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Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients (Review)

Webster AC, Pankhurst T, Rinaldi F, Chapman JR, Craig JC

Webster AC, Pankhurst T, Rinaldi F, Chapman JR, Craig JC.
Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients.
Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD004756.
DOI: 10.1002/14651858.CD004756.pub3.

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[Intervention Review]

Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients

Angela C Webster[1], Tanya Pankhurst[2], Fiona Rinaldi[3], Jeremy R Chapman[4], Jonathan C Craig[5]

[1]School of Public Health, University of Sydney, Sydney, Australia. [2]Department of Nephrology, University Hospital Birmingham, Birmingham, UK. [3]Wyeth Australia, Baulkhan Hills BC, Australia. [4]Renal Medicine, Westmead Hospital, Westmead, Australia. [5]Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia

Contact address: Angela C Webster, School of Public Health, University of Sydney, Edward Ford Building A27, Sydney, NSW, 2006, Australia. awebster@health.usyd.edu.au, angela.webster@gmail.com.

Editorial group: Cochrane Kidney and Transplant Group
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Citation: Webster AC, Pankhurst T, Rinaldi F, Chapman JR, Craig JC. Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD004756. DOI: 10.1002/14651858.CD004756.pub3.

ABSTRACT

Background

Registry data shows that between 15-35% kidney recipients will undergo treatment for at least one episode of acute rejection within the first post transplant year. Treatment options include pulsed steroid therapy, the use of an antibody preparation, the alteration of background immunosuppression, or combinations of these options. In 2002, in the US, 61.4% patients with an acute rejection episode received steroids, 20.4% received an antibody preparation and 18.2% received both.

Objectives

To determine the benefits and harms of mono- or polyclonal antibodies (Ab) used to treat acute rejection in kidney transplant recipients.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (in *The Cochrane Library,* issue 2, 2005), MEDLINE (1966-June 2005), EMBASE (1980-June 2005), and the specialised register of the Cochrane Renal Group (June 2005).

Selection criteria

Randomised controlled trials (RCTs) in all languages comparing all mono- and polyclonal antibody preparations, given in combination with any other immunosuppressive agents, for the treatment of acute graft rejection, when compared to any other treatment for acute rejection.

Data collection and analysis

Two reviewers independently assessed trials for eligibility and quality, and extracted data. Results are expressed as risk ratio (RR) with 95% confidence intervals (CI).

Main results

Twenty one trials (49 reports, 1387 patients) were identified. Trials were generally small, incompletely reported, especially for potential harms, and did not define outcome measures adequately. Fourteen trials (965 patients) compared therapies for first rejection episodes. Ab was better than steroid in reversing rejection (RR 0.57, 95% CI 0.38 to 0.87) and preventing graft loss (death censored RR 0.74, CI 0.58 to 0.95) but there was no difference in preventing subsequent rejection or death at one year. Seven trials (422 patients) investigated Ab treatment of steroid-resistant rejection. There was no benefit of muromonab-CD3 over ATG or ALG in either reversing rejection, preventing subsequent rejection, preventing graft loss or death.

Authors' conclusions

In reversing first rejection, any antibody is better than steroid and also prevents graft loss, but subsequent rejection and patient survival are not significantly different. In reversing steroid-resistant rejection the effects of different antibodies are also not significantly different. Given the clinical problem caused by acute rejection, data are very sparse, and clinically important differences in outcomes between widely used interventions have not been excluded. Standardised reproducible outcome criteria are needed.

PLAIN LANGUAGE SUMMARY

Antibody therapy is better that steroid treatment for reversing the first acute rejection episode, however antibody-treated patients are more likely to experience an immediate reaction of fever, chills and malaise than those receiving steroid.

Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD). Strategies to increase donor organ availability and to prolong the transplanted kidney's survival have become priorities in kidney transplantation. Fifteen to 35% of all kidney transplant recipients will experience one episode of acute rejection in the first year. Options for treating these episodes include pulsed steroid therapy, the use of an antibody preparation, the alteration of background immunosuppression, or combinations of these options. This review investigated the role of mono- or polyclonal antibodies (Ab) used to treat acute rejection in kidney transplant recipients. Twenty one trials (1387 patients) were included. Any antibody was better than steroid treatment for reversing the first acute rejection episode and preventing graft loss, but showed no significant difference in reversing steroid-resistant rejection episodes. Antibody-treated patients were 28 times more likely to experience an immediate reaction of fever, chills and malaise than those receiving steroid treatment. The main limitation of this review is that none of the included trials were performed using contemporary immunosuppressive regimens, with the most recent study performed in 2000.

BACKGROUND

Improvements in induction and maintenance immunosuppressive algorithms now mean that most recipients of kidney transplants can expect a greater than 90% chance of a functioning graft at one year. Despite this, registry data shows that between 15% to 35% patients will undergo treatment for at least one episode of acute rejection within the first post-transplant year (UNOS 2004) (ANZDATA 2005) and randomised controlled trials (RCTs) of immunosuppressive interventions show an average rejection risk of 20% to 40% in the control arms (Webster 2004; Webster 2005). The impact of acute rejection on both graft survival in the short and longer terms and on patient morbidity in the short and longer terms is widely recognised (Jamil 1999; Joseph 2001; Leggat 1997; Opelz 1997).

The treatment of acute rejection requires a short course of more intensive immunosuppression, added to baseline immunosuppression therapy. Options include pulsed steroid therapy, the use of an antibody preparation, the alteration of background immunosuppression, or combinations of these options (Denton 1999). In 2002 in the United States, 61.4% patients with an acute rejection episode received steroids, 20.4% received an antibody preparation and 18.2% received both (UNOS 2004).

The agents available for the treatment of rejection are not new: horse and rabbit-derived polyclonal antibodies against the human lymphocyte or thymocyte (anti-lymphocyte globulin - ALG and anti-thymocyte globulin - ATG) have been used for the last 35 years, although as methods for raising and purifying the antibody preparations have evolved, several distinct formulations have been licensed and used; horse antithymocyte globulin (ATGAM®, or ATG, Pharmacia and Upjohn Inc., Kalamazoo, MI, ATG-Fresenius S, Fresenius biotech GmbH), rabbit antithymocyte globulin (Thymoglobulin®, SangStat Medical Corp., Fremont, CA), NRATG/NRATS (Nashville rabbit antithymocyte globulin/Nashville rabbit antithymocyte serum), and T10B9 (Medimmune, Medimmune Inc., Gaithersburg, MD). A mouse monoclonal antibody against the CD3 receptor on activated T-cells (muromonab-CD3 - Orthoclone OKT3®, Ortho Pharmaceutical Corporation, Biotech Division, Raritan, NJ) also became commercially available in the late 1980s. These preparations remove the functional T-cell population from circulation, producing powerful saturation immunosuppression useful for induction immunosuppression and for the management of acute rejection. However, this profound immunosuppression may be complicated by immediate toxicity, higher rates of infection and malignancy and may be limited to a single course of therapy by the development of neutralising antibodies to their xenogeneic components (Kreis 1992; Soulillou 2001).

The aim of this systematic review was to identify and summarise the evidence for the efficacy and adverse effects of using monoclonal or polyclonal antibodies to treat acute rejection in kidney transplant recipients.

OBJECTIVES

1. To evaluate the relative and absolute effects of different classes of antibody preparation in preventing graft loss and resolving rejection episodes when used as a treatment for first episode of rejection in kidney transplant recipients.
2. To evaluate the relative and absolute effects of different classes of antibody preparation in preventing graft loss and resolving rejection episodes when used as a treatment for steroid-resistant rejection in kidney transplant recipients.
3. To determine how the benefits and adverse events vary for each type of antibody preparation.
4. To determine how the benefits and harms vary for different formulations of antibody within each type.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs were included where an antibody was compared to any other treatment with the aim of reversing acute rejection. Eligibility for inclusion was not restricted on the basis of report language, age of recipients, or combinations of baseline immunosuppressive co-interventions in either the control or intervention arm of the trials.

Types of participants

Adult and child kidney transplant recipients. Only studies involving kidney transplant as single organ were included; recipients of multi-organ transplants were excluded from this review.

Types of interventions

All mono and polyclonal antibody preparations, given in combination with any other immunosuppressive agents, for the treatment of acute graft rejection, when compared to any other treatment for acute rejection. Comparisons examined were:

- ATG versus ALG
- ATG versus a different ATG (rabbit versus horse etc)
- Monomurab CD3 versus ATG or ALG
- Any antibody versus non-antibody intervention
- Any antibody in dosage comparisons

The class effect of anti-lymphocyte preparations was initially assumed but differences in formulation were also examined (e.g. rabbit vs horse based ATG formulations). All dosage regimens were included.

Types of outcome measures

Data on the following outcomes were collected wherever possible;

- reversal of acute rejection,
- time to reversal,
- recurrent rejection after the intervention rejection episode had been treated,
- time to re-rejection,
- graft loss (censored and not censored for death),
- mortality,
- graft function (measured by serum creatinine or calculated glomerular filtration rate (GFR)),
- treatment failure necessitating a change in treatment either of the antibody or of the baseline immunosuppression,
- immediate adverse effects of treatment,
- occurrence of infection including cytomegalovirus disease (CMV),
- incidence of malignancy (including post-transplant lymphoproliferative disorder).

Definitions used by each trial for each outcome were recorded.

Search methods for identification of studies

The search was designed to identify all trials of antibody therapy in kidney transplant recipients. These were then divided into trials of induction therapy and trials of acute rejection treatment.

Relevant trials in all languages will be searched using the following sources (see Table 1 - *Electronic search strategies)*:

1. Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 2 2005) and the Cochrane Renal Group's trials register (June 2005).
2. MEDLINE (1966 to June 2005), using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994).
3. EMBASE (1980-June 2005) using the Cochrane Collaboration EMBASE search strategy (Lefebvre 1996).
4. Unpublished trials by contacting trial groups and pharmaceutical companies and authors of included trials
5. Hand searching reference lists from relevant clinical trials and conference proceedings and abstracts in transplant specific meetings (1998- June 2005), including, but not limited to:
   - The Transplantation Society (ITS)
   - American Society of Transplant Physicians (ASTP)
   - American Society of Transplant Surgeons (ASTS)
   - American Society of Nephrology (ASN)
   - Transplant Society of Australia and New Zealand (TSANZ)
   - European Dialysis & Transplant Association (EDTA)

Where duplicate publication is suspected authors will be contacted for clarification and if duplication is confirmed the initial full publication together with any subsequent publication which adds additional information (e.g. longer term follow-up data) will be included in the review.

Data collection and analysis

Selection criteria

The review was undertaken by five reviewers (Angela Webster (AW), Tanya Pankhurst (TP), Fiona Rinaldi (FR), Jeremy Chapman (JRC), Jonathan Craig (JCC)).

- Eligible studies were identified using the search strategy listed (AW, FR, TP).
- The titles and abstracts and, where necessary, the full text was independently screened by two reviewers (from the group AW, TP, FR).
- Studies not written in English were translated.
- Disagreement about inclusion was resolved by discussion between co-reviewers (AW, JRC, JCC).
- Data extraction was performed independently by reviewers, using a standardised form (AW, TP, FR). Discrepancies were resolved by discussion (all).
- Authors of published work were contacted for clarification of unclear data (AW and TP).
- Data was entered into RevMan 4.2 twice (AW and TP).

Quality of studies

Quality of included studies was assessed independently by at least two reviewers (AW,TP, FR) without blinding to journal or authorship, using the checklist created by the Cochrane Renal Group. Discrepancies were resolved by discussion. The quality items assessed were allocation concealment, intention-to-treat analysis, completeness of follow-up and blinding of investigators, subjects and outcomes assessment. Each item was assessed separately rather than combined in a scoring system.

Quality checklist

Allocation concealment

- Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
- Unclear (B): Randomisation stated but no information on method used is available
- Inadequate (C): Method of randomisation used such as alternate medical record numbers or unsealed envelopes.; Any information in the study that indicated that investigators or participants could influence intervention group

Blinding

- Blinding of investigators: Yes/no/not stated
- Blinding of participants: Yes/no/not stated
- Blinding of outcome assessor: Yes/no/not stated
- Blinding of data analysis: Yes/no/not stated

In trials where no placebo is used, or where the intervention and comparison arms use drugs with different dosing schedules then, unless otherwise clarified, both the investigators and the participants were considered non-blinded.

Intention-to-treat analysis (ITT)

- Yes: Specifically reported by authors that ITT was undertaken and this was confirmed on study assessment, or not stated but evident from study assessment that ITT was undertaken
- Unclear. Reported but unable to confirm on study assessment, or not reported and unable to confirm by study assessment.
- No: Lack of ITT confirmed on study assessment (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation) regardless of whether ITT reported or not

Participants who were randomised but then subsequently did not receive a kidney transplant or did not have acute rejection were considered to be justifiable exclusions to the ITT population.

Completeness of follow-up

Percentage of participants for whom data was complete at defined study end-point. Where interim analyses are reported 'not stated' was recorded

Statistical assessment

For dichotomous outcomes (e.g. rejection or no rejection) results were expressed as a risk ratio (RR) with 95% confidence intervals (CI). Data was pooled using the random effects model. The fixed

effect model was also analysed to ensure robustness of the chosen model and the susceptibility to outliers (Egger 2001). Where continuous scales of measurement were used to assess the effects of treatment (e.g. GFR), the mean difference (MD) was used. Heterogeneity was analysed using a Cohran Q test (chi^2 with N-1 degrees of freedom and a P value of 0.05 used for statistical significance) and with I^2 (with uncertainty intervals) (Higgins 2003).

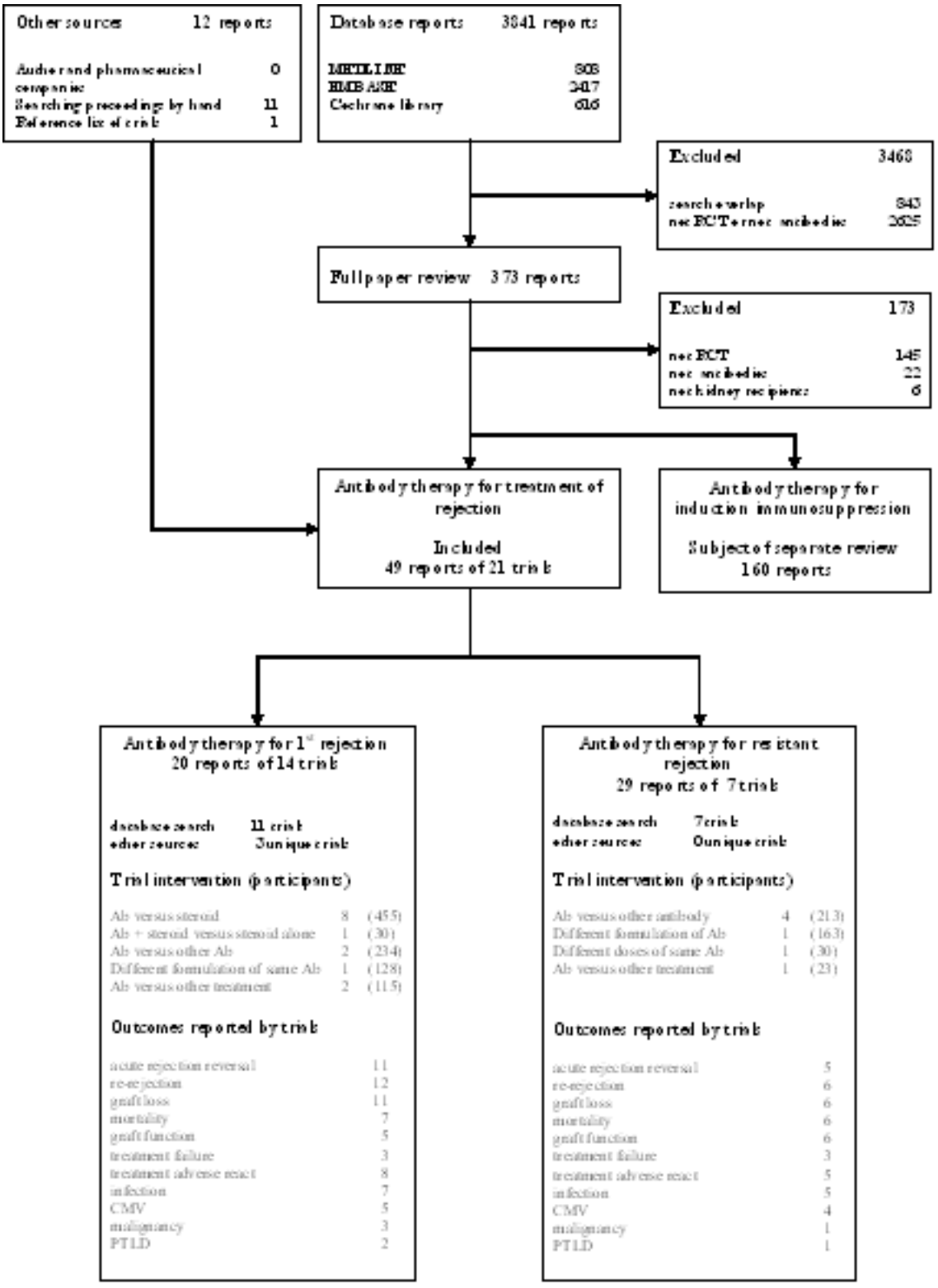
Possible sources of heterogeneity identified a priori were trial quality, specific formulation of antibody, and combination of baseline immunosuppression. Stratified analysis and meta-regression was planned to formally identify important clinical differences among the trials that might potentially be expected to alter the magnitude of treatment effect, but this was not possible because of the sparseness of the data.

RESULTS

Description of studies

A total of 49 reports of 21 trials were included in the review (Figure 1), representing a total of 1394 randomised participants. One of these trials was available in abstract form only (26 participants) (Hilbrands 1996) and the remaining twenty were reported in seven different journals, published between 1975-2005. Nineteen index reports were in English, one was in German (Barenbrock 1994) and one in French (Hourmant 1985).

Figure 1. Flow chart showing identification of trials for inclusion in the systematic review



Included trials

The included trials were heterogeneous. Patient characteristics, baseline immunosuppression, randomised interventions and outcomes definitions varied across trials. There were two main groups of trials, those which evaluated interventions for first rejection episodes and those which evaluated interventions in steroid-resistant rejection episodes. There were no trials identified where interleukin-2 receptor antagonists were investigated.

Fourteen trials (965 participants) investigated the treatment of first rejection episodes; eight (455 participants) compared antibody to steroid (Filo 1980; Glass 1983; Goldstein 1985; Hilbrands 1996; Hoitsma 1982; Shield 1979; Streem 1983; Theodorakis 1998) one (30 participants) compared antibody with steroid to steroid alone (Birkeland 1975), two (234 participants) compared antibody versus a different antibody (Baldi 2000; Waid 1992) one (128 participants) compared horse ATG with rabbit ATG (Johnson 1989) one (57 participants) compared ALG with intravenous immunoglobulin (Howard 1977) and one (58 participants) compared ALG with steroid and a switch to cyclosporin (Hourmant 1985).

For these 14 trials, ATG was rabbit-derived for three trials manufactured by Fresenius (Baldi 2000; Theodorakis 1998) and the formulation unstated in Hilbrands 1996, horse-derived for four trials, all Upjohn ATGAM (Filo 1980; Hoitsma 1982; Johnson 1989; Shield 1979) and ALG was entirely derived from horses manufactured by Merieux (Hourmant 1985) and the University of Minnesota (Glass 1983; Streem 1983), and unknown formulations two trials (Birkeland 1975; Howard 1977). Triple agent baseline immunosuppression with cyclosporin, azathioprine and steroids was used in only one trial (Baldi 2000), two trials used dual therapy with cyclosporin and steroid (Hilbrands 1996; Theodorakis 1998) and the remainder used azathioprine and steroids, either with (Hourmant 1985; Streem 1983) or without prior ALG induction therapy at the time of transplantation.

Six trials (259 participants) investigated the treatment of steroid-resistant acute rejection episodes; four (213 participants) trials compared muromonab-CD3 to treatment with another antibody (Barenbrock 1994; Hesse 1990; Mariat 1998; Midtvedt 2003) one compared dosage schedules of muromonab-CD3 (30 participants) (Midtvedt 1996) and one compared muromonab-CD3 to intravenous immunoglobulin (IVIg) (23 participants) (Casadei 1998). One additional trial compared rabbit and horse preparations of ATG (163 participants) in recipients with mixed acute rejection scenarios; 33% had a previous rejection episode, of which 40% had incomplete reversal at the time of randomisation to further treatment, and 11% had a first rejection episode that was steroid resistant (Gaber 1998). This trial was grouped with the six trials of steroid-resistant rejection, but analysed separately.

For these seven trials, ATG was rabbit-derived for three trials of Genzyme thymoglobulin (Gaber 1998; Mariat 1998; Midtvedt 2003) horse-derived for one trial of Upjohn ATGAM (Gaber 1998) not defined by one (Barenbrock 1994) and ALG was horse- derived, manufactured by Merieux (Hesse 1990). Triple agent baseline immunosuppression with cyclosporin, azathioprine and steroids was used for six trials (Barenbrock 1994; Casadei 1998; Gaber 1998; Mariat 1998; Midtvedt 1996; Midtvedt 2003) and one trial used dual therapy with cyclosporin and steroid from day seven (Hesse 1990). No trials used tacrolimus or mycophenolate, or other antibody induction agents in either intervention rationale.

Information on study population demographics was limited. Nine trials were conducted entirely in adult recipients (Barenbrock 1994; Casadei 1998; Gaber 1998; Hesse 1990; Mariat 1998; Midtvedt 1996; Midtvedt 2003; Streem 1983; Waid 1992) and two trials included a proportion (size not stated) of children (Filo 1980; Howard 1977). Six trials included a proportion (size not always stated) of patients with prior immunological sensitisation, as measured by panel reactive antibodies of >20 % (Baldi 2000; Filo 1980; Gaber 1998; Goldstein 1985; Hoitsma 1982; Mariat 1998) and the remaining trials did not clearly define their recipient population. The proportion of grafts from deceased and living donor sources, and of recipients with prior failed transplants is given in the table of included studies.

The reporting of outcomes was variable (Figure 1) with graft-focused outcomes reported more frequently (e.g. reversal of acute rejection, 16 trials) than patient-focused complications of treatment (e.g. CMV infection, nine trials) or specific adverse reactions. For many outcomes there was wide variation in the definitions used, the time post-treatment at which the data was collected, and the detail provided for each definition. The variation in definitions used is illustrated in (Figure 2; Figure 3). Data were often reported incompletely; although five trials reported mean time to rejection reversal and three trials the mean time to re-rejection, only one trial (Filo 1980) reported the standard deviation of the mean time, and so data could not be combined.

