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Adjunctive steroid therapy versus antibiotics alone for acute endophthalmitis after intraocular procedure

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[Intervention Review]

Adjunctive steroid therapy versus antibiotics alone for acute endophthalmitis after intraocular procedure

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ABSTRACT

Background

Endophthalmitis refers to severe infection within the eye that involves the aqueous humor or vitreous humor, or both, and that threatens vision. Most cases of endophthalmitis are exogenous (i.e. due to inoculation of organisms from an outside source), and most exogenous endophthalmitis is acute and occurs after an intraocular procedure. The mainstay of treatment is emergent administration of broad-spectrum intravitreous antibiotics. Due to their anti-inflammatory effects, steroids in conjunction with antibiotics have been proposed as being beneficial in endophthalmitis management.

Objectives

To assess the effects of antibiotics combined with steroids versus antibiotics alone for the treatment of acute endophthalmitis following intraocular surgery or intravitreous injection.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2021, Issue 8), MEDLINE Ovid (1946 to August 2021), Embase Ovid (1980 to August 2021), LILACS (Latin American and Caribbean Health Sciences Literature database) (1982 to August 2021), the ISRCTN registry; searched August 2021, ClinicalTrials.gov; searched August 2021, and the WHO International Clinical Trials Registry Platform; searched August 2021. We did not use any date or language restrictions in the electronic searches for trials.

Selection criteria

We included randomized controlled trials (RCTs) comparing the effectiveness of adjunctive steroids with antibiotics alone in the management of acute, clinically diagnosed endophthalmitis following intraocular surgery or intravitreous injection. We excluded trials with participants with endogenous endophthalmitis unless outcomes were reported by source of infection. We imposed no restrictions on the method or order of administration, dose, frequency, or duration of antibiotics and steroids.

Data collection and analysis

We used standard Cochrane methodology, and graded the certainty of the body of evidence for six outcomes using the GRADE classification.

Main results

We included four RCTs with a total of 264 eyes of 264 participants in this review update. The studies were conducted in South Africa, India, and the Netherlands. All studies used intravitreous dexamethasone for adjunctive steroid therapy and a combination of two intravitreous antibiotics that provided gram-positive and gram-negative coverage for the antibiotic therapy. We judged two trials to be at overall low

risk of bias, and the other two studies to be at overall unclear risk of bias due to lack of reporting of study methods. Only one study was registered in a clinical trial register.

While none of the included studies reported the primary outcome of complete resolution of endophthalmitis as defined in our protocol, one study reported combined anatomical and functional success (i.e. proportion of participants with intraocular pressure of at least 5 mmHg and visual acuity of at least 6/120). Very low certainty evidence suggested no difference in combined success when comparing adjunctive steroid to antibiotics alone (risk ratio (RR) 1.08, 95% confidence interval (CI) 0.80 to 1.45; 32 participants). Low certainty evidence from two studies suggested that adjunctive dexamethasone may result in having a good visual outcome (Snellen visual acuity 6/6 to 6/18) at 3 months compared with antibiotics alone (RR 1.95, 95% CI 1.05 to 3.60; 60 participants); however, the evidence was less conclusive at 12 months (RR 1.12, 95% CI 0.92 to 1.37; 2 studies; 195 participants; low certainty evidence). Investigators of one study reported improvement in visual acuity, but we could not estimate the effect of adjunctive steroid therapy because the study investigators did not provide any estimates of precision. Only one study examined intraocular pressure (IOP). The evidence suggests that adjunctive dexamethasone may reduce IOP slightly after 12 months of interventions (mean difference −1.90, 95% CI −3.78 to 0.07; 1 study; 167 participants; low certainty evidence). Three studies reported adverse events (retinal detachment, hypotony, proliferative vitreoretinopathy, seclusion of pupil, floaters, and pucker). The total numbers of adverse events were 14 out of 111 (12.6%) for those who received dexamethasone versus 12 out of 116 (10.3%) for those who did not. We could only perform a pooled analysis for the occurrence of retinal detachment: any difference between the two treatment groups was uncertain (RR 1.41, 95% CI 0.53 to 3.74; 227 participants; low certainty evidence). No study reported cost-related outcomes.

Authors' conclusions

The currently available evidence on the effectiveness of adjunctive steroid therapy versus antibiotics alone in the management of acute endophthalmitis after intraocular surgery is inadequate. We found no studies that had enrolled cases of acute endophthalmitis following intravitreous injection. A combined analysis of two studies suggests that use of adjunctive steroids may provide a higher chance of having a good visual outcome at three months than not using adjunctive steroids. However, considering that most of the confidence intervals crossed the null, and that this review was limited in scope and applicability to clinical practice, it is not possible to conclude whether the use of adjunctive steroids is effective at this time. Any future trials should examine whether adjunctive steroids may be useful in certain clinical settings such as type of causative organism or etiology. These studies should include outcomes that take patients' symptoms and clinical examination into account; report outcomes in a uniform and consistent manner; and follow up at short- and long-term intervals.

PLAIN LANGUAGE SUMMARY

Steroids plus antibiotics versus antibiotics alone for the treatment of acute endophthalmitis after eye surgery or injections into the eye

What is the aim of this review?

The aim of this Cochrane Review was to find out whether using steroids in addition to antibiotics is more effective than using antibiotics alone for acute endophthalmitis (infection inside the eyeball that can cause vision loss) after eye surgery or injections into the eye. We looked for all studies that answered this question and found four studies.

Key messages

It is uncertain whether using steroids in addition to antibiotics is helpful or harmful compared with using antibiotics alone to treat acute endophthalmitis after eye surgery or injections into the eye.

What was studied in the review?

Endophthalmitis is rare, but it is important for people undergoing surgery or injections to the eye to be aware of the risk and for their doctors to know how best to treat it because it can result in vision loss. It is most commonly caused by entry of bacteria into the eye during, or a few days after, surgery or injection. As soon as endophthalmitis is suspected, a sample of the fluid inside the eye is usually obtained (and the fluid drained in severe cases), and antibiotics that cover most types of bacteria are injected into the eye. Although the use of antibiotics is widely accepted, the use of additional steroids to treat endophthalmitis is the subject of debate. Steroids may help to decrease the inflammation inside the eye in people with endophthalmitis. We looked at whether giving steroids in addition to antibiotics affects patient outcomes.

What are the main results of the review?

We found four studies from South Africa, India, and the Netherlands. Almost all study participants had endophthalmitis after cataract surgery. All four studies compared injecting dexamethasone (a steroid) plus two antibiotics into the eye versus injecting only antibiotics into the eye. Low certainty evidence showed that more participants in the group receiving dexamethasone had a good visual outcome 3 months after treatment than in the antibiotics-only group, but the evidence was uncertain at 12 months. The effects of using steroids on resolution of endophthalmitis and harms were also uncertain. Given the uncertainty of evidence for most outcomes, it is not clear whether doctors should use steroids with antibiotics to treat endophthalmitis after a procedure in the eye.

How up-to-date is this review?

We searched for studies published up to 17 August 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Combined steroid and antibiotic therapy compared with antibiotics alone for acute endophthalmitis after intraocular procedure

Combined steroid and antibiotic therapy compared with antibiotics alone for acute endophthalmitis after intraocular procedure

Population: eyes with acute endophthalmitis following an intraocular procedure (e.g. surgery, intravitreous injection)

Settings: ophthalmology clinic or hospital

Intervention: steroids plus antibiotics

Comparison: antibiotics alone

Outcomes*	Illustrative comparative risks** (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Antibiotics alone	Combined steroid and antibiotic therapy				
Complete resolution of endophthalmitis at 3 months' follow-up	**813 per 1000**	**878 per 1000** (650 to 1000)	**RR 1.08** (0.80 to 1.45)	32 (1 study)	⊕⊖⊖⊖ **Very low[1,2,3]**	Assessed as combined anatomical and functional success, where anatomical success was defined as IOP of at least 5 mmHg, and functional success was defined as visual acuity of at least 6/120
Visual acuity 6/6 to 6/18 at 3 months' follow-up	**300 per 1000**	**585 per 1000** (315 to 1000)	**RR 1.95** (1.05 to 3.60)	60 (2 studies)	⊕⊕⊖⊖ **Low[1,2]**	
Visual acuity 6/6 to 6/18, or LogMAR 0.3 or better at 12 months' follow-up	**627 per 1000**	**710 per 1000** (704 to 750)	**RR 1.12** (0.92 to 1.37)	195 (2 studies)	⊕⊕⊖⊖ **Low[1,2]**	
Improvement in visual acuity at 3 months' follow-up	See comment					Investigators of 1 study reported improvement in visual acuity, but the effect of adjunctive steroid therapy could not be estimated because the study investigators did

						not provide standard deviations or standard errors.
Intraocular pressure at 12 months' follow-up	The mean IOP was 15.8 mmHg.	The mean IOP was on average **1.90 lower** (95% CI −3.78 to 0.07).	—	167 (1 study)	⊕⊖⊖⊖ **Low[4]**	
Adverse events at 3 to 12 months' follow-up	**52 per 1000**	**72 per 1000** (25 to 231)	**RR 1.41** (0.53 to 3.74)	227 (3 studies)	⊕⊕⊖⊖ **Low[1,2]**	Data are for **retinal detachment**. Other reported adverse events included hypotony (2/29 participants), proliferative vitreoretinopathy (1/29 participants), seclusion of pupil (1/29 participants), floaters (3/167 participants), and pucker (5/167 participants).
Costs associated with the interventions at 3 months' follow-up	No data were available for this outcome.					

*The primary follow-up time point for the review was 1 month; however, none of the included trials reported outcomes at this time point. Data are presented for the follow-up time point for which data were available.
The basis for the **assumed risk was the mean control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IOP:** intraocular pressure; **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.

[1]Downgraded (−1) for unclear risk of bias in the trials.
[2]Downgraded (−1) for imprecision (wide confidence interval).
[3]Downgraded (−1) for indirectness of the outcome definition.
[4]Downgraded (−2) for imprecision (very wide confidence interval).

BACKGROUND

Description of the condition

Endophthalmitis is a rare but potentially visually devastating condition that is defined as infection in the intraocular cavities (i.e. aqueous or vitreous humor, or both) (Durand 2013). A variety of pathogens, including bacteria, viruses, fungi, or parasites, can cause the infection; the culprit pathogens differ somewhat by the mechanism of infection (Keynan 2012). Most cases of endophthalmitis are exogenous; possible routes of infection include surgery, intravitreous injection, trauma, corneal infection, and glaucoma-filtering bleb infection (Sadaka 2012). Postoperative endophthalmitis is the most common type of exogenous endophthalmitis (Keynan 2012). While endophthalmitis is a possible complication of any intraocular surgery, 90% of postoperative endophthalmitis is due to cataract surgery, as it is the most frequent intraocular surgery (Lemley 2007). Endogenous endophthalmitis, which makes up 2% to 15% of endophthalmitis cases, occurs when organisms spread hematogenously from a distant infection site to the eye (Keynan 2012). The most common primary sites of infection are the liver, lung, and endocardium (Jackson 2014).

Epidemiology

The reported incidence of postoperative endophthalmitis varies widely, but available data indicate that the rate of endophthalmitis has been very low in recent years. Analyses of Medicare claims data in the USA showed that while the annual rate of post-cataract surgery endophthalmitis increased from 1.79 (95% confidence interval (CI) 1.46 to 2.18) to 2.62 (95% CI 2.22 to 3.07) cases per thousand surgeries between 1994 and 2000 (West 2005), it decreased from 1.32 (95% CI 1.27 to 1.38) to 1.11 (95% CI 1.06 to 1.16) per thousand surgeries between 2003 and 2004 (Keay 2012), and was stable between 2006 and 2011 (Du 2014). More recently, the Intelligent Research in Sight Registry found that the rate of endophthalmitis after cataract surgery was 0.08% (0.8 per 1000 surgeries) for 2013 and 2014 combined (Coleman 2015). Also, there were no cases of endophthalmitis following 21,501 office-based cataract surgeries performed at Kaiser Permanente Colorado from 2011 to 2014 (Ianchulev 2016). Reported incidences for other types of exogenous endophthalmitis are between 0.006% and 0.16% for intravitreous injection, between 0.3% and 0.7% for trabeculectomy, 2.0% for glaucoma drainage surgery, and between 0.9% and 17% for traumatic injury to the globe (Sadaka 2012; Stein 2008).

