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# Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer (Review)

Cheuk DKL, Chiang AKS, Chan GCF, Ha SY

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[Intervention Review]

# Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

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## ABSTRACT

### Background

Tumour lysis syndrome (TLS) is a serious complication of malignancies and can result in renal failure or death. Preliminary reports suggest that urate oxidase is effective in reducing serum uric acid, the build-up of which causes TLS. It is uncertain whether high-quality evidence exists to support its routine use in children with malignancies.

### Objectives

To assess the effects and safety of urate oxidase for the prevention and treatment of TLS in children with malignancies.

### Search methods

This is an update of the original review. We performed a comprehensive search of the Cochrane Central Register of Controlled Trials (CENTRAL) (in *The Cochrane Library* issue 1, 2013), MEDLINE (1966 to February 2013), Embase (1980 to February 2013), and CINAHL (1982 to February 2013). In addition, we searched the reference lists of all identified relevant papers. We also explored other internet sources (updated search on 26 February 2013): the NHS' National Research Register, the US National Institutes of Health Ongoing Trials Register, the metaRegister of Controlled Trials, and ProQuest Dissertations & Theses Database. We also screened conference proceedings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the International Society of Paediatric Oncology meetings from 1993 to 2012. Finally, we contacted experts in the field and the manufacturer of rasburicase, Sanofi-aventis.

### Selection criteria

Randomised controlled trials (RCT) and controlled clinical trials (CCT) of urate oxidase for the prevention or treatment of TLS in children under 18 years with any malignancy.

### Data collection and analysis

Two review authors independently extracted trial data and assessed individual trial quality. We used risk ratios (RR) for dichotomous data and mean difference (MD) for continuous data.

**Main results**

We included seven trials, involving 471 participants in the treatment groups and 603 participants in the control groups. One RCT and five CCTs compared urate oxidase and allopurinol. Three trials tested Uricozyme, and three trials tested rasburicase for the prevention of TLS.

The RCT showed no significant difference in mortality (both all-cause mortality and mortality due to TLS), renal failure, and adverse effects between the treatment and the control groups. The frequency of normalisation of uric acid at four hours (Fisher's exact test $P < 0.001$) and area under curve of uric acid at four days (MD -201.00 mg/dLhr, 95% confidence interval (CI) -258.05 mg/dLhr to -143.95 mg/dLhr; $P < 0.00001$) were significantly better in the treatment group. The trial did not evaluate the primary outcome (incidence of clinical TLS).

Pooled results of three CCTs showed significantly lower mortality due to TLS in the treatment group (RR 0.05, 95% CI 0.00 to 0.89; $P = 0.04$); all-cause mortality was not significantly different between the groups. Pooled results from five CCTs showed significantly lower incidence of renal failure in the treatment group (RR 0.26, 95% CI 0.08 to 0.89; $P = 0.03$). Results of CCTs also showed significantly lower uric acid in the treatment group at two days (three CCTs), three days (two CCTs), four days (two CCTs), and seven days (one CCT) after therapy, but not one day (three CCTs), five days (one CCT), and 12 days (one CCT) after therapy. Pooled results from three CCTs showed higher frequency of adverse effects in participants who received urate oxidase (RR 9.10, 95% CI 1.29 to 64.00; $P = 0.03$). One CCT evaluated the primary outcome; no significant difference was identified.

Another included RCT, with 30 participants, compared different doses of rasburicase (0.2 mg/kg versus 0.15 mg/kg), which demonstrated no significant difference in uric acid normalisation and uric acid level at four hours). Common adverse events of urate oxidase included hypersensitivity, haemolysis, and anaemia, but no significant difference between treatment groups was identified. No significant difference in mortality (all-cause mortality and mortality due to TLS) and renal failure was identified. The primary outcome was not evaluated.

All included trials were highly susceptible to biases.

**Authors' conclusions**

Although urate oxidase might be effective in reducing serum uric acid, it is unclear whether it reduces clinical tumour lysis syndrome, renal failure, or mortality. Adverse effects might be more common for urate oxidase compared with allopurinol. Clinicians should weigh the potential benefits of reducing uric acid and uncertain benefits of preventing mortality or renal failure from TLS against the potential risk of adverse effects.

## PLAIN LANGUAGE SUMMARY

**Urate oxidase for the prevention and treatment of complications from massive lysis (breakdown) of tumour cells in children with cancer**

Tumour lysis syndrome occurs when uric acid and other cellular substances are rapidly released into the circulation when tumour cells are broken down spontaneously or during treatment. Uric acid has low solubility (does not dissolve easily); therefore, it can build up in the kidney resulting in kidney failure and possibly death eventually. Urate oxidase is an enzyme that can be administered to patients at risk of tumour lysis syndrome to convert uric acid to a more soluble product, allantoin, which can be excreted by the kidneys more readily. Therefore, urate oxidase may be able to prevent or treat tumour lysis syndrome in patients with malignancies. However, the current systematic review of (randomised) controlled clinical trials found that although urate oxidase might be effective in reducing serum uric acid level, it has not been confirmed to reduce renal failure or mortality from tumour lysis syndrome in children with cancer. Adverse effects might be more common in patients who receive urate oxidase compared with allopurinol. Urate oxidase needs to be further evaluated, especially in high-risk patients, such as those with high-risk leukaemia and lymphoma.

## BACKGROUND

Tumour lysis syndrome (TLS) is a serious complication of malignancies that can occur spontaneously in the presence of rapidly proliferating tumour cells or during treatment because of rapid cell lysis, leading to release of intracellular components that may result in hyperkalaemia, hyperphosphataemia, hypocalcaemia, or hyperuricaemia. Hyperuricaemia and hyperphosphataemia can result in crystallisation in the renal tubules causing obstructive uropathy and renal failure. Other severe consequences of tumour lysis syndrome include cardiac arrhythmia and sudden death from hyperkalaemia (Navolanic 2003; Rampello 2006). The Cairo-Bishop definition for laboratory tumour lysis syndrome is the development of any two or more of the following four criteria within three days before or seven days after the initiation of chemotherapy: uric acid level $\geq$ 8 mg/dL, potassium level $\geq$ 6 mmol/L, phosphate level $\geq$ 6.65 mg/dL, and calcium level $\leq$ 7 mg/dL. A 25% increase from baseline for uric acid, potassium, or phosphate levels or a 25% decrease from baseline for calcium level is an alternative threshold (Cairo 2004). The Cairo-Bishop definition for clinical tumour lysis syndrome is the presence of laboratory tumour lysis syndrome and one or more of the following three criteria: serum creatinine level $\geq$ 1.5 times the upper limit of normal, cardiac arrhythmias, sudden death, or seizures.

Risk factors for tumour lysis syndrome include high proliferation rate, large tumour burden, and high chemosensitivity. A high white blood cell count in leukaemia (> 50 x $10^9$ /L) or a high lactate dehydrogenase level in lymphoma indicates high tumour burden. Certain malignancies, such as Burkitt's lymphoma, are associated with a very high risk of tumour lysis syndrome because of rapid tumour cell turnover (Wössmann 2003). The incidence of tumour lysis syndrome varies among studies. A retrospective review of acute lymphoblastic leukaemia, acute myeloid leukaemia, and non-Hodgkin's lymphoma found that the frequency of tumour lysis syndrome was 3.4%, 5.2%, and 6.1%, respectively, and it accounts for 0.9% of cancer mortality (Annemans 2003a). The mortality rate of tumour lysis syndrome has been estimated to be about 17.5% (Annemans 2003a). The medical costs of hyperuricaemia and tumour lysis syndrome are substantial. The cost of hyperuricaemia without tumour lysis syndrome has been estimated to be EURO672, and the cost of tumour lysis syndrome, EURO7342 (Annemans 2003a). The cost of tumour lysis syndrome requiring dialysis has been shown to be even higher (EURO17,706 on average) (Annemans 2003a).

Aggressive hydration and allopurinol, with or without urinary alkalinisation with bicarbonate, is the standard prophylaxis for tumour lysis syndrome. Allopurinol is a xanthine oxidase inhibitor, which prevents the formation of uric acid but does not catabolise (so degrade and detoxify) existing uric acid. Allopurinol is therefore not an effective treatment for established tumour lysis syndrome since it does not promote uric acid clearance. Because of the inhibition of xanthine oxidase, allopurinol increases the level of uric acid precursors, hypoxanthine and xanthine. As xanthine is less soluble than uric acid, it may precipitate in renal tubules causing xanthine nephropathy (kidney disease) or xanthine stones (Greene 1969).

Urate oxidase is an alternative agent used for the treatment or prophylaxis of hyperuricaemia in patients who are at high risk of tumour lysis syndrome. Urate oxidase converts uric acid to allantoin, which is five to 10 times more soluble than uric acid and readily excreted in urine. A non-recombinant form of urate oxidase has been available in Europe for more than 20 years, but it is associated with acute hypersensitivity reactions in 4.5% of patients (Yim 2003). Rasburicase, a relatively new, recombinant urate oxidase enzyme produced by a genetically modified *Saccharomyces cerevisiae* strain, has now replaced the older agent and is widely used. Reported advantages of urate oxidase over allopurinol include its ability to catabolise existing uric acid in established tumour lysis syndrome; no increased risk of xanthine stone formation; no requirement for dose adjustment in acute renal failure; lack of clinically relevant drug-drug interaction; and lower incidence of adverse reactions, such as skin rash, fever, eosinophilia, and Stevens Johnson syndrome (Gutierrez 2005; Sanofi 2011). Anecdotal reports and case series have indicated that urate oxidase may be effective in the prevention and treatment of tumour lysis syndrome (Bosly 2003; Coiffier 2003; Hummel 2003; Hutcherson 2006; Jeha 2005; Lascombes 1998; Lee 2003; Liu 2005; McDonnell 2006; Pui 2001a; Pui 2001b; Shin 2006; Trifilio 2006; Wang 2006), resulting in a significant reduction of serum uric acid level and a low incidence of renal failure requiring dialysis. In addition, the use of urate oxidase has been reported to be cost-effective for the prevention and treatment of tumour lysis syndrome in both children and adults (Annemans 2003b). However, it is not entirely certain whether the existing evidence is sufficiently rigorous to support the routine use of urate oxidase as prophylaxis in children with malignancies at risk of tumour lysis syndrome, or as a treatment for established laboratory or clinical tumour lysis syndrome. It is also uncertain whether single or multiple doses of urate oxidase should be used or which types of high-risk patients benefit most from prophylactic administration of urate oxidase. Although there are consensus guidelines developed for the management of tumour lysis syndrome (Coiffier 2008; Tosi 2008), they did not include the latest evidence from systematic review. Therefore, we examined the efficacy and safety of urate oxidase in children with malignancies in a systematic review of randomised controlled trials and controlled clinical trials (Cheuk 2010). This is an update of that systematic review.

## OBJECTIVES

To assess the effects and safety of urate oxidase for the prevention and treatment of TLS in children with malignancies.

# METHODS

## Criteria for considering studies for this review

### Types of studies

We included randomised controlled trials (RCTs) in the review. We also planned to include controlled clinical trials (CCTs) if no (or few) RCTs were available. A CCT is a study that compares one or more intervention groups to one or more control groups. We included historical controlled studies.

### Types of participants

We included participants under 18 years of age with all types of cancer, including haematological malignancies and solid tumours.

### Types of interventions

We included trials evaluating all preparations of urate oxidase. The control interventions could be placebo; no treatment; or other treatment, such as allopurinol. We also included trials comparing urate oxidase combined with other treatment versus the same other treatment alone, and trials comparing different doses or different preparations of urate oxidase.

### Types of outcome measures

For evaluation of urate oxidase as **prevention** for tumour lysis syndrome, we assessed the following outcome measures.

#### Primary outcome

1. Incidence of clinical tumour lysis syndrome according to Cairo-Bishop definition.

#### Secondary outcomes

1. Incidence of laboratory tumour lysis syndrome according to Cairo-Bishop definition.
2. Mortality associated with tumour lysis syndrome and combined with other reasons.
3. Incidence of renal failure requiring renal replacement therapy associated with tumour lysis syndrome.
4. Frequency of normalisation of serum uric acid level.
5. Duration before normalisation of serum uric acid level.
6. Change in serum uric acid level.
7. Area under curve (AUC) of uric acid level.
8. Frequency of adverse effects.

For the evaluation of urate oxidase as **treatment** for tumour lysis syndrome, we assessed the following outcome measures.

#### Primary outcome

1. Mortality associated with tumour lysis syndrome and combined with other reasons.

#### Secondary outcomes

1. Incidence of renal failure requiring renal replacement therapy associated with tumour lysis syndrome.
2. Frequency of normalisation of serum uric acid level.
3. Duration before normalisation of serum uric acid level.
4. Change in serum uric acid level.
5. Area under curve (AUC) of uric acid level.
6. Change in serum phosphate level.
7. Change in serum potassium level.
8. Change in serum creatinine level.
9. Change in serum calcium level.
10. Frequency of adverse effects.

## Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (issue 2, 2009 for the original review, and issue 1, 2013 for the update), MEDLINE/PubMed (1966 to August 2009 for the original review, and to February 2013 for the update), Embase (1980 to August 2009 for the original review, and to February 2013 for the update), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1982 to August 2009 for the original review, and to February 2013 for the update).

The search strategies used for the different electronic databases (using a combination of controlled vocabulary and text word terms) are shown in the Appendices (Appendix 1; Appendix 2; Appendix 3; Appendix 4).

We searched the reference lists of all identified relevant papers for further studies. We also explored other internet sources (updated search on 28 February 2013):

- the NHS' National Research Register (for the original review: www.update-software.com; for the update: www.nihr.ac.uk/Pages/NRRArchiveSearch.aspx);
- the US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov);
- metaRegister of Controlled Trials (www.controlled-trials.com/mrct); and
- ProQuest Dissertations & Theses Database (for the original review: wwwlib.umi.com/dissertations; for the update: search.proquest.com).

We also handsearched abstracts from the meetings of the ASCO (American Society of Clinical Oncology), ESMO (European Society for Medical Oncology), and SIOP (International Society of Paediatric Oncology) from 1993 to 2009 for the original review, and 2010 to 2012 for the update.

We also included articles published only in abstract form if we could contact the authors to provide essential details for appraisal and analysis. If the process of searching many different sources brought to light direct or indirect references to unpublished studies, we planned to obtain copies of such unpublished material. In addition, we contacted colleagues and experts in the field to ascertain any unpublished or ongoing studies. We also contacted the manufacturer of rasburicase, Sanofi-aventis, for published and unpublished clinical studies.

There was no language restriction in the search and inclusion of studies. However, we excluded multiple publications reporting the same group of participants or its subsets.

## Data collection and analysis

### Selection of studies

Two authors (the first and second authors) independently reviewed titles and abstracts of references retrieved from the searches and selected all potentially relevant studies. The same authors obtained copies of these articles and reviewed them independently against the above-mentioned inclusion and exclusion criteria for study selection. Authors were not blinded to the names of the trial authors, institutions, or journal of publication. We planned for the third author to resolve any discrepancies regarding selection of studies if necessary, but there was no discrepancy and the third author was not called upon.

### Data extraction and management

Two authors extracted data from included trials, independently. We planned for the third author to resolve any discrepancies regarding data extraction if necessary, but there was no discrepancy and the third author was not called upon.

We extracted the following data.

1. Study methods
   i) design (i.e. RCT or CCT)
   ii) randomisation method (including list generation)
   iii) method of allocation concealment
   iv) blinding method
   v) stratification factors
2. Participants
   i) inclusion/exclusion criteria
   ii) number of participants entering the trial, number of participants randomised, number of excluded participants (with reasons), and number of evaluable participants
   iii) age and gender distribution
   iv) type of malignancies
   v) treatments for the malignancies (chemotherapy, radiotherapy, autologous stem cell transplant, allogeneic stem cell transplant)
   vi) baseline renal function, uric acid level, potassium level, phosphate level, calcium level, lactate dehydrogenase (LDH) level, white blood cell (WBC) counts (for leukaemia), rate of decrease of WBC (for leukaemia), and sizes of the liver and spleen
3. Intervention and control
   i) type of uric oxidase
   ii) type of control treatment
   iii) details of administration of urate oxidase, including dosage and schedules
   iv) details of co-interventions
4. Follow-up data
   i) duration of follow-up
   ii) loss to follow up
5. Outcome data
   i) serial uric acid levels measurement
   ii) days to normalisation of uric acid level
   iii) number of criteria of laboratory tumour lysis syndrome according to Cairo-Bishop definition
   iv) number of criteria of clinical tumour lysis syndrome according to Cairo-Bishop definition
   v) change in serum potassium, calcium, phosphorus, and creatinine levels
   vi) adverse effects
6. Analysis data
   i) methods of analysis (intention-to-treat or per-protocol analysis)
   ii) comparability of groups at baseline (yes/no);
   iii) statistical methods

One author entered the data into Review Manager (RevMan) ( RevMan 2013); the other authors then checked the data.