Figure 2. Inclusion criteria and outcome definitions used in trials of antibody for the treatment of first rejection episodes.
*** direct quotation from the text of trial reports appears in quotation marks. ns= not stated and could not be clarified or deduced. MP= methylprednisolone**

Trial name	Days since transplant	Timing of randomisation	Criteria for rejection *	Criteria for rejection reversal *
Antibody versus steroid				
Sheild 1979	< 35	Rejection	Scoring algorithm of biochemical, and physical signs, with confirmatory "biopsy where possible"	Day 2 of "persistent creatinine fall"
Filo 1980	<90	Rejection	"Clinical signs, imaging and renal function tests"	Increase in creatinine within 24 -48 hours of bolus MP
Hoitsma 1982	< 90	Rejection	Increased creatinine, oliguria, sodium retention, weight gain, proteinuria, graft tenderness	Day 2 of 3 consecutive days of creatinine falling
Glass 1983	ns	Transplantation	Clinical criteria including creatinine rise for 3 sequential days	Improvement in creatinine and clinical signs at 7th day of treatment.
Streem 1983	ns	Transplantation	Rise in creatinine and diminished function on I-131 scan, with "supportive clinical findings" with confirmatory "biopsy where possible"	Day 2 of "persistent creatinine fall"
Goldstein 1985	6-90	Rejection	Scoring algorithm of biochemical, and physical signs, with confirmatory "biopsy where possible"	3 day progressive fall in creatinine, or investigator judged clinical reversal.
Hilbrands 1996	< 90	Rejection	ns	ns
Theodoraki 1998	ns	Rejection	Clinical +/- biopsy confirmation	Not assessed. Severity of rejection episode judged by AUC of serial 10 day creatinine measurements.
Antibody and steroid versus steroid alone				
Birkeland 1975	ns	Rejection	"Common clinical criteria", with biopsy where possible	Day 2 of progressive rise in creatinine clearance
Antibody versus other antibody				
Baldi 2000	ns	Rejection	20% increase in creatinine with clinical suggestive signs, and biopsy if > 10 days from transplantation	ns
Whid 1992	ns	Rejection	4 of 7 clinical and biochemical signs, subsequently confirmed by biopsy	Absence of cross-over, re-treatment or graft loss
Formulation comparisons				
Johnson 1989	ns	Rejection	Standard clinical indicators with supplementary "biopsy where possible"	1st of 3 consecutive days of creatinine falling
Antibody versus other treatment				
Hourmant 1985	> 90	90 days post-transplant	ns	ns
Howard 1977	ns	Rejection	Rise in creatinine of 0.3mg/dl and deterioration of renogram, "mostly confirmed by biopsy"	ns

Figure 3. Inclusion criteria and outcomes definitions used in trials of antibody for the treatment of resistant rejection episodes
*** direct quotation from the text of trial reports appears in quotation marks. ns = not stated and could not be clarified or d**

Trial name	Days since transplant*	Timing of randomisation *	Criteria for rejection *	Initial treatment of rejection *	Criteria for resistant rejection *
Antibody versus other antibody					
Hesse 1990	<42	ns	Rise in creatinine of >0.3mg/dl and biopsy	MP 500 mg for 2 days.	"Non response"
Barenbrock 1994	"early"	ns	"Typical clinical symptoms", renogram, and biopsy	MP 500-1000mg for 3 days	Lack of improvement in clinical and sonographic appearances
Mariat 1998	ns	At biopsy	Delayed graft function or rise in creatinine in presence of urine output < 1l/d, low sodium excretion, weight gain > 1 kg/d or graft tenderness	MP 15mg/kg, 2 doses alternate days	No decline in creatinine after 2 steroid boluses, followed by biopsy
Midtvedt 2003	ns	Day 5 of treatment	Rise in creatinine >20% in the absence of obvious cause and biopsy (Banff criteria)	MP 500mg then 250mg for 3 days	No decline in creatinine
Different formulations of antibody					
Gaber 1998	ns	At biopsy	Biopsy, Banff graded	MP 500mg, for 3 days	Creatinine increase of 10% after 3 days of methylprednisolone
Different doses of same antibody					
Midtvedt 1996	<90	Day 5 of treatment	Rise in creatinine > 20% in absence of obvious cause	MP boluses, cumulative dose 1-1.5g	No decline in creatinine after 5 days of treatment
Antibody versus other treatment					
Casadei 1998	ns	At biopsy	Clinical suspicion and biopsy	MP 500 mg for 3 days.	"Failure to show improved renal function" within 7 days of starting MP

Risk of bias in included studies

Reporting of details of trial methodology was incomplete for the majority of trials, often remaining unclear despite scrutiny of the trial reports and attempts to contact report authors and sponsoring pharmaceutical companies.

Allocation concealment

Eight trials (38%) reported adequate allocation concealment (Birkeland 1975; Filo 1980; Gaber 1998; Goldstein 1985; Hoitsma 1982; Mariat 1998; Midtvedt 2003; Waid 1992) three trials (14%) used inadequate allocation concealment (Glass 1983; Howard 1977; Midtvedt 1996) and the remaining 10 trials (48%) were randomised but gave no indication of the allocation method used.

Blinding

There were two blinded (investigators and participants) trials (Gaber 1998; Waid 1992).

Intention-to-treat

Intention-to-treat analysis was confirmed for seven trials (33%) (Baldi 2000; Filo 1980; Gaber 1998; Glass 1983; Mariat 1998; Midtvedt 2003; Waid 1992) not undertaken for seven trials (33%) (Birkeland 1975; Casadei 1998; Goldstein 1985; Howard 1977; Johnson 1989; Midtvedt 1996; Streem 1983) and unclear for the other seven trials (33%).

Completeness of follow-up

Completeness of follow-up was neither reported nor could be deduced for six trials (29%) (Hesse 1990; Hilbrands 1996; Hourmant 1985; Johnson 1989; Midtvedt 2003; Theodorakis 1998) and ranged between 83% to 100% for the remainder.

Effects of interventions

Readers are directed to the relevant forest plots as they are referred to in the text by brackets (outcome number). There are a large number of forest plots, though key results are illustrated in Analyses 1, 3 and 7.

Antibody therapy for the first rejection episode

Antibody versus steroid

Antibody was better than steroid alone in reversing an initial episode of rejection (Analysis 1.1 (failure to reverse rejection (6 trials)): RR 0.57, 95% CI 0.38 to 0.87), and also in preventing graft loss, whether censored for deaths or including death with a functioning graft, (Analysis 1.5 (censored for death, within 18 months of transplantation (7 trials)): RR 0.74 95% CI 0.58 to 0.95; Analysis 1.4 (graft loss or death with a functioning graft within 12 months of transplantation (7 trials)): RR 0.82, 95% CI 0.67 to 1.00). Recurrent rejection within the first year (Analysis 1.3 (8 trials): RR 0.67, 95% CI 0.43 to 1.04) favoured the use of antibody over steroid alone, but the estimates did not reach statistical significance.

For the trials of antibody versus steroid, there were no significant differences demonstrated in deaths, infections (all cause) or CMV disease within a year of treatment (Analysis 1.6, Analysis 1.7, Analysis 1.8, Analysis 1.9). No trials reported malignancy data, and the only adverse effects of treatment reported by more than one trial were a syndrome of fever, chills and malaise following drug administration, which significantly favoured steroid therapy (Analysis 1.10 (3 trials): RR 27.95, 95% CI 4.63 to 168.74) and avascular necrosis of the femoral head which was no different (Analysis 1.11 (2 trials): RR 1.05, 95% CI 0.12 to 9.34; P = 0.34, I^2 = 0%).

Muromonab-CD3 versus other antibody

For the two trials comparing muromonab-CD3 with another antibody, there was no evidence of significant advantage for muromonab-CD3 in reversing rejection (Analysis 3.1: RR 1.84, 95% CI 0.92 to 3.67; heterogeneity P = 0.54, I^2 = 0%), the requirement for additional treatment to achieve reversal (Analysis 3.2: RR 1.67, 95% CI 0.77 to 3.63; P = 0.60, I^2 = 0%), subsequent recurrent rejection (Analysis 3.3: RR 1.06, 95% CI 0.59 to 1.88; P = 0.45, I^2 = 0%), infection (Analysis 3.7: RR 1.53, 95% CI 0.69 to 3.40; P = 0.21, I^2 = 27.2%) or malignancy (Analysis 3.9: RR 0.26, 95% CI 0.03 to 2.30; P = 0.80, I^2 = 0%). However, muromonab-CD3 treated patients suffered three times more than those receiving either ATG or T10B9, from a syndrome of fever, chills and malaise following drug administration (Analysis 3.4: RR 3.12, 95% CI 1.87 to 5.21; P = 0.23, I^2 = 31.3%).

Four other RCTs compared three other different intervention algorithms using antibody in the treatment of first rejection episodes. Whether antibody and steroid were compared to steroid alone, (Analysis 2.1, Analysis 2.2, Analysis 2.3, Analysis 2.4, Analysis 2.5) or where rabbit was compared to horse derived ATG, (Analysis 4.1, Analysis 4.2) or where ALG was compared to other therapies, (Analysis 5.1, Analysis 5.2, Analysis 5.3, Analysis 5.4, Analysis 5.5, Analysis 5.6, Analysis 5.7, Analysis 6.1, Analysis 6.2, Analysis 6.3, Analysis 6.4, Analysis 6.5, Analysis 6.6) there were no significant differences in any outcomes assessed.

Antibody therapy for steroid-resistant rejection

OKT3 versus ATG or ALG

There was no advantage for OKT3 over ATG or ALG in either reversing resistant rejection (Analysis 7.1 (3 trials): RR 1.32, 95% CI 0.33 to 5.28) preventing subsequent rejection (Analysis 7.3 (3 trials): RR 0.99, 95% CI 0.61 to 1.59) or preventing graft loss (Analysis 7.4 censored for death (3 trials): RR 1.80, 95% CI 0.29 to 11.12; Analysis 7.5 including death with a functioning graft (3 trials): RR 1.08, 95% CI 0.38 to 3.10). Similarly, there were no significant differences identified in death, CMV disease, malignancy or mean serum creatinine at one year (Analysis 7.6, Analysis 7.7, Analysis 7.8, Analysis 7.10, Analysis 7.11) Patients taking muromonab-CD3 were three times more likely to experience a syndrome of fever, chills and malaise following drug administration (Analysis 7.9: RR 3.21, 95% CI 1.34 to 7.70) than those treated with either ATG or ALG. No other adverse effects were reported by more than one trial.

Other comparisons

There were three additional trials each comparing unique paired interventions. When rabbit ATG (thymoglobulin) was compared to horse ATG (ATGAM), rabbit prevented graft loss (Analysis 8.4 censored for death: RR 0.46, 95% CI 0.21 to 1.00) significantly more effectively than horse ATG, but the difference was not significant for failure to reverse rejection, recurrent rejection, deaths, infections or malignancy (Analysis 8.1, Analysis 8.2, Analysis 8.5, Analysis 8.6, Analysis 8.7, Analysis 8.8, Analysis 8.9, Analysis 8.10, Analysis 8.11). When muromonab-CD3 was compared at standard and half dose, or when muromonab-CD3 was compared to IVIg, there were no

significant differences in effect for any outcomes assessed (Analysis 9.1, Analysis 9.2, Analysis 9.3, Analysis 9.4, Analysis 9.5, Analysis 9.6, Analysis 9.7, Analysis 9.8, Analysis 9.9, Analysis 10.1, Analysis 10.2, Analysis 10.3, Analysis 10.4, Analysis 10.5, Analysis 10.6).

DISCUSSION

Summary of key findings

In kidney transplant recipients on dual baseline immunosuppressive therapy with either azathioprine and steroids or cyclosporin and steroids, antibody therapy is 43% more effective at reversing a first acute rejection episode, and 26% more effective at preventing graft loss than further steroid treatment, but significant benefit in patient survival has not been demonstrated.

In kidney transplant recipients on triple baseline immunosuppression with cyclosporin, azathioprine and steroids, experiencing acute rejection resistant to further steroid treatment, there is no evidence that the effects of muromonab-CD3 and ATG or ALG are different in reversal or recurrence of acute rejection, or patient or graft survival.

Antibody-treated patients were 28 times more likely to experience an immediate reaction of fever, chills and malaise than those receiving steroid, and muromonab-CD3 treated patients were three times more likely to experience this reaction than those treated with other antibodies, whether for the treatment of first rejection episode or steroid-resistant rejection. Other adverse effects of Ab therapy were inconsistently reported and could not be summarised because of sparsely reported data. We identified no trials investigating antibody therapy for the treatment of acute rejection where contemporary immunosuppressive agents such as tacrolimus, mycophenolate or sirolimus were employed.

Strengths and limitations

This systematic review was undertaken with widely inclusive criteria, in order to highlight and summarise the totality of RCT evidence available. This approach led to identification of 21 trials involving 1387 participants, including unpublished and non-English language data sources. This enhances the external and internal validity of our review, as confining a systematic review and meta-analysis to published or English language data alone has been demonstrated to over-estimate positive treatment effects (Egger 2001).

Our review is limited by the quantity and quality of existing published trials, so residual uncertainty about the true effects of these compounds remains. The reporting of key components for evaluating of the validity of RCTs was not comprehensive and not compatible with current standards of reporting. In many cases this reflected design features which are sub-optimal such as inadequate allocation concealment (10%), lack of blinding of outcome assessment, non-intention-to-treat principles, and substantial losses to follow-up. These features are associated with substantial bias in favour of the investigational intervention (Peduzzi 1993; Sackett 1979). Many clinically relevant outcomes were not reported at all or only within a very limited time frame; in particular it is uncertain whether these agents improve graft survival beyond one year. Additionally, the definitions and criteria used to define rejection, steroid-resistant rejection, and other outcomes were not always reported, were not provided in sufficient detail to be reproducible and where reported were not uniform across trials. Unfortunately these inconsistencies are not limited to trials on this topic, or to the field of transplantation, but are widely recognised by other investigators across diverse medical fields (Chan 2005; Hollis 1999; Loke 2001).

The relatively low number of small trials published in this area means that there is considerable imprecision around all estimates of effect. For example, our data suggest that antibody therapy for acute rejection may prevent further recurrent rejection episodes by around 33% compared to steroids, a clinically important difference, but the width of the 95% CI are consistent with a 57% reduction or a 4% increase. We have insufficient data to conclude with reasonable certainty that antibody treatment for acute rejection prevents further rejection, but this possibility is suggested by our data. Imprecision is a particular problem with estimating the harms of the interventions. Reporting of potential harms of treatment was very limited and inconsistently expressed, so the potential of meta-analysis to increase both power and precision through combining trial results to expose significant differences in harmful effects occurring at low frequency in individual trials was not realised. More than half the trials did not report treatment side effects, or other adverse events such as infection or malignancy. It should be recognised that absence of evidence does not equate to evidence of absence of effect, and we recognise that at present, with such scant trial data, these outcomes may be better informed by available registry data. The value of increasing available evidence of potential harms associated with interventions (compared with potential benefits alone) has been widely recognised and is also not a problem peculiar to this review, but is common to many RCTs (Cuervo 2003; Tunis 2003).

AUTHORS' CONCLUSIONS

Implications for practice

In treatment of rejection, especially where steroids have already failed, clinicians are faced with the option of using antibody therapy. There is no evidence from the pooled world literature of RCTs that OKT3, ATG or ALG differ in beneficial or harmful effects.

The majority of trials of first acute rejection following kidney transplantation were published 10 to 30 years ago and used dual baseline immunosuppression that is now used very infrequently. All of the seven trials investigating the treatment of resistant rejection used triple baseline immunosuppression with cyclosporin, azathioprine and steroids and this combination is no longer standard therapy in many countries; cyclosporin is used in only 25% new transplant patients in the USA, and azathioprine in fewer than 2%, and the cyclosporin/azathioprine combination used in only 3% in Australia and is not recommended in the UK (Chadban 2004; NICE 2004;UNOS 2004). Whether the effects of Ab therapy are different when used with baseline immunosuppression that differs from that of the trials we identified cannot be answered with current evidence, so the results of our analysis may or may not be generalisable to the contemporary clinical practice of many countries.

There have been no other systematic reviews of RCTs of antibody therapy in treating acute rejection in kidney recipients, although systematic reviews of antibodies used as induction immunosuppressive therapy, at the time of transplantation, with the aim of rejection prophylaxis have been undertaken (Szczech 1997; Szczech 1998; Webster 2004).

Implications for research

Our goal was to summarise the evidence for the use of antibody therapy in the treatment of acute rejection in renal transplant recipients. Our meta-analysis cannot answer the question of how best to treat rejection, but our systematic review does clearly establish and detail the entirety of trial evidence that is available and has demonstrated that there is little evidence on which to base clinical decision making, and no evidence for antibody use with tacrolimus, mycophenolate or sirolimus. To our knowledge, no peer-reviewed journal has published data from any RCT of any intervention for the treatment of acute rejection in kidney recipients for at least two years. There have, however, been numerous trials of newer immunosuppressive agents in primary, induction and maintenance therapy regimens designed with diverse primary outcomes. As the preparations for the treatment of rejection are not new, there is no economic drive from the pharmaceutical industry to encourage and back new trials. A definitive answer will not arise until trials ask the question. To increase both the amount and the quality of evidence available from RCTs in this area, the drive must come from researchers. Future trials investigating different antibody therapies, or antibody therapy versus switch in baseline immunosuppression would inform clinical care, but must clearly define outcomes and adequately report harms of treatment to improve on current knowledge and allow more informative cross-trial comparisons. In particular, the potential of antibody therapy to prevent graft loss compared with steroids alone to treat acute rejection needs to be confirmed.

ACKNOWLEDGEMENTS

ACW would like to acknowledge the help and support of all members of the Cochrane Renal Group. She also wishes to thank Dr N Webb, J Mahan, and Ms L Orton, who contributed to advice and comment at the initial protocol development stage of the review. ACW also wishes to thank all report authors who responded to our enquiries about their work and those who provided further information about their trials, particularly Drs Midtvedt, Almartine, Howard and Birkeland.

This review has been co-published with *Transplantation* April 2006, in press (Webster 2006).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Baldi 2000

Methods	Steroid resistant rejection Single centre Country: Belgium
Participants	n = 56 (28/28)

Baldi 2000 *(Continued)*

	Deceased donor: NS First transplant: NS
Interventions	Muromonab-CD3 versus ATG (4 mg/kg/d for 10 days) Baseline immunosuppression: cyclosporin (70), azathioprine (75) Other treatment: dexchlorpheniramine before muromonab-CD3
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Graft loss cause Death Death cause Serum creatinine Treatment failure Treatment side effects Infection CMV Malignancy
Notes	Maximum follow-up: 127 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Barenbrock 1994

Methods	First rejection Single centre Country: Germany
Participants	n = 38 (20/18) Deceased donor: 100% First transplant: NS
Interventions	Muromonab-CD3 versus ATG (5 mg/kg/d for 10 days) Baseline immunosuppression: cyclosporin (5-10 mg/kg/d), azathioprine Other treatment: H1 and H2 blockers
Outcomes	Serum creatinine Treatment side effects BP change
Notes	Maximum follow-up: 4 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Birkeland 1975

Methods	Steroid resistant rejection Single centre Country: Denmark
Participants	n = 30 Deceased donor: NS First transplant: NS
Interventions	ALG (20mg/kg, then 10 mg/kg for 21 days) with steroid versus steroid Baseline immunosuppression: azathioprine Other treatment: none
Outcomes	Acute rejection reversal Recurrent rejection Graft loss death censored Graft loss cause Death Death cause
Notes	Maximum follow-up: 77 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Casadei 1998

Methods	First rejection Single centre Country: Argentina
Participants	n = 23 Deceased donor: 65% First transplant: 100%
Interventions	Muromonab-CD3 (14 days) versus IVIg (500 mg/kg/d for 7 days) Baseline immunosuppression: cyclosporin (600), azathioprine Other treatment: diltiazem gancyclovir with muromonab-CD3
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Death Serum creatinine Treatment failure Treatment side effects
Notes	Maximum follow-up: 2 months

Risk of bias

Casadei 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Filo 1980

Methods	First rejection Single centre Country: USA
Participants	n = 114 Deceased donor: 100% First transplant: 100%
Interventions	ATG (10 mg/kg for 15 days) versus steroid (MP 30 mg/kg every other day up to 5 doses) Baseline immunosuppression: azathioprine Other treatment: diphenhydramine
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Death Death cause Treatment side effects
Notes	Maximum follow-up: 36 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Gaber 1998

Methods	33% previous rejection (40% unresolved), 11% first rejection 29 centres Country: USA
Participants	n = 163 Deceased donor: 66% First transplant: 94%
Interventions	ATG rabbit (1.5 mg/kg/d for 14 days) versus ATG horse (15 mg/kg/d for 14 days) Baseline immunosuppression: cyclosporin (NS), azathioprine (NS) Other treatment: acetaminophen, diphenhydramine
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Death Death cause

Gaber 1998 *(Continued)*

	Treatment failure Treatment side effects Infection Malignancy Cost effectiveness
Notes	Maximum follow-up: 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Glass 1983

Methods	Steroid resistant rejection Single centre Country: USA
Participants	n = 62 Deceased donor: NS First transplant: NS
Interventions	ALG (30 mg/kg/d 14 days) versus steroid (either 3 mg/kg/d or 30 mg/d) Baseline immunosuppression: azathioprine Other treatment: none
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Death Death cause Treatment side effects
Notes	Maximum follow-up: 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Goldstein 1985

Methods	Steroid resistant rejection 10 centres country: USA
Participants	n = 123 Deceased donor: 1005 First transplant: 87%

Goldstein 1985 *(Continued)*

Interventions	Muromonab-CD3 (14 days) versus steroid (MP 500 mg/d for 3 days) Baseline immunosuppression: azathioprine Other treatment: none
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Graft loss cause Death Treatment failure Treatment side effects
Notes	Maximum follow-up: 24 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Hesse 1990

Methods	First rejection Single centre Country: Germany
Participants	n = 60 Deceased donor: NS First transplant: NS
Interventions	Muromonab-CD3 versus ALG (5 mL/10 kg for 10 days) Baseline immunosuppression: cyclosporin (600), azathioprine (250) Other treatment: tavegu
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Death Death cause Serum creatinine Treatment side effects Infection CMV
Notes	Maximum follow-up: 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Hilbrands 1996

Methods	Steroid resistant rejection Single centre Country: Netherlands
Participants	n = 26 Deceased donor: NS First transplant: NS
Interventions	ATG (200 mg/d for 7 days) versus steroid (MP 1 g/d for 3 days) Baseline immunosuppression: cyclosporin (NS) Other treatment: none
Outcomes	Recurrent rejection Graft loss, not death censored Graft loss death censored
Notes	Maximum follow-up: 77 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Hoitsma 1982