Risk factors for exogenous endophthalmitis include host factors and factors associated with the procedure. Some preoperative risk factors are male gender, older age, black and Native American race, immunocompromized states (e.g. diabetes, chronic steroid use), and recent history of periocular infections (e.g. blepharitis, conjunctivitis) (Hatch 2009; Keay 2012; Keynan 2012). The main intraoperative risk factor is increased intraocular exposure to the patient's adnexal and ocular surface flora, which increases with surgical complexity and complications such as posterior capsule rupture and vitreous loss (Hatch 2009; Mamalis 2002). Possible reasons for the decline in the early 2000s therefore include improved surgical techniques, sterility, and prophylactic antibiotics (Barry 2013). A multicenter study across nine European countries showed that the use of antibiotic prophylaxis with intracameral cefuroxime at the end of cataract surgery decreased the rate of endophthalmitis from 0.35% to 0.05% (ESCRS Study 2007). Higher rates of endophthalmitis are also associated with surgeries performed by surgeons with lower annual volume and fewer years of experience (Keay 2012).

Clinical presentation and diagnosis

Postoperative endophthalmitis usually presents within one to two weeks after surgery (acute type), but can also present a few weeks or months after surgery (chronic type) (Keynan 2012). On average, endophthalmitis presents five days after intravitreous injection (Lyall 2012; Simunovic 2012). While endogenous endophthalmitis occasionally affects both eyes, exogenous endophthalmitis affects only the eye that was exposed to the insult (Jackson 2003; Keynan 2012). The most common symptoms, regardless of the mechanism, are eye pain, red eye, and decreased vision. People with exogenous endophthalmitis usually feel well otherwise and are afebrile (Durand 2013). On physical examination, endophthalmitis presents with eyelid and conjunctival swelling, injected conjunctiva, corneal edema, and poor view of the fundus due to inflammation in the aqueous or vitreous humor, or both (Durand 2013; Keynan 2012). Hypopyon, the accumulation of white blood cells in the anterior chamber, is found in over 80% of cases (Lalwani 2008).

The main concern following endophthalmitis is persistent vision loss despite treatment. Visual outcome is highly dependent on the causative organism, with any streptococci causing the worst outcomes, and coagulase-negative staphylococci causing milder cases (Durand 2013). Overall, approximately half of eyes affected by postcataract endophthalmitis do not regain a visual acuity of 20/40 or better, and 10% will lose useful vision (5/200 or worse) (EVS Group 1995). As streptococci cause a higher rate of postinjection endophthalmitis than postcataract endophthalmitis, postinjection endophthalmitis is associated with poorer visual outcomes (Simunovic 2012).

The diagnosis of endophthalmitis is made clinically, but is confirmed by a positive aqueous or vitreous culture. A vitreous specimen is preferable because it has a higher detection rate than an aqueous specimen (54.9% versus 22.5%) (Barza 1997). Nevertheless, a negative culture, which occurs in about 30% of cases, does not exclude the diagnosis (Durand 2013).

Specimen collection is performed by either needle aspirate (an office procedure) or by vitrectomy (performed in the operating room) (Durand 2013). Vitrectomy is considered a useful diagnostic as well as therapeutic method, as it is the fastest way of removing an infection from the vitreous humor. It is favored in patients with severe vision loss (i.e. worse than hand motion) and rapidly worsening vision, or those whose endophthalmitis is likely to be caused by more virulent strains (Barza 1997; Durand 2013).

Description of the intervention

Following specimen collection, endophthalmitis is immediately treated with antibiotics. Intravitreous administration of antibiotics is recommended, as other routes (e.g. topical, subconjunctival, intravenous) have been shown to be less effective (Durand 2013; Packer 2011). While the antibiotic regimen ideally targets the antibiotic sensitivities of the causative organism, it may not be possible to distinguish between different organisms from the presenting symptoms and signs alone. Broad-spectrum antibiotics (i.e. vancomycin plus ceftazidime or amikacin) are therefore typically used first. If there is no improvement in 48 hours, the

culture results dictate whether to give the patient another injection of vancomycin or ceftazidime (Durand 2013).

The use of steroids as adjunctive therapy for endophthalmitis remains controversial. The most commonly used and widely studied steroid is dexamethasone (Bui 2014).

How the intervention might work

Gram-positive bacteria cause the vast majority of cases of postoperative and postinjection endophthalmitis. Most of these cases are caused by coagulase-negative staphylococci, which are commonly found in the normal flora of the ocular surface (Callegan 2002; Keynan 2012). All gram-positive pathogens, except vancomycin-resistant *Enterococcus*, are susceptible to vancomycin. Most gram-negative pathogens that are responsible for bacterial endophthalmitis can be treated with an oxyimino-cephalosporin (e.g. ceftazidime) or an aminoglycoside (e.g. amikacin) (Han 1996; Kunimoto 1999). These antibiotics are bacteriocidal (i.e. they destroy bacteria directly), in contrast to bacteriostatic antibiotics, which work by inhibiting bacterial growth and replication.

It has been hypothesized that steroids may be beneficial in the treatment of endophthalmitis due to their anti-inflammatory effect. Experimental studies suggest that intraocular inflammation is incited by the growth of organisms and the antibiotic-induced release of bacterial cell walls and cell wall components. While an inflammatory response is crucial to the clearance of the infecting organism, this response may result in irreversible damage of the sensitive photoreceptor cells and other secondary damage (Callegan 2002; Callegan 2006). Steroids decrease inflammation by inhibiting migration of macrophages, disruption of vascular membranes, and production of inflammatory mediators (Sadaka 2012). In a rat model of endophthalmitis, a higher level of expression of inflammatory mediators tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), and interferon gamma (IFN-γ) was associated with worse clinical presentation (Petropoulos 2006). Targeting both the infection and subsequent inflammatory response could have synergistic effects and lead to more rapid resolution of endophthalmitis and improvement in vision.

One argument against using steroids as adjunctive therapy is that they may worsen infection control, especially with fungal infections, due to the immunosuppressive properties of steroids. However, a retrospective review of 20 people with postcataract or post-traumatic fungal endophthalmitis showed no difference in the visual outcomes of those who received intravitreous dexamethasone versus those who did not (Majji 1999). Furthermore, there was no statistically significant difference in mean vitreous vancomycin concentration among people with presumed postoperative bacterial endophthalmitis who were treated with versus without intravitreous dexamethasone (Gan 2005).

Why it is important to do this review

Although endophthalmitis is a rare complication of intraocular surgery and intravitreous injection, its treatment is an important clinical issue due to the large number of people who undergo these procedures and the poor visual outcomes after endophthalmitis. Antibiotics are well established as the mainstay of treatment, but the role of steroids remains unclear. Most literature on the use of steroids as adjunctive therapy are reports of preclinical or retrospective case studies; randomized controlled studies on this topic tend to have small sample sizes. By consolidating results across multiple studies in this review, we aimed to determine whether combination therapy with antibiotics and steroids has an obvious benefit over monotherapy with antibiotics. We also planned to address the question of whether there are certain clinical settings in which adjunctive therapy with steroids may be particularly useful in treating endophthalmitis.

OBJECTIVES

To assess the effects of antibiotics combined with steroids versus antibiotics alone for the treatment of acute endophthalmitis following intraocular surgery or intravitreous injection.

METHODS

Criteria for considering studies for this review

Types of studies

We conducted this review according to our published Cochrane protocol (Kim 2016). We included randomized controlled trials (RCTs) in our primary analyses.

Types of participants

We included trials with participants who had clinically diagnosed endophthalmitis within three months of undergoing any intraocular surgery or intravitreous injection (acute endophthalmitis). There was no restriction regarding the result of the vitreous or aqueous culture. We excluded trials with participants with endogenous endophthalmitis, unless outcomes were reported separately by source of infection.

Types of interventions

We included trials that compared antibiotics and steroids versus antibiotics alone for the management of acute postprocedure endophthalmitis. There was no restriction on the method of administration, dose, frequency, or duration of antibiotics or steroids. In participants who received both antibiotics and steroids, the two treatments could have been administered simultaneously, or one type of treatment could have been administered before the other treatment.

Types of outcome measures

Primary outcomes

The primary outcome of the review was complete resolution of endophthalmitis one month after the initiation of therapy. We considered complete resolution as resolution of associated symptoms or hypopyon, or both, but we also accepted definitions used by the investigators of the included trials. We based our primary analysis on one-month outcomes to evaluate whether using steroids as adjunctive therapy provides any benefit in the short term. We also compared outcomes at three, six, and 12 months whenever data were available.

Secondary outcomes

1. Proportion with best-corrected visual acuity (BCVA) 20/40 (LogMAR 0.30) or better one month after the initiation of therapy.

2. Improvement in BCVA, defined as a proportion with a gain of 2 lines or more from baseline on a LogMAR chart or equivalent, at one month.
3. Mean change in intraocular pressure (IOP) from baseline at one month. When the mean one-month change in IOP was not reported, we used the mean IOP at one month, as long as the baseline IOP was similar between intervention groups.
4. Proportion with IOP less than 21 mmHg at one month.

Adverse events

We evaluated ocular and systemic adverse effects relating to antibiotic or steroid use that were reported in the included trials.

Economic data

We did not conduct formal cost-effectiveness analyses, but we compared the costs associated with the interventions when data were available.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases. There were no study design, language, or publication year restrictions. The date of the search was 17 August 2021.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 8) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched August 2021) (Appendix 1)
- MEDLINE Ovid (1946 to August 2021) (Appendix 2)
- Embase Ovid (1980 to August 2021) (Appendix 3)
- LILACS (Latin American and Caribbean Health Science Information database (1982 to August 2021) (Appendix 4)
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched August 2021) (Appendix 5)
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched August 2021) (Appendix 6)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/ictrp; searched August 2021) (Appendix 7)

Searching other resources

We searched the reference lists of included trials to identify additional relevant trials. We did not search conference proceedings for the specific purposes of this review because they are searched annually by Cochrane Eyes and Vision, and all reports from trials identified are included in CENTRAL.

Data collection and analysis

Selection of studies

Two review authors (SE, KK) independently assessed the titles and abstracts of all records identified by the literature searches. We categorized each record as 'definitely relevant,' 'possibly relevant,' or 'definitely not relevant.' For records assessed as 'definitely relevant' or 'possibly relevant,' we obtained the full-text report and grouped them into studies. Two review authors independently reviewed each study and classified each study as 'include,' 'exclude,' or 'unsure.' Any discrepancies between review authors were resolved by discussion at each stage of selection. We documented studies that were excluded following review of the full-text reports, along with their reasons for exclusion, in the Characteristics of excluded studies table. For studies assessed as 'unsure' after review of the full-text reports, we contacted the study authors for clarification. In cases where we received no response after two weeks, we classified the study based on available information.

Data extraction and management

We extracted and recorded data-related study methods, participant characteristics, and outcomes from the selected trials onto standard paper data collection forms. We pilot-tested the forms on one study before using them for all of the included studies.

Two review authors (SE, KK) independently extracted the data, resolving any discrepancies by discussion. One review author entered the data into RevMan Web (RevMan Web 2022), and a second review author checked the data entry.

Assessment of risk of bias in included studies

Two review authors (SE, KK) independently assessed the risk of bias of each included study according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We considered the following risk of bias domains.

- Selection bias: random sequence generation, allocation concealment before randomization
- Performance bias: masking of study participants and personnel
- Detection bias: masking of outcome assessors
- Attrition bias: loss to follow-up
- Reporting bias: selective outcome reporting
- Other potential sources of bias (e.g. funding source, sponsor's involvement in trial)

We evaluated each domain for each trial as low, high, or unclear risk. Any discrepancies between review authors were resolved by discussion.

Measures of treatment effect

We measured treatment effects based on the types of data as described in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017), which included the following.

Dichotomous data

We reported the proportions of participants with complete resolution of endophthalmitis, improvement of BCVA, IOP less than 21 mmHg, and adverse effects. We calculated risk ratios (RRs) with 95% CIs to estimate treatment effects.

Continuous data

Outcomes with continuous data included mean IOP and mean change in IOP. We calculated mean differences with 95% CIs to estimate treatment effects.

Qualitative data

We described types of adverse effects and economic data qualitatively whenever quantitative description was not possible.

Unit of analysis issues

The individual (one study eye per participant) was the unit of analysis. There were no unit of analysis issues because each person was randomized to a treatment, and only one eye was affected.

Dealing with missing data

We contacted study investigators to request unpublished data, clarify unclearly reported data, and/or provide reasons for missing data or loss to follow-up. When we did not receive a response within two weeks, we used the information available in the published reports. We did not impute data for the purposes of this review. When we were unable to assume data were missing at random, we documented the outcomes with missing data and commented on potential implications in the Discussion section of the review. We referred to Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* for guidelines on how to interpret missing data (Higgins 2017).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by examining variations in study characteristics (e.g. methodology, participant characteristics, interventions compared, follow-up duration). We used the I^2 statistic to assess the degree of statistical heterogeneity across studies. When the I^2 statistic was greater than 50%, we considered the impact of heterogeneity to be substantial. We also performed a visual assessment of the forest plot to assess heterogeneity, with poor overlap of study estimates and CIs indicating heterogeneity.