### Assessment of risk of bias in included studies

Two authors (the first and second authors) independently assessed the methodological quality of each eligible trial. We planned for the third author to resolve any discrepancies regarding risk of bias assessment if necessary, but there was no discrepancy and the third author was not called upon. Where necessary, we sought additional information from the principal investigator of the trial concerned. We included the following items to assess the methodological quality of RCTs in the update of the review, according to the latest recommendation in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias); and
- other bias.

Similarly, we assessed controlled clinical trials for the above-mentioned types of biases; we expected them not to incorporate ran-

dom allocation of treatment groups or perform allocation concealment. Because of non-random treatment group allocation, they were also susceptible to confounding, and we examined possible confounding factors, including age of the participant, types of malignancies, baseline renal function, white blood cell (WBC) counts, lactate dehydrogenase (LDH) level, uric acid levels, and intensity of chemotherapy.

### Measures of treatment effect

We used risk ratio (RR) estimations with 95% confidence intervals (CI) for dichotomous outcomes. We did not calculate a RR if there was only one study available for a particular outcome, and there was no event in one of the groups. We used the Fisher's exact test (performed using SPSS version 19 (SPSS 2010)) to determine the P value in such situations. We used mean difference (MD) estimations with 95% CI for continuous outcomes. We analysed all participants in the treatment groups to which they were allocated (intention-to-treat (ITT) analyses) if there were no missing data; we planned to perform per-protocol analyses if information for intention-to-treat analyses was lacking. We did not impute missing data. We planned to consider cost-effectiveness of interventions if relevant data were available.

### Dealing with missing data

We contacted the authors of included studies to ask them to supply missing data. We assessed missing data and dropouts/attrition for each included study and assessed and discussed the extent to which the missing data could alter the results/conclusions of the review. If, for a particular outcome, less than 70% of participants allocated to the treatments were reported on at the end of the trial, we reported those data, but considered them prone to bias.

### Assessment of reporting biases

We planned to generate a funnel plot (effect size against standard error) if we found sufficient studies (more than five). Asymmetry could be due to publication bias, but could also be due to a relationship between trial size and effect size. In the event that we found a relationship, we planned to examine clinical diversity of the studies (Egger 1997). However, there were not enough studies available to prepare a reliable funnel plot.

### Data synthesis

Where the interventions were the same or similar enough, we synthesised results in a meta-analysis if there was no important clinical heterogeneity. If no significant statistical heterogeneity was present, we synthesised the data using a fixed-effect model. If there was unexplained heterogeneity, we used a random-effects model in the meta-analysis.

### Subgroup analysis and investigation of heterogeneity

If data permitted, we conducted subgroup analyses for the following:

1. different types of malignancies (acute leukaemia, lymphoma, solid tumour);
2. different number of doses of urate oxidase (single dose, two doses, three or more doses); and
3. different levels of risk of tumour lysis syndrome (participants with rapid cell turnover, high lactate dehydrogenase (LDH), or baseline hyperuricaemia).

If two or more included trials reported the same outcomes for the same subgroups, we combined their results in meta-analyses if no significant heterogeneity was present. We assessed clinical heterogeneity by comparing the distribution of important participant factors between trials (age, type of malignancies) and trial factors (randomisation concealment, blinding of outcome assessment, losses to follow up, treatment regimens). We assessed statistical heterogeneity of RCTs by examining the $I^2$ statistic (Higgins 2002), a quantity that describes approximately the proportion of variation in point estimates that is due to heterogeneity rather than sampling error. If significant heterogeneity was present (i.e. $I^2 \geq 50\%$ (Higgins 2011), we explored the trials to investigate possible explanations.

### Sensitivity analysis

We planned to conduct sensitivity analyses to assess the impact of study quality, including the following:

1. all studies; and
2. only those studies with adequate allocation concealment.

We also planned to conduct sensitivity analyses to assess the impact of heterogeneity, by excluding those with outlying results.

## RESULTS

### Description of studies

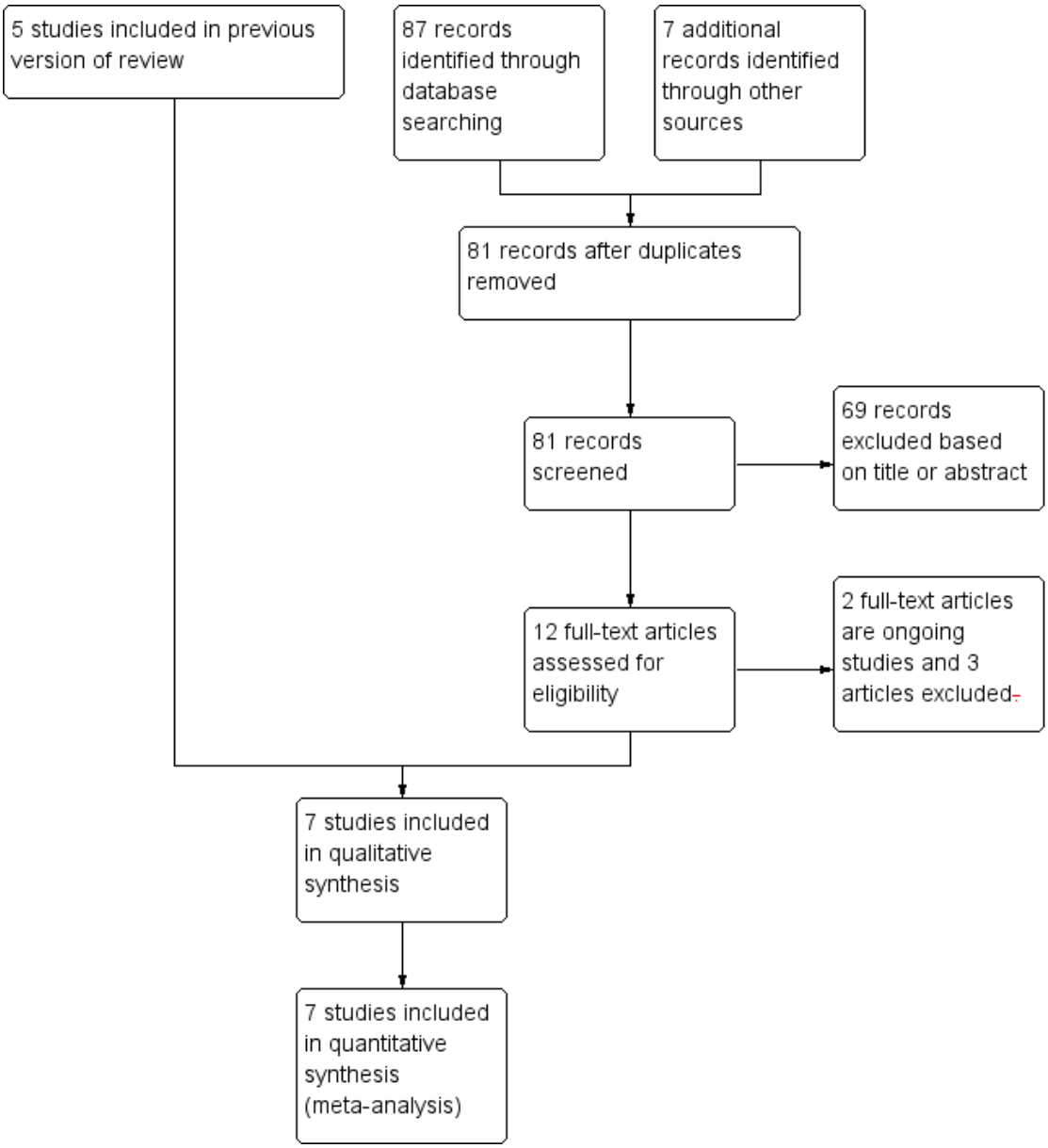
#### Results of the search

In August 2009, the electronic searches retrieved 68 articles from MEDLINE. We excluded 64 based on title or abstract, because of obvious irrelevance. We examined the full texts of the four remaining articles. Two were randomised controlled trials (RCTs) satisfying the inclusion criteria (Goldman 2001; Kikuchi 2009), and the other two were controlled clinical trials (CCTs) (Renyi 2007; Wossmann 2003). We included these two CCTs in the review because we only identified two RCTs. We also retrieved 100 articles from Embase. We excluded all but two articles after examining the title and abstract. The MEDLINE search also identified these

two articles (Kikuchi 2009; Renyi 2007). We retrieved 17 articles from the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*. We excluded 16 based on title or abstract, and we included one. This was one of the RCTs identified in MEDLINE (Goldman 2001). We retrieved 40 articles from CINAHL, excluding 37 based on title or abstract. The remaining three articles were the same as those identified and included from MEDLINE (Goldman 2001; Renyi 2007; Wossmann 2003). We identified and included one more CCT (Patte 2002) after checking the reference lists of the other included studies. We identified no additional completed or ongoing trials after checking internet sources and conference proceedings and contacting experts. There was no discrepancy in the independent selection of included studies among the two authors, and a third author was not necessary in this process.

With the updated electronic search strategy in February 2013, we retrieved 16 articles from CENTRAL, 53 articles from MEDLINE/PubMed, 18 articles from Embase, and no article from CINAHL. We found five studies from checking references of included studies and two studies from the US National Institutes of Health Ongoing Trials Register. We identified no studies by scanning the conference proceedings and contacting experts. In summary, we found a total of 94 studies in the update search in February 2013. After we removed duplicates, we screened 81 articles for eligibility. We excluded 69 articles based on title or abstract. We obtained the full text of the remaining 12 articles. We included seven studies in this review, including the five studies included in the original search (Goldman 2001; Kikuchi 2009; Patte 2002; Rényi 2007; Wössmann 2003) and two additional studies in the update (Sánchez Tatay 2010; Pui 1997). Two studies were ongoing (see the 'Characteristics of ongoing studies' tables) and did not have results available, and we excluded three studies (see the 'Characteristics of excluded studies' tables). There was no discrepancy in the independent selection of included studies among the two authors, and a third author was not necessary in this process. In summary (see Figure 1), we included seven studies (five identified in the original review and two in the update). Among the seven included studies, two were randomised controlled trials (RCTs) satisfying the inclusion criteria (Goldman 2001; Kikuchi 2009), and the other five were controlled clinical trials (CCTs) (Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003).

**Figure 1. Study flow diagram of review update**



### Included studies

All seven included trials evaluated urate oxidase as a preventive measure for tumour lysis syndrome. We identified no clinical trial investigating urate oxidase for treatment of tumour lysis syndrome. We give details of the included trials in the 'Characteristics of included studies' tables and summarise the details below.

Six included trials compared urate oxidase against allopurinol as the control treatment in parallel group designs (Goldman 2001; Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003). The remaining one included trial compared different doses of urate oxidase (Kikuchi 2009). Four trials used rasburicase (Goldman 2001; Kikuchi 2009; Rényi 2007; Sánchez Tatay 2010) while the remaining three trials used Uricozyme (Patte 2002; Pui 1997; Wössmann 2003). Four included trials (Goldman 2001; Patte 2002; Pui 1997; Rényi 2007) used a standard alkaline hyperhydration regimen in both the intervention and the control groups, while one trial (Wössmann 2003) used alkalinisation only in the control group. The remaining two trials (Kikuchi 2009; Sánchez Tatay 2010) did not mention alkalinisation. Six trials (Goldman 2001; Kikuchi 2009; Patte 2002; Pui 1997; Rényi 2007; Wössmann 2003) initiated urate oxidase before the start of chemotherapy, lasting for three to seven days. One trial (Sánchez Tatay 2010) did not mention the duration of therapy.

None of the five included non-randomised, controlled clinical trials used a concurrent control group. Four trials used a historical control group (Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003), and one trial used aggregate participant data from trials of other study groups as a retrospective analysis (Patte 2002).

The RCT (Goldman 2001) comparing rasburicase with allopurinol included a total of 27 children in the intervention group and 25 participants in the control group. This trial included children only (aged 0.3 to 17 years) (Goldman 2001). The RCT comparing different doses of rasburicase included a total of 15 participants in the low-dose group (0.15 mg/kg) and 15 participants in the high-dose group (0.2 mg/kg) (Kikuchi 2009). This trial also included children only (aged 0 to 17 years) (Kikuchi 2009). The five CCTs comparing urate oxidase with allopurinol included a total of 429 participants in the intervention groups and 563 participants in the control groups. All five CCTs included children only. Two of these trials reported a median age of 4.5 to 5.6 years in the intervention groups and 5.7 to 6 years in the control groups (Pui 1997; Rényi 2007). The remaining three trials (Patte 2002; Sánchez Tatay 2010; Wössmann 2003) did not mention the age distribution of the participants.

The types of malignancies included in all trials were similar. The RCT comparing rasburicase and allopurinol recruited participants with stage three or four non-Hodgkin's lymphoma, acute lymphoblastic leukaemia (ALL) with high white blood cell (WBC) counts, and participants with leukaemia or lymphoma with hyperuricaemia (Goldman 2001). The RCT comparing high-dose and low-dose rasburicase recruited participants with stage four non-Hodgkin's lymphoma, stage three non-Hodgkin's lymphoma with large lymph node or high lactate dehydrogenase (LDH), and acute leukaemia with high WBC (Kikuchi 2009). All five CCTs included participants with haematological malignancies who were at high risk of tumour lysis syndrome, with just minor differences in the inclusion criteria among these trials (for details, please refer to the 'Characteristics of included studies' tables).

For outcome measures, only one study reported incidence of clinical tumour lysis syndrome (Wössmann 2003). Five studies (Goldman 2001; Kikuchi 2009; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003) reported on all-cause mortality. Five studies (Goldman 2001; Kikuchi 2009; Patte 2002; Rényi 2007; Sánchez Tatay 2010) also reported on mortality due to tumour lysis syndrome. All seven included studies reported frequency of renal failure requiring renal replacement therapy (Goldman 2001; Kikuchi 2009; Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003), two studies reported frequency of normalisation of serum uric acid (Goldman 2001; Kikuchi 2009), one study reported area under curve (AUC) of serum uric acid (Goldman 2001), and four studies reported serial uric acid levels (Kikuchi 2009; Pui 1997; Rényi 2007; Sánchez Tatay 2010). Five studies reported adverse events (Goldman 2001; Kikuchi 2009; Pui 1997; Rényi 2007; Sánchez Tatay 2010).

### Excluded studies

We excluded three RCTs evaluating urate oxidase for prevention of tumour lysis syndrome as they recruited adult participants only and did not include paediatric participants (Cortes 2010; Ishizawa 2009; Vadhan-Raj 2012).

## Risk of bias in included studies

In general, none of the included trials were of high methodological quality. The two RCTs were quite small, recruiting only 30 to 52 participants (Goldman 2001; Kikuchi 2009). We describe the risk of bias in the 'Characteristics of included studies' tables, Figure 2, and Figure 3.

**Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies**

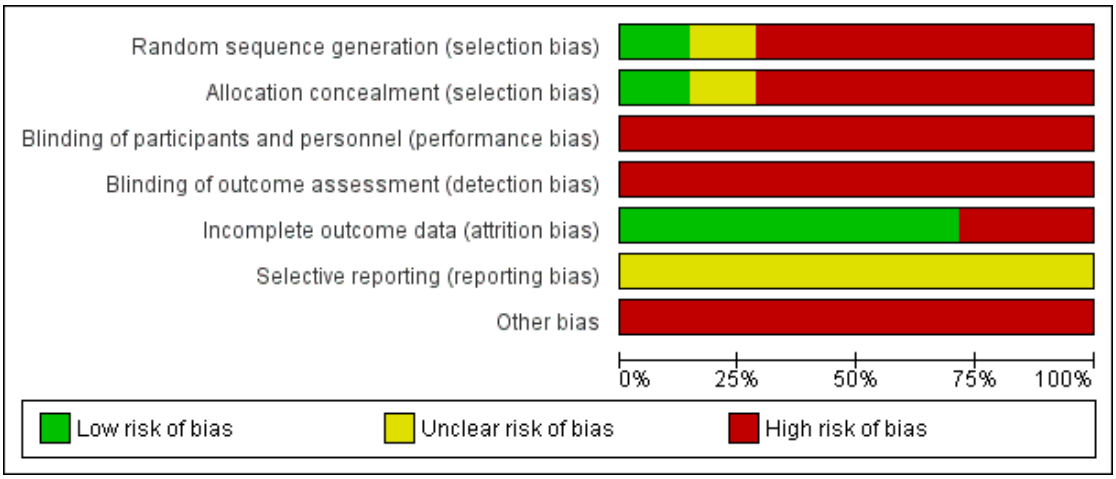
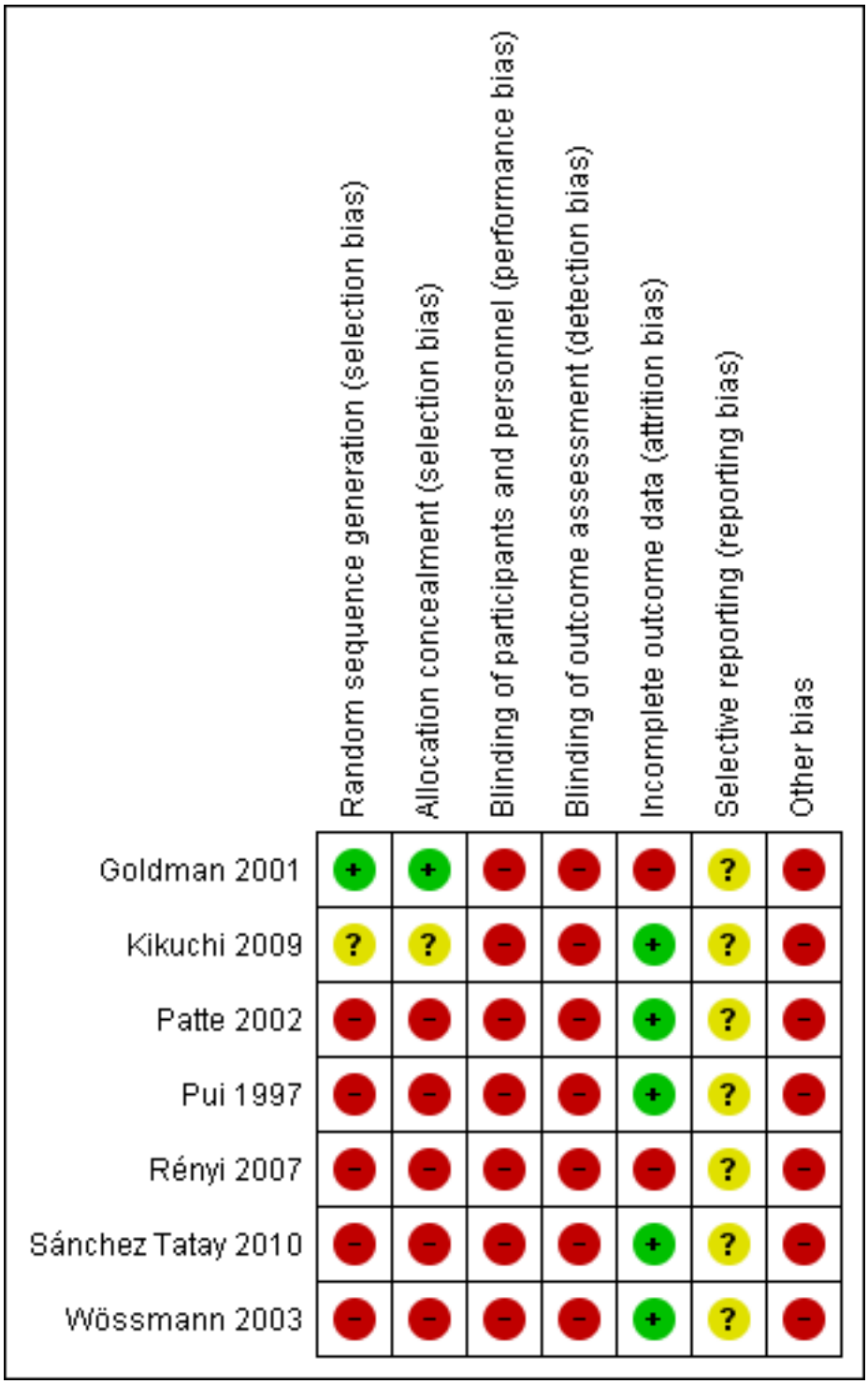


**Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study**



### Allocation

All five CCTs (Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003) included in this review were not randomised trials and selection bias was likely present. The RCT Kikuchi 2009 did not report random sequence generation or concealment. We were uncertain whether there was high risk of selection bias. Random sequence generation and randomisation concealment were likely to be adequate in the trial by Goldman as the randomisation code was computer-generated (Goldman 2001).

### Blinding

There was no blinding of participants, care providers, or outcome assessors in all five included CCTs (Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003). Also, two of the included RCTs (Goldman 2001; Kikuchi 2009) did not blind participants, care providers, or outcome assessors, which might introduce performance and detection biases.

### Incomplete outcome data

There were dropouts with incomplete data in both included RCTs (Goldman 2001; Kikuchi 2009). However, dropouts constituted a very low proportion of participants in one study (Kikuchi 2009) and were unlikely to cause significant attrition bias. Nevertheless, we considered the RCT by Goldman to have a high risk of bias as there were differences in the dropout rate between the intervention and the control groups, and more than 10% of the participants in the control group had incomplete follow up (Goldman 2001). One CCT also had incomplete data for a large proportion of participants and had high risk of attrition bias (Rényi 2007). The remaining four CCTs had no dropouts (Patte 2002; Pui 1997; Sánchez Tatay 2010; Wössmann 2003).

### Selective reporting

It was unclear whether there was selective reporting of outcomes in all included studies as the trial protocols were not available ( Goldman 2001; Kikuchi 2009; Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003).

### Other potential sources of bias

In all studies, there was a high risk of other bias. The intervention and comparison groups were not comparable at baseline in four studies, which might result in high risk of bias (Goldman 2001; Kikuchi 2009; Rényi 2007; Wössmann 2003). Two studies (Patte 2002; Sánchez Tatay 2010) did not report some important baseline characteristics, so the comparability of their intervention and comparison groups was not certain. For non-randomised controlled trials, failure of adjustment of potential confounders resulted in high risk of bias (Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003). The use of historical controls in four trials (Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003) may have biased the results in favour of the newer treatment because of improvement in supportive care. In one CCT (Patte 2002), chemotherapy treatments were different in different centres in different locations, and this may have caused bias.

## Effects of interventions

### Urate oxidase versus allopurinol

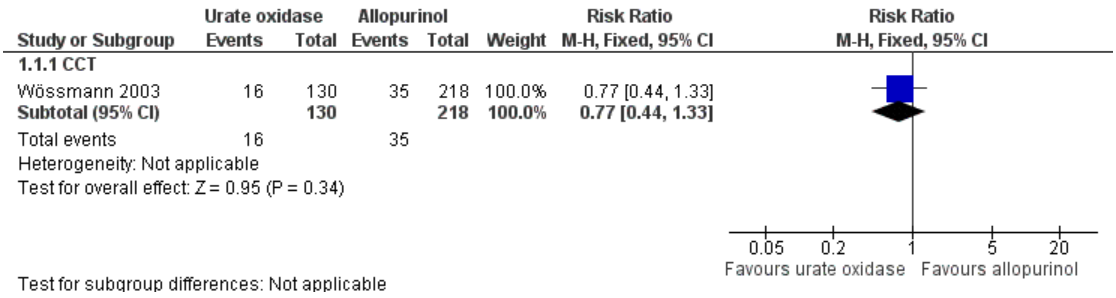
Six included studies compared urate oxidase with allopurinol for prevention of tumour lysis syndrome. One study was an RCT (Goldman 2001), and the other five studies were CCTs (Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003).

#### Primary outcome

##### Incidence of clinical tumour lysis syndrome

One CCT (Wössmann 2003) that reported this outcome did not find any significant difference between the group that received Uricozyme and the group that received allopurinol. (Sixteen out of 130 participants in the Uricozyme group versus 35 out of 218 participants in the allopurinol group developed tumour lysis syndrome (TLS); risk ratio (RR) 0.77, 95% confidence intervals (CI) 0.44 to 1.33; P = 0.34; intention-to-treat (ITT) analysis; Analysis 1.1; Figure 4.) This study also reported results for the subgroup of participants with acute B lymphoblastic leukaemia (B-ALL) and found no significant difference between the intervention and the control groups. (Five out of 53 participants in the Uricozyme group versus 16 out of 78 participants in the allopurinol group developed TLS; RR 0.46, 95% CI 0.18 to 1.18; P = 0.11; ITT analysis; Analysis 1.2.)

**Figure 4. Forest plot of comparison: 1 Urate oxidase compared with allopurinol, outcome: 1.1 Incidence of clinical tumour lysis syndrome**




### Secondary outcomes

#### Incidence of laboratory tumour lysis syndrome

None of the included trials reported this outcome.

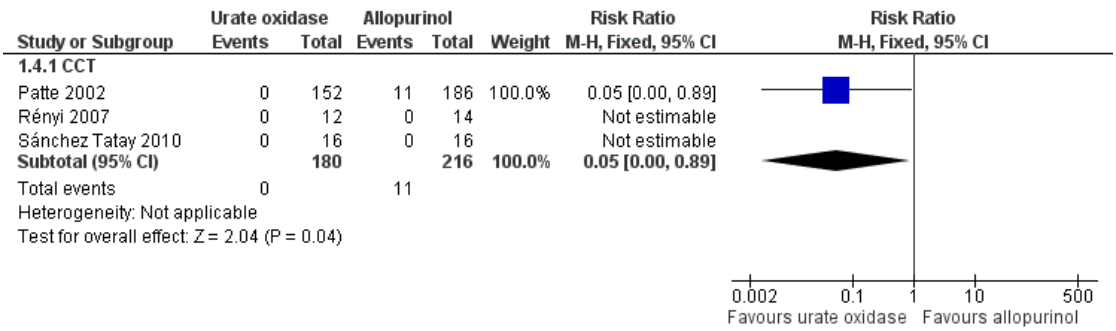
#### All-cause mortality

The RCT (Goldman 2001) showed slightly lower mortality in the group that received rasburicase compared with the group that received allopurinol, but this was not statistically significant. (None of the 27 participants in the rasburicase group versus 2 out of 25 participants in the allopurinol group died; Fisher's exact test P = 0.23; ITT analysis; Analysis 1.3.) The two participants in the allopurinol group died from *Pseudomonas* sepsis and intracerebral haemorrhage, respectively. All-cause mortality was available in three CCTs, two of which did not have any mortality (Rényi 2007; Sánchez Tatay 2010), and the third one reported four deaths in the control group (Wössmann 2003). The study reported the deaths to be treatment-related, but did not specify the actual cause. The pooled result of the three CCTs showed no significant difference in all-cause mortality between the intervention and the control groups. (None of the 158 participants in the urate oxidase group versus four out of 248 participants in the allopurinol group died; RR 0.19, 95% CI 0.01 to 3.42; P = 0.26; ITT analysis; Analysis 1.3.)

#### Mortality due to tumour lysis syndrome

The RCT (Goldman 2001) did not find any mortality due to tumour lysis syndrome in either the intervention group (total of 27 participants) or control group (total of 25 participants) (ITT analysis) (Analysis 1.4). However, pooled results of three CCTs (Patte 2002; Rényi 2007; Sánchez Tatay 2010) showed a significantly lower mortality due to tumour lysis syndrome in the group that received Uricozyme compared with the group that received allopurinol, (None of the 180 participants in the intervention group versus 11 out of 216 participants in the control group died due to TLS; RR 0.05, 95% CI 0.00 to 0.89; P = 0.04; ITT analysis; Analysis 1.4; Figure 5.)

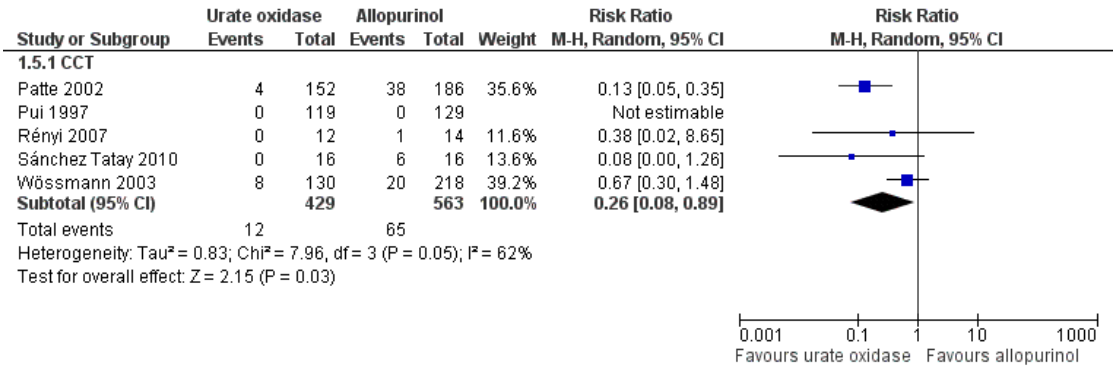
**Figure 5. Forest plot of comparison: 1 Urate oxidase compared with allopurinol, outcome: 1.4 Mortality due to tumour lysis syndrome**



### Renal failure requiring renal replacement therapy

The RCT (Goldman 2001) showed no significant difference in the frequency of renal failure between the intervention and the control groups. (None of the 27 participants in the rasburicase group versus one out of 25 participants in the allopurinol group had renal failure; Fisher's exact test P = 0.48; ITT analysis; Analysis 1.5.) In contrast, pooled results of five CCTs (Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003) showed significantly lower frequency of renal failure requiring renal replacement therapy in participants who received urate oxidase compared with those who received allopurinol. (Twelve out of 429 participants in the intervention group versus 65 out of 563 participants in the control group developed renal failure; $I^2$ = 62%; RR 0.26, 95% CI 0.08 to 0.89; P = 0.03; ITT analysis; Analysis 1.5; Figure 6.) One CCT (Wössmann 2003) reported results of a subgroup of participants with B-ALL and showed lower frequency of renal failure in the intervention group, but the difference was not statistically significant. (Two out of 53 participants in the intervention group versus 12 out of 78 participants in the control group developed renal failure; RR 0.25, 95% CI 0.06 to 1.05; P = 0.06; ITT analysis; Analysis 1.6.)

**Figure 6. Forest plot of comparison: 1 Urate oxidase compared with allopurinol, outcome: 1.5 Renal failure requiring renal replacement therapy**




### Normalisation of uric acid level

The RCT (Goldman 2001) showed significantly higher frequency of uric acid normalisation at four hours in the participants who received rasburicase compared with participants who received allopurinol. (Ten out of 10 participants in the intervention group versus zero out of nine participants in the control group had normalisation of uric acid level; Fisher's exact test P < 0.001; not ITT analysis.)

### Duration before normalisation of serum uric acid level

None of the included trials reported this outcome.

### Area under curve (AUC) of serum uric acid level

The RCT (Goldman 2001) reported a significantly lower AUC of serum uric acid at four days in the intervention group compared with the control group (mean AUC 128 mg/dLhr in 27 participants in the intervention group versus 329 mg/dLhr in 25 participants in the control group; mean difference (MD) -201.00 mg/dLhr, 95% CI -258.05 mg/dLhr to -143.95 mg/dLhr; P < 0.00001; ITT analysis; Analysis 1.7.) The RCT also reported results of different subgroups and found significantly lower AUC of serum uric acid at four days in the intervention group compared with the control group in participants with leukaemia (mean AUC 141 mg/dLhr in 20 participants in the intervention group versus 361 mg/dLhr in 19 participants in the control group; MD -220.00 mg/dLhr, 95% CI -286.67 mg/dLhr to -153.33 mg/dLhr; P < 0.00001; ITT analysis; Analysis 1.8), lymphoma (mean AUC 92 mg/dLhr in seven participants in the intervention group versus 224 mg/dLhr in six participants in the control group; MD -132.00 mg/dLhr, 95% CI -185.47 mg/dLhr to -78.53 mg/dLhr; P < 0.00001; ITT analysis; Analysis 1.9), baseline hyperuricaemia participants (mean AUC 162 mg/dLhr in 10 participants in the intervention group versus 440 mg/dLhr in nine participants in the control group; MD -278.00 mg/dLhr, 95% CI -373.69 mg/dLhr to -182.31 mg/dLhr; P < 0.00001; ITT analysis; Analysis 1.10), and participants with normal baseline uric acid (mean AUC 108 mg/dLhr in 17 participants in the intervention group versus 348

mg/dLhr in 16 participants in the control group; MD -240.00 mg/dLhr, 95% CI -340.95 mg/dLhr to -139.05 mg/dLhr, P < 0.00001; ITT analysis; Analysis 1.11.)

### Serial uric acid level

Three CCTs reported serial uric acid levels (Pui 1997; Rényi 2007; Sánchez Tatay 2010). All three CCTs reported results on the first two days after urate oxidase, while two studies (Rényi 2007; Sánchez Tatay 2010) reported results up to four days and one study (Rényi 2007) reported results up to 12 days. The pooled results showed significantly lower uric acid level in the intervention group compared with the control group at two days (mean uric acid level 1.02 mg/dL in 147 participants the intervention group versus 3.25 mg/dL in 147 participants in the control group; $I^2$ = 87%; MD -3.80 mg/dL, 95% CI -7.37 mg/dL to -0.24 mg/dL; P = 0.04; not ITT analysis; < 70% of participants had outcomes available for Rényi 2007; results susceptible to bias; Analysis 1.13), three days (mean uric acid level 0.52 mg/dL in 28 participants in the intervention group versus 4.66 mg/dL in 19 participants in the control group; $I^2$ = 89%; MD -3.13 mg/dL, 95% CI -6.12 mg/dL to -0.14 mg/dL; P = 0.04; not ITT analysis; < 70% of participants had outcomes available for Rényi 2007; results susceptible to bias; Analysis 1.14), four days (mean uric acid level 0.24 mg/dL in 28 participants in the intervention group versus 4.41 mg/dL in 17 participants in the control group; MD -4.60 mg/dL, 95% CI -6.39 mg/dL to -2.81 mg/dL; P < 0.00001; not ITT analysis; < 70% of participants had outcomes available for Rényi 2007; results susceptible to bias; Analysis 1.15), and seven days (mean uric acid level 1.43 mg/dL in 12 participants in the intervention group versus 3.17 mg/dL in four participants in the control group; MD -1.74 mg/dL, 95% CI -3.01 mg/dL to -0.47 mg/dL; P = 0.007; not ITT analysis; < 70% of patients had outcomes available for Rényi 2007; results susceptible to bias; Analysis 1.17), but not significant at one day (mean uric acid level 1.37 mg/dL in 147 participants in the intervention group versus 3.94 mg/dL in 151 participants in the control group; $I^2$ = 94%; MD -3.00 mg/dL, 95% CI -7.61 mg/dL to 1.60 mg/dL; P = 0.2; not ITT analysis; < 70% of participants had outcomes available for Rényi 2007; results susceptible to bias; Analysis 1.12), five days (mean uric acid level 0.44 mg/dL in 12 participants in the intervention group versus 1.46 mg/dL in two participants in the control group; MD -1.02 mg/dL, 95% CI -2.24 mg/dL to 0.20 mg/dL; P = 0.1; not ITT analysis; < 70% of participants had outcomes available for Rényi 2007; results susceptible to bias; Analysis 1.16), and 12 days (mean uric acid level 2.34 mg/dL in 12 participants in the intervention group versus 3.14 mg/dL in eight participants in the control group; MD -0.80 mg/dL, 95% CI -2.51 mg/dL to 0.91 mg/dL; P = 0.36; not ITT analysis; Analysis 1.18).