Methods	Steroid resistant rejection Single centre Country: Netherlands
Participants	n = 40 Deceased donor: 100% First transplant: 85%
Interventions	ATG (4-11 mg/kg/d for 21 days) versus steroid (prednisolone 200 mg/d for 3-5 days) Baseline immunosuppression: azathioprine Other treatment: none
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Death Serum creatinine Treatment side effects Infection CMV
Notes	Maximum follow-up: 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement

Hoitsma 1982 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Hourmant 1985

Methods	Steroid resistant rejection Single centre Country: France
Participants	n = 58 Deceased donor: 97% First transplant: 97%
Interventions	ALG (NS) versus steroid (NS) Baseline immunosuppression: cyclosporin (6 mg/kg/d), azathioprine Other treatment: none
Outcomes	None
Notes	Maximum follow-up: 18 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	High risk	C - Inadequate

Howard 1977

Methods	Steroid resistant rejection Single centre Country: USA
Participants	n = 57 Deceased donor: 39% First transplant: 100%
Interventions	ALG (20 mg/kg/d for 10 days) versus IVIg (20 mg/kg/d for 10 days) Baseline immunosuppression: azathioprine Other treatment: graft irradiation
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Death Death cause Infection CMV Malignancy
Notes	Maximum follow-up: 18 months

Risk of bias

Howard 1977 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Johnson 1989

Methods	Steroid resistant rejection Six centres Country: USA
Participants	n = 128 Deceased donor: NS First transplant: NS
Interventions	ATS (0.2 cc/kg for 14 days) versus ATG horse (NS) Baseline immunosuppression: cyclosporin (NS), azathioprine (NS) Other treatment: NS
Outcomes	Acute rejection reversal Graft loss, not death censored Death Death cause Treatment side effects
Notes	Maximum follow-up: 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Mariat 1998

Methods	First rejection Single centre Country: France
Participants	n = 60 Deceased donor: NS First transplant: 93%
Interventions	Muromonab-CD3 (5 mg/kg for 3 days, then 2.5 mg/kg for 7 days) versus ATG (50 mg/day) Baseline immunosuppression: cyclosporin (NS), azathioprine (NS) Other treatment: none
Outcomes	Recurrent rejection Graft loss, not death censored Graft loss death censored Graft loss cause Death Serum creatinine Treatment side effects Infection

Mariat 1998 *(Continued)*

	CMV
Notes	Maximum follow-up: 37 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Midtvedt 1996

Methods	First rejection Single centre Country: Norway
Participants	n = 23 Deceased donor: 65% First transplant: 100%
Interventions	Muromonab-CD3 half dose (2.5 mg for 10 days) versus Muromonab-CD3 standard dose Baseline immunosuppression: cyclosporin (NS), azathioprine (NS) Other treatment: cotrimoxazole
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Graft loss cause Death Death cause Treatment failure Infection CMV
Notes	Maximum follow-up: 18 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Midtvedt 2003

Methods	First rejection Single centre Country: Norway
Participants	n = 55 Deceased donor: 58% First transplant: NS
Interventions	Muromonab-CD3 (5 mg, then 2.5 mg, duration NS) versus ATG (2 mg/kg, then 1 mg/kg, duration NS)

Midtvedt 2003 *(Continued)*

	Baseline immunosuppression: cyclosporin (trough 150 µg/L), azathioprine Other treatment: co-trimoxazole, indomethacin, dexchlorpheniramine before muromonab-CD3
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Graft loss cause Death Death cause Serum creatinine Infection CMV Cost effectiveness
Notes	Maximum follow-up: 42 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Shield 1979

Methods	Steroid resistant rejection Two centres Country: USA
Participants	n = 20 Deceased donor: 0% First transplant: NS
Interventions	ATG (15 mg/kg) versus steroid (MP 1 g/day for 5 days) Baseline immunosuppression: azathioprine Other treatment: none
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Graft loss cause Death Serum creatinine Treatment side effects Infection
Notes	Maximum follow-up: 26 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Streem 1983

Methods	Steroid resistant rejection Single centre Country: USA
Participants	n = 23 Deceased donor: 100% First transplant: 100%
Interventions	ALG (15-20 mg/kg/d for 10 days) versus steroid (MP 1 g/d up to 6 days) Baseline immunosuppression: azathioprine Other treatment: none
Outcomes	Acute rejection reversal Recurrent rejection Graft loss, not death censored Graft loss death censored Graft loss cause Death Death cause Serum creatinine Treatment failure Treatment side effects Infection CMV
Notes	Maximum follow-up: 20 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Theodorakis 1998

Methods	Steroid resistant rejection Single centre Country: Germany
Participants	n = 50 Deceased donor: 100% First transplant: NS
Interventions	ATG (4 mg/kg for 7 days) verus steroid (MP 250 mg/d for 3 days) Baseline immunosuppression: cyclosporin (70), azathioprine (75)
Outcomes	Recurrent rejection Graft loss, not death censored,\ Serum creatinine
Notes	Maximum follow-up: 48 months

Risk of bias

Theodorakis 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Waid 1992

Methods	Steroid resistant rejection Single centre Country: USA
Participants	n = 178 Deceased donor: NS First transplant: 37%
Interventions	Muromonab-CD3 versus T10B9.1A31 (3 mg every 8 hours for 10 days) Baseline immunosuppression: cyclosporin (trough 50-150 ng/L) Other treatment: diphenhydramine, acetaminophen prior to muromonab-CD3
Outcomes	Acute rejection reversal Recurrent rejection Treatment failure Treatment side effects Infection CMV Malignancy
Notes	Maximum follow-up: 48 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

NS= not stated. In participants, numbers in brackets indicate groups in each intervention.
OKT3 given at 5 mg/d for 10 days unless otherwise stated. MP = methylprednisolone.
Baseline immunosuppression: Cyclosporin in mg/d. Azathioprine 150 mg/d unless otherwise stated. All patients were similarly described as being on tapering doses of steroids.

DATA AND ANALYSES

Comparison 1. Treatment of first rejection: antibody versus steroid (stratified by antibody type)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of reversal of acute rejection	6	344	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.38, 0.87]
1.1 Muromonab-CD3 versus steroid	1	120	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.14, 0.68]

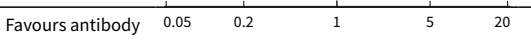
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.2 ATG versus steroid	3	139	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.26, 0.96]
1.3 ALG versus steroid	2	85	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.52, 1.75]
2 Additional treatment needed	3	83	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.27, 1.29]
2.1 ATG versus steroid	2	60	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.29, 1.43]
2.2 ALG versus steroid	1	23	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.01, 4.07]
3 Recurrent rejection up to 12 months post-therapy	8	413	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.43, 1.04]
3.1 Muromonab-CD3 versus steroid	1	103	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.69, 1.15]
3.2 ATG versus steroid	5	225	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.22, 1.21]
3.3 ALG versus steroid	2	85	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.34, 1.41]
4 Graft loss or death with a functioning graft within 12 months	7	380	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.67, 1.00]
4.1 muromonab-CD3 versus steroid	1	120	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.65, 1.10]
4.2 ATG versus steroid	3	155	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.48, 1.04]
4.3 ALG versus steroid	3	105	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.56, 1.54]
5 Graft loss censored for death within 18 months	7	380	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.58, 0.95]
5.1 Muromonab-CD3 versus steroid	1	120	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.53, 1.06]
5.2 ATG versus steroid	4	175	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.47, 1.06]
5.3 ALG versus steroid	2	85	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.42, 1.59]
6 Death within 12 months	6	318	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.57, 2.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 muromonab-CD3 versus steroid	1	120	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.53, 3.70]
6.2 ATG versus steroid	3	113	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.12, 4.43]
6.3 ALG versus steroid	2	85	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.31, 3.60]
7 Death from infection	3	164	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.21, 2.63]
7.1 ATG	1	79	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.08, 18.43]
7.2 ALG	2	85	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.15, 2.71]
8 Infection (total)	4	206	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.59, 1.31]
8.1 Muromonab-CD3 versus steroid	1	123	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.82, 1.35]
8.2 ATG versus steroid	2	60	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.11, 18.53]
8.3 ALG versus steroid	1	23	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.42, 1.60]
9 CMV infection (total)	3	83	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.09, 4.71]
9.1 ATG	2	60	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.39, 3.99]
9.2 ALG	1	23	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.70]
10 Treatment side effects: fever, chills, malaise following administration	3	185	Risk Ratio (M-H, Random, 95% CI)	27.95 [4.63, 168.74]
10.1 Muromonab-CD3 versus steroid	1	125	Risk Ratio (M-H, Random, 95% CI)	91.55 [5.77, 1453.49]
10.2 ATG versus steroid	2	60	Risk Ratio (M-H, Random, 95% CI)	15.12 [1.66, 137.67]
11 Treatment side effects: avascular necrosis	2	43	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.12, 9.34]
11.1 ATG	1	20	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 65.90]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
11.2 ALG	1	23	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.04]

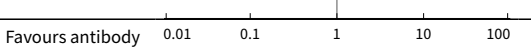
Analysis 1.1. Comparison 1 Treatment of first rejection: antibody versus steroid (stratified by antibody type), Outcome 1 Failure of reversal of acute rejection.

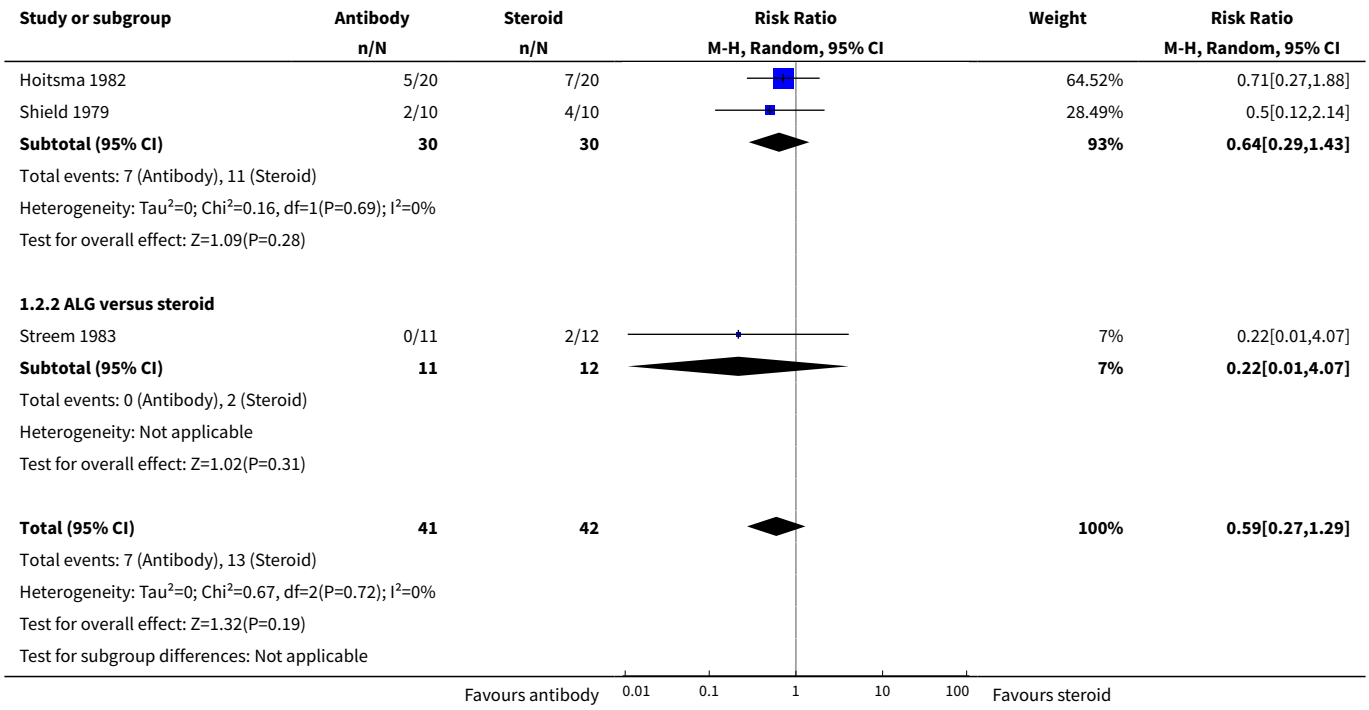
Study or subgroup	Antibody n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Muromonab-CD3 versus steroid					
Goldstein 1985	7/62	21/58		24.21%	0.31[0.14,0.68]
Subtotal (95% CI)	**62**	**58**		**24.21%**	**0.31[0.14,0.68]**
Total events: 7 (Antibody), 21 (Steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.94(P=0)					
1.1.2 ATG versus steroid					
Filo 1980	7/41	12/38		22.08%	0.54[0.24,1.23]
Hoitsma 1982	2/20	5/20		7.28%	0.4[0.09,1.83]
Shield 1979	2/10	4/10		7.9%	0.5[0.12,2.14]
Subtotal (95% CI)	**71**	**68**		**37.26%**	**0.5[0.26,0.96]**
Total events: 11 (Antibody), 21 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=0.12, df=2(P=0.94); I^2=0%					
Test for overall effect: Z=2.08(P=0.04)					
1.1.3 ALG versus steroid					
Glass 1983	13/35	10/27		31.87%	1[0.52,1.93]
Streem 1983	2/11	3/12		6.66%	0.73[0.15,3.57]
Subtotal (95% CI)	**46**	**39**		**38.53%**	**0.96[0.52,1.75]**
Total events: 15 (Antibody), 13 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%					
Test for overall effect: Z=0.14(P=0.89)					
Total (95% CI)	**179**	**165**		**100%**	**0.57[0.38,0.87]**
Total events: 33 (Antibody), 55 (Steroid)					
Heterogeneity: Tau^2=0.03; Chi^2=5.66, df=5(P=0.34); I^2=11.69%					
Test for overall effect: Z=2.61(P=0.01)					
Test for subgroup differences: Not applicable					



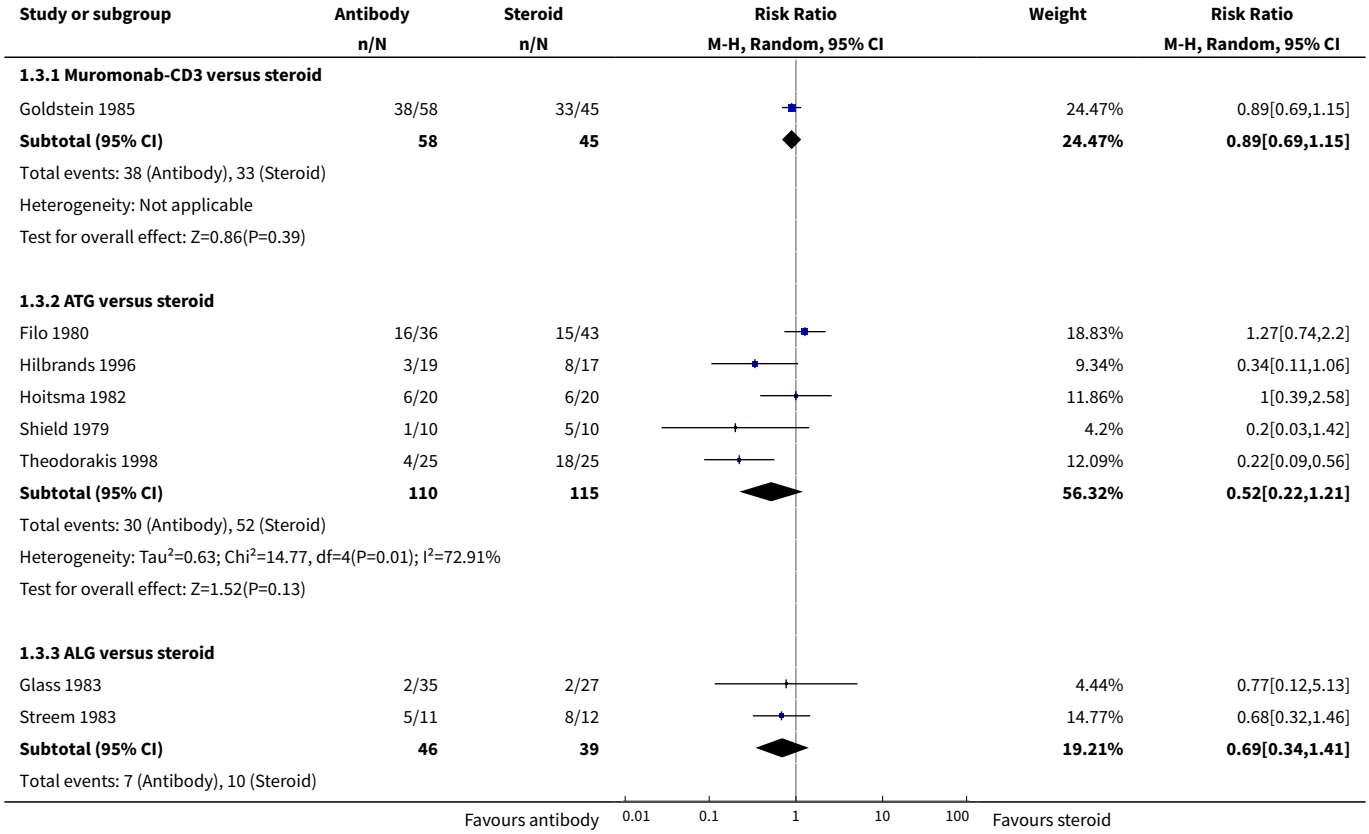
Analysis 1.2. Comparison 1 Treatment of first rejection: antibody versus steroid (stratified by antibody type), Outcome 2 Additional treatment needed.

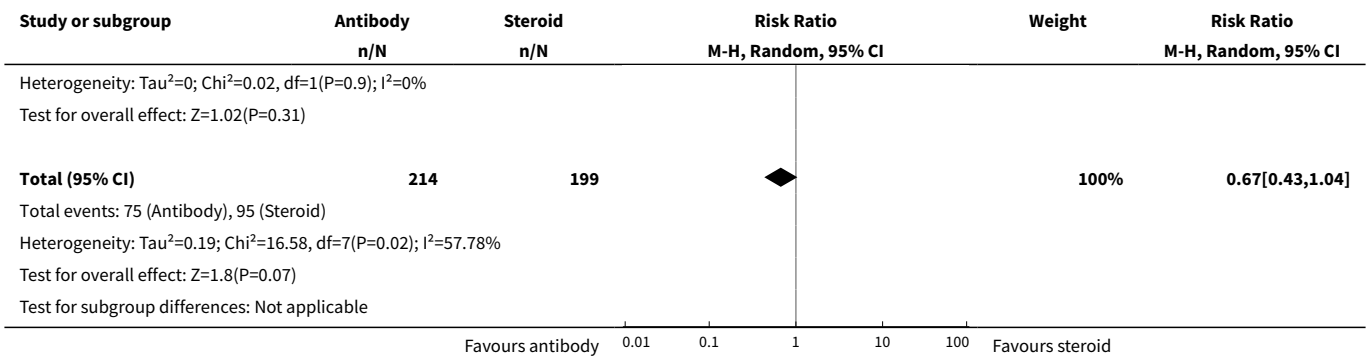
Study or subgroup	Antibody n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 ATG versus steroid					



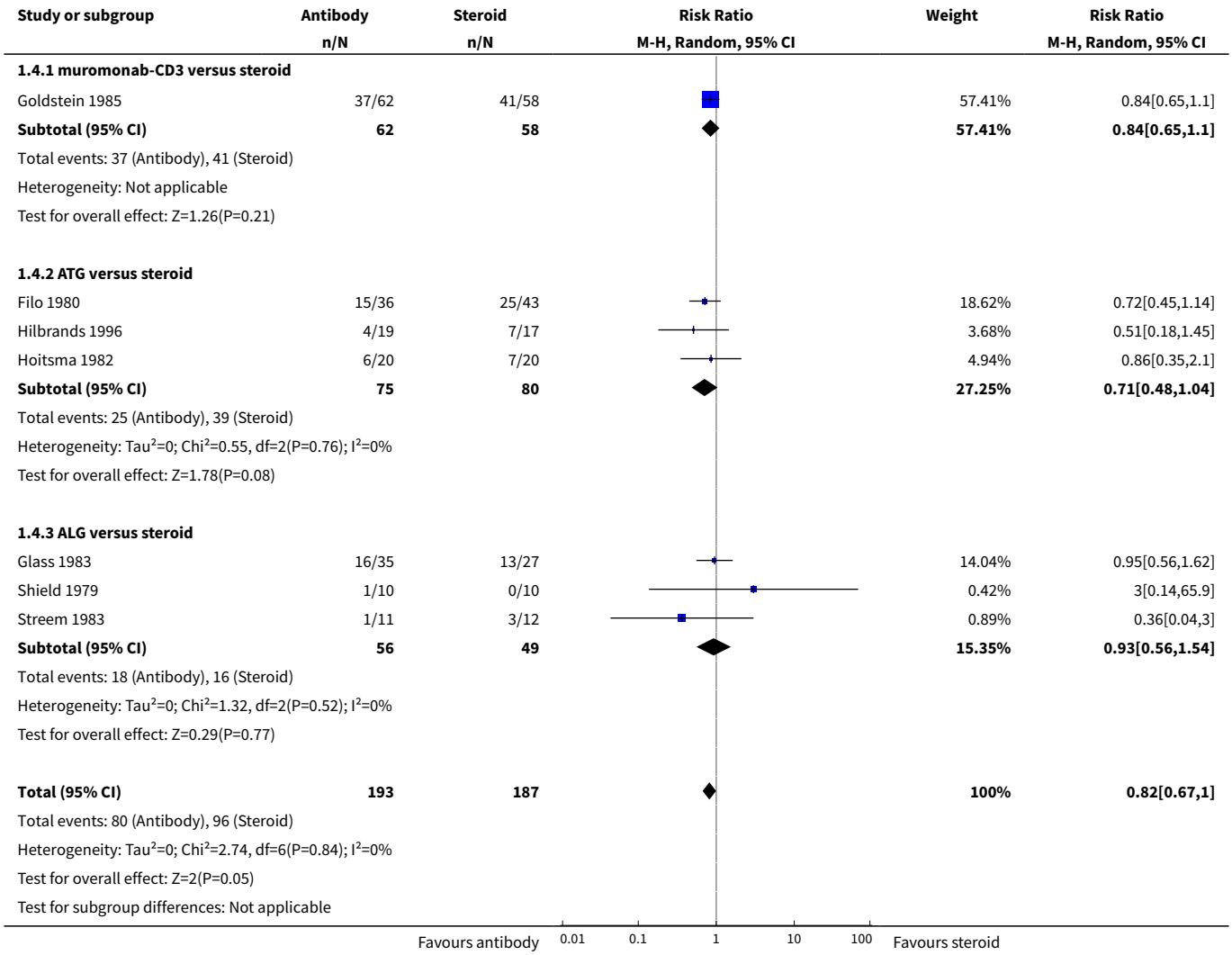


Analysis 1.3. Comparison 1 Treatment of first rejection: antibody versus steroid (stratified by antibody type), Outcome 3 Recurrent rejection up to 12 months post-therapy.