Assessment of reporting biases

Had we included 10 or more studies in a meta-analysis, we would have created funnel plots in RevMan Web to assess publication bias. We evaluated selective outcome reporting as part of the risk of bias assessment. We planned to compare outcomes reported in the included studies with outcomes reported in the study protocols, published design and methods papers, or clinical trial registry records, when these were available.

Data synthesis

We presented the results in a narrative summary when there was substantial clinical or methodological heterogeneity, or when statistical heterogeneity and assessment of the forest plots indicated that meta-analysis was not appropriate. In the absence of substantial heterogeneity, we combined the results of included studies and estimated treatment effects using meta-analysis with a random-effects model, or with a fixed-effect model when the outcome was available from fewer than three studies.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analysis and investigate heterogeneity by type of intraocular procedure (e.g. cataract, glaucoma, retina), mode of steroid delivery, mode of antibiotic delivery, class of antibiotic used, and use of pars plana vitrectomy, when sufficient data were available.

Sensitivity analysis

We planned to conduct sensitivity analyses to evaluate the impact of excluding studies at high risk of bias in one or more domains, studies with only unpublished outcome data, and industry-funded studies, when sufficient data were available.

Summary of findings and assessment of the certainty of the evidence

A summary of findings table provides key findings regarding the certainty of evidence, the magnitude of effect of the interventions examined, and the sum of available data on all primary and secondary outcomes. Two review authors (SE, KK) independently assessed the certainty of evidence for each outcome using the GRADE approach (GRADEpro GDT). Any discrepancies were resolved by discussion.

RESULTS

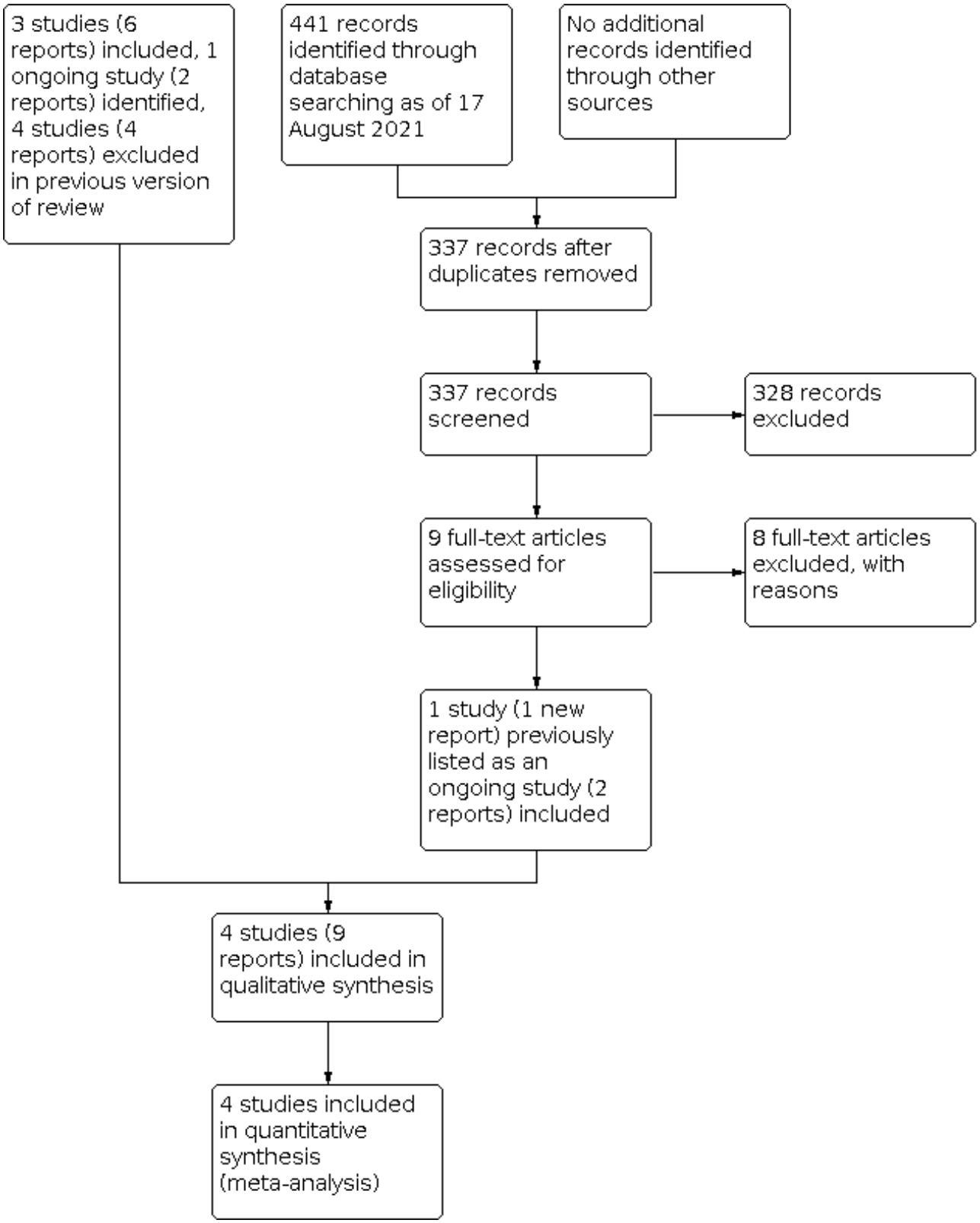
Description of studies

Results of the search

We presented the detailed results of the original search in the previously published version of this review (Kim 2017). Briefly, we included three studies (six reports); identified one ongoing study (two reports); and excluded four studies (four reports) from 1540 records identified by our search of the databases in December 2016.

We performed an updated electronic database search on 17 August 2021, which yielded 337 unique records. After title and abstract screening, we retrieved nine full-text reports for further review. We included one study (one report) and excluded eight studies (eight reports). The one newly included study was previously listed as an ongoing study (Manning 2018). Overall, we included four studies (nine reports) and excluded 12 studies (12 reports). A study flow diagram is shown in Figure 1.

Figure 1. Study flow diagram.



Included studies

This review includes four RCTs (Albrecht 2011; Das 1999; Gan 2005; Manning 2018). In all trials, one eye per participant was randomized. Two trials stratified participants based on etiology groups: the groups for Albrecht 2011 were "post cataract," "bleb-related," and "other" (trauma related, endogenous, post-pars plana

vitrectomy), while the groups for Das 1999 were "postoperative" and "post-traumatic." No studies were industry funded.

Types of participants

We included a total of 264 participants in this review update after the exclusion of 13 participants from the "bleb-related" group and 17 participants from the "other" group in Albrecht 2011, as well as 34 participants from the "post-traumatic" group in Das 1999. We excluded the "bleb-related" group because bleb-related endophthalmitis usually occurs months to years after glaucoma surgery. All of the included studies enrolled participants with a similar clinical diagnosis of suspected bacterial endophthalmitis. Except for one participant in the "postoperative group" who had a penetrating keratoplasty prior to being diagnosed with endophthalmitis, all participants in Das 1999 had postcataract endophthalmitis. The inclusion criteria for both Gan 2005 and Manning 2018 stated that the cataract surgery must have been performed within six weeks of the onset of endophthalmitis and with the expectation that postoperative visual acuity would be 20/100 or better, Gan 2005, or better than 20/100 (Manning 2018). Albrecht 2011 and Das 1999 did not report a maximum time period between the date of surgery and onset of endophthalmitis. However, Albrecht 2011 reported the mean delay of presentation as 20.25 days when including three chronic cases, and 8.6 days when excluding chronic cases. It was not possible to exclude the participants with chronic cases from this review. All of the included studies excluded any person with suspected fungal endophthalmitis. The studies were conducted in the following countries: South Africa (Albrecht 2011), India (Das 1999), and the Netherlands (Gan 2005; Manning 2018). Albrecht 2011 and Das 1999 enrolled participants who were similar in age (mean age of about 60), while Manning 2018 and Gan 2005 enrolled an older patient population (mean age of about 75 and 80, respectively). Both males and females were included in all studies. Baseline characteristics were similar between intervention groups in Albrecht 2011 and Manning 2018. The other two studies did not report statistics comparing baseline characteristics between intervention groups. The overall positive culture rates were 53%, 68%, and 69% for Albrecht 2011, Manning 2018, and Gan 2005, respectively. The positive culture rate for the postoperative group in Das 1999 was 56%.

Types of interventions

All trials used intravitreous dexamethasone with intravitreous antibiotics in the steroid group. The choice of antibiotics differed by study: vancomycin and ceftazidime in Albrecht 2011, vancomycin and amikacin in Das 1999, and vancomycin and gentamicin in Manning 2018 and Gan 2005. In each trial, the control group received the same intravitreous antibiotics as the steroid group. Participants in the control group for Manning 2018, Albrecht 2011, and Gan 2005 received antibiotics in a placebo solution, while participants in the control group in Das 1999 received intravitreous antibiotics without a placebo solution. No participants in Albrecht 2011 had a vitrectomy, while all participants in Das 1999 had vitrectomies. All participants with a baseline visual acuity at light perception only, and some participants with complications in Gan 2005 and Manning 2018 had vitrectomies. The trials also differed as to whether another injection of intravitreous dexamethasone and antibiotics was provided. Participants in Albrecht 2011 received a second injection of dexamethasone and antibiotics after 48 to 72 hours as required. Some participants in Das 1999 received another injection of intravitreous antibiotics, but no participants received additional intravitreous dexamethasone. In Gan 2005 and Manning 2018, the injection of antibiotics and dexamethasone or placebo was repeated once in all participants three to four days later. Other additional interventions are detailed in the Characteristics of included studies tables.

Types of outcomes

Primary outcome

No studies reported on our primary outcome, complete resolution of endophthalmitis. However, Das 1999 reported a somewhat similar outcome they termed "combined anatomical and functional success." This outcome was defined as the total percentage of participants with an IOP of at least 5 mmHg (i.e. anatomical success) and a BCVA of at least 6/120 (i.e. functional success). The time point for this outcome was unclear, but Das 1999 reported that visual acuity was measured at baseline as well as one, four, and 12 weeks after surgery. Other outcomes reported by Das 1999 involved quantitative inflammation scoring based on the clinical appearance of the cornea, anterior chamber, iris, and the vitreous. However, these outcomes were reported for postoperative and post-traumatic participants as a whole (while combined anatomical and functional success were reported for each group separately), and were not included in the evidence for this review.

Secondary outcomes

Although no study investigators reported the proportion of participants with BCVA of 20/40 (LogMAR 0.30) or better one month after the initiation of therapy as proposed in this review, Manning 2018 reported the percentage of participants in each visual outcome category and mean IOP at one year. Albrecht 2011 reported the percentage of participants in each of the following Snellen visual acuity groups at three months: group 1 (6/6 to 6/18), group 2 (6/24 to 6/60), group 3 (worse than 6/60). Gan 2005 reported the number of participants in each of the following Snellen visual acuity groups at three and 12 months: light perception (LP) to hand motion (HM), counting fingers (CF), 0.1 to 0.25, 0.4 to 1.0. We combined the three-month Snellen visual acuity data by converting the percentage of participants into number of participants for each visual acuity group for Albrecht 2011 and regrouping the visual acuities for Gan 2005 using the cut-offs reported in Albrecht 2011. The "post cataract" group from Albrecht 2011 and all participants from Gan 2005 were included in the meta-analysis. We also categorized 12-month visual acuities from Gan 2005 into the groups used for the three-month visual acuities (i.e. 6/6 to 6/18, 6/24 to 6/60, worse than 6/60). For both the three- and 12-month visual acuity outcomes, we compared only the proportion of participants in group 1 (6/6 to 6/18) with those not in group 1 because this comparison was the most clinically useful. Although Manning 2018 reported BCVA, neither Albrecht 2011 nor Gan 2005 specified whether the visual acuities that they reported were 'best-corrected.'

While no studies reported improvement in BCVA as a proportion with a gain of 2 lines or more, Albrecht 2011 reported mean number of lines of improvement on a Snellen visual acuity chart for the "post-cataract" group. For each participant, the number of lines of improvement was determined by comparing the visual acuity at three months with the visual acuity at admission. While the Snellen visual acuities at baseline, three months, and 12 months were provided for all participants in Gan 2005, it was not possible to

calculate the number of lines of improvement. Some participants had a baseline visual acuity of light perception, which does not have an equivalent visual acuity on the Snellen chart.