### Adverse events

The RCT (Goldman 2001) and three CCTs (Pui 1997; Rényi 2007; Sánchez Tatay 2010) reported frequency of adverse effects in the intervention and control groups. The RCT showed no significant differences between the intervention and the control groups. (One out of 27 participants in the intervention group versus none of the 25 participants in the control group had an adverse event; Fisher's exact test P = 1.0; ITT analysis.) The adverse event reported was haemolysis. The pooled results from CCTs showed significantly higher frequency of adverse effects in participants who received urate oxidase. (Thirteen out of 186 participants in the intervention group verses none of the 159 participants in the control group had adverse events; RR 9.10, 95% CI 1.29 to 64.00; P = 0.03; $I^2$ = 0%; ITT analysis; Analysis 1.19.) Adverse events reported in the intervention group included allergic reaction (six participants), methaemoglobinaemia (one participant), fever (two participants), nausea (one participant), abdominal pain (one participant), and mucositis (two participants). It should be noted that the Pui 1997 and Rényi 2007 studies included additional participants in this analysis (see the 'Characteristics of included studies' tables for more information).

## High-dose urate oxidase versus low-dose urate oxidase

One RCT (Kikuchi 2009) compared urate oxidase (rasburicase) given in high dose (0.2 mg/kg/day for five days) versus low dose (0.15 mg/kg/day for five days) .

### Primary outcome

### Incidence of clinical tumour lysis syndrome

The RCT did not report this outcome.

### Secondary outcomes

### Incidence of laboratory tumour lysis syndrome

The RCT did not report this outcome.

### All-cause mortality

The RCT (Kikuchi 2009) reported no significant difference in all-cause mortality between the high-dose and the low-dose groups. (None of the 15 participants in the high-dose group versus one of the 15 participants in the low-dose group died; Fisher's exact test P = 1.0; ITT analysis.) The death in the low-dose group was due to cerebral haemorrhage, brain oedema, and brain herniation.

#### Mortality due to tumour lysis syndrome

The RCT (Kikuchi 2009) reported no mortality due to TLS in both the high-dose group (15 participants) and the low-dose group (15 participants) (ITT analysis).

#### Renal failure requiring renal replacement therapy

The RCT (Kikuchi 2009) reported no renal failure due to TLS in both the high-dose group (15 participants) and the low-dose group (15 participants) (ITT analysis).

#### Normalisation of uric acid level

The RCT (Kikuchi 2009) showed no significant difference between the high-dose and the low-dose groups. (All participants (14) in the high-dose group versus 14 out of 15 participants in the low-dose group had normalisation of uric acid level; RR 1.07, 95% CI 0.89 to 1.28; P = 0.49; not ITT analysis; Analysis 2.1.)

#### Duration before normalisation of serum uric acid level

The included RCT did not report this outcome.

#### AUC of serum uric acid level

The included RCT did not report this outcome.

#### Serial uric acid level

The RCT (Kikuchi 2009) reported the percentage reduction of uric acid level at four hours and did not find any significant difference between the high-dose and the low-dose groups (mean percentage reduction in uric acid level 92.9% in 14 participants in the high-dose group versus 84.8% in 15 participants in the low-dose group; MD 8.10%, 95% CI -0.99% to 17.19%; P = 0.08; not ITT analysis; Analysis 2.2).

#### Adverse events

The RCT (Kikuchi 2009) did not show any significant difference in the frequency of adverse events between the high-dose group (two out of 15 participants) and the low-dose groups (four out of 15 participants) (ITT analysis) (Analysis 2.3). Adverse events included allergic reaction (three participants), haemolysis (one participant), and anaemia (two participants).

### Sensitivity analysis and cost-benefit analysis

We planned to do sensitivity analysis for heterogeneous results by excluding outlying results. We could not identify any obvious outliers, and therefore did not perform this sensitivity analysis. Since there was only one RCT with adequate allocation concealment, which we did not include in a pooled analysis, we did not perform sensitivity analysis for this. Since we identified no high-quality data on effectiveness, we did not perform a cost-benefit analysis.

## DISCUSSION

This is an update of the original systematic review. Conclusions regarding efficacy outcomes did not change, whereas for adverse effects they did. Although numerous uncontrolled studies have found that urate oxidase can lower serum uric acid levels quickly and sometimes dramatically, we found little evidence from randomised controlled trials (RCTs) or controlled clinical trials (CCTs) supporting its effectiveness in preventing or treating tumour lysis syndrome (TLS) in children with cancer. Only two RCTs (Goldman 2001; Kikuchi 2009) and five CCTs (Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003) were available on the prophylaxis of tumour lysis syndrome. There is currently no trial evaluating urate oxidase for treatment of established tumour lysis syndrome.

### Summary of main results

#### Urate oxidase versus allopurinol

Six included studies compared urate oxidase with allopurinol for the prevention of tumour lysis syndrome. One study was an RCT (Goldman 2001), and the other five studies were CCTs (Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003). One CCT (Wössmann 2003) reported the incidence of clinical tumour lysis syndrome and did not find significant difference between the group that received Uricozyme and the group that received allopurinol. The RCT (Goldman 2001) showed no significant difference in all-cause mortality between the group that received rasburicase and the group that received allopurinol. The pooled result of the three CCTs (Rényi 2007; Sánchez Tatay 2010; Wössmann 2003) also showed no significant difference in all-cause mortality between the intervention and the control groups. The RCT (Goldman 2001) did not find any mortality due to TLS in either the intervention group or the control group. However, the pooled result of the three CCTs (Patte 2002; Rényi 2007; Sánchez Tatay 2010) showed a significantly lower mortality due to TLS in the group that received Uricozyme compared with the group that received allopurinol. The RCT (Goldman 2001) showed no significant difference in the frequency of renal failure between the intervention and the control groups. In contrast, pooled results of five CCTs (Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003) showed significantly lower frequency of renal failure requiring renal replacement therapy in participants who received urate oxidase compared with those who received allopurinol. However, heterogeneity was present in this analysis.

The RCT (Goldman 2001) showed significantly higher frequency of uric acid normalisation at four hours in the participants who received rasburicase compared with participants who received allopurinol. All included trials did not report the duration before normalisation of serum uric acid level. The RCT (Goldman 2001) reported a significantly lower AUC of serum uric acid at 4 days in the intervention group compared with the control group. Three CCTs reported serial uric acid levels (Pui 1997; Rényi 2007; Sánchez Tatay 2010). All three CCTs reported results on the first two days after urate oxidase, while two studies (Rényi 2007; Sánchez Tatay 2010) reported results up to four days, and one study (Rényi 2007) reported results up to 12 days. The pooled results showed significantly lower uric acid levels in the intervention group compared with the control group at two days, three days, four days, and seven days, but the differences were not significant at one day, five days, and 12 days. Heterogeneity was present in some of these analyses. The RCT (Goldman 2001) and three CCTs (Pui 1997; Rényi 2007; Sánchez Tatay 2010) reported frequency of adverse effects in the intervention and the control groups. The RCT showed no significant differences between the intervention and the control groups. The adverse event reported was haemolysis. The pooled results from the three CCTs showed significantly higher frequency of adverse effects in participants who received urate oxidase. Adverse events reported in the intervention group included allergic reaction (six participants), methaemoglobinaemia (one participant), fever (two participants), nausea (one participant), abdominal pain (one participant), and mucositis (two participants).

### High-dose versus low-dose urate oxidase

We included one RCT that compared high-dose versus low-dose rasburicase (Kikuchi 2009). The trial did not report the incidence of TLS. The trial reported no significant difference in all-cause mortality between the high-dose and the low-dose groups. There was no mortality due to TLS in both the high-dose and the low-dose groups. There was no renal failure due to TLS in both groups. There was no significant difference in normalisation of uric acid level between the high-dose and the low-dose groups. The included RCT did not report the duration before normalisation of serum uric acid level or the AUC of serum uric acid level. The trial reported the percentage reduction of uric acid level at four hours and did not find significant difference between the two groups. There was no significant difference in the frequency of adverse events between the two groups. Adverse events included allergic reaction (three participants), haemolysis (one participant), and anaemia (two participants).

## Overall completeness and applicability of evidence

Although urate oxidase is widely used in paediatric cancer patients for prevention of tumour lysis syndrome, high-quality evidence of its efficacy is limited. The only RCT comparing urate oxidase with allopurinol (Goldman 2001) did not report the important outcome of clinical tumour lysis syndrome. Although participants who received rasburicase had significantly lower exposure to uric acid (lower AUC and higher chance of uric acid normalisation) compared with participants who received allopurinol in the RCT (Goldman 2001), we were not entirely certain whether this translated into significant clinical benefits. Although hyperuricaemia is related to tumour lysis syndrome, this trial failed to show any significant difference between the treatment and the control groups in all-cause mortality or mortality related to tumour lysis syndrome or renal failure requiring renal replacement therapy. Because of the paucity of evidence from RCT, we also included CCTs in the current systematic review. However, all five CCTs identified were of unsatisfactory methodological quality. Although mortality due to tumour lysis syndrome and incidence of renal failure were found to be significantly lower in participants who received urate oxidase, the conclusion from CCTs has to be treated with caution in view of high risk of biases.

On the other hand, due to inadequate sample size in the existing trials, the absence of significant clinical benefits of urate oxidase may be a false negative result. Therefore, we cannot ignore the potential benefits of urate oxidase in children with malignancy based on the current available evidence, especially in view of its probable effectiveness in reducing serum uric acid, which is an important surrogate outcome. Further trials of larger sample size are needed to clarify the role of urate oxidase. Assuming a mortality rate of 0.9% (Annemans 2003a) and that urate oxidase is effective in reducing mortality by half, the number of cancer patients needed to treat to prevent one death is 223, and the sample size required to achieve a power of 80% in detecting a reduction in mortality at a 5% level of significance is estimated to be 856 patients.

There was only one RCT comparing different doses of rasburicase (Kikuchi 2009). The results were consistent with previous uncontrolled studies and controlled clinical trials; comparing rasburicase at 0.15 mg/kg and 0.2 mg/kg showed a dramatic reduction in serum uric acid level in both arms. However, the RCT did not report the important outcome of incidence of clinical tumour lysis syndrome, and this small trial was not adequately powered to address the other clinically important outcomes of mortality or renal failure. Although there was no significant difference in any of the outcomes between the two groups, we are not certain whether a higher and lower dose of rasburicase are really equivalent because of the small sample size. Likewise, there is uncertainly about whether the higher dose is associated with more adverse effects.

Although not eligible for inclusion in this review, there is a study that has addressed the cost-effectiveness of rasburicase (Annemans 2003b). This study concluded that rasburicase was cost-effective for prevention of tumour lysis syndrome in children, and rasburicase for the treatment of tumour lysis syndrome in children was cost-saving. However, this conclusion was based on the assumption that rasburicase is 60% to 100% effective in the prevention

of tumour lysis syndrome, which was not in fact based on high-quality trial evidence. As the effectiveness of urate oxidase in the prevention or treatment of tumour lysis syndrome has yet to be established, its cost-effectiveness remains uncertain.

### Quality of the evidence

Apart from limitations in the number of RCTs reporting clinically relevant outcomes and inadequate power to evaluate these outcomes, the trials included in the current review had a number of methodological flaws and were prone to bias. We considered none of the included studies to have low risk of bias in all aspects assessed. In both RCTs, the treatment and the control groups were not comparable at baseline, which casts doubt on the success of randomisation and increased the probability of confounding. One of the RCTs included did not report the random sequence generation or allocation concealment, which are important to minimise selection bias (Kikuchi 2009). The other RCT had more drop-outs in the control arm than in the treatment arm, which might have caused attrition bias (Goldman 2001). None of the included RCTs attempted to blind the participants, physicians, or outcome assessors, which might have introduced performance and detection biases. Trial protocols were not available, and it was uncertain whether there was reporting bias in the RCTs.

In addition, all five CCTs included were also of unsatisfactory methodological quality (Patte 2002; Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003). There was a high risk of selection bias as participants were not randomly allocated to treatment groups. Performance and detection biases were also likely as there was no blinding. Reporting bias was uncertain as trial protocols were not available. There was a high risk of attrition bas in one CCT, which had a lot of missing data (Rényi 2007). The results from the four historical controlled trials (Pui 1997; Rényi 2007; Sánchez Tatay 2010; Wössmann 2003) were prone to bias from the advancement of supportive care with time. The remaining CCT (Patte 2002) was actually a retrospective review of data from trials of chemotherapy protocols comparing different treatments from different study groups at different locations; therefore, it suffered from bias due to different practices in different centres. The intervention and comparison groups were not comparable at baseline in two studies, which might result in high risk of bias (Rényi 2007; Wössmann 2003). Two studies (Patte 2002; Sánchez Tatay 2010) did not report some important baseline characteristics, so comparability of the intervention and comparison groups was uncertain. None of the included CCTs took into consideration and adjusted for potential confounding factors in their analyses; hence, their results were susceptible to confounding by known and unknown factors.

### Potential biases in the review process

We focused our search to major English electronic databases; therefore, non-English literature might be underrepresented and missed in the review. Because the search was focused on RCTs and CCTs, we could have missed some further historical controlled trials. Publication bias was also possible.

### Agreements and disagreements with other studies or reviews

As far as we know, this is the only systematic review evaluating the effectiveness of urate oxidase for prevention and treatment of tumour lysis in children with cancer. There was a review on tumour lysis syndrome with targeted therapy and the role of rasburicase (Bose 2011). The authors performed a search on MEDLINE in February 2011 and included RCTs, CCTs, and single-arm studies of rasburicase in both children and adults. That review had a similar conclusion to the current review, that although there was a wealth of evidence suggesting that rasburicase is effective in correcting hyperuricaemia, prospective trials showing that it improves hard outcomes, such as acute renal failure, need for dialysis, and mortality, are lacking. More randomised controlled trials evaluating clinically relevant outcomes are needed.

## AUTHORS' CONCLUSIONS

### Implications for practice

Thus far, the paucity of high-quality studies precludes firm recommendations. Although there is some evidence that urate oxidase might be more effective than allopurinol in reducing the frequency of hyperuricaemia and the exposure to high serum uric acid, it is still uncertain whether the routine use of urate oxidase is effective for the prevention or treatment of tumour lysis syndrome, or a reduction in mortality or renal failure associated with tumour lysis syndrome in children with cancer. The potential benefit of urate oxidase might be its effectiveness in reducing serum uric acid, which is an important surrogate outcome. It is unclear which type of urate oxidase (rasburicase or Uricozyme) is superior in terms of efficacy and what dosage regimen or treatment duration is optimal. On the other hand, urate oxidase may be associated with potential adverse effects, such as haemolysis or hypersensitivity. Clinicians who wish to use urate oxidase should weigh the potential benefits of reducing serum uric acid levels and the uncertain benefits in preventing renal failure or mortality from tumour lysis syndrome against the potential risk of adverse effects.

### Implications for research

There is a paucity of evidence from randomised controlled trials assessing urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer. The existing trials

are of small size and low methodological quality. Further high-quality RCTs of larger sample size are needed to assess the effectiveness of urate oxidase in children, especially high-risk patients who are more likely to benefit. High-risk patients can include those with high tumour burden or turn-over (such as high initial white blood cell counts for leukaemia, or Burkitt lymphoma, high-stage lymphoma, or lymphoma with bulky disease), and patients with baseline hyperuricaemia, renal impairment, hypocalcaemia, or hypophosphataemia. Trials should assess patient-orientated outcomes, such as incidence of clinical tumour lysis syndrome, mortality, or frequency of renal failure. Although blinding of participants and clinicians for comparison of intravenous urate oxidase and oral allopurinol is difficult, it can be attempted with the use of a double placebo, to minimise performance biases. The effectiveness and safety of different forms of urate oxidase in different dosage regimens should also be investigated further.

## ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

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

**Goldman 2001**

| | |
|---|---|
| Methods | Design: RCT<br>Randomisation method: stratified randomisation, computer-generated randomisation code<br>Stratification factor: according to uric acid level (< 8 mg/dL or ≥ 8 mg/dL) |
| Participants | Inclusion criteria: paediatric participants < 18 years with leukaemia and lymphoma deemed to have a high risk of tumour lysis syndrome: Murphy stage III or IV non-Hodgkin's lymphoma, ALL with WBC ≥ 25,000/uL, childhood lymphoma or leukaemia with uric acid level of ≥ 8 mg/dL. Participants must have received chemotherapeutic agents not investigational in nature, with minimum life expectancy of 4 weeks, and ECOG performance scale ≤ 3 or Karnofsky scale ≥ 30%<br>Exclusion criteria: participants previously treated with rasburicase or Uricozyme, treatment with allopurinol within 7 days, significant history of documented asthma, atopy, or G6PD deficiency<br>Number of participants (intervention/comparison): 27/25<br>Number of boys (intervention/comparison): 16/18<br>Age (intervention/comparison): (mean) 7.1 (range = 0.3 to 17)/7.8 (range = 0.5 to 16) years<br>Underlying haematological malignancies (intervention/comparison): leukaemia 20/9; lymphoma 7/6<br>Baseline creatinine (intervention/comparison): (mean) 0.6 (SD 0.33)/0.61 (SD 0.3) mg/dL<br>Baseline uric acid (intervention/comparison): (mean) 7.7 (SD 3.5)/6.8 (SD 3.4) mg/dL<br>Baseline potassium (intervention/comparison): (mean) 4.18 (SD 0.71)/3.85 (SD 0.52) mg/dL<br>Baseline phosphate (intervention/comparison): (mean) 4.62 (SD 1.39)/4.15 (SD 1.11) mg/dL<br>Baseline calcium (intervention/comparison): (mean) 8.92 (SD 0.74)/8.67 (SD 0.7) mg/dL<br>Baseline LDH (intervention/comparison): (mean) 1599 (SD 1022)/1393 (SD 1438) U/L<br>Baseline WBC (intervention/comparison): (mean) 83.2 (SD 81)/91 (SD 115) x109/L |
| Interventions | Intervention (type of urate oxidase): rasburicase<br>Comparison (type of control): allopurinol<br>Treatment regime in intervention group: rasburicase 0.2 mg/kg ivi over 30 minutes daily for 5 to 7 days<br>Treatment regime in comparison group: allopurinol 300 mg/m²/day or 10 mg/kg/day divided every 8 hours for 5 to 7 days<br>Cointerventions: hydration 3 L/m²/day, iv sodium bicarbonate at investigator's discretion |
| Outcomes | • All-cause mortality<br>• Mortality due to tumour lysis syndrome<br>• Incidence of renal failure requiring renal replacement therapy |

**Goldman 2001** (*Continued*)

| | |
|---|---|
| | • Frequency of normalisation of serum uric acid level<br>• Area under curve (AUC) of serum uric acid level<br>• Frequency of adverse effects (haemolysis) |
| Notes | Duration of follow up: 2 weeks<br>Number of dropouts (intervention/comparison): 1 (haemolysis)/3 (2 died; 1 did not start chemotherapy)<br>Potential confounders were not described or adjusted<br>The 2 groups may not be comparable at baseline because serum uric acid level was higher in the treatment group<br>Whether outcomes were clearly defined: yes |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "...treatment (rasburicase or allopurinol) was randomly allocated to patients according to a computer-generated randomization code schema" |
| Allocation concealment (selection bias) | Low risk | Quote: "Via telephone entry, treatment (rasburicase or allopurinol) was randomly allocated to patients according to a computer-generated randomization code schema" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Participants knew which treatment they were allocated, and care providers knew which treatment a participant was allocated |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Outcome assessors knew which treatment participants were assigned as this was an open-label trial |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 4% of participants in the treatment group and 12% of participants in the control group did not complete treatment or follow up |
| Selective reporting (reporting bias) | Unclear risk | The study protocol was not available, and it was unclear whether there was selective reporting of outcomes |
| Other bias | High risk | The 2 groups may not be comparable at baseline because serum uric acid level was higher in the treatment group, which might introduce bias |

**Kikuchi 2009**

| | |
|---|---|
| Methods | Design: RCT<br>Randomisation method: central randomisation, details not available<br>Stratification factor: baseline body weight (< 10 or ≥ 10 kg) |
| Participants | Inclusion criteria: paediatric participants < 18 years with newly diagnosed haematological malignancies with hyperuricaemia (uric acid > 7.5 mg/dL for participants ≥ 13 years; uric acid > 6.5 mg/dL for participants < 13 years) or with a high tumour burden (defined as non-Hodgkin's lymphoma stage IV; NHL stage III with ≥ 1 lymph node or mass > 5 cm, or LDH ≥ 3 times the upper limit of normal) or acute leukaemia with WBC ≥ 50,000/mm³ and LDH ≥ 3 times the upper limit of normal<br>ECOG performance scale ≤ 3 or Lansky score ≥ 30<br>Life expectancy ≥ 45 days<br>Exclusion criteria: administration of allopurinol within 72 hours; known history of severe allergy, severe asthma, or both; low birth weight (< 2500 g) or gestational age < 37 weeks; previous therapy with urate oxidase; positive HBsAg, HCV antibodies, HIV-1 or HIV-2 antibodies; severe disorders of the liver or kidney (ALT > 5 times the upper limit of normal, total bilirubin > 3 times the upper limit of normal; creatinine > 3 times the upper limit of normal); uncontrollable infection including viral infection; G6PD deficiency; known family history of G6PD deficiency; known history of methaemoglobinaemia and haemolysis<br>Number of participants (low-dose group/high-dose group): 15/15<br>Number of boys (low-dose group/high-dose group): 9/10<br>Age (low-dose group/high-dose group): (median) 11 (range = 1 to 17)/7 (range = 0 to 16) years<br>Underlying haematological malignancies (low-dose group/high-dose group): acute leukaemia 9/13; lymphoma 6/2<br>Baseline hyperuricaemia (low-dose group/high-dose group): 8/5<br>Baseline creatinine (low-dose group/high-dose group): (mean) 52.3 (SD 22.6)/44.4 (SD 19.1) mg/dL |
| Interventions | Intervention (type of urate oxidase): rasburicase in both groups (0.15 mg/kg versus 0.2 mg/kg)<br>Treatment regime in low-dose group: rasburicase 0.15 mg/kg ivi over 30 minutes daily for 5 days<br>Treatment regime in high-dose group: rasburicase 0.2 mg/kg ivi over 30 minutes daily for 5 days<br>Cointerventions: chemotherapy started 4 to 24 hours after the first dose of rasburicase in both groups |
| Outcomes | • All-cause mortality<br>• Mortality due to tumour lysis syndrome<br>• Incidence of renal failure requiring renal replacement therapy<br>• Frequency of normalisation of serum uric acid level<br>• Serial uric acid levels<br>• Frequency of adverse events |
| Notes | Duration of follow up: 5 weeks<br>Number of dropouts (low-dose group/high-dose group): 1 (3 concomitant grade 4 adverse events)/1 (lack of WBC result at baseline) |

**Kikuchi 2009** (*Continued*)

| | |
|---|---|
| | The 2 groups may not be comparable at baseline because body weight was higher in the low-dose group; baseline hyperuricaemia and diagnosis of lymphoma were more frequent in the low-dose group<br>Whether outcomes were clearly defined: yes |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Participants were randomly allocated to the 2 treatment groups by central randomisation, but details were not available |
| Allocation concealment (selection bias) | Unclear risk | This was not mentioned |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Participants knew which treatment they were allocated, and care providers knew which treatment a participant was allocated |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Outcome assessors knew which treatment participants were assigned as this was an open-label trial |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 6.7% of each group of participants did not complete treatment or follow up, which were explained. The low proportion of dropout is unlikely to cause significant bias |
| Selective reporting (reporting bias) | Unclear risk | The study protocol was not available, and it was unclear whether there was selective reporting of outcomes |
| Other bias | High risk | The 2 groups may not be comparable at baseline because body weight was higher in the low-dose group; baseline hyperuricaemia and diagnosis of lymphoma were more frequent in the low-dose group |

**Patte 2002**

| | |
|---|---|
| Methods | Design: CCT<br>Stratification factor: not applicable |
| Participants | Inclusion criteria: paediatric participants with stage III and IV B-cell NHL or L3 ALL treated with the LMB89 protocol (intervention group), paediatric participants with stage IV B-cell NHL or ALL treated with UKCCSG protocol (comparison group 1), or paediatric participants with stage IV B-cell NHL or ALL treated with POG protocol (comparison group 2) |

**Patte 2002** (*Continued*)

| | |
|---|---|
| | Exclusion criteria: participants not treated in France excluded from intervention group<br>Number of participants (intervention/comparison 1/comparison 2): 152/63/123<br>Number of boys (intervention/comparison 1/comparison 2): not available<br>Age (intervention/comparison 1/comparison 2): not available<br>Underlying haematological malignancies: only data for intervention group available: B-NHL stage III 257 out of 410; B-NHL stage IV 57 out of 410; L3 ALL 96 out of 410<br>Baseline renal failure (intervention/comparison 1/comparison 2): 21/410/not available<br>Baseline elevated LDH $\geq$ 2 x normal (intervention/comparison 1/comparison 2): 234/410/not available |
| Interventions | Intervention (type of urate oxidase): Uricozyme<br>Comparison 1 and 2 (type of control): allopurinol<br>Treatment regime in intervention group: Uricozyme 50 to 100 U/kg/day for 5 to 7 days<br>Treatment regime in comparison groups: not available<br>Cointerventions: intervention group: alkaline hyperhydration 3 L/m²/day to obtain urine output 100 to 120 ml/m²/hour and urine pH 7; not stated in comparison groups |
| Outcomes | • Mortality due to tumour lysis syndrome<br>• Incidence of renal failure requiring renal replacement therapy |
| Notes | Duration of follow up: 7 days<br>Number of dropouts (intervention/comparison 1/comparison 2): 0/0/0<br>Potential confounders were not described or adjusted<br>Comparability of the treatment groups at baseline was uncertain because some important baseline characteristics of comparison groups were not available<br>Whether outcomes were clearly defined: yes |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | High risk | This was not a randomised controlled trial |
| Allocation concealment (selection bias) | High risk | This was not a randomised controlled trial, and no allocation concealment was used |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Blinding was not used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Blinding was not used |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | The outcome data were complete for the groups of participants analysed |

**Patte 2002** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | The study protocol was not available, and it was unclear whether there was selective reporting of outcomes |
| Other bias | High risk | Comparability of the treatment groups at baseline was uncertain because baseline characteristics of comparison groups were not available. Potential confounders were not adjusted. Chemotherapy treatments were different in different centres in different locations, which may cause bias |

**Pui 1997**

| | |
|---|---|
| Methods | Design: CCT<br>Stratification factor: not applicable |
| Participants | Inclusion criteria: paediatric participants with non-B-cell ALL<br>Exclusion criteria: participants with history of allergy, G6PD deficiency or pregnancy, or who had not received methotrexate or 6-mercaptopurine as preinduction therapy<br>Number of participants (intervention/comparison): 119/129<br>Number of boys (intervention/comparison): not available<br>Age (intervention/comparison): (median) 5.6/5.7 years<br>Underlying haematological malignancies (intervention/comparison): all non-B-cell ALL<br>Baseline WBC (intervention/comparison): (median) 11.7/13.8 x$10^9$ /L<br>Baseline uric acid (intervention/comparison): (median) 4.3/4.3 mg/dL<br>Baseline lactate dehydrogenase (intervention/comparison): (median) 1243/957 U/L<br>Baseline BUN (intervention/comparison): (median) 8.0/8.0 mg/dL<br>Baseline creatinine (intervention/comparison): (median) 0.5/0.5 mg/dL<br>Baseline calcium (intervention/comparison): (median) 9.4/9.4 mg/dL<br>Baseline phosphate (intervention/comparison): (median) 4.9/4.7 mg/dL |
| Interventions | Intervention (type of urate oxidase): Uricozyme<br>Comparison (type of control): allopurinol<br>Treatment regime in intervention group: Uricozyme 100 units/kg ivi over 30 minutes daily for 5 days<br>Treatment regime in comparison group: allopurinol 300 mg/m²/day po for 5 to 13 days<br>Cointerventions: hydration with $NaHCO_3$ to maintain urine pH $\geq$ 6.5; oral phosphate binders (aluminium hydroxide or calcium carbonate) were given to participants as indicated |
| Outcomes | • Incidence of renal failure requiring renal replacement therapy<br>• Serial uric acid levels<br>• Frequency of adverse effects |
| Notes | Duration of follow up: 13 days<br>Number of dropouts (intervention/comparison): 0/0<br>Potential confounders were adjusted |

**Pui 1997** (*Continued*)

| | |
|---|---|
| | The intervention and the control groups appeared comparable at baseline<br>Whether outcomes were clearly defined: yes<br>The report of adverse events included additional 15 participants who had received an incomplete course of Uricozyme |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | High risk | This was not a randomised controlled trial |
| Allocation concealment (selection bias) | High risk | This was not a randomised controlled trial, and no allocation concealment was used |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Blinding was not used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Blinding was not used |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | The outcome data were complete for the groups of participants analysed |
| Selective reporting (reporting bias) | Unclear risk | The study protocol was not available, and it was unclear whether there was selective reporting of outcomes |
| Other bias | High risk | Potential confounders were not adjusted. Use of historical control may bias the results in favour of the newer treatment because of improvement in supportive care |

**Rényi 2007**

| | |
|---|---|
| Methods | Design: CCT<br>Stratification factor: not applicable |
| Participants | Inclusion criteria: paediatric participants aged 6 months to 18 years with a recent diagnosis of B-cell lineage ALL with an initial WBC $\geq$ 25,000/uL, or high-grade non-Hodgkin's lymphoma, or any type of ALL or NHL with a plasma uric acid $\geq$ 480 mmol/L and LDH > 500 IU/L, or either a creatinine or an LDH concentration > twice the upper limit of normal<br>Exclusion criteria: history of clinically significant atopic allergy, bronchial asthma, G6PD deficiency or any type of haemolytic anaemia, previous treatment with rasburicase or non-recombinant urate oxidase, hypersensitivity reaction against ingredients of the present |

| | |
|---|---|
| | preparation used in the study, participation in another drug experiment, pregnancy or lactation<br>Number of participants (intervention/comparison): 12/14<br>Number of boys (intervention/comparison): 6/6<br>Age (intervention/comparison): (median) 4.5/6<br>Underlying haematological malignancies (intervention/comparison): leukaemia 8/13; lymphoma 4/1<br>Baseline creatinine (intervention/comparison): median 65 (range = 32 to 85)/80 (range = 17 to 353) umol/L<br>Baseline uric acid (intervention/comparison): median 323 (range = 139 to 1059)/207 (range = 51 to 785) umol/L<br>Baseline phosphate (intervention/comparison): median 1.32 (range = 0.97 to 1.64)/1.62 (range = 0.98 to 1.33) mmol/L<br>Baseline LDH (intervention/comparison): 1909 (range = 497 to 9760)/3193 (236 to 20,560) U/L<br>Baseline WBC (intervention/comparison): 51.8 (range = 2 to 651)/56 (range = 0.4 to 551) x109/L |
| Interventions | Intervention (type of urate oxidase): rasburicase<br>Comparison (type of control): allopurinol<br>Treatment regime in intervention group: rasburicase 0.2 mg/kg ivi over 30 minutes daily for 5 days from day 1 of antineoplastic treatment<br>Treatment regime in comparison group: allopurinol 300 mg/m²/day or 10 mg/kg/day divided every 8 hours for 5 to 7 days<br>Cointerventions: hydration 3 L/m²/day, iv sodium bicarbonate 20 to 40 mmol/L to maintain urine pH 6.5 to 7 |
| Outcomes | • All-cause mortality<br>• Mortality due to tumour lysis syndrome<br>• Incidence of renal failure requiring renal replacement therapy<br>• Serial uric acid levels<br>• Frequency of adverse effects |
| Notes | Duration of follow up: 12 days<br>Number of dropouts (intervention/comparison): 0/0<br>Potential confounders were not described or adjusted<br>The 2 groups may not be comparable at baseline because the treatment group had more participants with lymphoma, higher uric acid level, lower LDH level, lower serum creatinine, and phosphorus<br>Whether outcomes were clearly defined: yes<br>The report of adverse events included additional 24 participants who had received rasburicase in other centres |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | High risk | This was not a randomised controlled trial |

**Rényi 2007** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment (selection bias) | High risk | This was not a randomised controlled trial, and no allocation concealment was used |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Blinding was not used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Blinding was not used |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Serum uric acid data at 24 to 288 hours post-treatment were missing in 6 to 12 participants (43% to 86%) |
| Selective reporting (reporting bias) | Unclear risk | The study protocol was not available, and it was unclear whether there was selective reporting of outcomes |
| Other bias | High risk | The 2 groups may not be comparable at baseline because the treatment group had more participants with lymphoma, higher uric acid level, lower LDH level, lower serum creatinine, and phosphorus. Potential confounders were not adjusted. Use of historical control may bias the results in favour of the newer treatment because of improvement in supportive care |