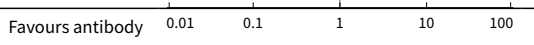


Analysis 1.4. Comparison 1 Treatment of first rejection: antibody versus steroid (stratified by antibody type), Outcome 4 Graft loss or death with a functioning graft within 12 months.



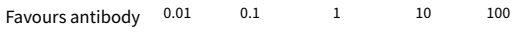
Analysis 1.5. Comparison 1 Treatment of first rejection: antibody versus steroid (stratified by antibody type), Outcome 5 Graft loss censored for death within 18 months.

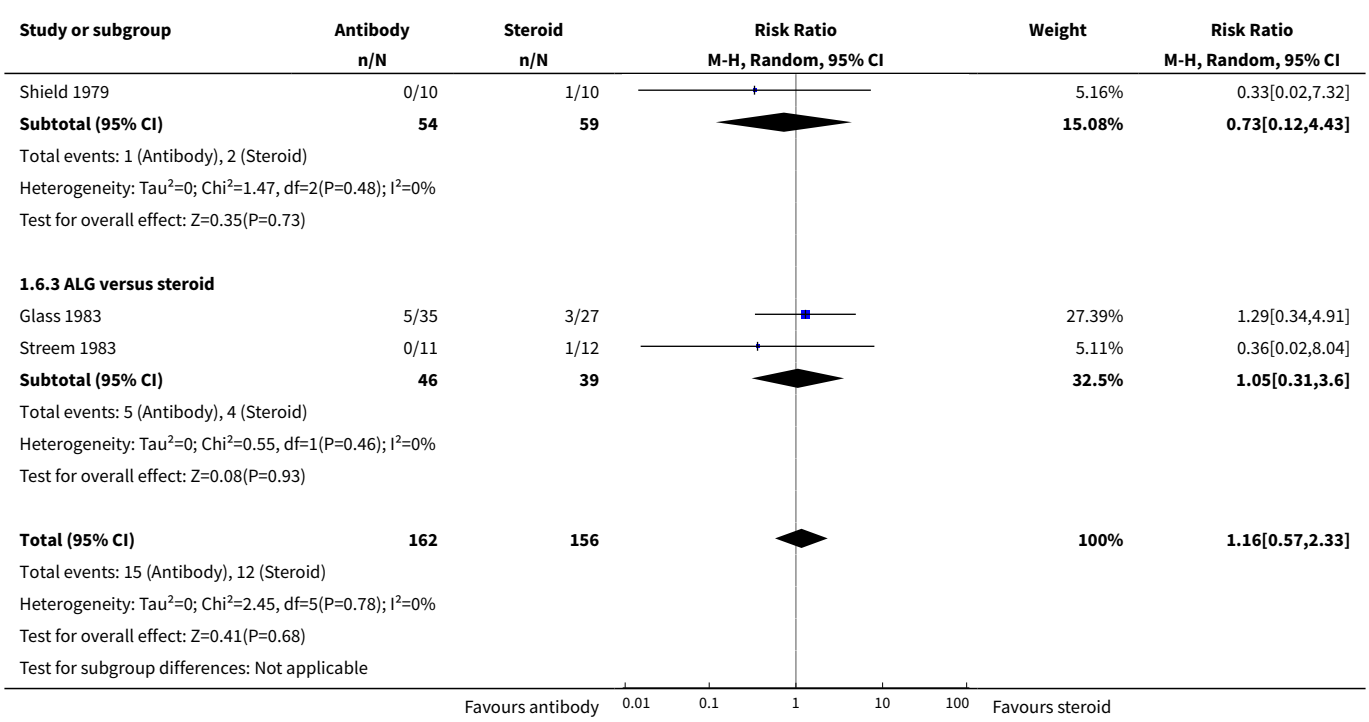
Study or subgroup	Antibody n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Muromonab-CD3 versus steroid					
Goldstein 1985	28/62	35/58		49.84%	0.75[0.53,1.06]
Subtotal (95% CI)	**62**	**58**		**49.84%**	**0.75[0.53,1.06]**
Total events: 28 (Antibody), 35 (Steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.65(P=0.1)					
1.5.2 ATG versus steroid					
Filo 1980	14/36	25/43		25.51%	0.67[0.41,1.08]
Hilbrands 1996	3/19	6/17		3.97%	0.45[0.13,1.52]
Hoitsma 1982	6/20	6/20		6.6%	1[0.39,2.58]
Shield 1979	1/10	0/10		0.62%	3[0.14,65.9]
Subtotal (95% CI)	**85**	**90**		**36.7%**	**0.71[0.47,1.06]**
Total events: 24 (Antibody), 37 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=1.95, df=3(P=0.58); I^2=0%					
Test for overall effect: Z=1.7(P=0.09)					
1.5.3 ALG versus steroid					
Glass 1983	11/35	10/27		12.3%	0.85[0.42,1.7]
Streem 1983	1/11	2/12		1.16%	0.55[0.06,5.21]
Subtotal (95% CI)	**46**	**39**		**13.46%**	**0.82[0.42,1.59]**
Total events: 12 (Antibody), 12 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%					
Test for overall effect: Z=0.6(P=0.55)					
Total (95% CI)	**193**	**187**		**100%**	**0.74[0.58,0.95]**
Total events: 64 (Antibody), 84 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=2.22, df=6(P=0.9); I^2=0%					
Test for overall effect: Z=2.41(P=0.02)					
Test for subgroup differences: Not applicable					



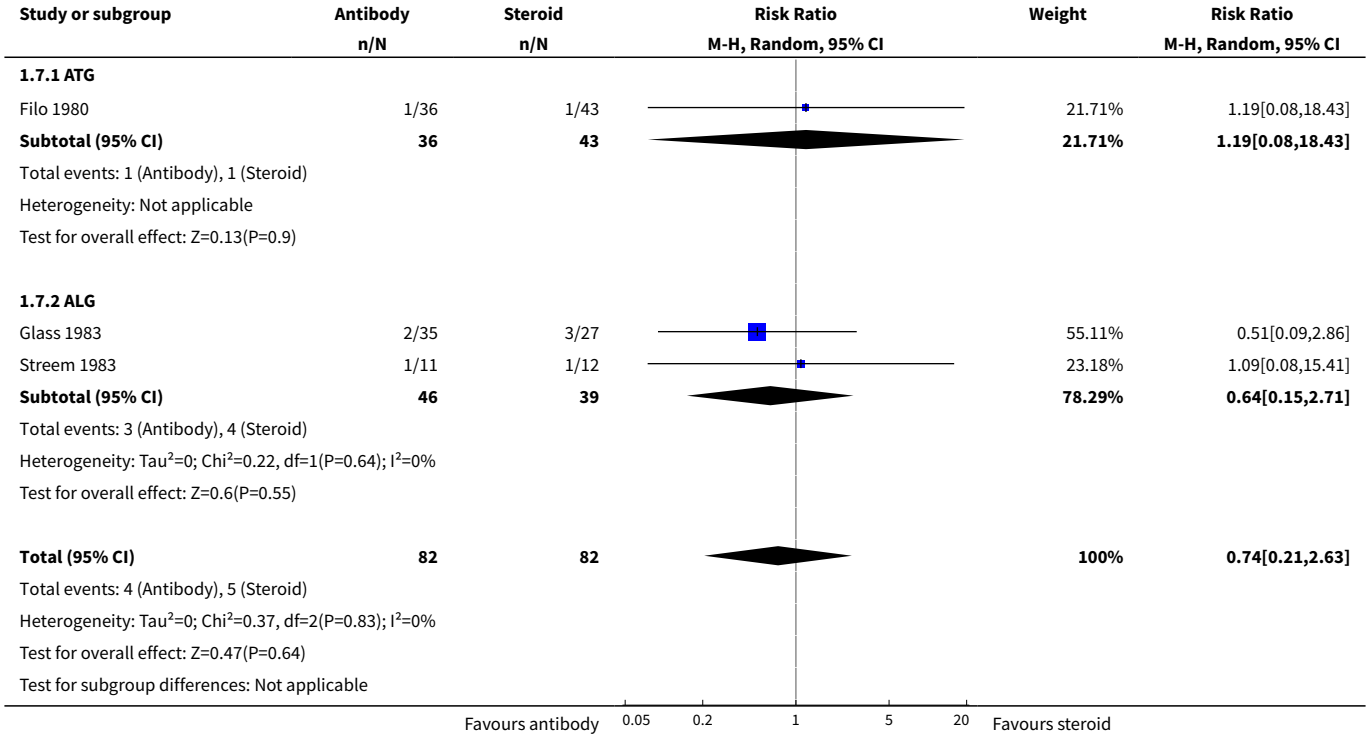
Analysis 1.6. Comparison 1 Treatment of first rejection: antibody versus steroid (stratified by antibody type), Outcome 6 Death within 12 months.

Study or subgroup	Antibody n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 muromonab-CD3 versus steroid					
Goldstein 1985	9/62	6/58		52.42%	1.4[0.53,3.7]
Subtotal (95% CI)	**62**	**58**		**52.42%**	**1.4[0.53,3.7]**
Total events: 9 (Antibody), 6 (Steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
1.6.2 ATG versus steroid					
Filo 1980	1/24	0/29		4.94%	3.6[0.15,84.54]
Hoitsma 1982	0/20	1/20		4.98%	0.33[0.01,7.72]

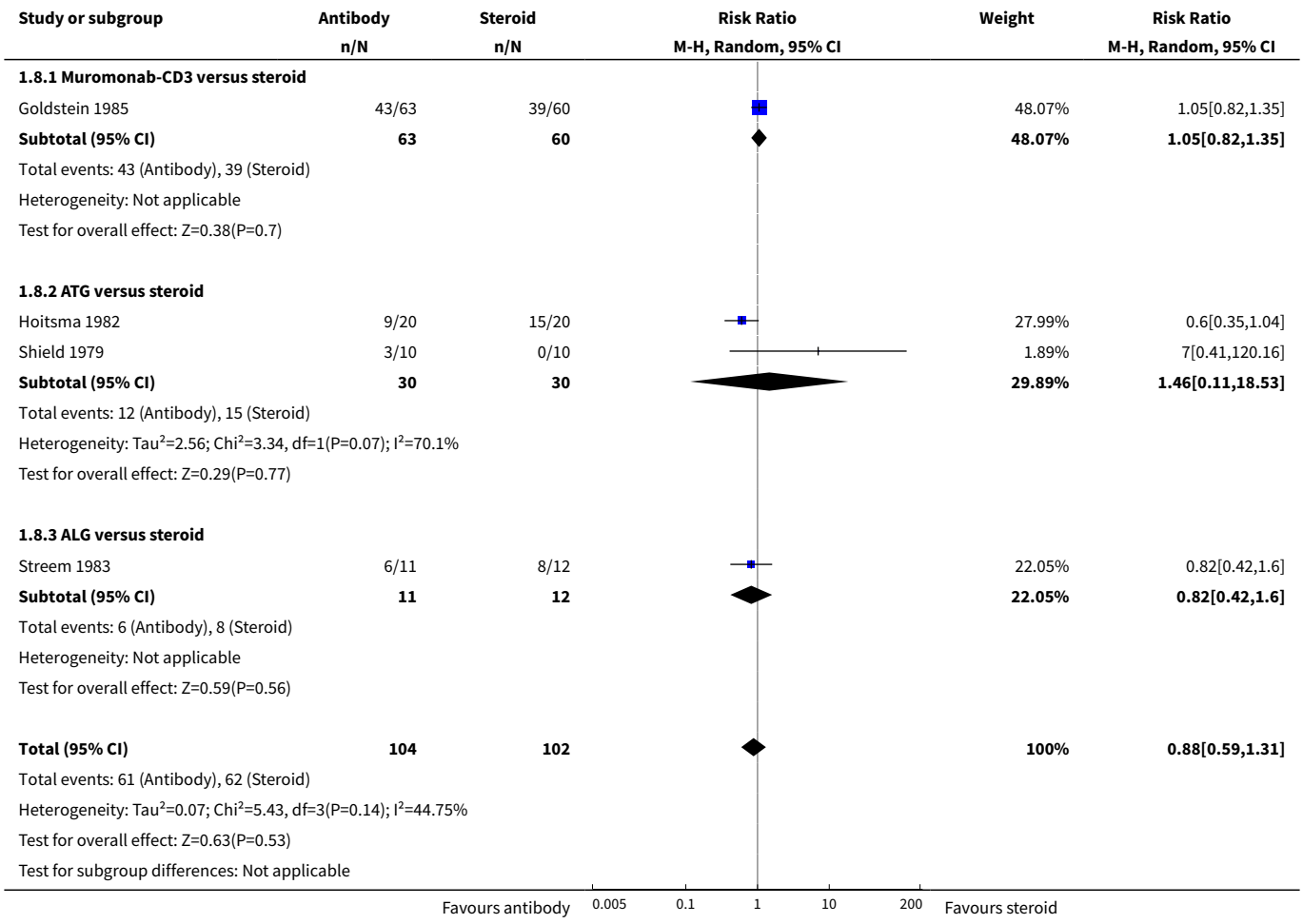




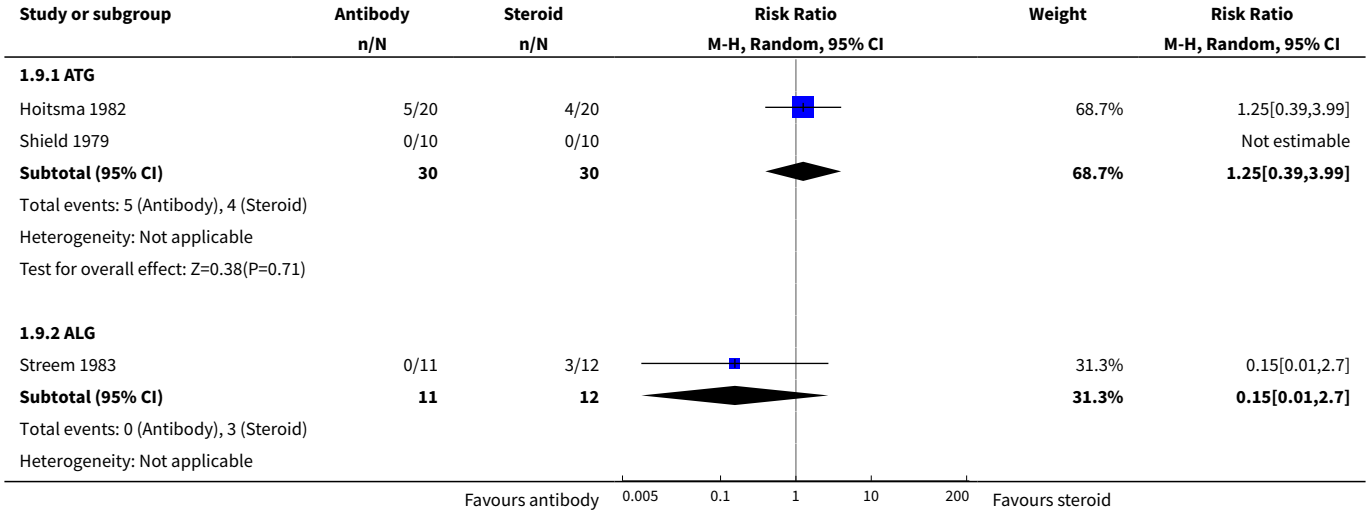
Analysis 1.7. Comparison 1 Treatment of first rejection: antibody versus steroid (stratified by antibody type), Outcome 7 Death from infection.

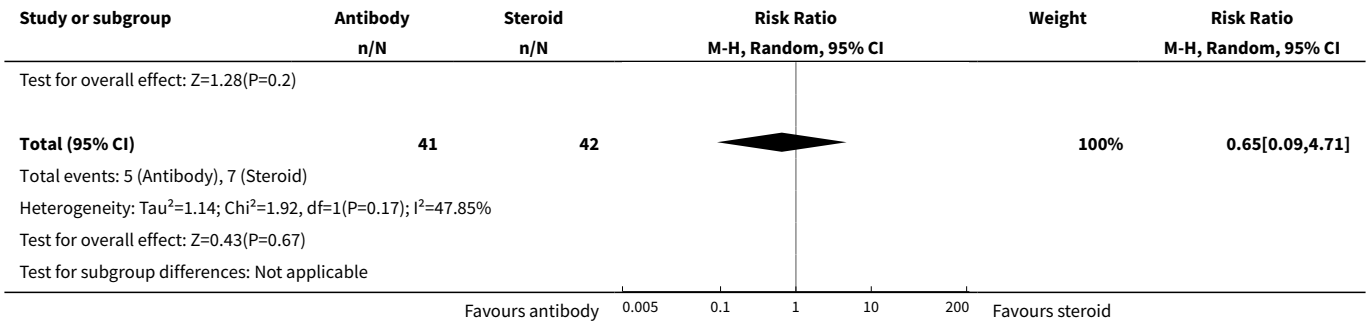


Analysis 1.8. Comparison 1 Treatment of first rejection: antibody versus steroid (stratified by antibody type), Outcome 8 Infection (total).

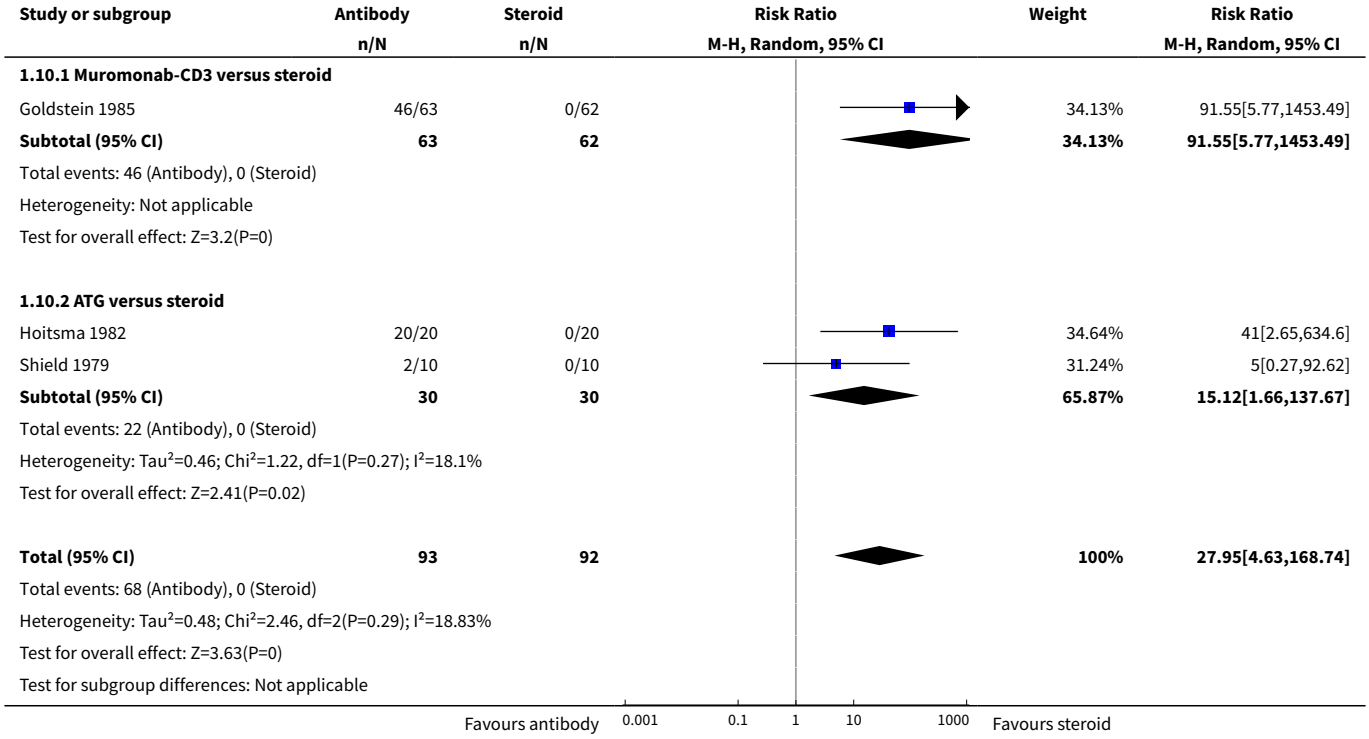


Analysis 1.9. Comparison 1 Treatment of first rejection: antibody versus steroid (stratified by antibody type), Outcome 9 CMV infection (total).

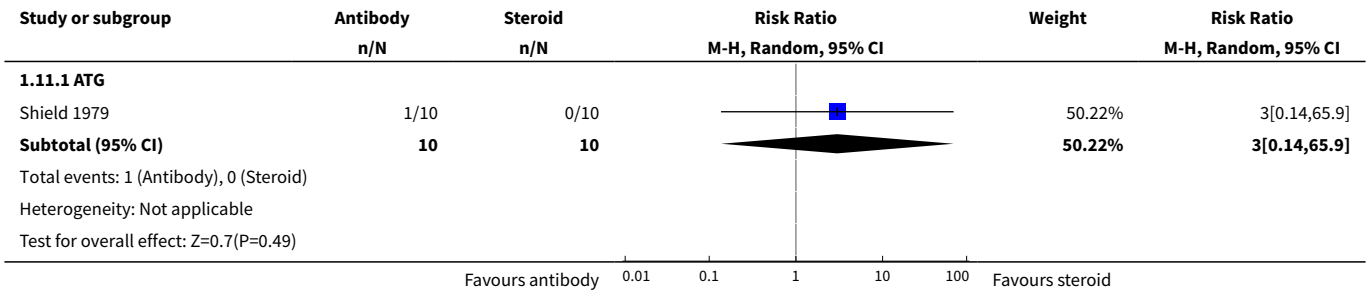


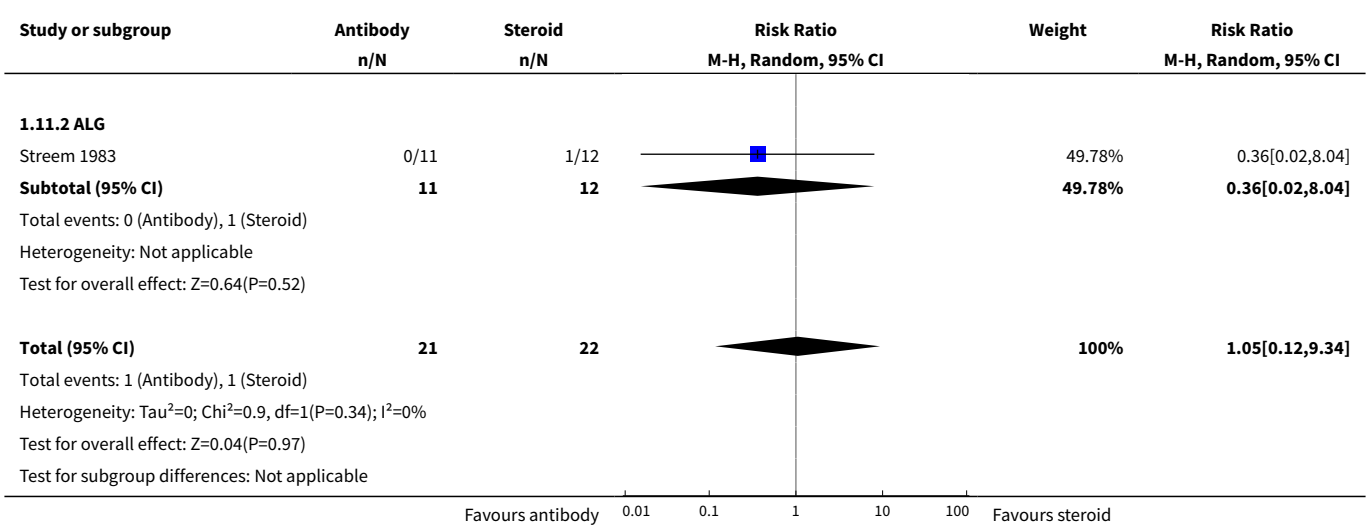


Analysis 1.10. Comparison 1 Treatment of first rejection: antibody versus steroid (stratified by antibody type), Outcome 10 Treatment side effects: fever, chills, malaise following administration.