Except for what was included in the "combined anatomical and functional success" outcome, no outcomes related to visual acuity or IOP were reported by Das 1999. The remaining three studies did not report outcomes related to IOP.

Adverse events

Three studies reported adverse events in participants (Albrecht 2011; Gan 2005; Manning 2018). Das 1999 did not report any adverse events.

Economic data

No studies reported costs associated with the interventions.

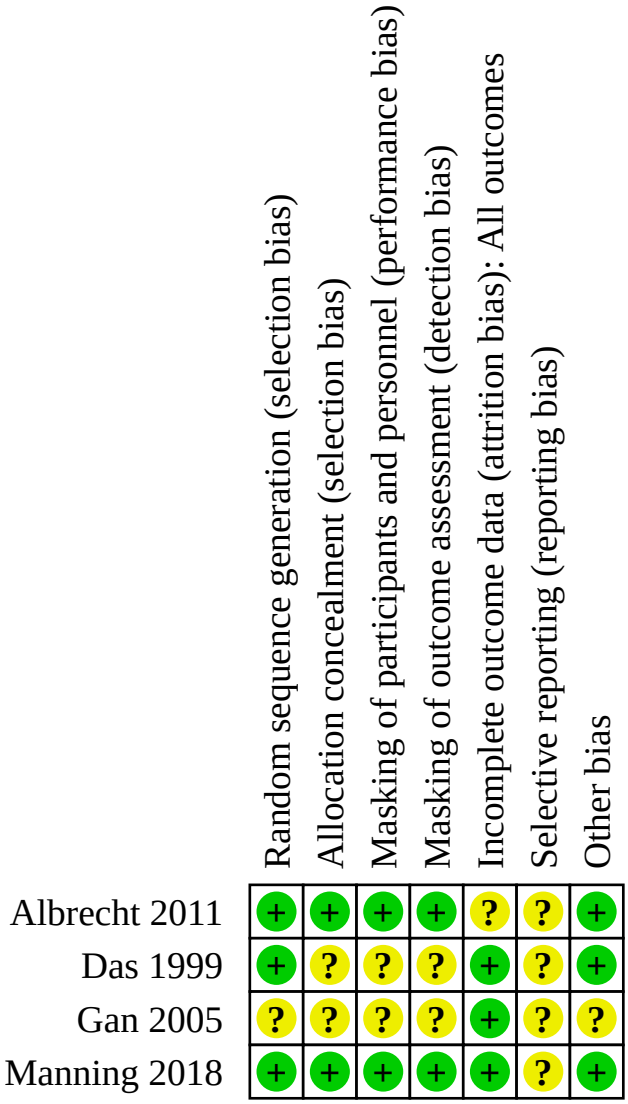
Excluded studies

We excluded 13 studies after full-text review; reasons for their exclusion are provided in the Characteristics of excluded studies table. In summary, we excluded seven studies because they were not RCTs and five studies because they investigated the use of adjunctive corticosteroids for the purpose of prophylaxis. The remaining study was excluded because it examined early versus delayed intravitreal corticosteroids for the treatment of acute postoperative endophthalmitis (Koehrer 2016).

Risk of bias in included studies

A risk of bias summary assessment is shown in Figure 2.

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



Allocation

We assessed three trials as at low risk of bias for reporting of random sequence generation procedures (Albrecht 2011; Das 1999; Manning 2018), and two trials at low risk of bias for allocation concealment before randomization (Albrecht 2011; Manning 2018). In two studies, allocation was performed by the pharmacy based on computer-generated random sequences (Albrecht 2011; Manning 2018). In Das 1999, randomly generated assignments were placed in sealed envelopes and opened by circulating nurses just before the preparation of the intraocular solutions. However, the risk of allocation concealment was unclear because the article does not mention whether the envelopes were sequentially numbered or opaque or whether they were opened sequentially. No information on random sequence generation or allocation concealment, or both, was provided in Gan 2005, so we assessed the risk of selection bias as unclear.

Masking (performance bias and detection bias)

We assessed Albrecht 2011 as at low risk of performance bias because a label hid the injection assignment from the participants and the surgeon. After receiving clarification from the trial author over email that visual acuities were measured by nursing staff without any knowledge of the trial, we also assessed Albrecht 2011 as at low risk of detection bias. We judged Manning 2018 as having low risk of performance and detection bias because the study authors claimed that participants, study personnel, and

outcome assessors were masked with the use of similar vials containing indistinguishable clear fluids. We classified the risk of performance and detection bias as unclear for the other two trials because the masking of participants and personnel administering the injection, as well as outcome assessors, was not clearly described.

Incomplete outcome data

Das 1999 reported no losses to follow-up or adverse events, therefore we assessed the risk of attrition bias as low. We also assessed Gan 2005 as having a low risk of attrition bias because only one participant was lost to follow-up at 12 months, and the numbers of adverse events were similar between the steroid and placebo groups. In Manning 2018, all participants who were randomized were included in the intention-to-treat analysis, except for the erroneous inclusion of one participant each group; we judged this study as having low risk of attrition bias. We assessed the risk of attrition bias as unclear for Albrecht 2011 because four out of 62 participants in the placebo group were lost to follow-up, and the reasons for loss to follow-up were not reported (and were unknown to the trial author when asked by email). A modified intention-to-treat analysis was performed in which participants were analyzed by assigned treatment groups, but those without outcome information at three months' follow-up were removed.

Selective reporting

A clinical trial registry record was available for one study, but it was unclear if the prespecified outcomes were fully reported in the final paper (Manning 2018). We judged this study as at unclear risk of bias. We assessed the three remaining trials as at unclear risk of reporting bias because no trial protocols or clinical trial registry records were available to compare the planned outcomes with the reported outcomes. Furthermore, Das 1999 reported visual acuity outcomes differently than described in the methods section of the study report. Instead of reporting visual acuity measurements at one, four, and 12 weeks postoperatively, Das 1999 reported a combined rate of functional success (visual acuity of at least 6/120) and anatomical success (IOP of at least 5 mmHg). It was not possible to verify whether the rate of functional and anatomical success was a planned outcome because we did not have access to the original study protocol.

Other potential sources of bias

One study stopped enrolling participants prematurely because the manufacturer of dexamethasone withdrew it from the markets (Gan 2005). We assessed the risk of bias as unclear for this study. We identified no other potential risk of bias in the remaining studies (Albrecht 2011; Das 1999; Manning 2018); none of these studies reported industry funding or other funding sources that could have introduced a conflict of interest.

Effects of interventions

See: **Summary of findings 1** Combined steroid and antibiotic therapy compared with antibiotics alone for acute endophthalmitis after intraocular procedure

Of a total of 264 randomized participants, 259 participants were analyzed, of which 127 participants received intravitreous steroids in addition to intravitreous antibiotics and 132 participants received only intravitreous antibiotics.

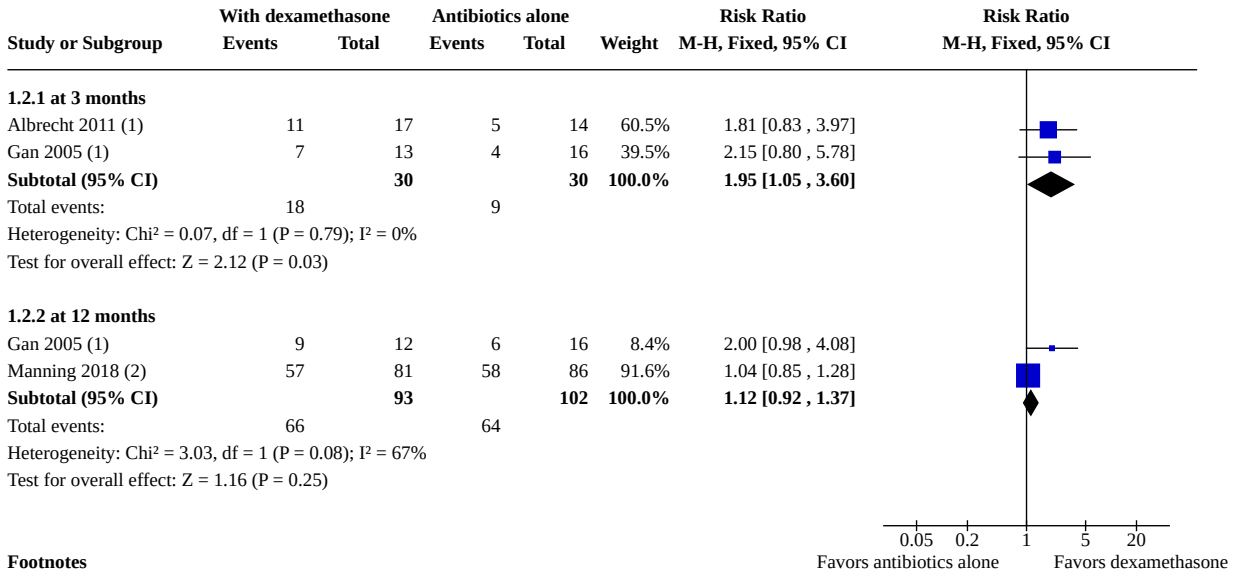
Resolution of endophthalmitis

In one study, 26 (32.1%) participants in the dexamethasone group and 27 (31.4%) participants in the placebo group showed no bacterial growth in vitreous biopsy at one year (risk ratio (RR) 1.02, 95% confidence interval (CI) 0.66 to 1.60; 167 participants; Analysis 1.1) (Manning 2018). However, it was not explicitly reported if those participants were culture-positive or -negative at baseline, resulting in no analysis performed for this outcome. While no other included study reported on complete resolution of endophthalmitis, Das 1999 reported on the rate of combined anatomical and functional success. Anatomical success was defined as IOP of at least 5 mmHg, and functional success as visual acuity of at least 6/120. Among participants with postoperative endophthalmitis, 87.5% (14 out of 16) of those who received intravitreous dexamethasone and intravitreous antibiotics achieved anatomical and functional success, compared with 81.5% (13 out of 16) of the intravitreous antibiotics-alone group (RR 1.08, 95% CI 0.80 to 1.45; Analysis 1.1). For an unknown reason, the percentage of participants who achieved combined success in the dexamethasone group was slightly higher (i.e. 93.8%; 15 out of 16) if calculated from Das 1999's Table 3 compared to the percentage reported in the results text of the study. We chose to include the percentage from the results text in the review. We graded the certainty of the evidence as very low (−1 for risk of bias, −1 for indirectness, −1 for imprecision).

Visual acuity

Three studies assessed visual acuity outcomes in people with endophthalmitis after cataract surgery (Albrecht 2011; Gan 2005; Manning 2018). In two studies (Albrecht 2011; Gan 2005), participants who received intravitreous dexamethasone and antibiotics were more likely to have a good visual outcome (6/6 to 6/18) compared with those in the antibiotics-alone group at three months (RR 1.95, 95% CI 1.05 to 3.60; 2 studies; N = 60; Analysis 1.2; Figure 3). Two studies reported visual acuity at 12 months following treatment (Gan 2005; Manning 2018). The estimated risk ratio of having a good visual outcome (6/6 to 6/18, or LogMAR 0.3 or better) at 12 months was 1.12 (95% CI 0.92 to 1.37; 2 studies; N = 195; Analysis 1.2; Figure 3). Although I^2 may represent substantial heterogeneity (I^2 = 67%) in this analysis, we have presented the pooled estimate because only two studies are included (i.e. low power), and the direction of effect is the same in the two studies. We assessed the certainty of evidence as low for this outcome, downgrading for risk of bias (−1) and imprecision (−1) due to wide confidence intervals.

Figure 3. Forest plot of comparison: 1 Adjunctive intravitreal dexamethasone versus antibiotics alone, outcome: 1.2 Snellen visual acuity 6/6 to 6/18.



Footnotes

(1) Snellen visual acuity 6/6 to 6/18

(2) logMAR 0.3 or better

Albrecht 2011 was the only study to report an outcome related to improvement in visual acuity. For participants in the postcataract group, there was no statistically significant difference in the mean number of Snellen lines of improvement at three months between those who received intravitreous dexamethasone and those who received placebo (4.1 versus 2.7, P = 0.33). Albrecht 2011 did not provide standard deviations (SDs) or standard errors, therefore we could not calculate the estimated mean difference and 95% CI.

Das 1999 reported no visual acuity outcomes except for what was included in the combined anatomical and functional success outcome.