**Sánchez Tatay 2010**

| | |
|---|---|
| Methods | Design: CCT<br>Stratification factor: not applicable |
| Participants | Inclusion criteria: paediatric participants with haematological malignancies with tumour lysis syndrome or at risk of tumour lysis syndrome, with at least 1 of the following criteria: WBC > 50,000/uL or lactate dehydrogenase > 500 U/L; uric acid level ≥8 mg/dL or creatinine > 2 mg/dL; history of tumour lysis syndrome in previous cycles of chemotherapy<br>Exclusion criteria: participants with history of hypersensitivity to rasburicase or allopurinol, asthma, atopy, G6PD deficiency, or other metabolic causes of haemolytic anaemia<br>Number of participants (intervention/comparison): 16/16<br>Number of boys (intervention/comparison): not available<br>Age (intervention/comparison): not available<br>Underlying haematological malignancies (intervention/comparison): not available<br>Baseline uric acid (intervention/comparison): (median) 10.6 (SD 3.2)/11.3 (SD 5.8) mg/dL<br>Baseline creatinine (intervention/comparison): (median) 0.93 (SD 0.81)/1.01 (SD 0. |

**Sánchez Tatay 2010** (*Continued*)

| | |
|---|---|
| | 51) mg/dL<br>Baseline phosphate (intervention/comparison): (median) 6.28 (SD 2.29)/6.72 (SD 5. 02) mg/dL |
| Interventions | Intervention (type of urate oxidase): rasburicase<br>Comparison (type of control): allopurinol<br>Treatment regime in intervention group: rasburicase 0.2 mg/kg ivi daily (duration of treatment was not mentioned)<br>Treatment regime in comparison group: allopurinol 10 mg/kg/day divided every 8 hours (duration of treatment was not mentioned)<br>Cointerventions: not mentioned |
| Outcomes | • All-cause mortality<br>• Mortality due to tumour lysis syndrome<br>• Incidence of renal failure requiring renal replacement therapy<br>• Serial uric acid levels<br>• Frequency of adverse effects |
| Notes | Duration of follow up: 4 days<br>Number of dropouts (intervention/comparison): 0/0<br>Potential confounders were not described or adjusted<br>Comparability of the treatment groups at baseline was uncertain because some important baseline characteristics of comparison groups were not available<br>Whether outcomes were clearly defined: yes |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | High risk | This was not a randomised controlled trial |
| Allocation concealment (selection bias) | High risk | This was not a randomised controlled trial, and no allocation concealment was used |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Blinding was not used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Blinding was not used |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | The outcome data were complete for the groups of participants analysed |
| Selective reporting (reporting bias) | Unclear risk | The study protocol was not available, and it was unclear whether there was selective reporting of outcomes |

**Sánchez Tatay 2010** (*Continued*)

| | | |
|---|---|---|
| Other bias | High risk | Comparability of the treatment groups at baseline was uncertain because some important baseline characteristics of comparison groups were not available. Potential confounders were not adjusted. Use of historical control may bias the results in favour of the newer treatment because of improvement in supportive care |

**Wössmann 2003**

| | |
|---|---|
| Methods | Design: CCT<br>Stratification factor: not applicable |
| Participants | Inclusion criteria: paediatric participants ≤ 18 years with B-ALL or stage III and IV B-NHL and LDH ≥ 500 U/L treated in the trials NHL-BFM 90 and 95, during the period November 1997 to December 2001 (intervention group) or April 1990 to March 1996 (comparison group)<br>Exclusion criteria: nil<br>Number of participants (intervention/comparison): 130/218<br>Number of boys (intervention/comparison): N/A<br>Age (intervention/comparison): N/A<br>Underlying haematological malignancies: B-ALL 53/78; B-NHL 77/140<br>Baseline elevated LDH > 1000 U/L (intervention/comparison): 49.6%/47.2% |
| Interventions | Intervention (type of urate oxidase): Uricozyme<br>Comparison (type of control): allopurinol and alkalinisation<br>Treatment regime in intervention group: Uricozyme 3 x 50 U/kg/day for 3 to 4 days<br>Treatment regime in comparison group: allopurinol 10 mg/kg/day + alkalinisation to maintain urine pH 7<br>Cointerventions: hydration 3 to 4.5 L/m²/day |
| Outcomes | • Incidence of clinical tumour lysis syndrome<br>• All-cause mortality<br>• Incidence of renal failure requiring renal replacement therapy |
| Notes | Duration of follow up not reported<br>Number of dropouts (intervention/comparison): 0/0<br>Potential confounders were not described or adjusted<br>The 2 groups may not be comparable at baseline because the treatment group had fewer participants who were critically ill or had complications after initial surgery<br>Whether outcomes were clearly defined: yes |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|

**Wössmann 2003** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | High risk | This was not a randomised controlled trial |
| Allocation concealment (selection bias) | High risk | This was not a randomised controlled trial, and no allocation concealment was used |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Blinding was not used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Blinding was not used |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | The outcome data were complete for the groups of participants analysed |
| Selective reporting (reporting bias) | Unclear risk | The study protocol was not available, and it was unclear whether there was selective reporting of outcomes |
| Other bias | High risk | The 2 groups may not be comparable at baseline because the treatment group had fewer participants who were critically ill or had complications after initial surgery. Potential confounders were not adjusted. Use of historical control may bias the results in favour of the newer treatment because of improvement in supportive care |

*ALL:acutelymphoblasticleukaemia.*
*ALT:alanineaminotransferase.*
*B−NHL:Bcellnon−Hodgkinlymphoma.*
*BUN:bloodureanitrogen.*
*CCT:controlledclinicaltrial.*
*ECOG:EasternCooperativeOncologyGroup.*
*G6PD:glucose−6−phosphatedehydrogenasedeficiency.*
*HBsAg:hepatitisBvirussurfaceantigen.*
*HCV:hepatitisCvirus.*
*iv:intravenous.*
*ivi:intravenousinfusion.*
*LDH:lactatedehydrogenase.*
*N/A:informationnotavailable.*
*NHL:non−Hodgkinlymphoma.*
*Po:takenorally.*
*RCT:randomisedcontrolledtrial.*
*SD:standarddeviation.*
*WBC:whitebloodcell(count).*

*UKCCSG:UnitedKingdomChildren'sCancerStudyGroup.*

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

| Study | Reason for exclusion |
|---|---|
| Cortes 2010 | This was an RCT recruiting adult participants only and no paediatric participants |
| Ishizawa 2009 | This was an RCT recruiting adult participants only and no paediatric participants |
| Vadhan-Raj 2012 | This was an RCT recruiting adult participants only and no paediatric participants |

*RCT:randomisedcontrolledtrial.*

## Characteristics of ongoing studies *[ordered by study ID]*

**NCT00199043**

| | |
|---|---|
| Trial name or title | Randomised phase III trial of effectivity and safety of rasburicase compared with allopurinol for treatment of hyperuricemia in patients with acute lymphoblastic leukemia or high-grade NHL with high risk of tumour lysis syndrome (> 15 yrs) |
| Methods | RCT |
| Participants | Participants aged above 15 years, participating in the GMALL B-ALL/NHL-Study 2002; the GMALL-Study 07/2003; or the GMALL-Study Elderly 1/2003 that fulfil the following criteria: bulky disease (> 7.5 cm) , high LDH (> 2 times the upper limit of normal), uric acid > 8 mg/dl (> 475 µmol/L) at diagnosis, and leukocytes > 30000/µL |
| Interventions | Arm 1: allopurinol<br>Arm 2: rasburicase |
| Outcomes | Primary outcomes: renal function, uric acid, electrolytes, adverse events, mortality in pre-phase and the 2 following cycles of chemotherapy, time and dose compliance of chemotherapy<br>Secondary outcomes: response rate, incidence of tumour lysis syndrome |
| Starting date | May 2003 |
| Contact information | Dieter Hoelzer, University Hospital, Medical Dept. II, Frankfurt, Germany, 60590 |
| Notes | Study completed. Results not available yet. Not all participants are eligible for this review (for example, elderly participants may be included in this study) |

**NCT01200485**

| | |
|---|---|
| Trial name or title | A randomized phase 2 study to evaluate the efficacy of rasburicase in patients at risk for TLS during two cycles of chemotherapy |
| Methods | RCT |
| Participants | Participants that are high risk for TLS or potential/intermediate risk for TLS as described below: (a) High risk: Hyperuricaemia of malignancy (uric acid levels > 7.5 mg/dL); or diagnosis of very aggressive lymphoma/leukaemia based on Revised European-American Lymphoma (REAL) classification; acute myeloid leukaemia, CML in blast crisis; high-grade myelodysplastic syndrome only if they have > 10% bone marrow blast involvement and given aggressive treatment similar to acute myeloid leukaemia. (B) Potential risk: Diagnosis of aggressive lymphoma/leukaemia based on REAL classification, plus 1 or more of the following criteria: lactate dehydrogenase >/= 2 times the upper limit of normal; stage III to IV disease; stage I to II disease with at least 1 lymph node/tumour > 5 cm in diameter. For participants with potential/intermediate risk for TLS, only those planned to receive alternating regimens (or non-standard regimens) in 2 cycles (example; R-Hyper-CVAD alternating with MTX/ARA-C) will be eligible |
| Interventions | Arm A: Cycle 2 chemotherapy, rasburicase 0.15 mg/kg IV day 1, additional dose on days 2 to 5 at physician's discretion<br>Arm B: Cycle 2 chemotherapy, allopurinol 300 mg/day IV days 1 to 5 + rasburicase 0.15 mg/kg IV day 1 if uric acid blood levels dictate single dose or more |
| Outcomes | Primary outcome: Incidence of laboratory tumour lysis syndrome during cycle 2 (as defined by the Cairo-Bishop criteria) |
| Starting date | May 2011 |
| Contact information | Saroj Vadhan-Raj, UT MD Anderson Cancer Center, Houston, Texas, United States, 77030<br>Telephone: +1 713 792 7966 |
| Notes | Ongoing study recruiting participants. Not all participants are eligible for this review (for example, elderly participants may be included in this study) |

*CML:chronicmyelogenousleukaemia.*

*R−Hyper−CVAD:chemotherapyregimenconsistingofrituximab,cyclophosphamide,vincristine,adriamycin,dexamethasone.*

*LDH:lactatedehydrogenase.*

*MTX/ARA−C:methotrexateandcytarabine.*

*NHL:non−Hodgkinlymphoma.*

*RCT:randomisedcontrolledtrial.*

*TLS:tumourlysissyndrome.*

## DATA AND ANALYSES

### Comparison 1. Urate oxidase compared with allopurinol

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Incidence of clinical tumour lysis syndrome | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.1 CCT | 1 | 348 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.44, 1.33] |
| 2 Incidence of clinical tumour lysis syndrome in B-ALL subgroup | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.1 CCT | 1 | 131 | Risk Ratio (M-H, Fixed, 95% CI) | 0.46 [0.18, 1.18] |
| 3 All-cause mortality | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.1 CCT | 3 | 406 | Risk Ratio (M-H, Fixed, 95% CI) | 0.19 [0.01, 3.42] |
| 4 Mortality due to tumour lysis syndrome | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 4.1 CCT | 3 | 396 | Risk Ratio (M-H, Fixed, 95% CI) | 0.05 [0.00, 0.89] |
| 5 Renal failure requiring renal replacement therapy | 5 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 5.1 CCT | 5 | 992 | Risk Ratio (M-H, Random, 95% CI) | 0.26 [0.08, 0.89] |
| 6 Renal failure requiring renal replacement therapy in B-ALL subgroup | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.1 CCT | 1 | 131 | Risk Ratio (M-H, Fixed, 95% CI) | 0.25 [0.06, 1.05] |
| 7 AUC of serum uric acid level at 4 days | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 7.1 RCT | 1 | 52 | Mean Difference (IV, Fixed, 95% CI) | -201.0 [-258.05, -143.95] |
| 8 AUC of serum uric acid level at 4 days in leukaemia participants | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 8.1 RCT | 1 | 39 | Mean Difference (IV, Fixed, 95% CI) | -220.0 [-286.67, -153.33] |
| 9 AUC of serum uric acid level at 4 days in lymphoma participants | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 9.1 RCT | 1 | 13 | Mean Difference (IV, Fixed, 95% CI) | -132.0 [-185.47, -78.53] |
| 10 AUC of serum uric acid level at 4 days in hyperuricemic participants | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 10.1 RCT | 1 | 19 | Mean Difference (IV, Fixed, 95% CI) | -278.0 [-373.69, -182.31] |
| 11 AUC of serum uric acid level at 4 days in normouricemic participants | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 11.1 RCT | 1 | 33 | Mean Difference (IV, Fixed, 95% CI) | -240.0 [-340.95, -139.05] |
| 12 Serum uric acid level at 1 day | 3 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 12.1 CCT | 3 | 298 | Mean Difference (IV, Random, 95% CI) | -3.00 [-7.61, 1.60] |

| | | | | |
|---|---|---|---|---|
| 13 Serum uric acid level at 2 days | 3 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 13.1 CCT | 3 | 294 | Mean Difference (IV, Random, 95% CI) | -3.80 [-7.37, -0.24] |
| 14 Serum uric acid level at 3 days | 2 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 14.1 CCT | 2 | 47 | Mean Difference (IV, Random, 95% CI) | -3.13 [-6.12, -0.14] |
| 15 Serum uric acid level at 4 days | 2 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 15.1 CCT | 2 | 45 | Mean Difference (IV, Fixed, 95% CI) | -4.6 [-6.39, -2.81] |
| 16 Serum uric acid level at 5 days | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 16.1 CCT | 1 | 14 | Mean Difference (IV, Fixed, 95% CI) | -1.02 [-2.24, 0.20] |
| 17 Serum uric acid level at 7 days | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 17.1 CCT | 1 | 16 | Mean Difference (IV, Fixed, 95% CI) | -1.74 [-3.01, -0.47] |
| 18 Serum uric acid level at 12 days | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 18.1 CCT | 1 | 20 | Mean Difference (IV, Fixed, 95% CI) | -0.80 [-2.51, 0.91] |
| 19 Frequency of adverse events | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 19.1 CCT | 3 | 345 | Risk Ratio (M-H, Fixed, 95% CI) | 9.10 [1.29, 64.00] |

## Comparison 2. High-dose urate oxidase compared with low-dose urate oxidase

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Normalisation of serum uric acid | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.1 RCT | 1 | 29 | Risk Ratio (M-H, Fixed, 95% CI) | 1.07 [0.89, 1.28] |
| 2 Percentage reduction in serum uric acid level at 4 hours | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 2.1 RCT | 1 | 29 | Mean Difference (IV, Fixed, 95% CI) | 8.10 [-0.99, 17.19] |
| 3 Frequency of adverse events | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.1 RCT | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.5 [0.11, 2.33] |

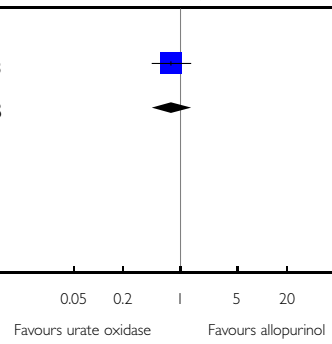
### Analysis 1.1. Comparison 1 Urate oxidase compared with allopurinol, Outcome 1 Incidence of clinical tumour lysis syndrome.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 1 Incidence of clinical tumour lysis syndrome

| Study or subgroup | Urate oxidase n/N | Allopurinol n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 CCT | | | | | |
| Wössmann 2003 | 16/130 | 35/218 | | 100.0 % | 0.77 [ 0.44, 1.33 ] |
| **Subtotal (95% CI)** | **130** | **218** | | **100.0 %** | **0.77 [ 0.44, 1.33 ]** |
| Total events: 16 (Urate oxidase), 35 (Allopurinol) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.95 (P = 0.34) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

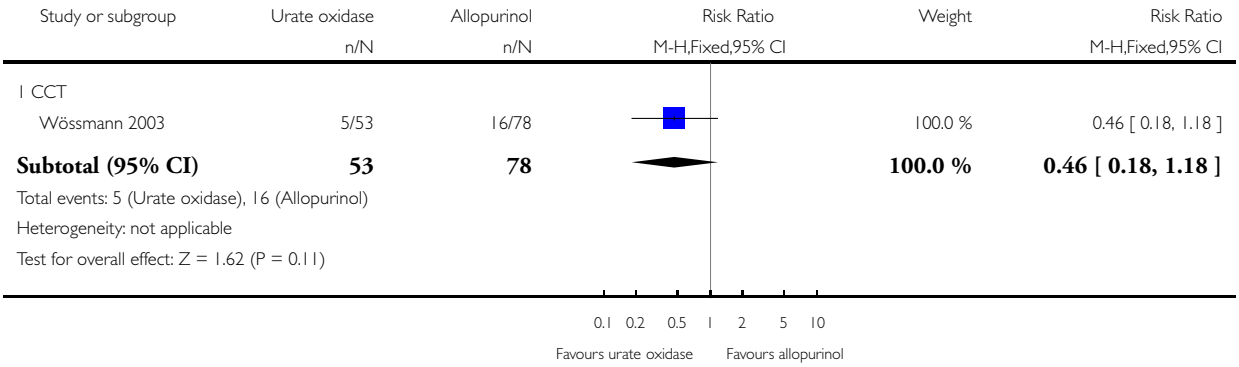


### Analysis 1.2. Comparison 1 Urate oxidase compared with allopurinol, Outcome 2 Incidence of clinical tumour lysis syndrome in B-ALL subgroup.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 2 Incidence of clinical tumour lysis syndrome in B-ALL subgroup