Analysis 1.11. Comparison 1 Treatment of first rejection: antibody versus steroid (stratified by antibody type), Outcome 11 Treatment side effects: avascular necrosis.

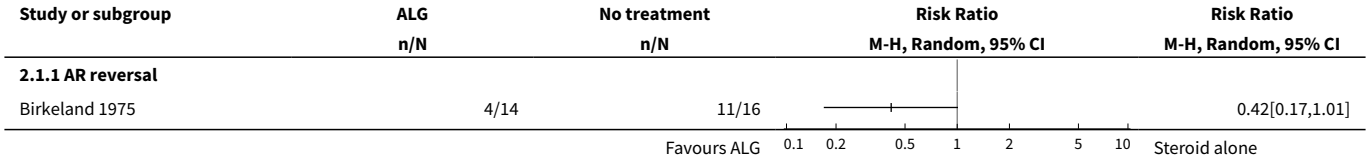




Comparison 2. Treatment of first rejection: ALG + steroid versus steroid alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of reversal of acute rejection (AR) episode	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 AR reversal	1		Risk Ratio (M-H, Random, 95% CI)	0.42 [0.17, 1.01]
2 Recurrent rejection within 3 months post-therapy	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Graft loss or death with a functioning graft within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Graft loss censored for death within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Death within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 2.1. Comparison 2 Treatment of first rejection: ALG + steroid versus steroid alone, Outcome 1 Failure of reversal of acute rejection (AR) episode.



Analysis 2.2. Comparison 2 Treatment of first rejection: ALG + steroid versus steroid alone, Outcome 2 Recurrent rejection within 3 months post-therapy.

Study or subgroup	ALG n/N	No treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Birkeland 1975	0/14	8/16		0%	0.07[0,1.06]

Favours ALG 0.002 0.1 1 10 500 Favours no treatment

Analysis 2.3. Comparison 2 Treatment of first rejection: ALG + steroid versus steroid alone, Outcome 3 Graft loss or death with a functioning graft within 12 months.

Study or subgroup	ALG n/N	No treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Birkeland 1975	3/16	3/16		0%	1[0.24,4.23]

Favours ALG 0.2 0.5 1 2 5 Favours no treatment

Analysis 2.4. Comparison 2 Treatment of first rejection: ALG + steroid versus steroid alone, Outcome 4 Graft loss censored for death within 12 months.

Study or subgroup	ALG n/N	No treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Birkeland 1975	3/14	4/16		0%	0.86[0.23,3.19]

Favours ALG 0.2 0.5 1 2 5 Favours no treatment

Analysis 2.5. Comparison 2 Treatment of first rejection: ALG + steroid versus steroid alone, Outcome 5 Death within 12 months.

Study or subgroup	ALG n/N	No treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Birkeland 1975	9/14	12/16		0%	0.86[0.53,1.39]

Favours ALG 0.5 0.7 1 1.5 2 Favours no treatment

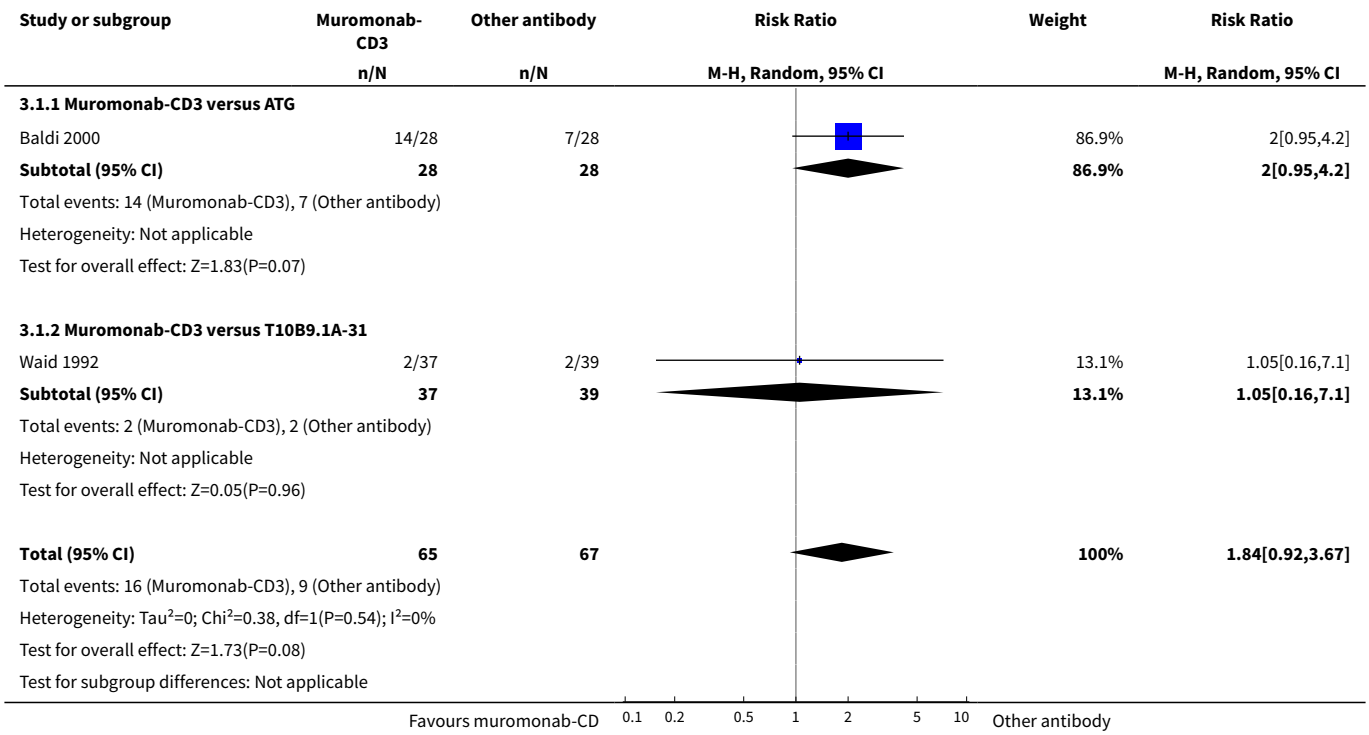
Comparison 3. Treatment of first rejection: muromonab-CD3 versus other antibody (stratified by comparator)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of acute rejection reversal	2	132	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.92, 3.67]
1.1 Muromonab-CD3 versus ATG	1	56	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.95, 4.20]
1.2 Muromonab-CD3 versus T10B9.1A-31	1	76	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.16, 7.10]

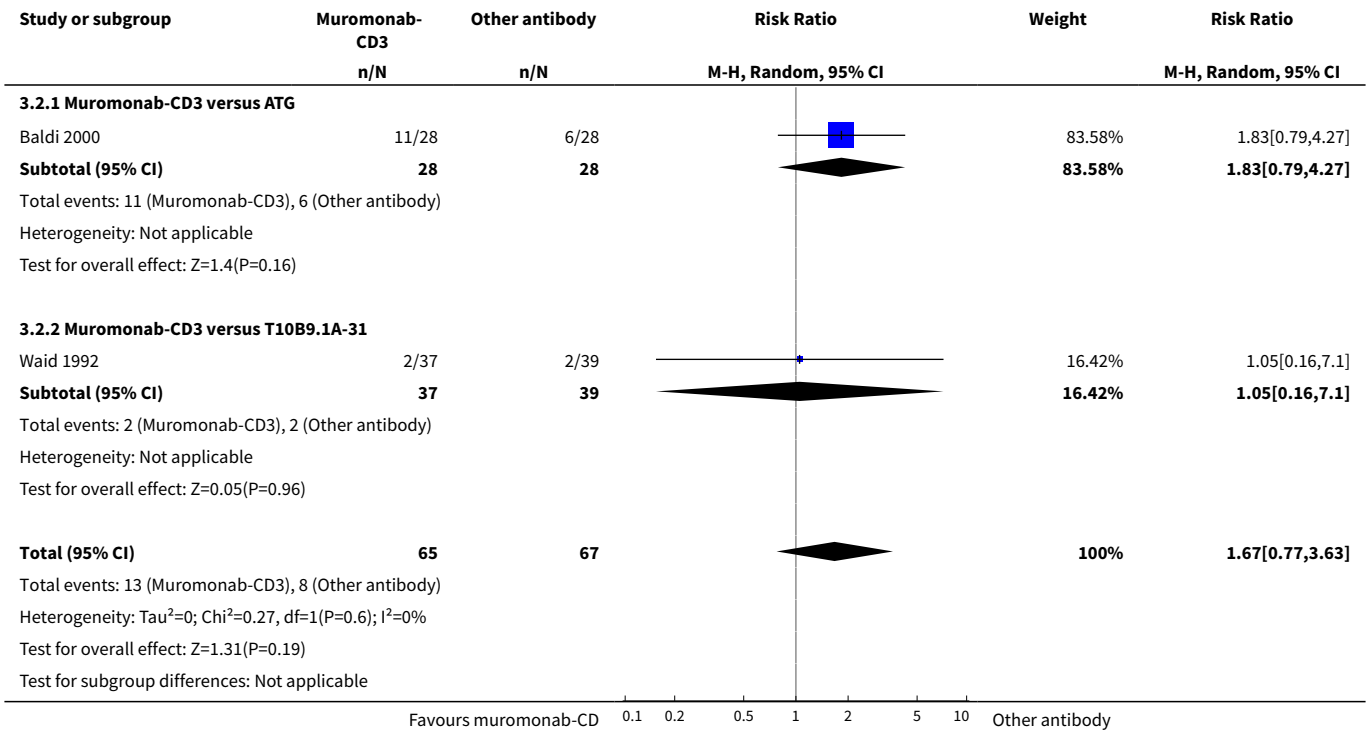
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Additional treatment needed	2	132	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.77, 3.63]
2.1 Muromonab-CD3 versus ATG	1	56	Risk Ratio (M-H, Random, 95% CI)	1.83 [0.79, 4.27]
2.2 Muromonab-CD3 versus T10B9.1A-31	1	76	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.16, 7.10]
3 Recurrent rejection up to 12 months post-therapy	2	129	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.59, 1.88]
3.1 Muromonab-CD3 versus ATG	1	53	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.61, 2.56]
3.2 Muromonab-CD3 versus T10B9.1A-31	1	76	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.30, 2.06]
4 Treatment side effects: fevers, chills, malaise following administration	2	132	Risk Ratio (M-H, Random, 95% CI)	3.12 [1.87, 5.21]
4.1 Muromonab-CD3 versus ATG	1	56	Risk Ratio (M-H, Random, 95% CI)	4.33 [2.12, 8.87]
4.2 Muromonab-CD3 versus T10B9.1A-31	1	76	Risk Ratio (M-H, Random, 95% CI)	2.55 [1.54, 4.20]
5 Treatment side effects: gastrointestinal	2	132	Risk Ratio (M-H, Random, 95% CI)	8.23 [0.90, 75.11]
5.1 Muromonab-CD3 versus ATG	1	56	Risk Ratio (M-H, Random, 95% CI)	33.0 [2.08, 524.54]
5.2 Muromonab-CD3 versus T10B9.1A-31	1	76	Risk Ratio (M-H, Random, 95% CI)	4.04 [1.86, 8.79]
6 Treatment side effects: neurological	2	132	Risk Ratio (M-H, Random, 95% CI)	13.10 [1.43, 120.05]
6.1 Muromonab-CD3 versus ATG	1	56	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 70.64]
6.2 Muromonab-CD3 versus T10B9.1A-31	1	76	Risk Ratio (M-H, Random, 95% CI)	29.51 [4.23, 206.05]
7 Infection (total)	2	86	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.69, 3.40]
7.1 Muromonab-CD3 versus ATG at 2 months	1	56	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.53, 2.31]
7.2 Muromonab-CD3 versus T10B9.1A-31 at 12 months	1	30	Risk Ratio (M-H, Random, 95% CI)	2.55 [0.88, 7.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 CMV infection (total)	2	132	Risk Ratio (M-H, Random, 95% CI)	2.25 [0.31, 16.08]
8.1 Muromonab-CD3 versus ATG	1	56	Risk Ratio (M-H, Random, 95% CI)	1.2 [0.41, 3.48]
8.2 Muromonab-CD3 versus T10B9.1A-31	1	76	Risk Ratio (M-H, Random, 95% CI)	9.47 [0.53, 170.09]
9 Malignancy (total)	2	132	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.03, 2.30]
9.1 Muromonab-CD3 versus ATG	1	56	Risk Ratio (M-H, Random, 95% CI)	0.2 [0.01, 3.99]
9.2 Muromonab-CD3 versus T10B9.1A-31	1	76	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.35]

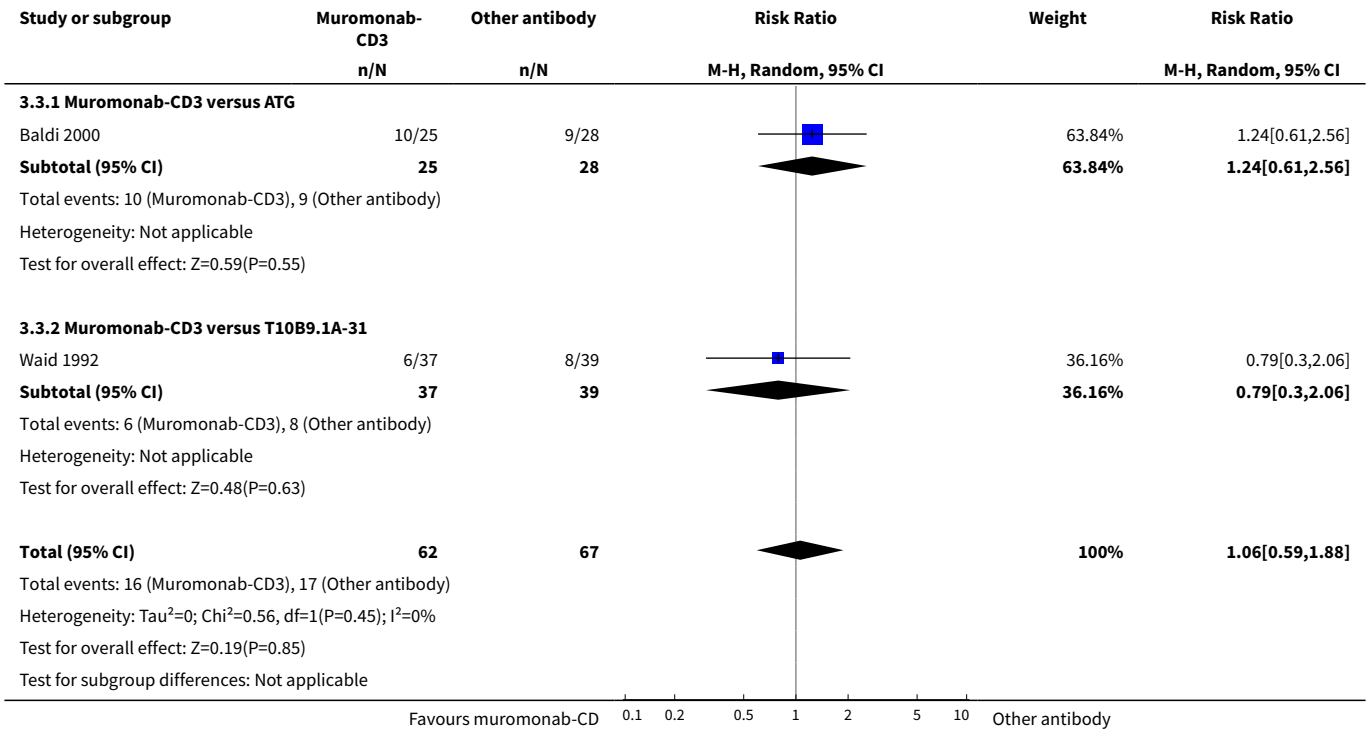
Analysis 3.1. Comparison 3 Treatment of first rejection: muromonab-CD3 versus other antibody (stratified by comparator), Outcome 1 Failure of acute rejection reversal.



Analysis 3.2. Comparison 3 Treatment of first rejection: muromonab-CD3 versus other antibody (stratified by comparator), Outcome 2 Additional treatment needed.

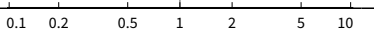


Analysis 3.3. Comparison 3 Treatment of first rejection: muromonab-CD3 versus other antibody (stratified by comparator), Outcome 3 Recurrent rejection up to 12 months post-therapy.



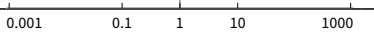
Analysis 3.4. Comparison 3 Treatment of first rejection: muromonab-CD3 versus other antibody (stratified by comparator), Outcome 4 Treatment side effects: fevers, chills, malaise following administration.

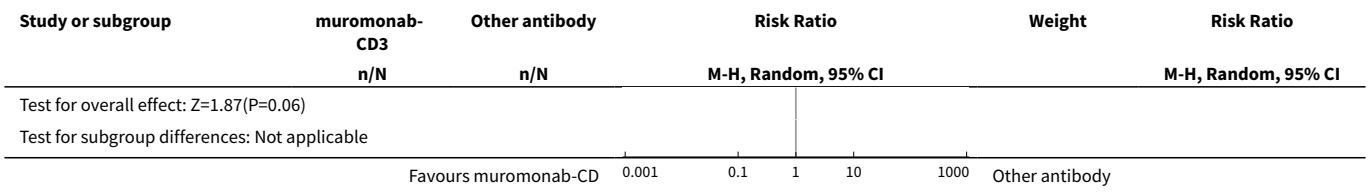
Study or subgroup	Muromonab-CD3 n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Muromonab-CD3 versus ATG					
Baldi 2000	26/28	6/28		38.15%	4.33[2.12,8.87]
Subtotal (95% CI)	**28**	**28**		**38.15%**	**4.33[2.12,8.87]**
Total events: 26 (Muromonab-CD3), 6 (Other antibody)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.01(P<0.0001)					
3.4.2 Muromonab-CD3 versus T10B9.1A-31					
Waid 1992	29/37	12/39		61.85%	2.55[1.54,4.2]
Subtotal (95% CI)	**37**	**39**		**61.85%**	**2.55[1.54,4.2]**
Total events: 29 (Muromonab-CD3), 12 (Other antibody)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.66(P=0)					
Total (95% CI)	**65**	**67**		**100%**	**3.12[1.87,5.21]**
Total events: 55 (Muromonab-CD3), 18 (Other antibody)					
Heterogeneity: Tau^2=0.05; Chi^2=1.45, df=1(P=0.23); I^2=31.27%					
Test for overall effect: Z=4.35(P<0.0001)					
Test for subgroup differences: Not applicable					



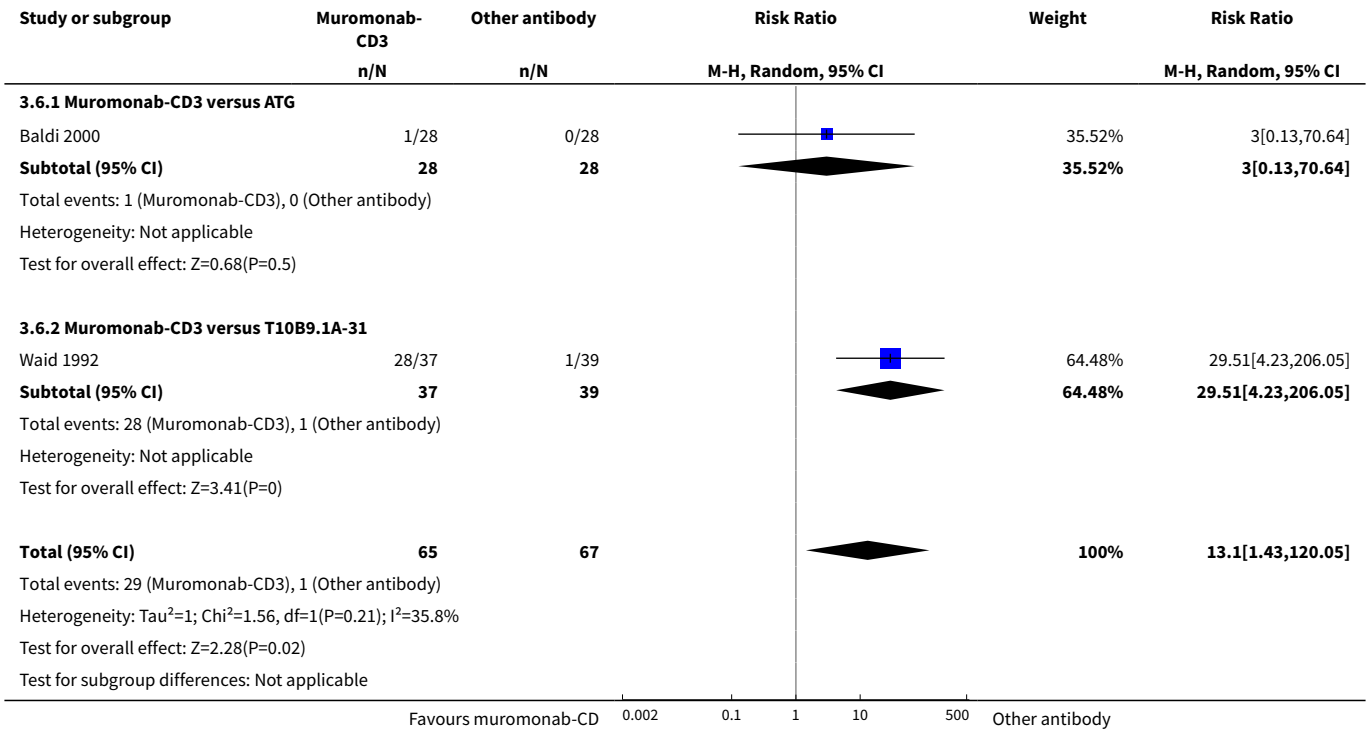
Analysis 3.5. Comparison 3 Treatment of first rejection: muromonab-CD3 versus other antibody (stratified by comparator), Outcome 5 Treatment side effects: gastrointestinal.