Intraocular pressure

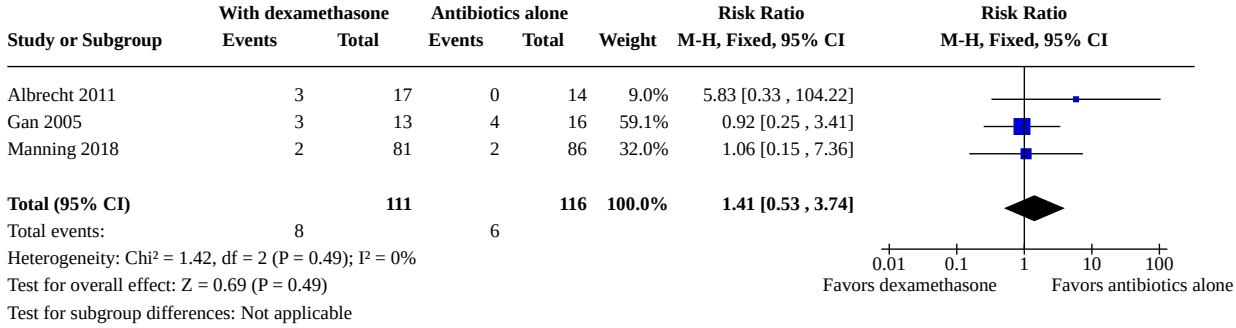
No study reported IOP outcome data at our prespecified time point of three months. One study showed that after 12 months of therapy, IOP changed to 13.9 mmHg (SD 4.5) from 16.3 mmHg (SD 8.7) at baseline in the dexamethasone group, and to 15.8 mmHg (SD 8.1) from 16.3 mmHg (SD 8.0) at baseline in the antibiotics-alone group (mean difference −1.90, 95% CI −3.78 to 0.07; N = 167; Analysis 1.3) (Manning 2018). Except for what was included in the combined anatomical and functional success outcome in Das 1999, no other studies reported outcomes related to IOP.

We graded the certainty of the evidence for this outcome as low (−2 for imprecision).

Adverse events

Three studies reported the occurrence of adverse events, as described in Table 1 (Albrecht 2011; Gan 2005; Manning 2018). The total numbers of adverse events were 14 out of 111 (12.6%) for those who received dexamethasone versus 12 out of 116 (10.3%) for those who received antibiotics alone. All three retinal detachments (RDs) reported by Albrecht 2011 followed complicated cataract surgery and the use of intravitreous steroids. Since RDs were the only adverse events shared by the three studies, we performed a pooled analysis for this outcome with the postcataract group from Albrecht 2011 and all participants in Gan 2005 and Manning 2018 (Figure 4). The difference in the occurrence of retinal detachment between those who received dexamethasone and those who did not was uncertain (RR 1.41, 95% CI 0.53 to 3.74; Analysis 1.4); we judged the certainty of the evidence for this outcome to be low (−1 for risk of bias, −1 for imprecision).

Figure 4. Forest plot of comparison: 1 Adjunctive intravitreal dexamethasone versus antibiotics alone, outcome: 1.3 Retinal detachment.



Gan 2005 also reported the number of participants who underwent a secondary procedure in each intervention group. Three participants in the dexamethasone group underwent a secondary procedure (one vitrectomy and gas for RD, one vitrectomy and silicone oil for persistent inflammation and proliferative vitreoretinopathy, one vitrectomy and silicone oil for RD) compared to four participants in the placebo group (three vitrectomy and silicone oil for RD, one vitrectomy for hypotony).

Similarly, Manning 2018 reported the number of participants who underwent reoperations in each intervention group. Each group had six participants who underwent a vitrectomy; however, each participant had varying indications. Two participants underwent vitrectomies for floaters in the dexamethasone group compared with one participant in the placebo group. Two participants underwent vitrectomies for pucker in the dexamethasone group compared with three participants in the placebo group. Lastly, each group had two participants who underwent vitrectomies for RD.

Das 1999 did not report any adverse events.

Economic data

No trial reported costs associated with the interventions.

DISCUSSION

Summary of main results

In this review, we have presented the results of four RCTs that compared the effects of adjunctive steroid therapy versus antibiotics alone in people with suspected bacterial endophthalmitis after an intraocular procedure. All studies used intravitreous dexamethasone for adjunctive steroid therapy and a combination of intravitreous antibiotics with gram-positive and gram-negative bacterial coverage for the antibiotic therapy. Overall, the included trials provided insufficient evidence to either support or refute the use of adjunctive steroids for the treatment of postoperative endophthalmitis (Summary of findings 1). None of the included studies reported the primary outcome of complete resolution of endophthalmitis as defined in our protocol. One study investigated the effect of adjunctive steroid therapy on the rate of combined functional and anatomical success (as defined by visual acuity and IOP parameters) compared with antibiotics alone, and found no evidence of a difference between groups (Das 1999). A pooled analysis of two studies revealed that adjunctive dexamethasone resulted in a good visual outcome (i.e. Snellen visual acuity of 6/6 to 6/18) at three months compared with antibiotics alone (Albrecht 2011; Gan 2005). Conversely, there was little to no difference between participants who received adjunctive dexamethasone and those who received antibiotics alone in achieving a good visual outcome (visual acuity of 6/6 to 6/18, or LogMAR 0.3 or better) at 12 months (Gan 2005; Manning 2018). One study reported no difference in visual acuity improvement from baseline between the participants treated with versus those treated without steroids (Albrecht 2011). Although one study stratified causative organisms for endophthalmitis between the two intervention groups at one year, the effect of the interventions could not be analyzed because their baseline biopsy results were not provided. Only one study examined IOP, with results suggesting a slight reduction in IOP after 12 months with the use of adjunctive dexamethasone compared with antibiotics alone (Manning 2018). Three studies reported adverse events; the only adverse event shared between the studies was retinal detachment (Albrecht 2011; Gan 2005; Manning 2018). The effect of adjunctive steroid therapy on the occurrence of retinal detachment was uncertain. No study investigated costs associated with the interventions, therefore this outcome remains unknown.

Overall completeness and applicability of evidence

By expanding the inclusion criteria of this review to include participants with acute endophthalmitis after any type of intraocular procedure, we hoped that we would find trials that examined the treatment of endophthalmitis following a variety of intraocular procedures. However, almost all of the included trials reported outcomes for participants who were diagnosed with endophthalmitis after cataract surgery. Also, none of the included studies examined the effect of adjunctive steroid therapy by causative organism. We were therefore unable to address whether adjunctive steroids are useful in certain clinical settings (e.g. specific procedures or causative organisms).

It should be noted that there were some differences in treatment regimens between the different studies, as well as what is considered current practice, which may limit the applicability of the evidence. Currently, a vitrectomy is recommended as soon as endophthalmitis is suspected and prior to intravitreous antibiotics for patients with a presenting visual acuity of light perception only (Barry 2013). Barry and colleagues also favor a vitrectomy for certain cases of acute endophthalmitis even if the presenting visual acuity is better than light perception (Barry 2013). If the patient does not improve within the first 24 to 48

hours, a vitrectomy would usually be considered (if not performed already), or a partial vitrectomy would be expanded to a full vitrectomy (Barry 2013). However, a vitrectomy was performed in the appropriate set of participants in Gan 2005 and Manning 2018. All participants had a vitrectomy prior to intravitreous injection in Das 1999, and no participants had a vitrectomy in Albrecht 2011. There were also differences in the choice of intravitreous antibiotics. All studies used vancomycin, but the second antibiotic used was ceftazidime in Albrecht 2011, amikacin in Das 1999, and gentamicin in Gan 2005 and Manning 2018. Current guidelines recommend using vancomycin and ceftazidime or, rarely, amikacin. Despite their synergistic effects against gram-positive bacteria when used with vancomycin, aminoglycosides, including amikacin and gentamicin, are less frequently used because of their risk for retinal toxicity. Although gentamicin also provides gram-negative (including *Pseudomonas*) coverage, the use of gentamicin could make these two studies less applicable to current practice than the other two studies. Also, the variability in treatment regimen following the additional injection is less than ideal. There are no guidelines on whether to give a second steroid injection, but it is recommended that a second injection of intravitreous antibiotics (antibiotic choice dependent on culture results) be considered in 24 to 48 hours if there is no improvement (Barry 2013). A repeat intravitreous antibiotic injection was only given when necessary in Albrecht 2011 and Das 1999, while all participants had a repeat injection three to four days later in Gan 2005 and Manning 2018.

Inconsistency in the types of outcomes reported and follow-up intervals made it difficult to combine the studies. Unfortunately, there is no standard way of quantifying resolution or successful management of endophthalmitis. Das 1999's measure of combined anatomical and functional success may be appropriate in a research setting, but may not be useful for determining whether treatment is successful in a clinical setting. Other potential ways of quantifying success are by clinical examination and patient-reported eye pain (or other quality of life measures). With regard to visual acuity outcomes, we performed pooled analysis on the proportion of participants in each of the Snellen visual acuity groups (as defined by Albrecht 2011 or Manning 2018) at three and 12 months. The evidence regarding visual acuity would have been more complete if visual acuity outcomes at additional time intervals had been reported and shared among studies. Had we been able to examine how visual acuity changed over time between the two intervention groups, we would have a better understanding of whether adjunctive steroid therapy is harmful or beneficial at certain points in the recovery process.

Quality of the evidence

We found two studies at an overall low risk of bias, Albrecht 2011 and Manning 2018, while the other two studies had some methodological limitations (Das 1999; Gan 2005). We considered the evidence for the effect of adjunctive steroid therapy on combined anatomical and functional success to be of very low certainty, downgrading for unclear risk of bias for most outcomes, indirectness of outcome, and imprecision of results with uncertainty in the direction of the true effect. We graded the certainty of the evidence as low for the proportion of participants with visual acuity of 6/6 to 6/18, or LogMAR 0.3 or better, at three and 12 months due to unclear risk of bias and imprecision. We judged the certainty of the evidence for intraocular pressure as low due to imprecision of results. Lastly, we graded the certainty of the evidence for the occurrence of retinal detachment as low due to unclear risk of bias and imprecision of results.

Potential biases in the review process

We did not identify any specific biases. It is likely that all relevant studies have been included in this review, as we used a highly sensitive strategy to search bibliographic databases, clinical trial databases, and reference lists of included studies. Also, two review authors performed major steps of the review process independently in order to minimize bias and errors.

Agreements and disagreements with other studies or reviews

While only four RCTs have compared adjunctive steroid therapy with antibiotics alone for the treatment of acute postoperative endophthalmitis, several non-randomized studies have studied this comparison. Most studies found that the use of intravitreous steroids had no significant effect on final visual outcome (Dev 2005; Eifrig 2003; Hall 2008; Miller 2004; Pijl 2010). Due to the retrospective nature of these studies, there was a wide range in the follow-up periods within and among studies, ranging from months to years. Three studies included only patients with postcataract endophthalmitis (Dev 2005; Hall 2008; Pijl 2010), while the other two studies examined those with endophthalmitis caused by a specific organism regardless of etiology: *Streptococcus pneumoniae* in Miller 2004 and *Pseudomonas aeruginosa* in Eifrig 2003. The one study that showed a harmful effect of adjunctive steroid therapy was Shah 2000, which found that administering adjunctive steroids in participants with postcataract endophthalmitis resulted in a significant worsening of visual acuity. This negative effect was seen when comparing mean visual acuities at one, three, and six months, as well as comparing the percentage of participants with a 3-line improvement by one and three months. The Shah 2000 study investigators proposed steroid-induced toxicity or blunting of the immune response, or both, as possible reasons for their findings. In contrast, one small retrospective case series on culture-positive *Staphylococcus aureus* endophthalmitis (note: 26% of participants had non-acute postoperative endophthalmitis) showed that the addition of intravitreous dexamethasone to intravitreous antibiotics had a significantly beneficial effect on final visual outcome (Mao 1993). Similar to our study, a significant effect was found when examining the proportion with good visual outcome (i.e. visual acuity of 20/50 or better) at last follow-up time point (mean: 13 months, range: one month to 4.5 years). Another study that observed a beneficial effect of adjunctive steroids examined the use of systemic and topical steroids (Koul 1989), unlike our review. This retrospective, multicenter study in Sweden reported that participants treated with a combination of topical and systemic steroids in conjunction with intravitreous antibiotics had better final visual acuities than those treated with no steroids or only topical steroids. Only a few studies compared the occurrence of adverse events. Dev 2005 reported no difference in the need for a second procedure to manage endophthalmitis and the occurrence of late postoperative complications, while Eifrig 2003 reported no difference in the need for enucleation or evisceration.