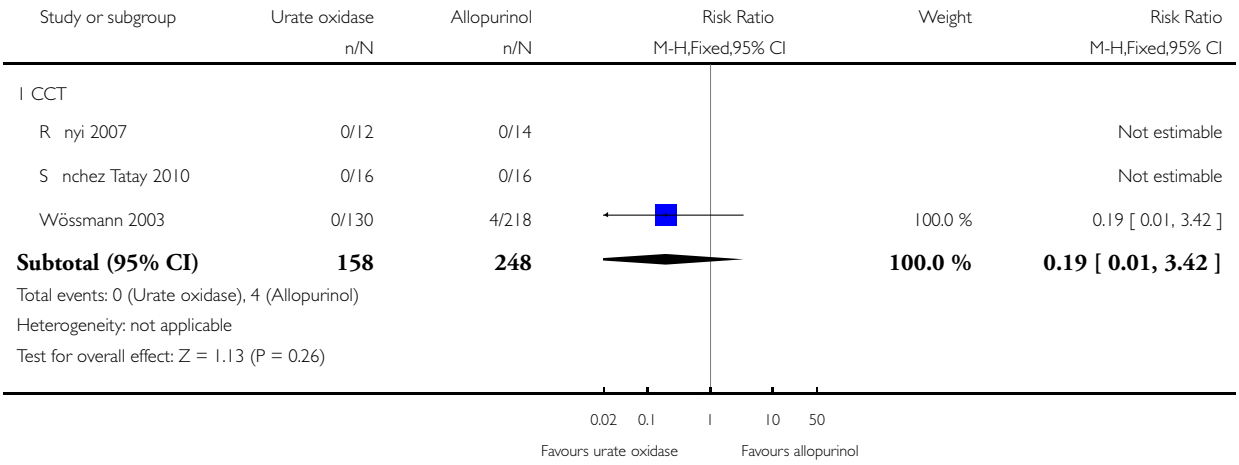


### Analysis 1.3. Comparison 1 Urate oxidase compared with allopurinol, Outcome 3 All-cause mortality.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 3 All-cause mortality



### Analysis 1.4. Comparison 1 Urate oxidase compared with allopurinol, Outcome 4 Mortality due to tumour lysis syndrome.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 4 Mortality due to tumour lysis syndrome

| Study or subgroup | Urate oxidase n/N | Allopurinol n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 CCT | | | | | |
| Patte 2002 | 0/152 | 11/186 | | 100.0 % | 0.05 [ 0.00, 0.89 ] |
| R nyi 2007 | 0/12 | 0/14 | | | Not estimable |
| S nchez Tatay 2010 | 0/16 | 0/16 | | | Not estimable |
| **Subtotal (95% CI)** | **180** | **216** | | **100.0 %** | **0.05 [ 0.00, 0.89 ]** |
| Total events: 0 (Urate oxidase), 11 (Allopurinol) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.04 (P = 0.042) | | | | | |

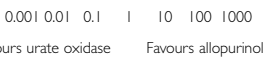
## Analysis 1.5. Comparison 1 Urate oxidase compared with allopurinol, Outcome 5 Renal failure requiring renal replacement therapy.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 5 Renal failure requiring renal replacement therapy

| Study or subgroup | Urate oxidase n/N | Allopurinol n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 CCT | | | | | |
| Patte 2002 | 4/152 | 38/186 | | 35.6 % | 0.13 [ 0.05, 0.35 ] |
| Pui 1997 | 0/119 | 0/129 | | | Not estimable |
| R nyi 2007 | 0/12 | 1/14 | | 11.6 % | 0.38 [ 0.02, 8.65 ] |
| S nchez Tatay 2010 | 0/16 | 6/16 | | 13.6 % | 0.08 [ 0.00, 1.26 ] |
| Wössmann 2003 | 8/130 | 20/218 | | 39.2 % | 0.67 [ 0.30, 1.48 ] |
| **Subtotal (95% CI)** | **429** | **563** | | **100.0 %** | **0.26 [ 0.08, 0.89 ]** |
| Total events: 12 (Urate oxidase), 65 (Allopurinol) | | | | | |
| Heterogeneity: $Tau^2 = 0.83$; $Chi^2 = 7.96$, df = 3 (P = 0.05); $I^2 = 62\%$ | | | | | |
| Test for overall effect: Z = 2.15 (P = 0.031) | | | | | |



### Analysis 1.6. Comparison 1 Urate oxidase compared with allopurinol, Outcome 6 Renal failure requiring renal replacement therapy in B-ALL subgroup.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 6 Renal failure requiring renal replacement therapy in B-ALL subgroup

| Study or subgroup | Urate oxidase n/N | Allopurinol n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 CCT | | | | | |
| Wössmann 2003 | 2/53 | 12/78 | | 100.0 % | 0.25 [ 0.06, 1.05 ] |
| **Subtotal (95% CI)** | **53** | **78** | | **100.0 %** | **0.25 [ 0.06, 1.05 ]** |
| Total events: 2 (Urate oxidase), 12 (Allopurinol) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.89 (P = 0.058) | | | | | |

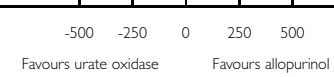

### Analysis 1.7. Comparison 1 Urate oxidase compared with allopurinol, Outcome 7 AUC of serum uric acid level at 4 days.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 7 AUC of serum uric acid level at 4 days

| Study or subgroup | Urate oxidase N | Mean(SD) | Allopurinol N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 RCT | | | | | | | |
| Goldman 2001 | 27 | 128 (70) | 25 | 329 (129) | | 100.0 % | -201.00 [ -258.05, -143.95 ] |
| **Subtotal (95% CI)** | **27** | | **25** | | | **100.0 %** | **-201.00 [ -258.05, -143.95 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 6.91 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

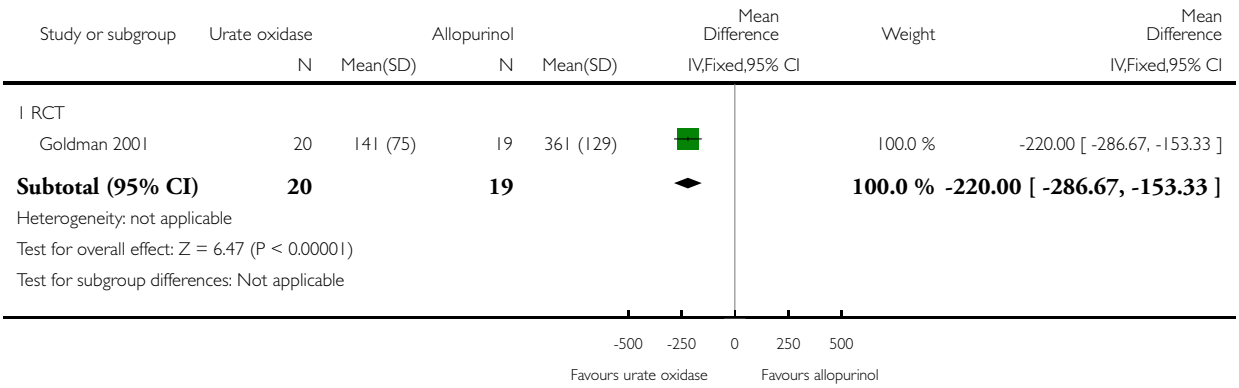


## Analysis 1.8. Comparison 1 Urate oxidase compared with allopurinol, Outcome 8 AUC of serum uric acid level at 4 days in leukaemia participants.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 8 AUC of serum uric acid level at 4 days in leukaemia participants

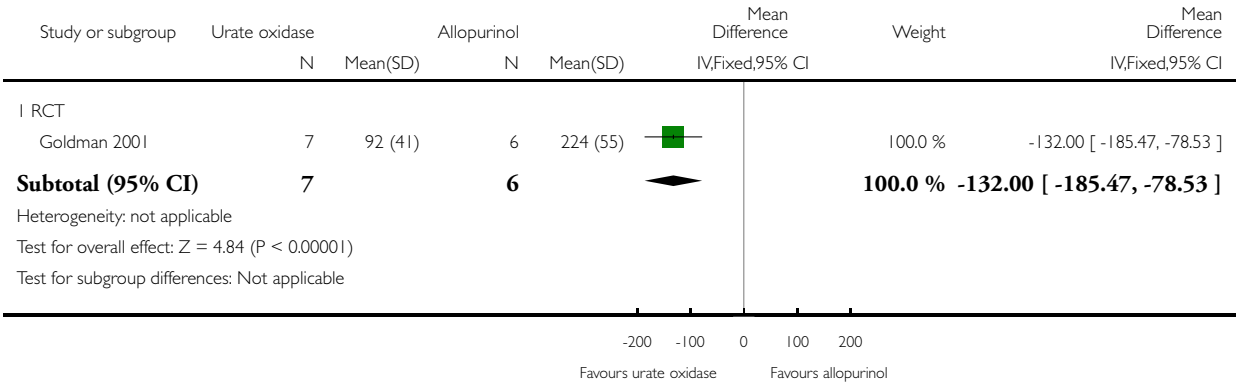


### Analysis 1.9. Comparison 1 Urate oxidase compared with allopurinol, Outcome 9 AUC of serum uric acid level at 4 days in lymphoma participants.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 9 AUC of serum uric acid level at 4 days in lymphoma participants

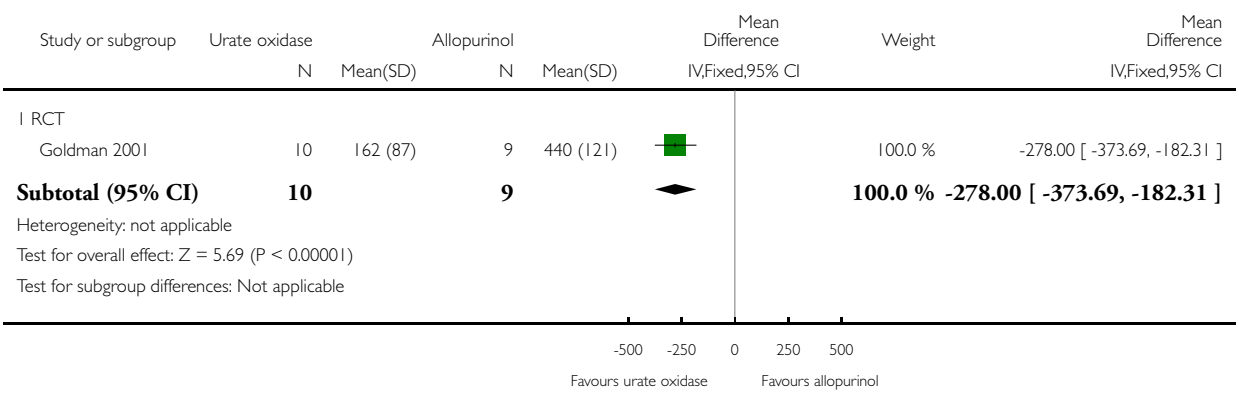



### Analysis 1.10. Comparison 1 Urate oxidase compared with allopurinol, Outcome 10 AUC of serum uric acid level at 4 days in hyperuricemic participants.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 10 AUC of serum uric acid level at 4 days in hyperuricemic participants

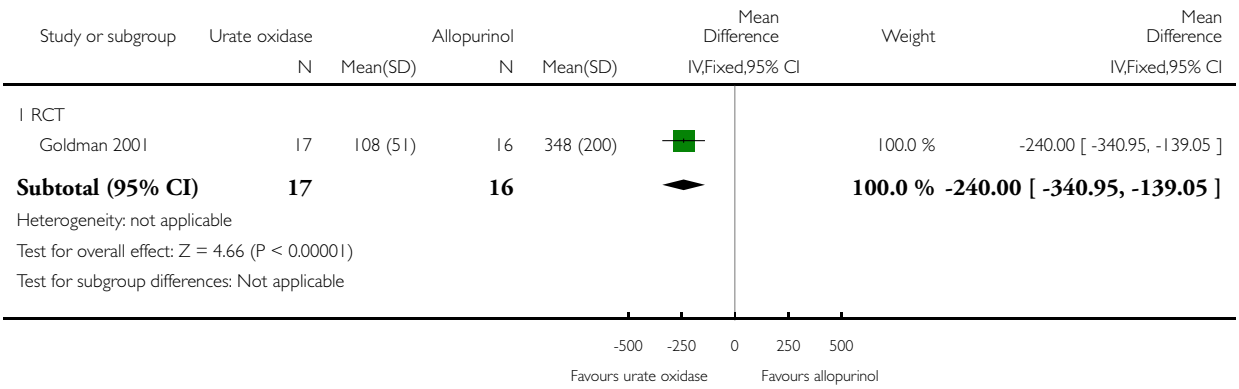


### Analysis 1.11. Comparison 1 Urate oxidase compared with allopurinol, Outcome 11 AUC of serum uric acid level at 4 days in normouricemic participants.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 11 AUC of serum uric acid level at 4 days in normouricemic participants



## Analysis 1.12. Comparison 1 Urate oxidase compared with allopurinol, Outcome 12 Serum uric acid level at 1 day.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 12 Serum uric acid level at 1 day

| Study or subgroup | Urate oxidase N | Mean(SD) | Allopurinol N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 CCT | | | | | | | |
| Pui 1997 | 119 | 1 (3.81) | 129 | 3.4 (5.64) | | 36.1 % | -2.40 [ -3.59, -1.21 ] |
| R nyi 2007 | 12 | 6.17 (3.38) | 6 | 4.12 (4.54) | | 28.6 % | 2.05 [ -2.06, 6.16 ] |
| S nchez Tatay 2010 | 16 | 0.5 (1.7) | 16 | 8.2 (2.8) | | 35.4 % | -7.70 [ -9.31, -6.09 ] |
| **Subtotal (95% CI)** | **147** | | **151** | | | **100.0 %** | **-3.00 [ -7.61, 1.60 ]** |

Heterogeneity: $Tau^2$ = 14.92; $Chi^2$ = 35.69, df = 2 (P<0.00001); $I^2$ =94%

Test for overall effect: Z = 1.28 (P = 0.20)

Test for subgroup differences: Not applicable

## Analysis 1.13. Comparison 1 Urate oxidase compared with allopurinol, Outcome 13 Serum uric acid level at 2 days.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 13 Serum uric acid level at 2 days

| Study or subgroup | Urate oxidase N | Mean(SD) | Allopurinol N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 CCT | | | | | | | |
| Pui 1997 | 119 | 1.1 (3.57) | 129 | 2.8 (4.73) | | 41.3 % | -1.70 [ -2.74, -0.66 ] |
| R nyi 2007 | 12 | 0.98 (1.38) | 2 | 4.63 (3.91) | | 21.3 % | -3.65 [ -9.12, 1.82 ] |
| S nchez Tatay 2010 | 16 | 0.5 (1.5) | 16 | 6.7 (3.9) | | 37.5 % | -6.20 [ -8.25, -4.15 ] |
| **Subtotal (95% CI)** | **147** | | **147** | | | **100.0 %** | **-3.80 [ -7.37, -0.24 ]** |

Heterogeneity: $Tau^2 = 7.74$; $Chi^2 = 14.89$, df = 2 (P = 0.00058); $I^2 = 87\%$

Test for overall effect: Z = 2.09 (P = 0.037)

Test for subgroup differences: Not applicable

## Analysis 1.14. Comparison 1 Urate oxidase compared with allopurinol, Outcome 14 Serum uric acid level at 3 days.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 14 Serum uric acid level at 3 days

| Study or subgroup | Urate oxidase N | Mean(SD) | Allopurinol N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 CCT | | | | | | | |
| R nyi 2007 | 12 | 0.67 (0.64) | 3 | 2.32 (1.03) | | 51.5 % | -1.65 [ -2.87, -0.43 ] |
| S nchez Tatay 2010 | 16 | 0.4 (0.7) | 16 | 5.1 (3.2) | | 48.5 % | -4.70 [ -6.31, -3.09 ] |
| **Subtotal (95% CI)** | **28** | | **19** | | | **100.0 %** | **-3.13 [ -6.12, -0.14 ]** |

Heterogeneity: $Tau^2 = 4.12$; $Chi^2 = 8.79$, df = 1 (P = 0.003); $I^2 = 89\%$

Test for overall effect: Z = 2.05 (P = 0.040)