Study or subgroup	muromonab-CD3 n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Muromonab-CD3 versus ATG					
Baldi 2000	16/28	0/28		33.86%	33[2.08,524.54]
Subtotal (95% CI)	**28**	**28**		**33.86%**	**33[2.08,524.54]**
Total events: 16 (muromonab-CD3), 0 (Other antibody)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.48(P=0.01)					
3.5.2 Muromonab-CD3 versus T10B9.1A-31					
Waid 1992	23/37	6/39		66.14%	4.04[1.86,8.79]
Subtotal (95% CI)	**37**	**39**		**66.14%**	**4.04[1.86,8.79]**
Total events: 23 (muromonab-CD3), 6 (Other antibody)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.52(P=0)					
Total (95% CI)	**65**	**67**		**100%**	**8.23[0.9,75.11]**
Total events: 39 (muromonab-CD3), 6 (Other antibody)					
Heterogeneity: Tau^2=1.77; Chi^2=2.64, df=1(P=0.1); I^2=62.19%					

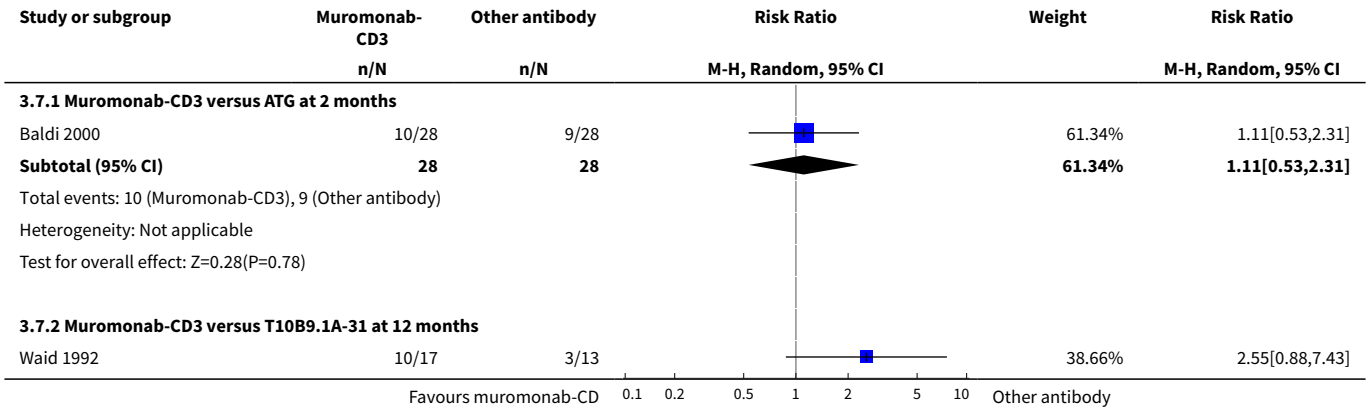


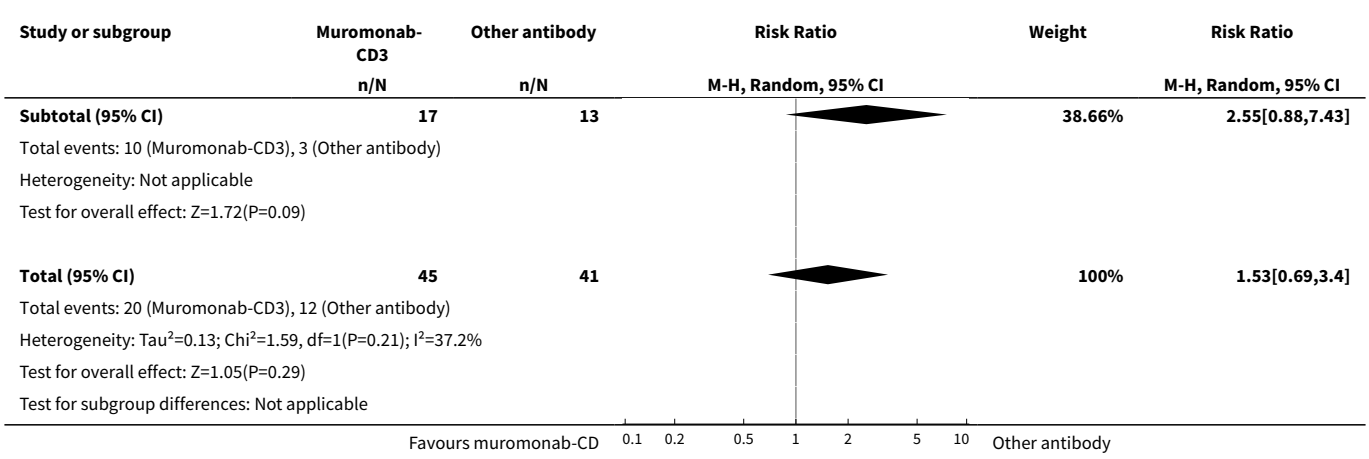


Analysis 3.6. Comparison 3 Treatment of first rejection: muromonab-CD3 versus other antibody (stratified by comparator), Outcome 6 Treatment side effects: neurological.

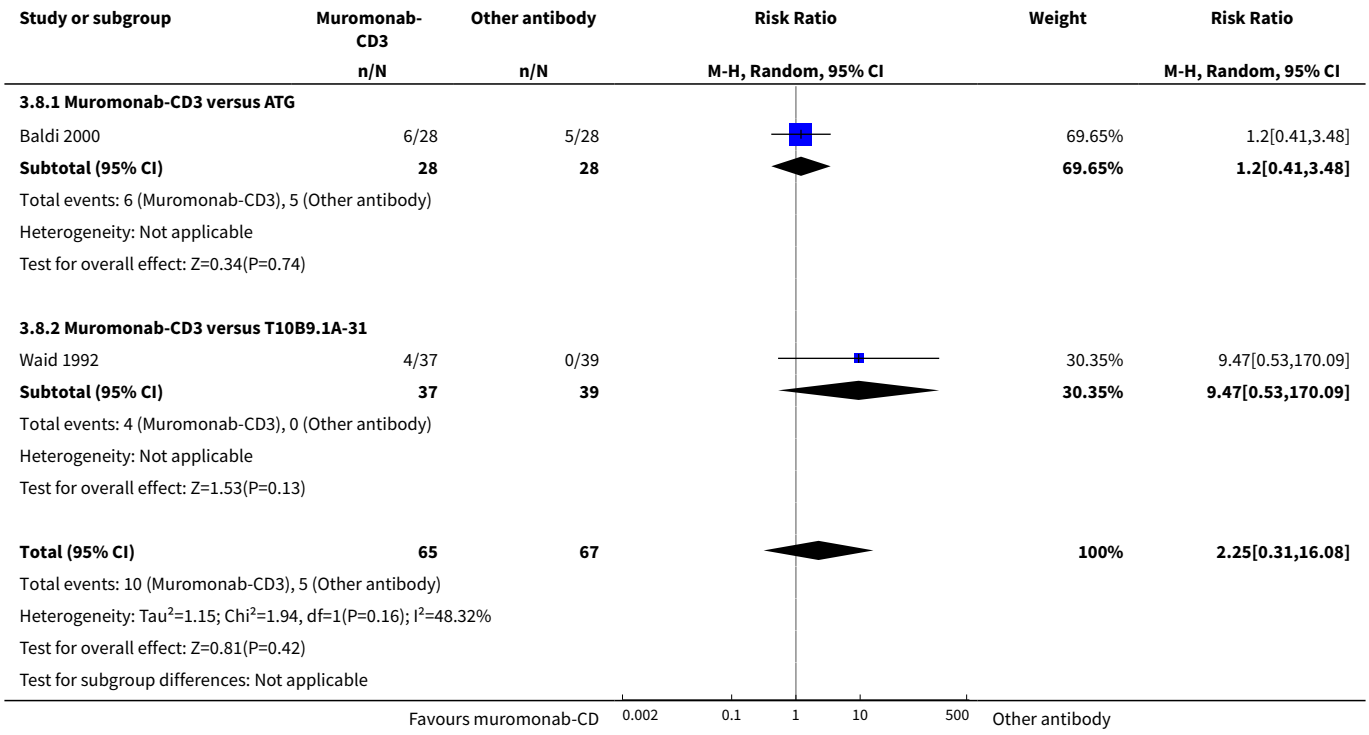


Analysis 3.7. Comparison 3 Treatment of first rejection: muromonab-CD3 versus other antibody (stratified by comparator), Outcome 7 Infection (total).

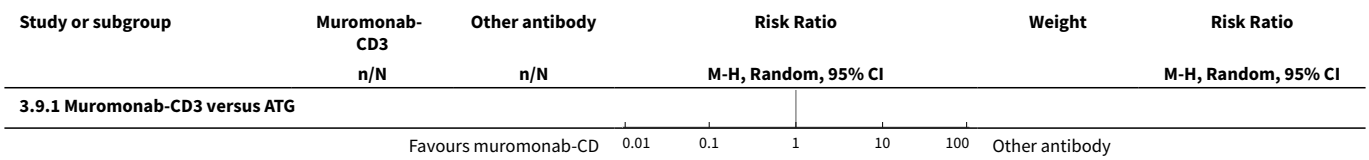


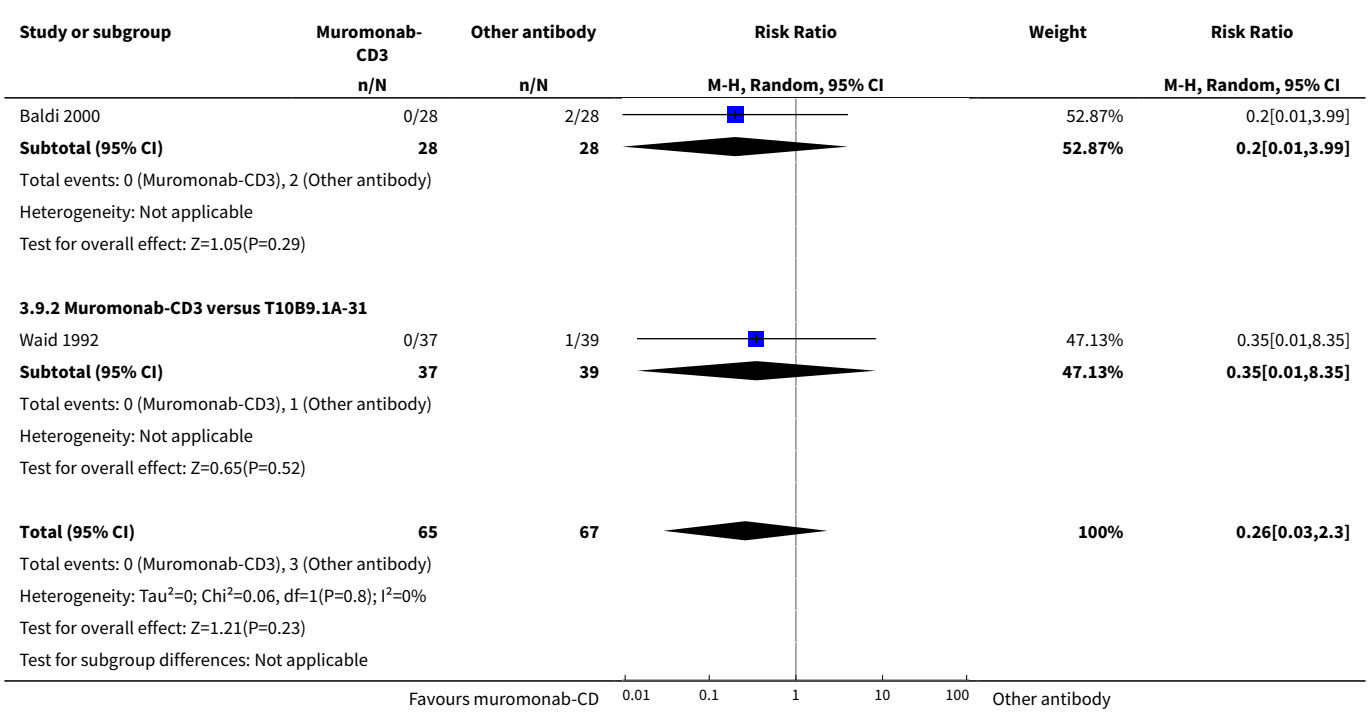


Analysis 3.8. Comparison 3 Treatment of first rejection: muromonab-CD3 versus other antibody (stratified by comparator), Outcome 8 CMV infection (total).



Analysis 3.9. Comparison 3 Treatment of first rejection: muromonab-CD3 versus other antibody (stratified by comparator), Outcome 9 Malignancy (total).

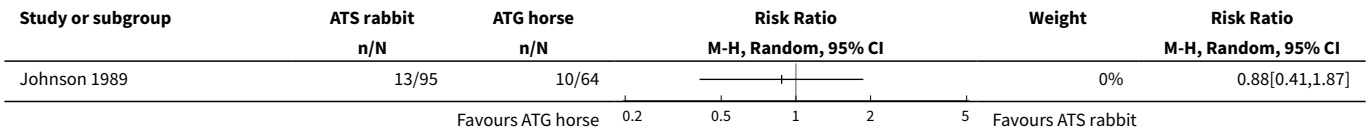




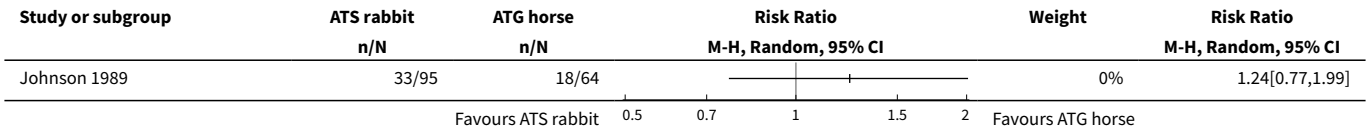
Comparison 4. Treatment of first rejection: ATS rabbit versus ATG horse

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Failure of reversal of acute rejection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Recurrent rejection post-therapy	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 4.1. Comparison 4 Treatment of first rejection: ATS rabbit versus ATG horse, Outcome 1 Failure of reversal of acute rejection.



Analysis 4.2. Comparison 4 Treatment of first rejection: ATS rabbit versus ATG horse, Outcome 2 Recurrent rejection post-therapy.

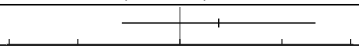


Comparison 5. Treatment of first rejection: ALG versus IV immunoglobulin (IVIg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of reversal of acute rejection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Recurrent rejection post-therapy	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Graft loss or death with a functioning graft within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Graft loss censored for death within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Death within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6 Death from infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7 Malignancy (total)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

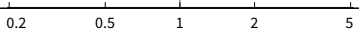
Analysis 5.1. Comparison 5 Treatment of first rejection: ALG versus IV immunoglobulin (IVIg), Outcome 1 Failure of reversal of acute rejection.

Study or subgroup	ALG n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Howard 1977	3/25	1/20		0%	2.4[0.27,21.35]



Analysis 5.2. Comparison 5 Treatment of first rejection: ALG versus IV immunoglobulin (IVIg), Outcome 2 Recurrent rejection post-therapy.

Study or subgroup	ALG n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Howard 1977	7/25	9/20		0%	0.62[0.28,1.38]

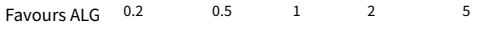


Analysis 5.3. Comparison 5 Treatment of first rejection: ALG versus IV immunoglobulin (IVIg), Outcome 3 Graft loss or death with a functioning graft within 12 months.

Study or subgroup	ALG n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Howard 1977	10/25	8/20		0%	1[0.49,2.05]

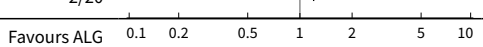
Analysis 5.4. Comparison 5 Treatment of first rejection: ALG versus IV immunoglobulin (IVIg), Outcome 4 Graft loss censored for death within 12 months.

Study or subgroup	ALG n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Howard 1977	9/25	7/20		0%	1.03[0.47,2.27]



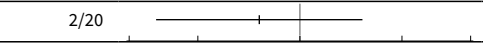
Analysis 5.5. Comparison 5 Treatment of first rejection: ALG versus IV immunoglobulin (IVIg), Outcome 5 Death within 12 months.

Study or subgroup	ALG n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Howard 1977	3/25	2/20		0%	1.2[0.22,6.5]



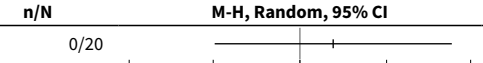
Analysis 5.6. Comparison 5 Treatment of first rejection: ALG versus IV immunoglobulin (IVIg), Outcome 6 Death from infection.

Study or subgroup	ALG n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Howard 1977	1/25	2/20		0%	0.4[0.04,4.1]



Analysis 5.7. Comparison 5 Treatment of first rejection: ALG versus IV immunoglobulin (IVIg), Outcome 7 Malignancy (total).

Study or subgroup	ALG n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Howard 1977	1/25	0/20		0%	2.42[0.1,56.46]



Comparison 6. Treatment of first rejection: ATG versus further steroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of acute rejection reversal	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Recurrent rejection up to 3 months post-therapy	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Graft loss or death with a functioning graft within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Graft loss censored for death within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Death within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6 Death cause: infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 6.1. Comparison 6 Treatment of first rejection: ATG versus further steroid, Outcome 1 Failure of acute rejection reversal.

Study or subgroup	ATG n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Filo 1980	7/41	12/38		0%	0.54[0.24,1.23]

Favours steroid 0.2 0.5 1 2 5 Favours ATG

Analysis 6.2. Comparison 6 Treatment of first rejection: ATG versus further steroid, Outcome 2 Recurrent rejection up to 3 months post-therapy.

Study or subgroup	ATG n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Filo 1980	16/36	15/43		0%	1.27[0.74,2.2]

Favours ATG 0.2 0.5 1 2 5 Favours steriod

Analysis 6.3. Comparison 6 Treatment of first rejection: ATG versus further steroid, Outcome 3 Graft loss or death with a functioning graft within 12 months.

Study or subgroup	ATG n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Filo 1980	15/36	25/43		0%	0.72[0.45,1.14]

Favours ATG 0.2 0.5 1 2 5 Favours steroid

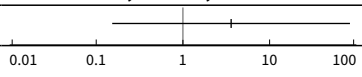
Analysis 6.4. Comparison 6 Treatment of first rejection: ATG versus further steroid, Outcome 4 Graft loss censored for death within 12 months.

Study or subgroup	ATG n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Filo 1980	14/36	25/43		0%	0.67[0.41,1.08]

Favours ATG 0.2 0.5 1 2 5 Favours steroid

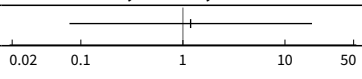
Analysis 6.5. Comparison 6 Treatment of first rejection: ATG versus further steroid, Outcome 5 Death within 12 months.

Study or subgroup	ATG n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Filo 1980	1/24	0/29		0%	3.6[0.15,84.54]



Analysis 6.6. Comparison 6 Treatment of first rejection: ATG versus further steroid, Outcome 6 Death cause: infection.

Study or subgroup	ATG n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Filo 1980	1/36	1/43		0%	1.19[0.08,18.43]



Comparison 7. Treatment of steroid-resistant rejection: antibody versus other antibody (stratified by antibody type)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Failure of acute rejection reversal	3	136	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.33, 5.28]
1.1 Muromonab-CD3 versus ATG	2	115	Risk Ratio (M-H, Random, 95% CI)	2.43 [0.45, 13.00]
1.2 Muromonab-CD3 versus ALG	1	21	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.05, 4.28]
2 Additional treatment required	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Muromonab-CD3 versus ATG	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Muromonab-CD3 versus ALG	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Recurrent rejection	3	175	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.61, 1.59]
3.1 Muromonab-CD3 versus ATG	2	115	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.80, 1.88]
3.2 Muromonab-CD3 versus ALG	1	60	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.31, 1.15]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4 Graft loss censored for death (< 1 year)	3	136	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.29, 11.12]
4.1 muromonab-CD3 versus ATG	2	115	Risk Ratio (M-H, Random, 95% CI)	4.00 [0.88, 18.17]
4.2 muromonab-CD3 versus ALG	1	21	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.01, 3.41]
5 Graft loss or death with a functioning graft (< 1year)	3	136	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.38, 3.10]
5.1 Muromonab-CD3 versus ATG	2	115	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.60, 3.58]
5.2 Muromonab-CD3 versus ALG	1	21	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.26]
6 Death within 12 months	3	175	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.09, 1.65]
6.1 Muromonab-CD3 versus ATG	2	115	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.08, 2.05]
6.2 Muromonab-CD3 versus ALG	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]
7 Death cause: infection	2	76	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.17, 2.65]
7.1 Muromonab-CD3 versus ATG	1	55	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.06, 14.65]
7.2 Muromonab-CD3 versus ALG	1	21	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.13, 2.92]
8 CMV infection	3	175	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.60, 1.28]
8.1 Muromonab-CD3 versus ATG	2	115	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.61, 1.42]
8.2 Muromonab-CD3 versus ALG	1	60	Risk Ratio (M-H, Random, 95% CI)	0.7 [0.31, 1.59]
9 Treatment side effects: fever, chills, malaise following administration	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 Muromonab-CD3 versus ATG	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Muromonab-CD3 versus ALG	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

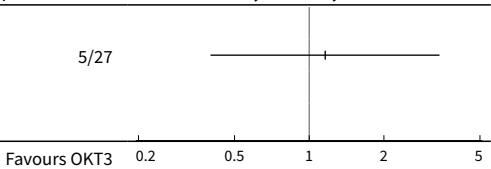
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Malignancy (total)	2	115	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.28, 15.66]
11 Serum creatinine at 12 months (umol/L)	3	120	Mean Difference (IV, Random, 95% CI)	10.04 [-16.68, 36.77]

Analysis 7.1. Comparison 7 Treatment of steroid-resistant rejection: antibody versus other antibody (stratified by antibody type), Outcome 1 Failure of acute rejection reversal.