More recently, Robbins 2020 performed a retrospective, non-randomized comparative study in which they evaluated visual outcomes in patients with endophthalmitis who were treated with or without systemic corticosteroid therapy. Investigators found

that in 133 eyes with endophthalmitis, 33 (25%) received oral steroids (and 32 of these eyes also received topical steroids). Oral steroid use was associated with an improvement in visual acuity of 3 lines or more after endophthalmitis and a greater improvement comparing visual acuity at presentation to six-month follow-up. However, in a retrospective chart review of 63 eyes with endophthalmitis, Moisseiev 2017 found similar improvements in mean visual acuity in the 19 eyes (30%) that received intravitreal antibiotics and dexamethasone versus the eyes that received intravitreal antibiotics alone. Given the heterogeneity of even more recent results and innovations in intraocular surgery techniques and new antibiotics, Soliman 2019 was interested in evaluating current treatment patterns for endophthalmitis. In their multicenter study describing international practice patterns, Soliman 2019 found that in 237 eyes diagnosed with acute endophthalmitis after intraocular surgery or intravitreal injections, all received intravitreal antibiotics on the day of presentation, but only a minority received adjunctive steroid therapies, with 25.3% receiving intravitreal steroids and 21.9% receiving systemic steroids.

In a narrative review of the literature, Rahmani 2018 came to similar conclusions as those of this review, noting that limited small studies have not shown improvement in long-term visual outcomes with the use of intravitreal steroids. Furthermore, Rahmani 2018 pointed out that although adjunctive steroids are commonly used at the time of diagnosis for more severe cases of endophthalmitis, surgeons should exercise caution and consider the potential for inadequate first-line antibiotic coverage, and think about waiting until the pathogen and drug sensitivities are identified before using intravitreal steroids.

Considering the paucity of data and heterogeneity of the results, it is not possible to conclude whether intravitreous dexamethasone is beneficial or harmful in the treatment of acute endophthalmitis after intraocular procedure from these studies. A recent review concluded that since most of the current literature does not show an effect of adjunctive steroid therapy, and Shah 2000 showed a detrimental effect, the routine use of adjunctive intravitreous steroids for acute endophthalmitis is not supported at this time (Bui 2014). We agree with Bui 2014 that RCTs at low risk of bias and with adequate power should be completed to clarify whether adjunctive steroid therapy may be helpful in certain clinical settings and should be avoided in others.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence for the effectiveness of steroids in conjunction with intravitreous antibiotics for the treatment of acute endophthalmitis following intraocular procedure is insufficient to provide support either for or against their usage. One trial indirectly measured treatment success by determining whether participants achieved improvements in visual acuity or intraocular pressure, but the effect of adjunctive steroid therapy on this outcome was uncertain. We found low certainty evidence suggesting there is a higher chance of having a good visual outcome at three months in the adjunctive steroid group compared with antibiotics alone, and no evidence of a difference between groups at 12 months. Furthermore, the effect of adjunctive steroids on the rate of complications (e.g. retinal detachment) remains unexplored. Although this review showed a possible beneficial effect on visual acuity with adjunctive steroid use, most of the current evidence on this topic is inconsistent and has major limitations. We therefore cannot conclude at this time if adjunctive steroid therapy is beneficial or harmful in the treatment of acute postprocedure endophthalmitis when compared to antibiotics alone.

Implications for research

This review highlights the limited amount of randomized controlled trial (RCT) data available for assessing the effect of adjunctive steroids for postprocedure endophthalmitis treatment, as well as potential ways to expand the current literature. Most of the RCTs and comparative, non-randomized studies that have been conducted to date have focused on treatment of endophthalmitis after cataract surgery. This is understandable considering that the large majority of endophthalmitis occurs after cataract surgery; however, we believe that studying the effect of adjunctive steroids on other intraocular surgeries, as well as intraocular injections, is also important. Furthermore, two of the four included studies combined patients of different etiologies (e.g. post-traumatic) for some outcomes, which could make the patient population more heterogeneous than desired. Conducting such larger RCTs may also allow for examination of the effect of adjunctive steroid therapy by type of causative organism. Studying the comparison of adjunctive steroid therapy and antibiotics alone in more specific patient populations may not only help us understand whether steroids should be administered for endophthalmitis, but also for which cases of endophthalmitis.

One of the major limitations of this review was inconsistency of the outcomes reported by the trials and the time intervals at which these outcomes were collected. Since the reporting of most outcomes differed across studies, few meta-analyses were possible. Any future trials should therefore report outcomes in ways that facilitate comparing findings with previous research. We also believe that it is important to formulate an outcome that considers the patient's symptoms (e.g. pain, discharge) and clinical examination (e.g. inflammatory changes) to measure the success of a treatment option. Ideally, a standardized measure would be created and adopted by multiple trials. An example of such an outcome is the inflammation score in Das 1999. Unfortunately, since Das 1999 reported this outcome for postoperative and post-traumatic patients as a whole, we decided not to include this outcome in the review. Any future studies should also have earlier (i.e. a month or earlier) and later (i.e. several years) follow-up intervals to determine whether adjunctive steroid therapy is beneficial or harmful throughout the post-treatment period.

To maximize the applicability of future trials, we recommend employing the treatment regimen that is considered standard practice with regard to the use of vitrectomy as well as antibiotic and steroid choice, dosage, and frequency. Also, researchers should conduct trials with sufficient power to detect important clinical differences and implement methods to minimize bias. This requires that researchers not only use methods that reduce the risk of bias (e.g. random sequence generation; allocation concealment; masking of participants, personnel, and outcome assessors; accounting for missing participants), but also report how they performed these methods.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Albrecht 2011

Study characteristics

Methods	**Study design:** randomized controlled trial **Number randomized:** 62 participants in total, 32 in postcataract endophthalmitis group (17 steroid, 15 placebo), 13 in bleb-related endophthalmitis group (4 steroid, 9 placebo), 17 in other-endophthalmitis group (9 steroid, 8 placebo) **Exclusions after randomization:** admission visual acuity was not recorded for 1 participant in other-endophthalmitis group who received steroids **Losses to follow-up:** 1 participant in postcataract group placebo group, 2 participants in bleb-related placebo group, 1 participant in other placebo group **Number analyzed:** 57 participants in total, 31 in postcataract group (17 steroid, 14 placebo), 11 in bleb-related group (4 steroid, 7 placebo), 15 in other group (8 steroid, 7 placebo) **Unit of analysis:** participant (1 eye per participant)

Albrecht 2011 *(Continued)*

	Notes: other-endophthalmitis group included 8 trauma-related (4 steroid, 4 placebo), 3 endogenous (1 steroid, 2 placebo), and 5 post-pars plana vitrectomy endophthalmitis (4 steroid, 2 placebo) participants
Participants	**Country:** South Africa **Setting:** Groote Schuur Hospital (Cape Town) **Study period:** January 2001 to December 2005 **Mean age (years):** 59 (steroid), 61 (placebo) **Gender:** 11 men and 19 women (steroid); 18 men and 14 women (placebo) **Inclusion criteria:** all people with presumed bacterial endophthalmitis **Exclusion criteria:** 1. Suspected fungal/parasitic/viral/non-bacterial endophthalmitis 2. People who underwent vitrectomy for endophthalmitis **Equivalence of baseline characteristics**: yes
Interventions	**Intervention (n = 30):** intravitreal dexamethasone 0.4 mg/1 mL with intravitreal vancomycin 1 mg/0.1 mL and ceftazidime 2.225 mg/0.1 mL (replaced with amikacin 0.4 mg/1 mL for participants allergic to penicillin) **Comparator (n = 32):** intravitreal placebo 0.1 mL balanced salt solution with intravitreal vancomycin 1 mg/0.1 mL and ceftazidime 2.225 mg/0.1 mL **Additional interventions (all participants):** "Vitreous and aqueous samples were sent for microbiological analysis. A subconjunctival injection of vancomycin (25 mg/0.5 ml), ceftazidime (50 mg/0.5 ml) and betamethasone (1.5 mg/0.5 ml) was also administered at the end of the procedure. Post injection, patients received topical ofloxacin and topical dexamethasone. Patients were re-injected after 48-72 h if needed." **Length of follow-up:** 2 to 4 months
Outcomes	**Outcomes:** 1. Visual acuity using standard Snellen chart, grouped into the following categories (group 1: 6/6 to 6/18, group 2: 6/24 to 6/60, group 3: < 6/60) 2. Number of lines improvement on the Snellen chart 3. Any adverse events 4. Any medication side effects **Other findings reported:** % positive culture rate overall, most common organism cultured, mean delay in presentation of endophthalmitis **Adverse events reported:** rhegmatogenous retinal detachment **Intervals at which outcomes were assessed:** baseline, 3 months
Notes	**References to other relevant studies:** none **Trial registration:** none reported **Funding source:** none reported **Declarations of interest:** none reported
Risk of bias	

Albrecht 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The pharmacy randomised the patients within the three groups using standard computer generated randomisation tables."
Allocation concealment (selection bias)	Low risk	Allocation was performed by the pharmacy.
Masking of participants and personnel (performance bias)	Low risk	"A double-blinding label (dexamethasone/placebo) masked the dexamethasone/placebo injection to both surgeon and patient."
Masking of outcome assessment (detection bias)	Low risk	Visual acuities were measured by nursing staff who had no knowledge of the trial, so they were unaware of the participants' intervention assignments. (Information provided by the study author via email.)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of the total 62 participants, 4 participants in the placebo group were lost to follow-up, and the admission visual acuity was not recorded for a participant in the steroid group. The reasons for loss to follow-up were not reported (and were unknown to the study author when asked by email). These participants were excluded from the final analysis (after randomization).
Selective reporting (reporting bias)	Unclear risk	We did not have access to the original study protocol to compare planned versus reported outcomes.
Other bias	Low risk	None identified.

Das 1999

Study characteristics	
Methods	**Study design:** randomized controlled trial **Number randomized:** 68 participants, 34 in postoperative endophthalmitis group, 34 in post-traumatic endophthalmitis group **Exclusions after randomization:** 5 participants in total (because initial vitreous smear or final vitreous culture was positive for fungus), 2 in postoperative group, 3 in post-traumatic group **Losses to follow-up:** none reported **Number analyzed:** 63 participants in total, 32 in postoperative group (16 with steroid, 16 without steroid), 31 in post-traumatic group (13 with steroid, 18 without steroid) **Unit of analysis:** participant (1 eye per participant)
Participants	**Country:** India **Setting:** Retina Vitreous Services, L V Prasad Eye Institute (Hyderabad) **Study period:** January 1993 to December 1994 **Mean age (years):** 55.1 (postoperative/with steroid), 64.5 (postoperative/without steroid), 20.8 (post-traumatic/with steroid), 12.2 (post-traumatic/without steroid) **Gender:** 11 men/boys and 5 women/girls (postoperative/with steroid); 11 men/boys and 5 women/girls (postoperative/without steroid); 10 men/boys and 3 women/girls (post-traumatic/with steroid); 10 men/boys and 8 women/girls (post-traumatic/without steroid)

Das 1999 *(Continued)*

	Inclusion criteria: all people with suspected bacterial endophthalmitis **Exclusion criteria:** 1. If it was "considered an absolute necessity to administer oral corticosteroid at any time postoperatively, the patient will be withdrawn from the study"; no trial participant was excluded for this reason 2. Positive fungal culture or smear **Equivalence of baseline characteristics**: not reported
Interventions	**Intervention (n = 29):** intravitreal dexamethasone 0.4 mg/1 mL with vitrectomy and intravitreal vancomycin 1 mg and amikacin 0.4 mg **Comparator (n = 34):** vitrectomy and intravitreal vancomycin 1 mg and amikacin 0.4 mg **Additional interventions (all participants):** "Both intravitreal antibiotics and dexamethasone were injected only after obtaining the vitreous biopsy microscopy report from the microbiology laboratory. The usual time taken for the microscopy report was 10–15 minutes ... . All the eyes received subconjunctival antibiotics (same as the intravitreal antibiotics) at the end of the surgery; subconjunctival steroid was not given to any of the eyes in the study. All the patients also received intravenous antibiotics (gentamicin and cefazolin) for a period of 7 days ... . Four patients in the postoperative group and six patients in the post-trauma group received a second injection of intravitreal antibiotics after the culture report was available. This was usually after 72 hours, and was culture adjusted. Intravitreal dexamethasone was not repeated." **Length of follow-up:** 3 months
Outcomes	**Outcomes:** 1. Mean inflammation score (based on clinical picture of cornea, anterior chamber, iris, and vitreous) that ranged from 0 to 4 in each category 2. % with visual acuity of at least 6/120 (functional success) 3. % with intraocular pressure of at least 5 mmHg (anatomical success) 4. Magnitude of change in inflammation score 5. Relative % change in inflammation score **Other findings reported:** % positive culture rate overall and per group **Adverse events reported:** none reported **Intervals at which outcomes were assessed:** baseline, 1, 4, and 12 weeks
Notes	**References to other relevant studies:** none **Trial registration:** none reported **Funding source:** grants from the Hyderabad Eye Resarch Foundation (Hyderabad, India) **Declarations of interest:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation was done using the standard randomisation table."
Allocation concealment (selection bias)	Unclear risk	"The sealed envelopes were opened by the circulating nurse just before the preparation of the IOABs [intraocular antibiotics]." It is unclear if the envelopes were sequentially numbered or opaque, and if the envelopes were opened sequentially.

