ab,ti OR betamethasone*:ab,ti OR betamethasone*:ab,ti OR paramethasone*:ab,ti
#15	'corticotropin'/exp
#14	antiinflammator*:ab,ti OR 'anti-inflammatory':ab,ti OR 'anti-inflammatories':ab,ti
#13	'antiinflammatory agent'/exp
#12	adrenocorticosteroid*:ab,ti
#11	glucocorticoid*:ab,ti
#10	'glucocorticoid'/exp
#9	corticosteroid*:ab,ti OR 'adrenal cortex hormone':ab,ti OR 'adrenal cortex hormones':ab,ti
#8	'corticosteroid'/exp
#7	steroid*:ab,ti

(Continued)

#6	'steroid'/exp
#5	#1 OR #2 OR #3 OR #4
#4	'Epstein Barr virus'/de
#3	'Epstein Barr':ab,ti OR 'Epstein-barr':ab,ti OR EBV:ab,ti
#2	'infectious mononucleosis':ab,ti OR 'glandular fever':ab,ti
#1	'infectious mononucleosis'/exp OR 'Epstein Barr virus infection'/de

WHAT'S NEW

Date	Event	Description
8 December 2015	Amended	Minor edits to text to improve readability.

HISTORY

Protocol first published: Issue 3, 2003
Review first published: Issue 3, 2006

Date	Event	Description
14 August 2015	New citation required but conclusions have not changed	A new team of authors updated this review.
14 August 2015	New search has been performed	Searches updated. We identified 186 records in the updated search. After processing the results according to the inclusion criteria, we did not identify any new studies that could be included in the review.
28 February 2011	New search has been performed	Searches conducted. No new trials were included or excluded in this updated review.
7 May 2008	New search has been performed	Searches updated. No new trials were identified and the conclusions of the original review remain unchanged.
28 April 2008	Amended	Converted to new review format.
4 November 2005	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

For this 2015 update, Emtithal Rezk (ER) the contact person, provided guidance and revised the review.

Ammar Hamzeh (AH) identified this review required updating, wrote and screened the abstract, AH with Yazan Nofal (YN) wrote the plain language summary and YN screened it.

Mohammad Ali Alkheder (MAA) wrote and screened the acknowledgements, MAA with Muhammed Fayez Aboujaib (MFA) wrote and screened the discussion, the what's new, and the history, MAA, MFA, and YN entered data into RevMan 5.3. MAA, MFA , and YN wrote contributions of authors. MAA and YN wrote and screened authors' conclusions.

MFA and AH evaluated citation titles and abstracts identified from the electronic databases using the inclusion criteria. MFA obtained the full text of all potentially relevant studies for assessment and excluded any further papers that on more detailed review did not match the inclusion criteria, wrote and screened the methods, checked the correct use of grammar in this review.

YN with Muhammad Firas Al Hammad (MFAH) drafted the protocol and wrote and screened the results. YN wrote and screened the background and the objectives, revised the review and checked the screening, drafted the review, screened contributions of authors. YN and AH coordinated the group work.

MAA commented on the abstract, the plain language summary, the background, and the protocol. (MFA) commented on the plain language summary, the background, the results, and the authors' conclusions. (YN) commented on the abstract, the plain language summary, the methods, the results, the discussion, the authors' conclusions, the acknowledgements, the what's new, and the history. (MFAH) commented on the plain language summary and the background. (AH) commented on the background, the results, the authors' conclusions, and the what's new.
(MFA, YN, AH, MAA) checked that everything in the research has been written according to the new Checklist.

DECLARATIONS OF INTEREST

Emtithal Rezk: none known.
Yazan H Nofal: none known.
Ammar Hamzeh: none known.
Mohammad A AlKheder: none known.
Muhammad F Al Hammad: none known.
Muhammed F Aboujaib: none known.

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Internal sources

- Association for Evidence Based Medicine, Syrian Arab Republic.

  www.a4ebm.org provided training courses
- Faculty of Human Medicine, Damascus University, Syrian Arab Republic.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Infectious Mononucleosis [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Humans; Young Adult