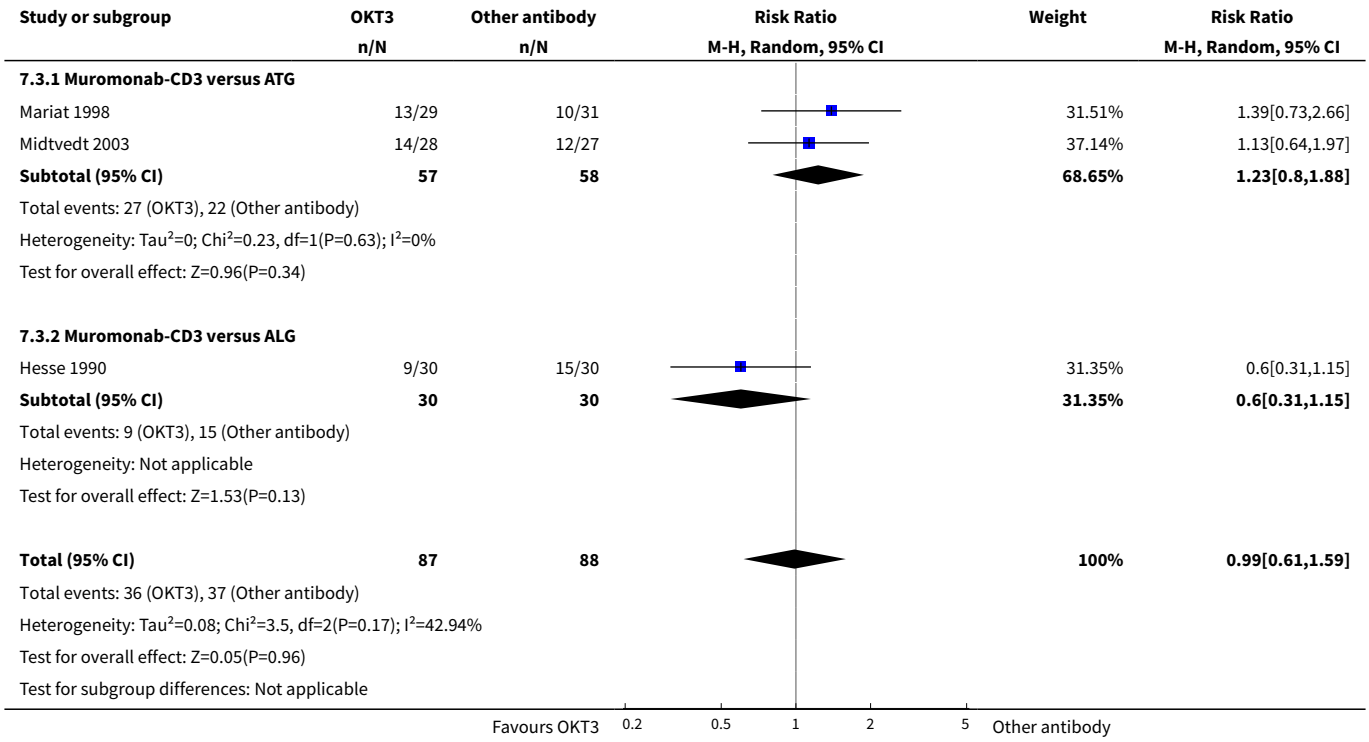
Study or subgroup	OKT3 n/N	ATG n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Muromonab-CD3 versus ATG					
Mariat 1998	4/29	1/31		39.38%	4.28[0.51,36.05]
Midtvedt 2003	1/28	1/27		24.8%	0.96[0.06,14.65]
Subtotal (95% CI)	**57**	**58**		**64.18%**	**2.43[0.45,13]**
Total events: 5 (OKT3), 2 (ATG)					
Heterogeneity: Tau^2=0; Chi^2=0.72, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=1.04(P=0.3)					
7.1.2 Muromonab-CD3 versus ALG					
Hesse 1990	1/11	2/10		35.82%	0.45[0.05,4.28]
Subtotal (95% CI)	**11**	**10**		**35.82%**	**0.45[0.05,4.28]**
Total events: 1 (OKT3), 2 (ATG)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
Total (95% CI)	**68**	**68**		**100%**	**1.32[0.33,5.28]**
Total events: 6 (OKT3), 4 (ATG)					
Heterogeneity: Tau^2=0.08; Chi^2=2.11, df=2(P=0.35); I^2=5.36%					
Test for overall effect: Z=0.4(P=0.69)					
Test for subgroup differences: Not applicable					

Analysis 7.2. Comparison 7 Treatment of steroid-resistant rejection: antibody versus other antibody (stratified by antibody type), Outcome 2 Additional treatment required.

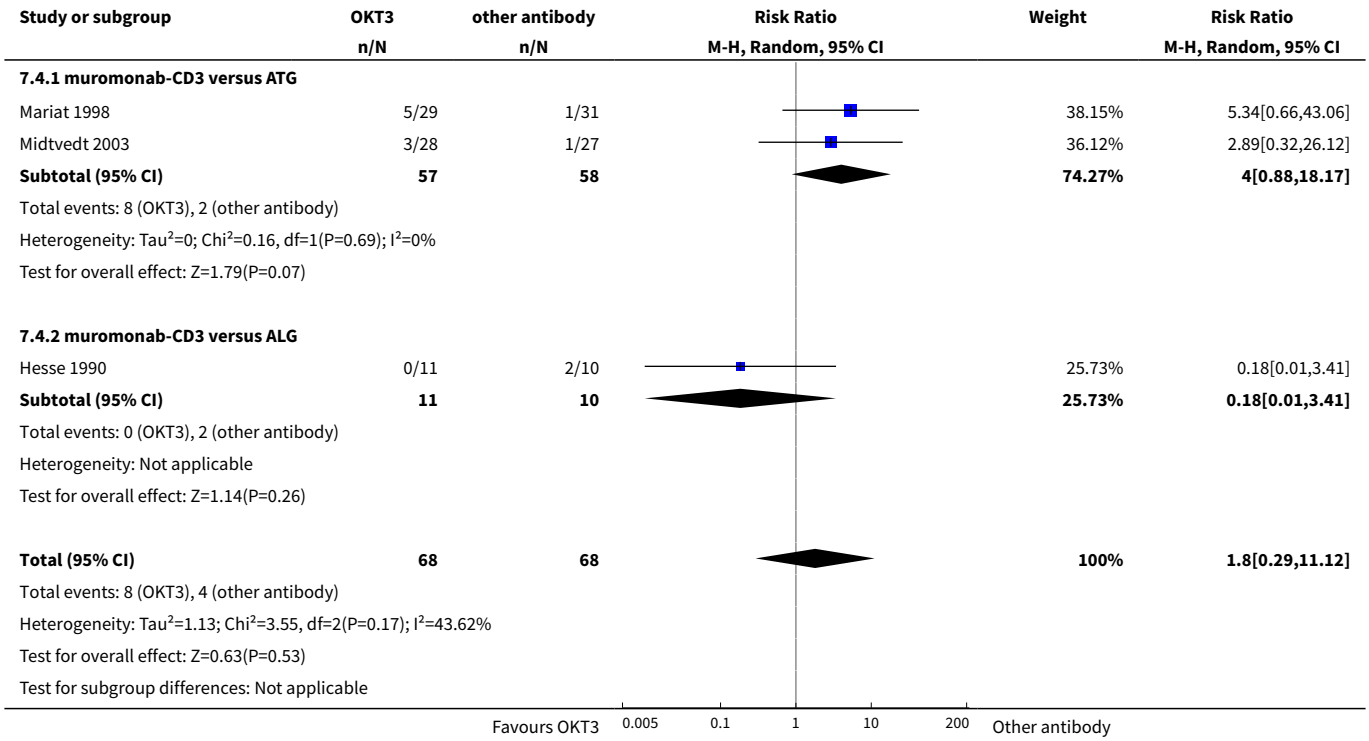
Study or subgroup	OKT3 n/N	ATG n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.2.1 Muromonab-CD3 versus ATG				
Midtvedt 2003	6/28	5/27		1.16[0.4,3.35]
7.2.2 Muromonab-CD3 versus ALG				



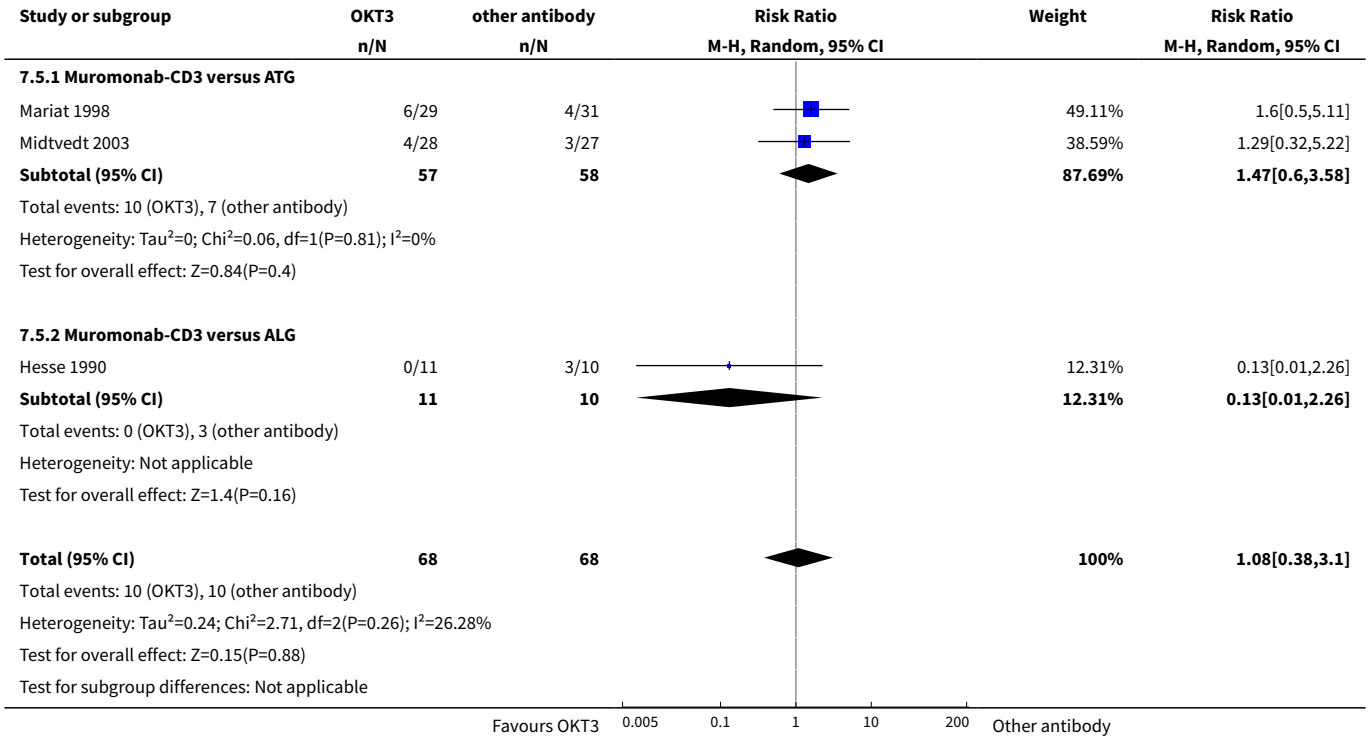
Analysis 7.3. Comparison 7 Treatment of steroid-resistant rejection: antibody versus other antibody (stratified by antibody type), Outcome 3 Recurrent rejection.



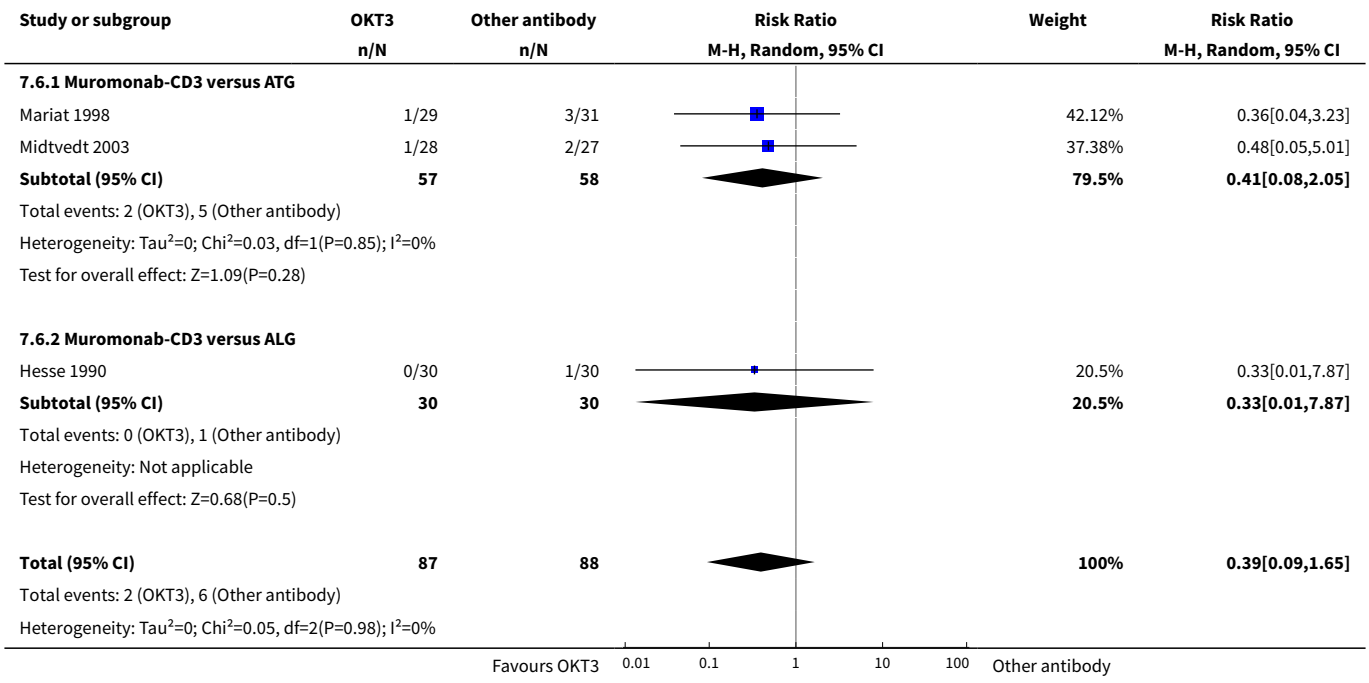
Analysis 7.4. Comparison 7 Treatment of steroid-resistant rejection: antibody versus other antibody (stratified by antibody type), Outcome 4 Graft loss censored for death (< 1 year).

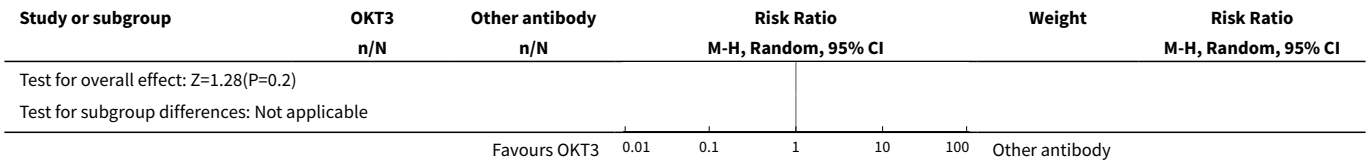


Analysis 7.5. Comparison 7 Treatment of steroid-resistant rejection: antibody versus other antibody (stratified by antibody type), Outcome 5 Graft loss or death with a functioning graft (< 1year).

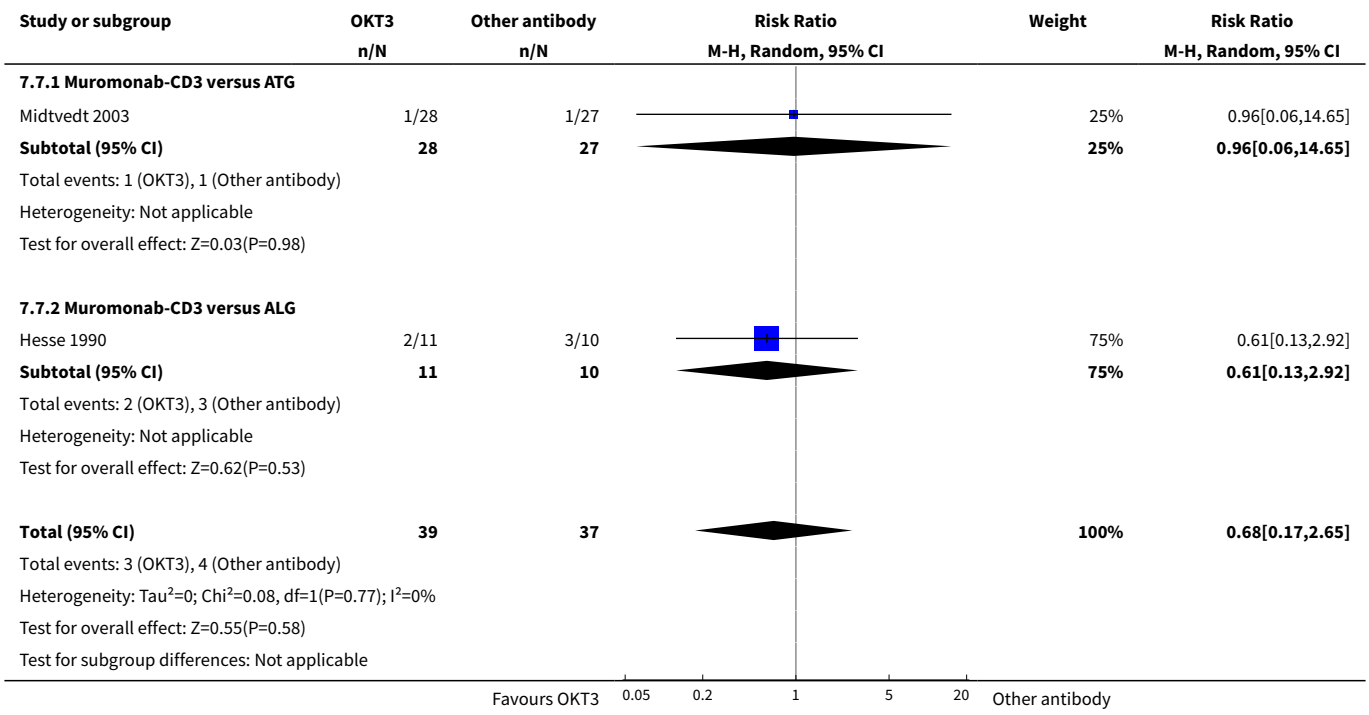


Analysis 7.6. Comparison 7 Treatment of steroid-resistant rejection: antibody versus other antibody (stratified by antibody type), Outcome 6 Death within 12 months.

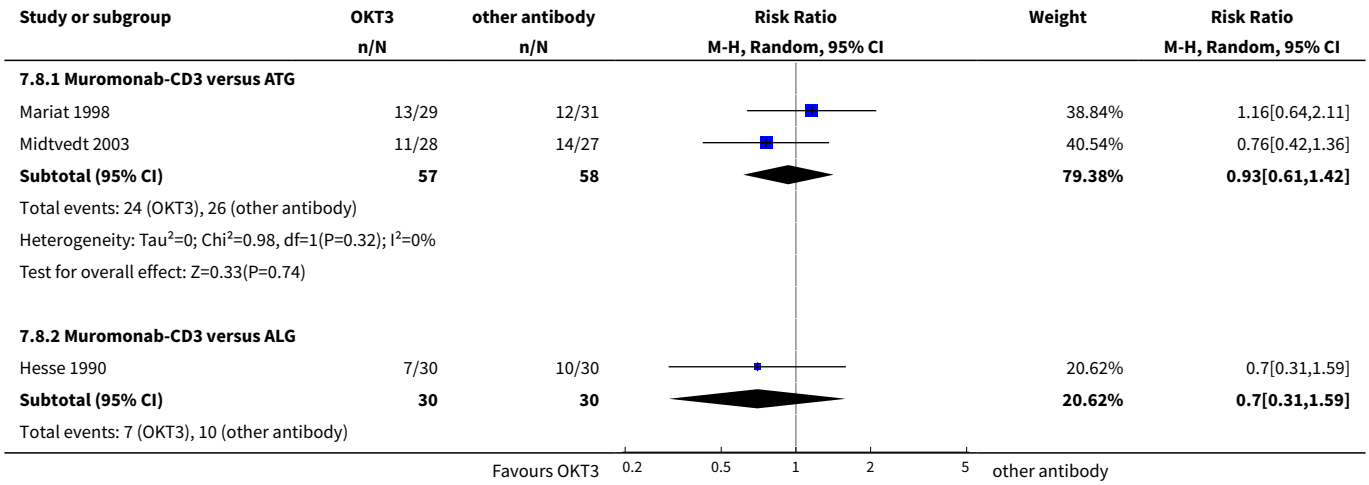


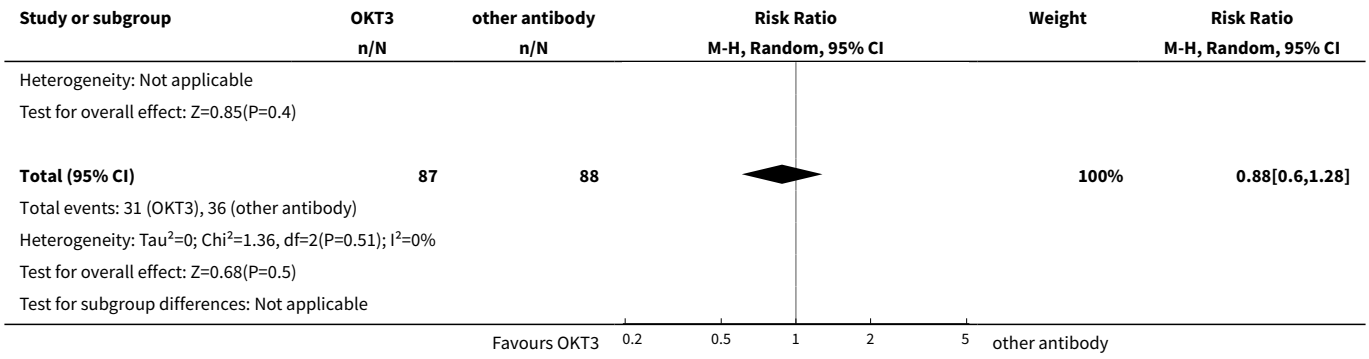


Analysis 7.7. Comparison 7 Treatment of steroid-resistant rejection: antibody versus other antibody (stratified by antibody type), Outcome 7 Death cause: infection.

