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Cochrane Commentaries

Corticosteroid therapy for nephrotic syndrome in children

Edited by Angela Webster (angela.webster@sydney.edu.au)
Written by Deirdre Hahn (deidre.hahn@health.nsw.gov.au) and Elisabeth Hodson (elisabeth.hodson@health.nsw.gov.au)

What is this review about?

This systematic review summarizes the randomized controlled trials (RCTs) evaluating the benefits and harms of corticosteroids in children with their initial episode of steroid-sensitive nephrotic syndrome (SSNS) and in children with frequently relapsing disease (FRNS). This is the fourth update of the review, which was first published in 2000 and updated in 2003, 2005 and 2007 with the addition of new studies.

What are the findings?

Initial episode of SSNS

In previous versions of this review, studies found that prednisone duration exceeding 3 months compared with 2 or 3 months significantly reduced the risk of relapse and of FRNS. However, three RCTs published in 2013 and 2015 found no significant benefit of increasing prednisone duration beyond 2 or 3 months. When these new studies were included in meta-analyses, the number of children developing FRNS were significantly reduced in children treated for 3 months or more compared with 2 months (six studies, 582 children: risk ratio 0.68; 95% confidence interval (CI) 0.47–1.00), but not in children treated for 5–6 months *versus* 3 months (five studies, 591 children: RR 0.78; 95% CI 0.50–1.22). However, there was now substantial heterogeneity among the studies (I^2 36–83%), which had not been present in the earlier versions of the review. Studies at high or unclear risk of bias for allocation concealment and blinding may overestimate the benefit of an intervention. In subgroup analyses (Figs 1,2) we found that studies at low risk of bias for allocation concealment showed no

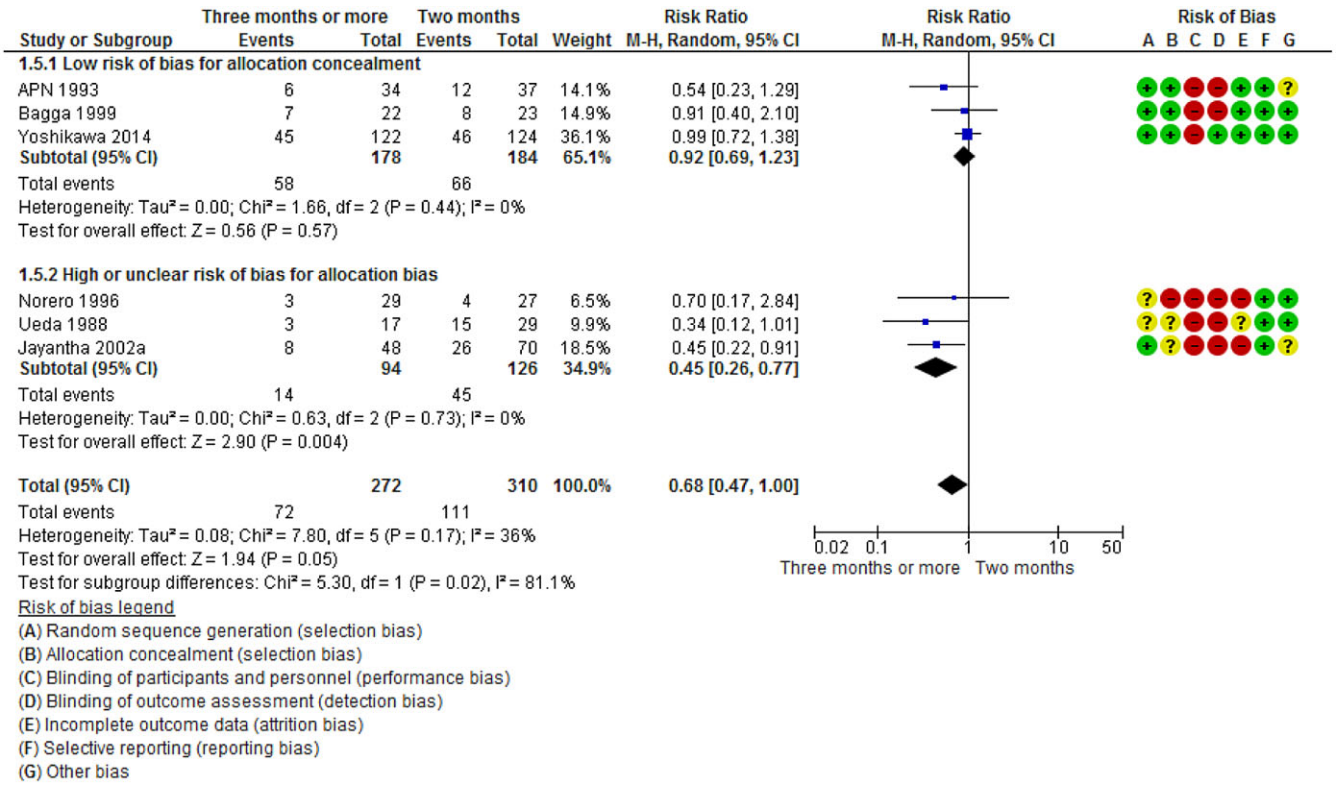

Fig. 1 The risk of developing frequently relapsing nephrotic syndrome in trials comparing three months or more of prednisone therapy *versus* 2 months in the first episode of steroid-sensitive nephrotic syndrome. In the risk of bias assessment, green indicates low risk of bias, red indicates high risk of bias and yellow indicates unclear risk of bias. CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel statistical method.