Das 1999 *(Continued)*

Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not described.
Masking of outcome assessment (detection bias)	Unclear risk	"The inflammation score (IS) was done by two independent observers—one ophthalmologist and one senior optometrist, experienced with eye examination by slit lamp and indirect ophthalmoscope ... . The IS [at the follow-up visits] was done by same two independent observers to quantitate the degree of inflammation at each evaluation." However, it is not clearly stated whether these observers were aware of the intervention assignment. Also, masking of personnel assessing visual acuity and intraocular pressure was not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up or adverse events were reported.
Selective reporting (reporting bias)	Unclear risk	We did not have access to the original study protocol to compare planned versus reported outcomes. Outcomes for inflammation score were reported as described in the methods section. Visual acuity outcomes were not reported in results section as described in the methods section; instead, a combined rate of functional success (i.e. visual acuity of at least 6/120) and anatomical success (i.e. IOP of at least 5 mmHg) was reported in the results section.
Other bias	Low risk	None identified.

Gan 2005

Study characteristics	
Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 29 participants in total, 13 in steroid group, 16 in placebo group **Exclusions after randomization:** none reported **Losses to follow-up:** 1 participant in steroid group at 12 months **Number analyzed:** 29 participants in total, 13 in steroid group (1 participant lost to follow-up at 12 months not included in 12-month analysis), 16 in placebo group **Unit of analysis:** participant (1 eye per participant)
Participants	**Country:** the Netherlands **Setting:** The Rotterdam Eye Hospital (Rotterdam) **Study period:** April 1999 to June 2000 (terminated prematurely because study drug dexamethasone sodium diphosphate was no longer available) **Median age (years):** 82 (steroid), 76 (placebo) **Gender:** 8 males and 5 females (steroid), 4 males and 12 females (placebo) **Inclusion criteria:** "consecutive patients with a diagnosis of suspected bacterial post-cataract endophthalmitis" (defined as: "(1) severe, sudden visual deterioration and (2) an inflammatory response deemed excessive (relative to the anticipated course after surgery) with cells and hypopyon in the anterior chamber or posterior segment with loss of fundus detail") **Exclusion criteria:**

Gan 2005 *(Continued)*

1. Cataract surgery performed more than 6 weeks ago
2. "cataract surgery had been performed without the expectation of a postoperative vision of 20/100 or better"
3. Administration of systemic or subconjunctival antibiotics
4. Suspicion of fungal infection

Equivalence of baseline characteristics: not reported

Interventions	**Intervention (n = 13):** intravitreal dexamethasone sodium diphosphate 0.4 mg (Decadron 20 mg/mL with 1 mg/mL paraben as preservative, resulting in 0.025 mg paraben in 0.1 mL) with intravitreal 0.2 mg vancomycin in 0.1 mL phosphate-buffered saline and 0.05 mg gentamicin in 0.1 mL phosphate-buffered saline **Comparator (n = 16):** placebo in 0.1 mL phosphate-buffered saline with intravitreal 0.2 mg vancomycin in 0.1 mL phosphate-buffered saline and 0.05 mg gentamicin in 0.1 mL phosphate-buffered saline **Additional interventions (all participants):** "A limited core vitrectomy with an anterior chamber infusion was performed in patients with light perception only [prior to intravitreal injection] ... . The intravitreal injection of 0.2 mg vancomycin and dexamethasone or placebo was repeated once after 3 or 4 days ... . If the Gram-staining or culture of the first biopsy material yielded Gram-negative bacteria, 1 mg ceftazidime was immediately injected intravitreally, followed by continuous intravenous infusion of ceftazidime (6 g per day). After the first biopsy, patients used Predforte eye drops 6 times a day in a tapering schedule over the next 6 weeks and atropine 1% for 4 weeks. Additional procedures were allowed ... if the treating surgeon thought it to be in the patients' best interest." **Length of follow-up:** 12 months
Outcomes	**Outcomes:** 1. Snellen visual acuity 2. % with functionally lost eye (i.e. final vision of hand motion or less) 3. % who underwent secondary procedure **Other findings reported:** % positive culture rate overall and per group, most common organisms cultured **Adverse events reported:** retinal detachment, hypotony, seclusion of pupil, pucker, dropped intraocular lens **Intervals at which outcomes were assessed:** baseline and 3, 12 months
Notes	**References to other relevant studies:** none **Trial registration:** none reported **Funding source:** none reported **Declarations of interest:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomized to either intravitreal dexamethasone or placebo as adjunct to standard antibiotic treatment." However, the randomization method was not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described.

Gan 2005 *(Continued)*

Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not described.
Masking of outcome assessment (detection bias)	Unclear risk	Masking of outcome assessment was not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in steroid group did not return for her last follow-up visit at 12 months, so her visual acuity data at 12 months were not included in the analysis.
Selective reporting (reporting bias)	Unclear risk	We did not have access to the original study protocol to compare planned versus reported outcomes.
Other bias	Unclear risk	The major limitation of the study was the small sample size; the study stopped enrolling participants prematurely because the manufacturer of dexamethasone withdrew it from the market.

Manning 2018

Study characteristics	
Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 169 participants in total, 82 in dexamethasone group, 87 in placebo group **Exclusions after randomization:** 2 in total, 1 in each group (both were due to erroneous inclusion after secondary intraocular lens) **Losses to follow-up:** 17 in total, 10 in dexamethasone group, 7 in placebo group (all of them were included in the analysis) **Number analyzed:** 167 participants in total, 81 in dexamethasone group, 86 in placebo group **Unit of analysis:** participant (1 eye per participant)
Participants	**Country:** the Netherlands **Setting:** The Rotterdam Eye Hospital (Rotterdam) **Study period:** 1 November 2004 to 1 March 2014, although from 15 March 2005 to 28 June 2005 and from 20 July 2007 to 26 December 2008 study drug was unavailable (total of 20 months) **Mean ± SD age (years):** 74.6 ± 9.3 (dexamethasone), 75.8 ± 9.3 (placebo) **Gender:** 37 males and 44 females (dexamethasone), 40 males and 46 females (placebo) **Inclusion criteria:** 1. Post-cataract surgery bacterial endophthalmitis defined as (i) a decrease in VA and (ii) an inflammatory response deemed excessive (relative to the anticipated course after surgery) with cells or hypopyon in the anterior chamber or posterior segment with reduction or loss of fundus detail 2. Strong, and increasing, irritation of anterior chamber and/or vitreous during postoperative 8 weeks' interval **Exclusion criteria:** 1. Cataract surgery had been performed more than 6 weeks previously

Manning 2018 *(Continued)*

2. The expected postoperative VA was 20/100 (LogMAR 0.7) or worse, due to the presence of any visually consequential comorbidity
3. Systemic or subconjunctival antibiotics had been administered
4. Suspicion of fungal infection

Equivalence of baseline characteristics: no significant differences were reported in baseline characteristics between groups (see Table 1, alpha = 0.05)

Interventions	**Intervention (n = 82):** intravitreal injection of 0.2 mg vancomycin in 0.1 mL phosphate-buffered saline and 0.05 mg gentamicin in 0.1 mL phosphate-buffered saline, followed by 400 µg dexamethasone sodium diphosphate in 0.1 mL sodium hydroxide-buffered saline, without preservatives with only 0.5 mg/mL sodium edetate. The intravitreal injection of 0.2 mg vancomycin and dexamethasone was repeated once within 3 to 4 days. **Comparator (n = 87):** intravitreal injection of 0.2 mg vancomycin in 0.1 mL phosphate-buffered saline and 0.05 mg gentamicin in 0.1 mL phosphate-buffered saline, followed by placebo in 0.1 mL sodium hydroxide-buffered saline, without preservatives and with only 0.5 mg/mL sodium edetate. The intravitreal injection of 0.2 mg vancomycin and placebo was repeated once within 3 to 4 days. **Length of follow-up:** 12 months
Outcomes	**Outcomes:** 1. Best-corrected visual acuity 2. IOP **Other findings reported:** endophthalmitis-microbiological findings, reoperations **Adverse events reported:** floaters (2 in dexamethasone group, 1 in placebo group), pucker (2 in dexamethasone group, 3 in placebo group), retinal detachment (2 each group) **Intervals at which outcomes were assessed:** baseline, 4 and 10 weeks, 6 and 12 months after inclusion
Notes	**References to other relevant studies:** none **Trial registration:** Netherlands Trial Register (NTR 189) **Funding source:** "This study was supported by the Research Foundation Rotterdam Eye Hospital and the Foundation Dutch Ophthalmological Research, solely to produce the study drug and placebo." **Declarations of interest:** no conflicts of interest for anyone (personal communication)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized to receive either intravitreal dexamethasone or placebo, adjunctive to intravitreal antibiotic treatment." "The list had been generated in SPSS: blocked in groups of 10 stratified by center"
Allocation concealment (selection bias)	Low risk	Allocation was performed by the pharmacy: "In batches randomized per 10 patients, the trial pharmacist prepared two vials for each patient in a plastic bag (each patient had either two dexamethasone vials or two placebo vials, in similar vials containing indistinguishable clear fluids) and stored in the refrigerator in the operation centres."
Masking of participants and personnel (performance bias)	Low risk	Participants were given similar vials containing indistinguishable clear fluids. The authors claimed that participants and study personnel were masked by the plastic bag to the study medication assigned to the participant; placebo or treatment intervention was indistinguishable.

Manning 2018 *(Continued)*

Masking of outcome assessment (detection bias)	Low risk	Study personnel and outcome assessors were masked by the plastic bag to the study medication assigned to the participant; placebo or treatment intervention was indistinguishable.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was followed. All participants who were randomized (except erroneous inclusion of 1 participant each group) were included in the analysis and were analyzed according to their randomized allocation regardless of the intervention they actually received.
Selective reporting (reporting bias)	Unclear risk	The trial protocol mentions visual acuity and panbacterial PCR as primary outcomes. The study only investigated visual outcome as primary outcome. "Panbacterial PCR is not mentioned nor used in this study. Pathogens were identified by bacterial culture."
Other bias	Low risk	None identified.

IOP: intraocular pressure
PCR: polymerase chain reaction
SD: standard deviation
VA: visual acuity

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

Study	Reason for exclusion
Aragona 2021	This was a review and not an RCT.
Bandello 2020	This study looked at endophthalmitis prophylaxis following phacoemulsification comparing antibiotics plus steroids versus steroids alone.
Baum 1976	This was an interventional case series that discussed the clinical outcomes of 8 people with bacterial endophthalmitis, all of whom received the same therapeutic regimen.
Breucker 1968	A retrospective study that compared the clinical outcomes of treatment without versus with oral prednisone therapy in people with exogenous endophthalmitis
Dhaliwal 2019	Not an RCT; a letter to editor and did not present primary study
Doft 1994	This study was a prospective comparison of immediate vitrectomy versus vitreous tap and treatment with or without intravenous antibiotics. All participants received oral corticosteroids.
Gomes 2017a	This study compared aqueous humor concentrations of topical antibiotics alone versus topical antibiotics plus corticosteroids for endophthalmitis prophylaxis before phacoemulsification.
Gomes 2017b	This study compared moxifloxacin versus moxifloxacin plus dexamethasone for endophthalmitis prophylaxis after phacoemulsification.
Koehrer 2016	This study compared early versus delayed dexamethasone use as adjunctive therapy for acute postoperative endophthalmitis.
Loukovaara 2019	A retrospective case series, not an RCT
NCT03363295	This terminated study planned to compare moxifloxacin versus no moxifloxacin for prophylaxis.

Study	Reason for exclusion
Rehak 2007	A prospective, non-randomized study examining the role of adjunctive systemic steroids in the treatment of acute postoperative endophthalmitis; 12 of 34 consecutive patients received systemic prednisolone in addition to a vitrectomy and intravitreous antibiotics.