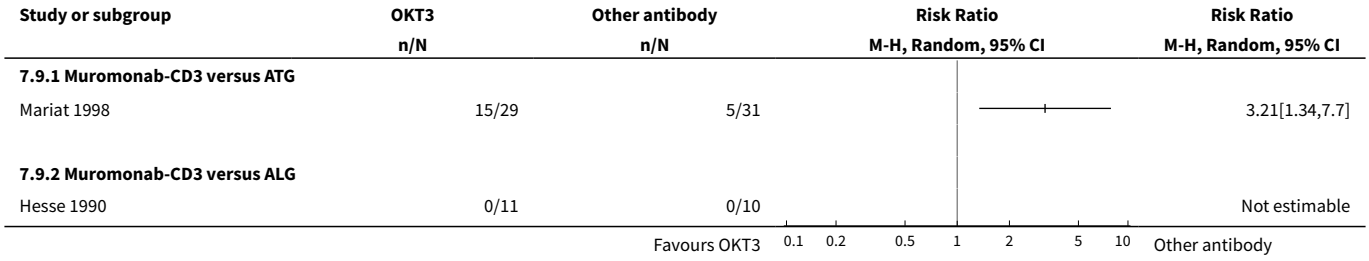


Analysis 7.8. Comparison 7 Treatment of steroid-resistant rejection: antibody versus other antibody (stratified by antibody type), Outcome 8 CMV infection.

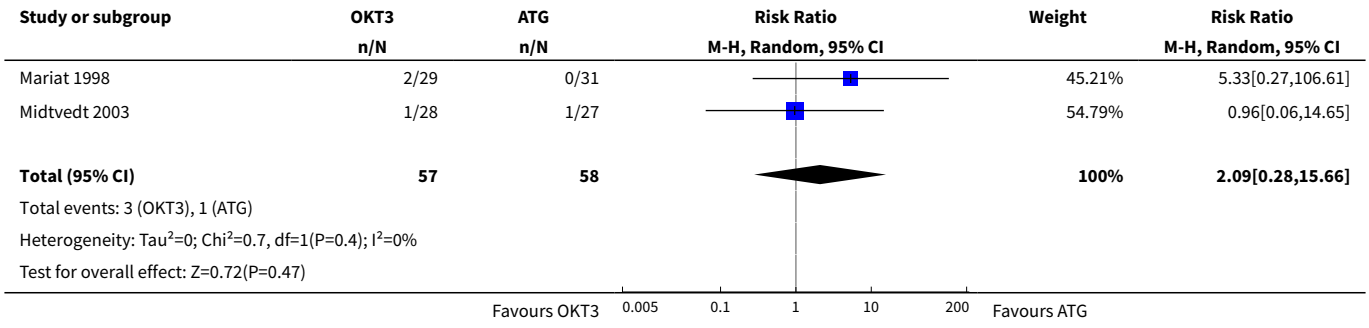




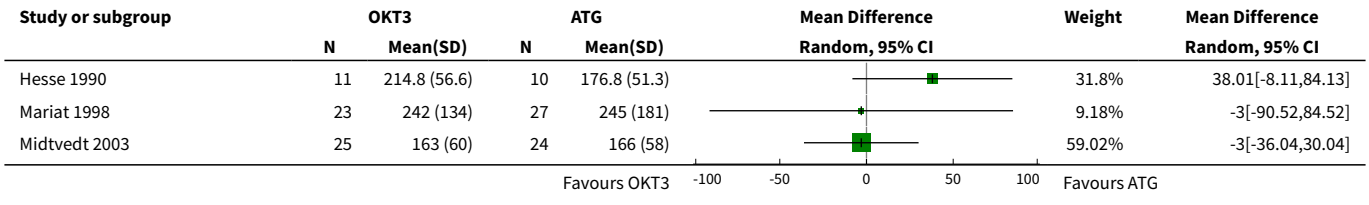
Analysis 7.9. Comparison 7 Treatment of steroid-resistant rejection: antibody versus other antibody (stratified by antibody type), Outcome 9 Treatment side effects: fever, chills, malaise following administration.

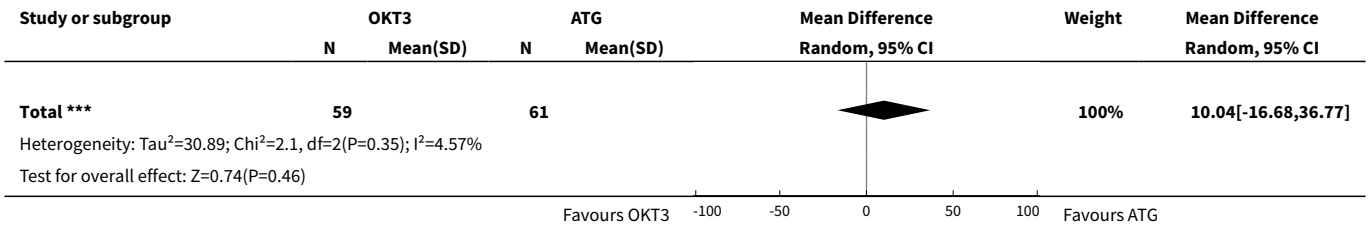


Analysis 7.10. Comparison 7 Treatment of steroid-resistant rejection: antibody versus other antibody (stratified by antibody type), Outcome 10 Malignancy (total).



Analysis 7.11. Comparison 7 Treatment of steroid-resistant rejection: antibody versus other antibody (stratified by antibody type), Outcome 11 Serum creatinine at 12 months (umol/L).

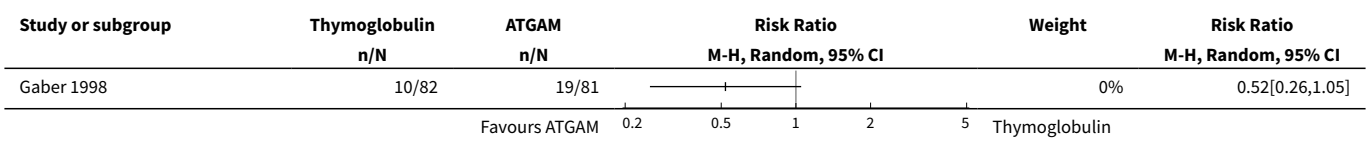




Comparison 8. Treatment of steroid-resistant rejection: ATG rabbit (thymoglobulin) versus ATG horse (ATGAM)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of acute rejection reversal	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Recurrent rejection up to 3 months post-therapy	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Graft loss or death with a functioning graft within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Graft loss censored for death within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Death within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6 Cause of death: infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7 Treatment side effects: leucopoenia	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8 Infection (total) at 2 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9 CMV infection (total)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10 Malignancy (total)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11 PTLD/Lymphoma	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 8.1. Comparison 8 Treatment of steroid-resistant rejection: ATG rabbit (thymoglobulin) versus ATG horse (ATGAM), Outcome 1 Failure of acute rejection reversal.



Analysis 8.2. Comparison 8 Treatment of steroid-resistant rejection: ATG rabbit (thymoglobulin) versus ATG horse (ATGAM), Outcome 2 Recurrent rejection up to 3 months post-therapy.

Study or subgroup	Thymoglobulin n/N	ATGAM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gaber 1998	10/82	16/81		0%	0.62[0.3,1.28]

Favs thymoglobulin — Favours ATGAM

Analysis 8.3. Comparison 8 Treatment of steroid-resistant rejection: ATG rabbit (thymoglobulin) versus ATG horse (ATGAM), Outcome 3 Graft loss or death with a functioning graft within 12 months.

Study or subgroup	Thymoglobulin n/N	ATGAM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gaber 1998	14/82	20/80		0%	0.68[0.37,1.26]

Favs thymoglobulin — Favours ATGAM

Analysis 8.4. Comparison 8 Treatment of steroid-resistant rejection: ATG rabbit (thymoglobulin) versus ATG horse (ATGAM), Outcome 4 Graft loss censored for death within 12 months.

Study or subgroup	Thymoglobulin n/N	ATGAM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gaber 1998	8/82	17/80		0%	0.46[0.21,1]

Favs Thymoglobulin — Favours ATGAM

Analysis 8.5. Comparison 8 Treatment of steroid-resistant rejection: ATG rabbit (thymoglobulin) versus ATG horse (ATGAM), Outcome 5 Death within 12 months.

Study or subgroup	Thymoglobulin n/N	ATGAM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gaber 1998	6/82	3/81		0%	1.98[0.51,7.63]

Favs thymoglobulin — Favours ATGAM

Analysis 8.6. Comparison 8 Treatment of steroid-resistant rejection: ATG rabbit (thymoglobulin) versus ATG horse (ATGAM), Outcome 6 Cause of death: infection.

Study or subgroup	Thymoglobulin n/N	ATGAM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gaber 1998	3/82	0/81		0%	6.92[0.36,131.79]

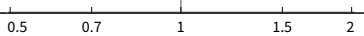
Favs thymoglobulin — Favours ATGAM

Analysis 8.7. Comparison 8 Treatment of steroid-resistant rejection: ATG rabbit (thymoglobulin) versus ATG horse (ATGAM), Outcome 7 Treatment side effects: leucopoenia.

Study or subgroup	Thymoglobulin n/N	ATGAM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gaber 1998	47/82	24/81		0%	1.93[1.32,2.84]

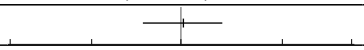
Analysis 8.8. Comparison 8 Treatment of steroid-resistant rejection: ATG rabbit (thymoglobulin) versus ATG horse (ATGAM), Outcome 8 Infection (total) at 2 months.

Study or subgroup	Thymoglobulin n/N	ATGAM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gaber 1998	41/82	41/81		0%	0.99[0.73,1.34]



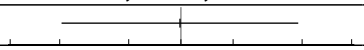
Analysis 8.9. Comparison 8 Treatment of steroid-resistant rejection: ATG rabbit (thymoglobulin) versus ATG horse (ATGAM), Outcome 9 CMV infection (total).

Study or subgroup	Thymoglobulin n/N	ATGAM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gaber 1998	65/82	63/80		0%	1.01[0.86,1.18]



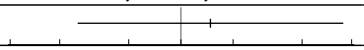
Analysis 8.10. Comparison 8 Treatment of steroid-resistant rejection: ATG rabbit (thymoglobulin) versus ATG horse (ATGAM), Outcome 10 Malignancy (total).

Study or subgroup	Thymoglobulin n/N	ATGAM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gaber 1998	3/82	3/81		0%	0.99[0.21,4.75]



Analysis 8.11. Comparison 8 Treatment of steroid-resistant rejection: ATG rabbit (thymoglobulin) versus ATG horse (ATGAM), Outcome 11 PTLD/Lymphoma.

Study or subgroup	Thymoglobulin n/N	ATGAM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gaber 1998	3/82	2/81		0%	1.48[0.25,8.64]

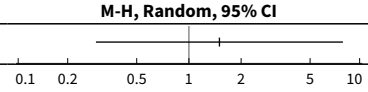


Comparison 9. Treatment of steroid-resistant rejection: OKT3 half versus OKT3 standard dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of acute rejection reversal	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Recurrent rejection post-therapy	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Graft loss or death with a functioning graft within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Graft loss censored for death within 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Death within 18 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6 Cause of death: infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7 Serum creatinine 18 months after treatment (umol/L)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8 Bacterial infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9 CMV infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

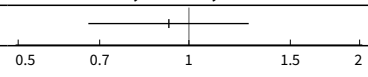
Analysis 9.1. Comparison 9 Treatment of steroid-resistant rejection: OKT3 half versus OKT3 standard dose, Outcome 1 Failure of acute rejection reversal.

Study or subgroup	OKT3 half dose n/N	OKT3 standard dose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Midtvedt 1996	3/15	2/15		0%	1.5[0.29,7.73]



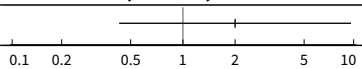
Analysis 9.2. Comparison 9 Treatment of steroid-resistant rejection: OKT3 half versus OKT3 standard dose, Outcome 2 Recurrent rejection post-therapy.

Study or subgroup	OKT3 half dose n/N	OKT3 standard dose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Midtvedt 1996	12/15	13/15		0%	0.92[0.67,1.27]



Analysis 9.3. Comparison 9 Treatment of steroid-resistant rejection: OKT3 half versus OKT3 standard dose, Outcome 3 Graft loss or death with a functioning graft within 12 months.

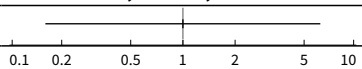
Study or subgroup	OKT3 half dose n/N	OKT3 standard dose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Midtvedt 1996	4/15	2/15		0%	2[0.43,9.32]



Favours half dose — Favours standard

Analysis 9.4. Comparison 9 Treatment of steroid-resistant rejection: OKT3 half versus OKT3 standard dose, Outcome 4 Graft loss censored for death within 12 months.

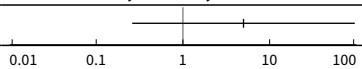
Study or subgroup	OKT3 half dose n/N	OKT3 standard dose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Midtvedt 1996	2/15	2/15		0%	1[0.16,6.2]



Favours half dose — Favours standard

Analysis 9.5. Comparison 9 Treatment of steroid-resistant rejection: OKT3 half versus OKT3 standard dose, Outcome 5 Death within 18 months.

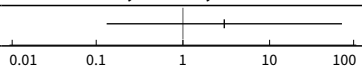
Study or subgroup	OKT3 half dose n/N	OKT3 standard dose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Midtvedt 1996	2/15	0/15		0%	5[0.26,96.13]



Favours half dose — Favours standard

Analysis 9.6. Comparison 9 Treatment of steroid-resistant rejection: OKT3 half versus OKT3 standard dose, Outcome 6 Cause of death: infection.

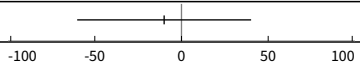
Study or subgroup	OKT3 half dose n/N	OKT3 standard dose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Midtvedt 1996	1/15	0/15		0%	3[0.13,68.26]



Favours half dose — Favours standard

Analysis 9.7. Comparison 9 Treatment of steroid-resistant rejection: OKT3 half versus OKT3 standard dose, Outcome 7 Serum creatinine 18 months after treatment (umol/L).

Study or subgroup	OKT3 half dose N	Mean(SD)	OKT3 standard dose N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Midtvedt 1996	11	185 (62)	13	195 (63)		0%	-10[-60.15,40.15]



Favours half dose — Favours standard

Analysis 9.8. Comparison 9 Treatment of steroid-resistant rejection: OKT3 half versus OKT3 standard dose, Outcome 8 Bacterial infection.

Study or subgroup	OKT3 half dose n/N	OKT3 standard dose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Midtvedt 1996	1/15	0/15		0%	3[0.13,68.26]

Favours half dose 0.01 0.1 1 10 100 Favours standard

Analysis 9.9. Comparison 9 Treatment of steroid-resistant rejection: OKT3 half versus OKT3 standard dose, Outcome 9 CMV infection.

Study or subgroup	OKT3 half dose n/N	OKT3 standard dose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Midtvedt 1996	8/15	8/15		0%	1[0.51,1.95]

Favours half dose 0.2 0.5 1 2 5 Favours standard

Comparison 10. Treatment of steroid-resistant rejection: OKT3 versus IV immunoglobulin (IVIg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of acute rejection reversal	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Recurrent rejection within 2 months post-therapy	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Graft loss or death with a functioning graft within 2 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Graft loss censored for death within 2 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Death within 2 years	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6 Treatment side effects: fever, chills, malaise following administration	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

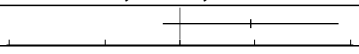
Analysis 10.1. Comparison 10 Treatment of steroid-resistant rejection: OKT3 versus IV immunoglobulin (IVIg), Outcome 1 Failure of acute rejection reversal.

Study or subgroup	OKT3 n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Casadei 1998	2/12	3/11		0%	0.61[0.12,3]

Favours IVIg 0.1 0.2 0.5 1 2 5 10 Favours OKT3

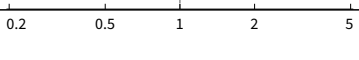
Analysis 10.2. Comparison 10 Treatment of steroid-resistant rejection: OKT3 versus IV immunoglobulin (IVIg), Outcome 2 Recurrent rejection within 2 months post-therapy.

Study or subgroup	OKT3 n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Casadei 1998	9/14	5/15		0%	1.93[0.85,4.36]



Analysis 10.3. Comparison 10 Treatment of steroid-resistant rejection: OKT3 versus IV immunoglobulin (IVIg), Outcome 3 Graft loss or death with a functioning graft within 2 months.

Study or subgroup	OKT3 n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Casadei 1998	3/15	3/15		0%	1[0.24,4.18]



Analysis 10.4. Comparison 10 Treatment of steroid-resistant rejection: OKT3 versus IV immunoglobulin (IVIg), Outcome 4 Graft loss censored for death within 2 months.

Study or subgroup	OKT3 n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Casadei 1998	2/15	1/15		0%	2[0.2,19.78]

Analysis 10.5. Comparison 10 Treatment of steroid-resistant rejection: OKT3 versus IV immunoglobulin (IVIg), Outcome 5 Death within 2 years.

Study or subgroup	OKT3 n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Casadei 1998	1/15	2/15		0%	0.5[0.05,4.94]

Analysis 10.6. Comparison 10 Treatment of steroid-resistant rejection: OKT3 versus IV immunoglobulin (IVIg), Outcome 6 Treatment side effects: fever, chills, malaise following administration.

Study or subgroup	OKT3 n/N	IVIg n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Casadei 1998	15/15	0/15		0%	31[2.02,475.12]

ADDITIONAL TABLES

Table 1. Electronic search strategies

Database	Search terms
CENTRAL	#1. Kidney Transplantation, this term only in MeSH #2. (kidney or renal) next transplant* #3. (kidney or renal) near recipient* #4. (#1 OR #2 OR #3) #5. Antibodies, Monoclonal explode all trees in MeSH #6. monoclonal next antibod* #7. polyclonal near antibod* #8. muromonab-cd3 #9. "muromonab cd3" #10. "muromonab cd 3" #11. thymoglobulin* #12. okt3 #13. okt-3 #14. "okt 3" #15. Antilymphocyte Serum explode all trees in MeSH #16. antilymphocyte* #17. antithymocyte* #18. alg #19. lymphocyt* next antibod* #20. thymocyte* next antibod* #21. lymphocyte* next antiserum #22. thymocyte next antiserum #23. atg #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. (#4 AND #24)
MEDLINE	1. kidney transplantation/ 2. ((kidney or renal) adj (transplant$ or recipient$)).tw. 3. 1 or 2 4. exp antibodies, monoclonal/ 5. monoclonal antibod$.tw. 6. (polyclonal adj3 antibod$).tw. 7. exp antilymphocyte serum/ 8. antilymphocyte.tw. 9. alg.tw. 10. lymphocyte$ antibod$.tw. 11. lymphocyte antiserum$.tw. 12. muromonab cd$.tw. 13. thymoglobulin$.tw. 14. antithymocyte.tw. 15. atg.tw. 16. okt3.tw. 17. okt 3.tw. 18. thymocyte antibod$.tw. 19. thymocyte antiserum$.tw. 20. or/4-19 21. 3 and 20 22. randomized controlled trial.pt. 23. controlled clinical trial.pt. 24. randomized controlled trials/ 25. random allocation/ 26. double blind method/ 27. single blind method/ 28. or/22-27 29. animals/ not (animals/ and human/) 30. 28 not 29 31. clinical trial.pt.

Table 1. Electronic search strategies *(Continued)*

	32. exp clinical trials/ 33. (clinic$ adj25 trial$).ti,ab. 34. cross-over studies/ 35. (crossover or cross-over or cross over).tw. 36. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 37. placebos/ 38. placebo$.ti,ab. 39. random$.ti,ab. 40. research design/ 41. or/31-40 42. 41 not 29 43. 30 or 42 44. 21 and 43
EMBASE	1. exp kidney transplantation/ 2. exp monoclonal antibody/ 3. monoclonal antibod$.tw. 4. (polyclonal adj3 antibod$).tw. 5. lymphocyte antibody/ 6. antilymphocyte$.tw. 7. lymphocyte antibod$.tw. 8. lymphocyte antiserum$.tw. 9. alg.tw. 10. muromonab-cd3/ 11. muromonab cd 3.tw. 12. muromonab cd3.tw. 13. okt3/ 14. okt3.tw. 15. okt 3.tw. 16. atg$.tw. 17. thymocyte antibody/ 18. antithymocyte$.tw. 19. thymocyte antibod$.tw. 20. thymocyte antiserum$.tw. 21. or/2-20 22. 1 and 21 23. exp clinical trial/ 24. comparative study/ 25. drug comparison/ 26. major clinical study/ 27. randomization/ 28. crossover procedure/ 29. double blind procedure/ 30. single blind procedure/ 31. placebo/ 32. prospective study/ 33. ((clinical or controlled or comparative or placebo or prospective or randomi#ed) adj3 (trial or study)).ti,ab. 34. (random$ adj7 (allocat$ or allot$ or assign$ or basis$ or divid$ or order$)).ti,ab. 35. ((singl$ or doubl$ or trebl$ or tripl$) adj7 (blind$ or mask$)).ti,ab. 36. (cross?over$ or (cross adj1 over$)).ti,ab. 37. ((allocat$ or allot$ or assign$ or divid$) adj3 (condition$ or experiment$ or intervention$ or treatment$ or therap$ or control$ or group$)).ti,ab. 38. or/23-32 39. or/33-37 40. 38 or 39 41. 22 and 40

WHAT'S NEW

Date	Event	Description
14 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Writing of protocol and review - AW, TP, FR, JRc, JCC
Screening of titles and abstracts - AW, TP, FR
Assessment for inclusion - AW, TP, FR
Quality assessment - AW, TP, FR
Data extraction - AW, TP, FR
Data entry into RevMan - AW, TP
Data analysis - AW, TP
Disagreement resolution - AW, JRC, JCC

DECLARATIONS OF INTEREST

Cochrane renal group (ACW, JCC): The Cochrane renal group receives financial support from several sources. These funds go into a general fund managed by the Children's Hospital at Westmead. These funds are used to support key activities including hand-searching, the development of a trials registry, training and support for reviewers conducting reviews, and consumer participation in the group. Those contributing funds have no rights of authorship or publication. The authors of the review retain the right to interpretation of the results and the right to publish.

TP: has received educational support from Roche and Novartis in the form of sponsorship to attend scientific meetings. She also received a grant from the Cochrane renal group to enable her to work on this review.

FR: now works for Wyeth Australia. At the time of her principal contribution to this review she was working for the Cochrane Renal Group.

JRC: has advisory board and clinical trial involvement with Novartis, Roche, Janssen-Cilag, Fujisawa and Wyeth, and has also been an invited speaker at national and international meetings sponsored by these companies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Kidney Transplantation; Acute Disease; Antibodies [*therapeutic use]; Antibodies, Monoclonal [therapeutic use]; Antilymphocyte Serum [therapeutic use]; Drug Resistance; Graft Rejection [*drug therapy]; Immunologic Factors [therapeutic use]; Immunosuppressive Agents [*therapeutic use]; Muromonab-CD3 [therapeutic use]; Randomized Controlled Trials as Topic; Rituximab [therapeutic use]

MeSH check words

Humans