Test for subgroup differences: Not applicable

## Analysis 1.15. Comparison 1 Urate oxidase compared with allopurinol, Outcome 15 Serum uric acid level at 4 days.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 15 Serum uric acid level at 4 days

| Study or subgroup | Urate oxidase N | Mean(SD) | Allopurinol N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 CCT | | | | | | | |
| R nyi 2007 | 12 | 0.3 (0.3) | 1 | 1.43 (0) | | | Not estimable |
| S nchez Tatay 2010 | 16 | 0.2 (0.6) | 16 | 4.8 (3.6) | | 100.0 % | -4.60 [ -6.39, -2.81 ] |
| **Subtotal (95% CI)** | **28** | | **17** | | | **100.0 %** | **-4.60 [ -6.39, -2.81 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 5.04 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

## Analysis 1.16. Comparison 1 Urate oxidase compared with allopurinol, Outcome 16 Serum uric acid level at 5 days.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 16 Serum uric acid level at 5 days

| Study or subgroup | Urate oxidase N | Mean(SD) | Allopurinol N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 CCT | | | | | | | |
| R nyi 2007 | 12 | 0.44 (0.48) | 2 | 1.46 (0.86) | | 100.0 % | -1.02 [ -2.24, 0.20 ] |
| **Subtotal (95% CI)** | **12** | | **2** | | | **100.0 %** | **-1.02 [ -2.24, 0.20 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 1.64 (P = 0.10)

Test for subgroup differences: Not applicable


## Analysis 1.17. Comparison 1 Urate oxidase compared with allopurinol, Outcome 17 Serum uric acid level at 7 days.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

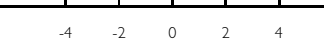
Outcome: 17 Serum uric acid level at 7 days

| Study or subgroup | Urate oxidase N | Mean(SD) | Allopurinol N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 CCT | | | | | | | |
| R nyi 2007 | 12 | 1.43 (1.06) | 4 | 3.17 (1.14) | | 100.0 % | -1.74 [ -3.01, -0.47 ] |
| **Subtotal (95% CI)** | **12** | | **4** | | | **100.0 %** | **-1.74 [ -3.01, -0.47 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 2.69 (P = 0.0072)

Test for subgroup differences: Not applicable



## Analysis 1.18. Comparison 1 Urate oxidase compared with allopurinol, Outcome 18 Serum uric acid level at 12 days.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 18 Serum uric acid level at 12 days

| Study or subgroup | Urate oxidase N | Mean(SD) | Allopurinol N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 CCT | | | | | | | |
| R nyi 2007 | 12 | 2.34 (1.49) | 8 | 3.14 (2.14) | | 100.0 % | -0.80 [ -2.51, 0.91 ] |
| **Subtotal (95% CI)** | **12** | | **8** | | | **100.0 %** | **-0.80 [ -2.51, 0.91 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.92 (P = 0.36)

Test for subgroup differences: Not applicable

## Analysis 1.19. Comparison 1 Urate oxidase compared with allopurinol, Outcome 19 Frequency of adverse events.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 1 Urate oxidase compared with allopurinol

Outcome: 19 Frequency of adverse events

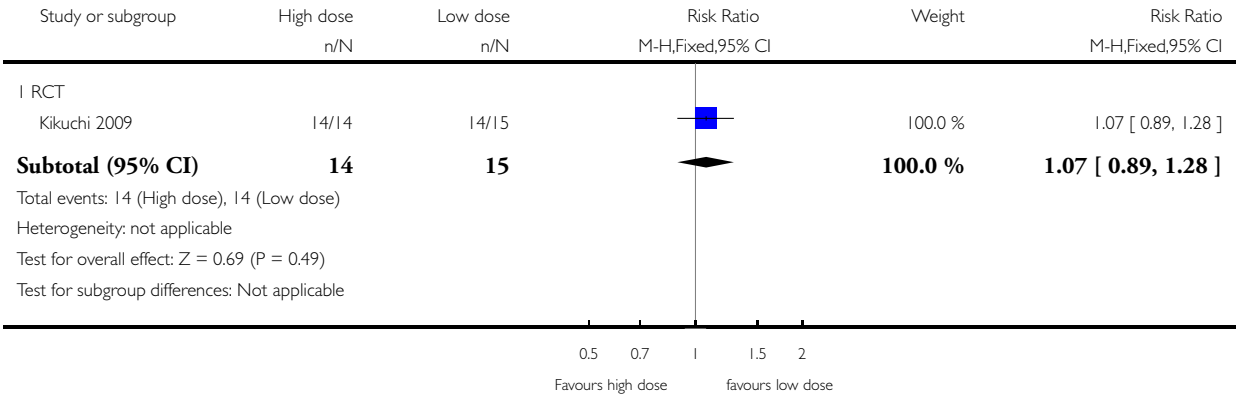
| Study or subgroup | Urate oxidase n/N | Allopurinol n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 CCT | | | | | |
| Pui 1997 | 7/134 | 0/129 | | 41.7 % | 14.44 [ 0.83, 250.35 ] |
| R nyi 2007 | 6/36 | 0/14 | | 58.3 % | 5.27 [ 0.32, 87.82 ] |
| S nchez Tatay 2010 | 0/16 | 0/16 | | | Not estimable |
| **Subtotal (95% CI)** | **186** | **159** | | **100.0 %** | **9.10 [ 1.29, 64.00 ]** |
| Total events: 13 (Urate oxidase), 0 (Allopurinol) | | | | | |
| Heterogeneity: $Chi^2 = 0.25$, df = 1 (P = 0.62); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 2.22 (P = 0.027) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

### Analysis 2.1. Comparison 2 High-dose urate oxidase compared with low-dose urate oxidase, Outcome 1 Normalisation of serum uric acid.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 2 High-dose urate oxidase compared with low-dose urate oxidase

Outcome: 1 Normalisation of serum uric acid

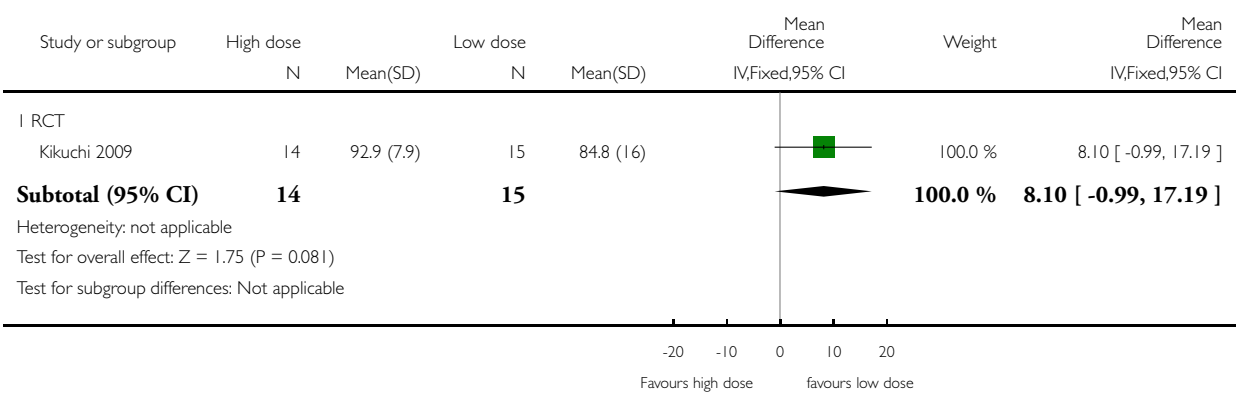



### Analysis 2.2. Comparison 2 High-dose urate oxidase compared with low-dose urate oxidase, Outcome 2 Percentage reduction in serum uric acid level at 4 hours.

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 2 High-dose urate oxidase compared with low-dose urate oxidase

Outcome: 2 Percentage reduction in serum uric acid level at 4 hours

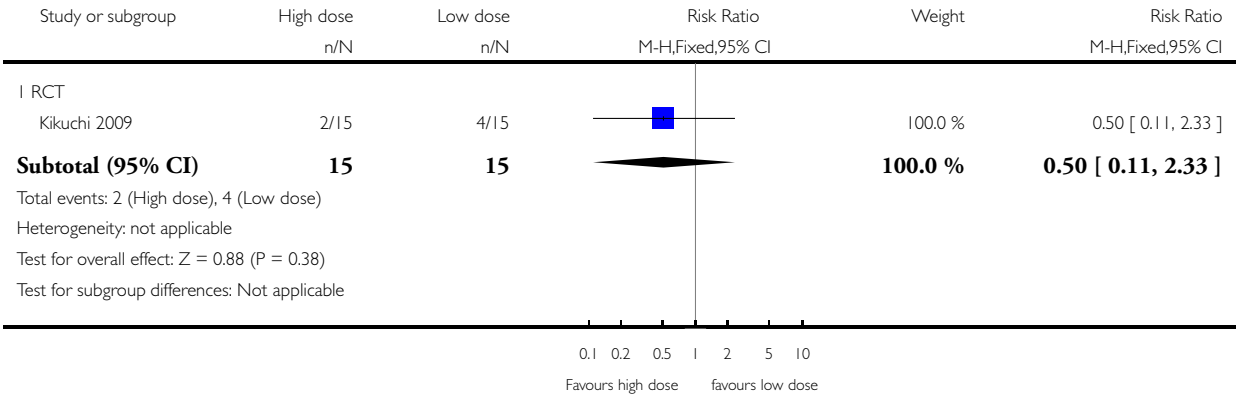


**Analysis 2.3. Comparison 2 High-dose urate oxidase compared with low-dose urate oxidase, Outcome 3 Frequency of adverse events.**

Review: Urate oxidase for the prevention and treatment of tumour lysis syndrome in children with cancer

Comparison: 2 High-dose urate oxidase compared with low-dose urate oxidase

Outcome: 3 Frequency of adverse events




# APPENDICES

## Appendix 1. Search strategy for Cochrane Central Register of Controlled Trials (CENTRAL)

The following text words were used:
urate oxidase OR uricase OR uricas* rasburicase OR rasburicas* OR elitek OR fasturtec OR fasturt* OR uox
The search was performed in title, abstract or keywords
[*=zero or more characters]

## Appendix 2. Search strategy for PubMed

**1.** For **Urate oxidase** the following MeSH headings and text words were used:
urate oxidase OR uricase OR uricas* OR oxidase, urate OR EC 1.7.3.3. OR rasburicase OR rasburicas* OR elitek OR fasturtec OR fasturt* OR uox
**2.** For **Children** the following MeSH headings and text words were used:
infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery OR infant, newborn
**3.** For **Cochrane RCTs/CCTs** the following MeSH headings and text words were used in the original version of the review:
(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:NoExp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT humans [mh]))
For the update in 2013 the following search strategy for identifying **RCTs and CCTs** was used:
((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) AND (humans[mh])
Final search: 1 AND 2 AND 3
[CCT = controlled clinical trial; RCT = randomized controlled trial; mh = Medical Subject Heading (MeSH) term; pt =publication type; tw: text word]

## Appendix 3. Search strategy for Embase (OVID)

**1.** For **Urate oxidase** the following Emtree terms and text words were used:
1. urate oxidase.mp. or Urate Oxidase/
2. (rasburicase or uox).mp.
3. (uricase or elitek).mp.
4. (9002-12-4 or 352311-12-7).rn. or EC 1733.mp.
5. (uricas$ or rasburicas$ or fasturtec or fasturt$).mp.
6. or/1-5
**2.** For **Children** the following Emtree terms and text words were used:
1. infant/ or infancy/ or newborn/ or baby/ or child/ or preschool child/ or school child/
2. adolescent/ or juvenile/ or boy/ or girl/ or puberty/ or prepuberty/ or pediatrics/
3. primary school/ or high school/ or kindergarten/ or nursery school/ or school/
4. or/1-3
5. (infant$ or (newborn$ or new born$) or (baby or baby$ or babies) or neonate$).mp.
6. (child$ or (school child$ or schoolchild$) or (school age$ or schoolage$) or (pre school$ or preschool$)).mp.
7. (kid or kids or toddler$ or adoles$ or teen$ or boy$ or girl$).mp.
8. (minors$ or (under ag$ or underage$) or juvenil$ or youth$).mp.
9. (puber$ or pubescen$ or prepubescen$ or prepubert$).mp.
10. (pediatric$ or paediatric$ or peadiatric$).mp.
11. (school or schools or (high school$ or highschool$) or primary school$ or nursery school$ or elementary school or secondary school$ or kindergar$).mp.
12. or/5-11
13. 4 or 12
**3.** For **RCTs/CCTs** the following Emtree terms and text words were used in the original version of the review:
1. Clinical Trial/

2. Controlled Study/
3. Randomized Controlled Trial/
4. Double Blind Procedure/
5. Single Blind Procedure/
6. Comparative Study/
7. RANDOMIZATION/
8. Prospective Study/
9. PLACEBO/
10. Phase 2 Clinical Trial/
11. phase 3 clinical study.mp.
12. phase 4 clinical study.mp.
13. Phase 3 Clinical Trial/
14. Phase 4 Clinical Trial/
15. or/1-14
16. allocat$.mp.
17. blind$.mp.
18. control$.mp.
19. placebo$.mp.
20. prospectiv$.mp.
21. random$.mp.
22. ((singl$ or doubl$ or trebl$ or tripl$) and (blind$ or mask$)).mp.
23. (versus or vs).mp.
24. (randomized controlled trial$ or randomised controlled trial$).mp.
25. controlled clinical trial$.mp.
26. clinical trial$.mp.
27. or/16-27
28. Human/
29. Nonhuman/
30. ANIMAL/
31. Animal Experiment/
32. or/29-31
33. 32 not 28
34. (15 or 27) not 33

For the update in 2013 the following search strategy for identifying **RCTs and CCTs** was used:

1. Randomized Controlled Trial/
2. Controlled Clinical Trial/
3. randomized.ti,ab.
4. placebo.ti,ab.
5. randomly.ti,ab.
6. trial.ti,ab.
7. groups.ti,ab.
8. drug therapy.sh.
9. or/1-8
10. Human/
11. 9 and 10

Final search: 1 and 2 and 3 (Urate oxidase AND Children AND RCT)

[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; sh = subject heading; ti,ab = title, abstract; / = Emtree term; $ = zero or more characters; rn = registry number; RCT = randomized controlled trial; CCT = controlled clinical trial]

## Appendix 4. Search strategy for CINAHL

**1.** For **Urate oxidase** the following text words were used:
urate oxidase OR rasburicase OR uox OR uricase OR elitek OR fasfurtec
**2.** For **Children** the following text words were used:
neonate OR infant OR newborn OR baby OR child OR preschool OR school OR adolescent OR juvenile OR boy OR girl OR puberty OR pediatric OR kindergarten OR nursery OR kid OR minors
**3.** For **RCTs/CCTs** the following text words were used:
trial OR control OR placebo OR random OR prospective study OR comparative study
In the final search the three searches were combined: 1 AND 2 AND 3

# WHAT'S NEW

Last assessed as up-to-date: 26 February 2013.

| Date | Event | Description |
|---|---|---|
| 1 August 2013 | New citation required and conclusions have changed | Two new studies were found and included in the update. Conclusions regarding efficacy outcomes did not change, whereas for adverse effects they did |
| 26 February 2013 | New search has been performed | The search for eligible studies was updated to February 2013 |

# HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 6, 2010

| Date | Event | Description |
|---|---|---|
| 17 June 2008 | Amended | Converted to new review format. |

# CONTRIBUTIONS OF AUTHORS

Cheuk DKL: protocol development, searching for trials, quality assessment of trials, data extraction, data input, data analyses, development of final review, corresponding author.

Chiang AKS: protocol development, quality assessment of trials, data extraction, data input, data analyses, development of final review.

Chan GCF: protocol development, development of final review.

Ha SY: protocol development, development of final review.

## DECLARATIONS OF INTEREST

Daniel KL Cheuk: nothing to declare.

Alan KS Chiang: nothing to declare.

Godfrey CF Chan: nothing to declare.

Shau Yin Ha: nothing to declare.

## SOURCES OF SUPPORT


### Internal sources

- The Library of The University of Hong Kong, Hong Kong.

The Library of The University of Hong Kong provided support in retrieving full-texts of studies.

### External sources

- No sources of support supplied


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We used the mean difference for continuous outcomes instead of the weighted mean difference. We updated the 'Risk of bias' assessment according to the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (version 5.1.0). We still reported outcomes with less than 70% of participants' data, but we considered them to be prone to bias. We did not calculate RR if there was only one study available for a particular outcome and there was no event in one of the groups; we used the Fisher's exact test (performed using SPSS 19) to determine the P value in such situations. In this update, we changed the unit of uric acid measurements to mg/dL, instead of micromol/L in the original review, as mg/dL appeared to be more widely used.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Allopurinol [therapeutic use]; Antimetabolites [therapeutic use]; Area Under Curve; Controlled Clinical Trials as Topic; Neoplasms [*drug therapy]; Randomized Controlled Trials as Topic; Renal Insufficiency [prevention & control]; Tumor Lysis Syndrome [mortality; *prevention & control]; Urate Oxidase [adverse effects; *therapeutic use]; Uric Acid [blood]

### MeSH check words

Adolescent; Child; Humans