RCT: randomized controlled trial

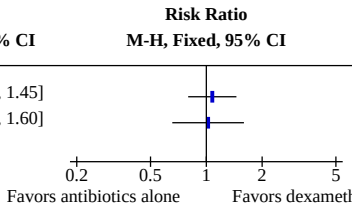
DATA AND ANALYSES

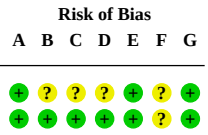
Comparison 1. Adjunctive intravitreal dexamethasone versus antibiotics alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Resolution of endophthalmitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2 Visual acuity	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 at 3 months	2	60	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [1.05, 3.60]
1.2.2 at 12 months	2	195	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.92, 1.37]
1.3 Intraocular pressure (IOP)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Retinal detachment	3	227	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.53, 3.74]

Analysis 1.1. Comparison 1: Adjunctive intravitreal dexamethasone versus antibiotics alone, Outcome 1: Resolution of endophthalmitis

Study or Subgroup	With dexamethasone Events	Total	Antibiotics alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
Das 1999 (1)	14	16	13	16	1.08 [0.80 , 1.45]
Manning 2018 (2)	26	81	27	86	1.02 [0.66 , 1.60]



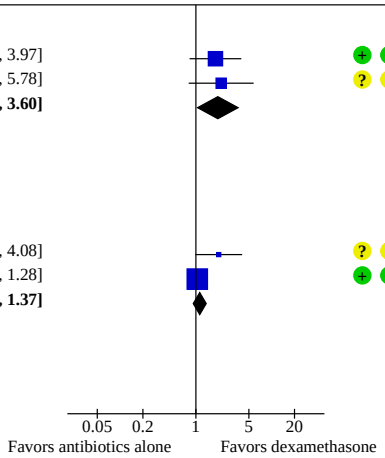


Footnotes
(1) Combined anatomical and functional success rate
(2) No bacterial growth in vitreous biopsy at one year

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Masking of participants and personnel (performance bias)
(D) Masking of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Adjunctive intravitreal dexamethasone versus antibiotics alone, Outcome 2: Visual acuity

Study or Subgroup	With dexamethasone Events	Total	Antibiotics alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
1.2.1 at 3 months								
Albrecht 2011 (1)	11	17	5	14	60.5%	1.81 [0.83 , 3.97]		+ + + + ? ? +
Gan 2005 (1)	7	13	4	16	39.5%	2.15 [0.80 , 5.78]		? ? ? ? + ? ?
Subtotal (95% CI)		**30**		**30**	**100.0%**	**1.95 [1.05 , 3.60]**		
Total events:	18		9					
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%								
Test for overall effect: Z = 2.12 (P = 0.03)								
1.2.2 at 12 months								
Gan 2005 (1)	9	12	6	16	8.4%	2.00 [0.98 , 4.08]		? ? ? ? + ? ?
Manning 2018 (2)	57	81	58	86	91.6%	1.04 [0.85 , 1.28]		+ + + + + ? +
Subtotal (95% CI)		**93**		**102**	**100.0%**	**1.12 [0.92 , 1.37]**		
Total events:	66		64					
Heterogeneity: Chi² = 3.03, df = 1 (P = 0.08); I² = 67%								
Test for overall effect: Z = 1.16 (P = 0.25)								

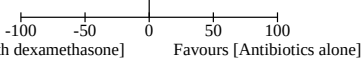


Footnotes
(1) Snellen visual acuity 6/6 to 6/18
(2) logMAR 0.3 or better

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Masking of participants and personnel (performance bias)
(D) Masking of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Adjunctive intravitreal dexamethasone versus antibiotics alone, Outcome 3: Intraocular pressure (IOP)

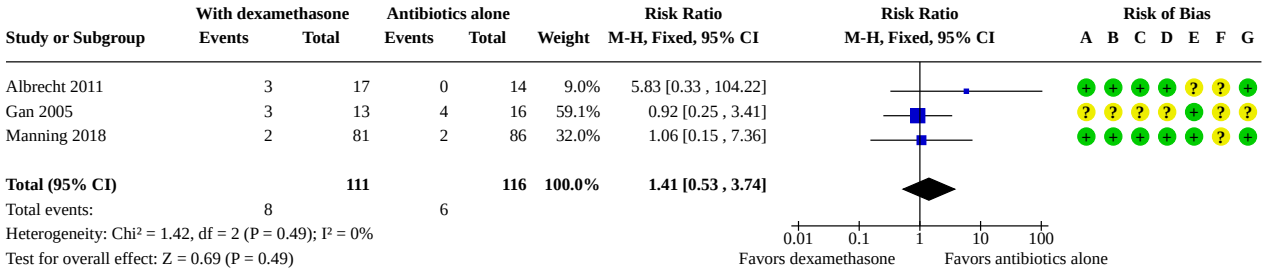
Study or Subgroup	With dexamethasone Mean	SD	Total	Antibiotics alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Manning 2018 (1)	13.9	4.5	81	15.8	8.1	86	-1.90 [-3.87 , 0.07]		+ + + + + ? +



Footnotes
(1) At 12 months

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Masking of participants and personnel (performance bias)
(D) Masking of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Adjunctive intravitreal dexamethasone versus antibiotics alone, Outcome 4: Retinal detachment



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Masking of participants and personnel (performance bias)
(D) Masking of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. Adverse events

Adverse event	Study ID	With dexamethasone	Antibiotics alone
Retinal detachment	Albrecht 2011 [a]	3/17 (17.6%)	0/14 (0%)
	Gan 2005	3/13 (23.1%)	4/16 (25.0%)
	Manning 2018	2/81 (2.5%)	2/86 (2.3%)
Hypotony	Gan 2005	1/13 (7.7%)	1/16 (6.3%)
Proliferative vitreoretinopathy	Gan 2005	1/13 (7.7%)	0/16 (0%)
Seclusion of pupil	Gan 2005	0/13 (0%)	1/16 (6.3%)
Floaters	Manning 2018	2/81 (2.5%)	1/86 (1.2%)
Pucker	Manning 2018	2/81 (2.5%)	3/86 (3.5%)

[a]Includes participants from the "post cataract" endophthalmitis group only.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Endophthalmitis] explode all trees
#2 endophthalmiti*
#3 ophthalmia
#4 #1 or #2 or #3
#5 MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#6 antibiotic*

#7 MeSH descriptor: [Anti-Infective Agents] explode all trees
#8 chloramphenicol*
#9 ciprofloxacin*
#10 gentamicin*
#11 levofloxacin*
#12 neomycin*
#13 ofloxacin*
#14 polymyxin*
#15 cefazolin*
#16 cefuroxime*
#17 moxifloxacin*
#18 norfloxacin*
#19 vancomycin*
#20 cephtazidime*
#21 amikacin*
#22 tobramycin*
#23 gatifloxacin*
#24 #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 or #23
#25 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#26 steroid*
#27 glucocorticoid*
#28 dexamethasone*
#29 betamethasone*
#30 triamcinolone*
#31 prednisolone*
#32 fluorometholone*
#33 #25 or #27 or #28 or #29 or #30 or #31 or #32
#34 #4 and #24 and #33

Appendix 2. MEDLINE Ovid search strategy

1. exp endophthalmitis/
2. endophthalmiti$.tw.
3. ophthalmia.tw.
4. or/1-3
5. exp anti bacterial agents/
6. antibiotic$.tw.
7. exp Anti-Infective Agents/
8. chloramphenicol$.tw.
9. ciprofloxacin.tw.
10. gentamicin$.tw.
11. levofloxacin$.tw.
12. neomycin$.tw.
13. ofloxacin$.tw.
14. polymyxin$.tw.
15. cefazolin$.tw.
16. cefuroxime$.tw.
17. moxifloxacin$.tw.
18. norfloxacin$.tw.
19. vancomycin$.tw.
20. cephtazidime$.tw.
21. amikacin$.tw.
22. tobramycin$.tw.
23. gatifloxacin$.tw.
24. or/5-23
25. exp Adrenal Cortex Hormones/
26. steroid$.tw.
27. glucocorticoid$.tw.
28. dexamethasone$.tw.
29. betamethasone$.tw.
30. triamcinolone$.tw.
31. prednisolone$.tw.

32. fluorometholone$.tw.
33. or/25-32
34. 4 and 24 and 33

Appendix 3. Embase Ovid search strategy

1. exp endophthalmitis/
2. endophthalmiti$.tw.
3. ophthalmia.tw.
4. or/1-3
5. exp antibiotic agent/
6. antibiotic$.tw.
7. chloramphenicol$.tw.
8. ciprofloxacin.tw.
9. gentamicin$.tw.
10. levofloxacin$.tw.
11. neomycin$.tw.
12. ofloxacin$.tw.
13. polymyxin$.tw.
14. cefazolin$.tw.
15. cefuroxime$.tw.
16. moxifloxacin$.tw.
17. norfloxacin$.tw.
18. vancomycin$.tw.
19. cephtazidime$.tw.
20. amikacin$.tw.
21. tobramycin$.tw.
22. gatifloxacin$.tw.
23. or/5-22
24. exp Steroids/
25. steroid$.tw.
26. glucocorticoid$.tw.
27. dexamethasone$.tw.
28. betamethasone$.tw.
29. triamcinolone$.tw.
30. prednisolone$.tw.
31. fluorometholone$.tw.
32. or/24-31
33. 4 and 23 and 32

Appendix 4. LILACS search strategy

endophthalmitis and antibiotic OR chloramphenicol OR ciprofloxacin OR gentamicin OR levofloxacin OR neomycin OR ofloxacin OR polymyxin cefazolin OR cefuroxime OR moxifloxacin OR norfloxacin OR vancomycin OR cephtazidime OR amikacin OR tobramycin OR gatifloxacin and steroid OR glucocorticoid OR dexamethasone OR betamethasone OR triamcinolone OR prednisolone OR fluorometholone

Appendix 5. ISRCTN search strategy

endophthalmitis AND (antibiotic OR chloramphenicol OR ciprofloxacin OR gentamicin OR levofloxacin OR neomycin OR ofloxacin OR polymyxin cefazolin OR cefuroxime OR moxifloxacin OR norfloxacin OR vancomycin OR cephtazidime OR amikacin OR tobramycin OR gatifloxacin) AND (steroid OR glucocorticoid OR dexamethasone OR betamethasone OR triamcinolone OR prednisolone OR fluorometholone)

Appendix 6. ClinicalTrials.gov search strategy

Interventional Studies | endophthalmitis | antibiotic OR chloramphenicol OR ciprofloxacin OR gentamicin OR levofloxacin OR neomycin OR ofloxacin OR polymyxin OR cefazolin OR cefuroxime OR moxifloxacin OR norfloxacin OR vancomycin OR amikacin OR tobramycin OR gatifloxacin OR cephtazidime

Appendix 7. WHO ICTRP search strategy

endophthalmitis = Condition AND antibiotic OR chloramphenicol OR ciprofloxacin OR gentamicin OR levofloxacin OR neomycin OR ofloxacin OR polymyxin OR cefazolin OR cefuroxime OR moxifloxacin OR norfloxacin OR vancomycin OR cephtazidime OR amikacin OR tobramycin OR gatifloxacin = Intervention

WHAT'S NEW

Date	Event	Description
17 August 2021	New search has been performed	New search performed.
17 August 2021	New citation required but conclusions have not changed	One relevant study was identified, which was previously listed as an ongoing study (Manning 2018).

HISTORY

Protocol first published: Issue 3, 2016
Review first published: Issue 2, 2017

CONTRIBUTIONS OF AUTHORS

Screening search results: SE, KK
Organizing retrieval of papers: SE, KK
Screening retrieved papers against inclusion criteria: SE, KK
Appraising risk of bias of papers: SE, KK
Abstracting data from papers: SE, KK
Managing data for the review: SE, KK
Interpretation of data: SE, KK, ALC
Writing the review: SE, KK, ALC

Final approval of the document to be published: all review authors

DECLARATIONS OF INTEREST

SE: None known.

KK: None known.

ALC: None known.

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- No sources of support provided

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- Public Health Agency, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We intended to include participants with clinically diagnosed, culture-positive endophthalmitis following intraocular procedure. However, we realized that due to the emergent nature of endophthalmitis, initial treatment with antibiotics with or without steroids is administered before the culture results are known. Also, none of the included trials reported outcomes separately for culture-positive and culture-

negative cases (except for inflammation scoring in Das 1999, which was not included in the evidence for this review). We therefore amended the Types of participants section to state that participants would be included regardless of their culture result.

Insufficient data and the small number of trials precluded the performance of subgroup analyses. We also did not perform any sensitivity analyses because no included studies fitted any of the following criteria: high risk of bias in one or more domains, only unpublished outcome data, or industry funded.

For the review update, we did not search for comparative, non-randomized studies (e.g. cohort studies) because we identified relevant RCTs in the previously published review (Kim 2017).

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [therapeutic use]; Dexamethasone [therapeutic use]; *Endophthalmitis [drug therapy]; *Eye Diseases; *Retinal Detachment; Steroids [therapeutic use]

MeSH check words

Humans