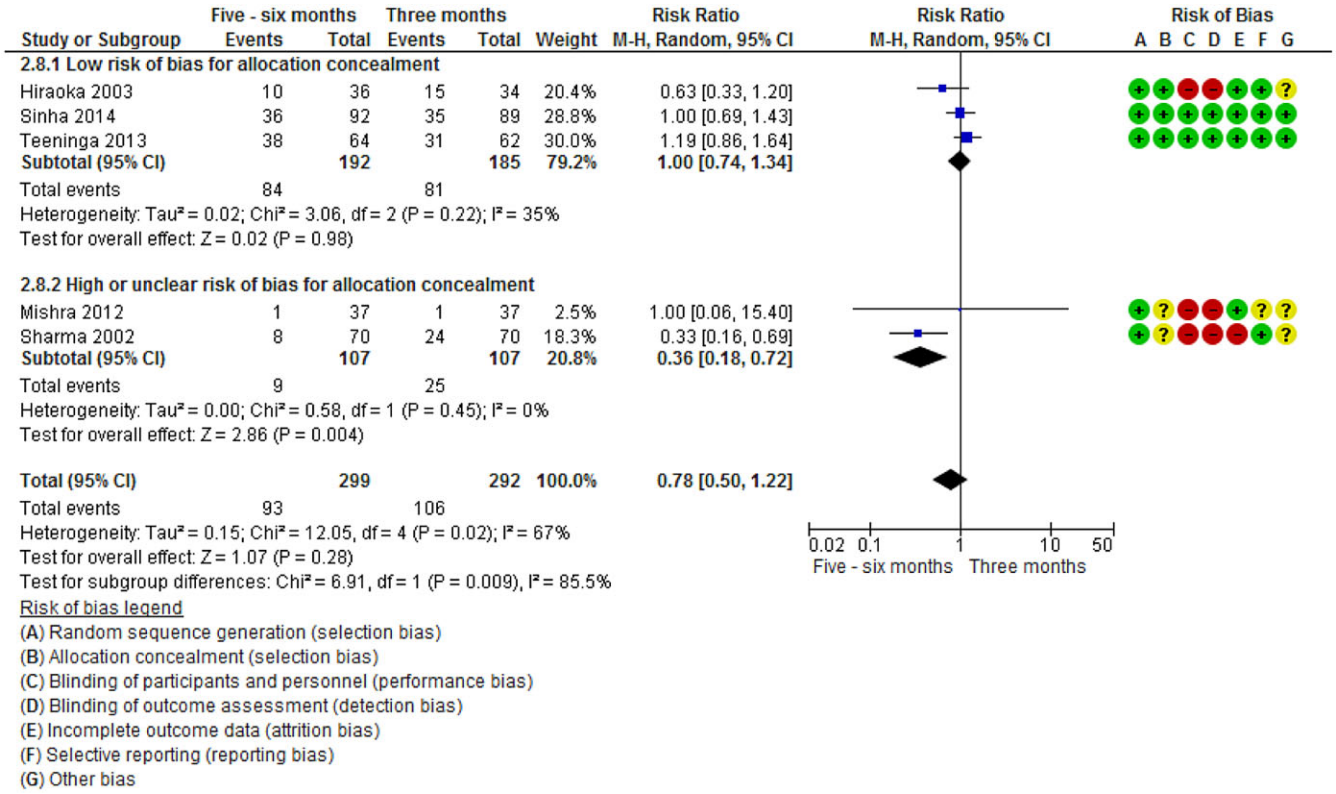

Fig. 2 The risk of developing frequently relapsing nephrotic syndrome in trials comparing 5 or 6 months of prednisone therapy *versus* 3 months in the first episode of steroid-sensitive nephrotic syndrome. In the risk of bias assessment, green indicates low risk of bias, red indicates high risk of bias and yellow indicates unclear risk of bias. CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel statistical method.

significant differences in the risk of FRNS between extended duration prednisone *versus* 2 or 3 months. However, in studies at high or unclear risk of bias, extended duration prednisone significantly reduced the risk of FRNS *versus* 2 or 3 months. Similar results were found in subgroup analyses based on study performance, detection and attrition bias. Thus, the heterogeneity among the studies can be explained by differences in methodological quality (risk of bias). Therefore, in the initial episode of SSNS, there is no significant benefit of extending prednisone therapy beyond 2 or 3 months based on data from new well-designed studies.

Relapsing SSNS

In four studies (219 children) from emerging countries, administering prednisone daily at the onset of an infection for 5–7 days reduced the risk of relapse compared with alternate day-therapy (three studies) or placebo (one study). Because of different study designs and end points, the data could not be combined in meta-analyses. The results of a fourth study from the UK with a planned enrolment of 300 children are awaited.

What are the findings based on?

The systematic review included 34 RCTs with 3033 participants; 21 studies evaluated prednisone therapy in the initial episode of SSNS while 14 studies evaluated different regimens in relapsing SSNS. The methodological quality of studies overall was moderate. Of the 34 studies, 18 and 16 studies reported adequate sequence generation and allocation concealment, respectively. In the initial episode of SSNS, eight studies evaluated 2 months of prednisone compared with 3 months or more while seven studies evaluated three months of prednisone compared with 5 or 6 months. None of these studies evaluated lower induction doses of prednisone than the International Study of Kidney Disease in Children recommended dose of 60 mg/m^2/day. Four studies examined other durations or doses of prednisone. Two studies compared prednisone alone with prednisone with cyclosporin or azithromycin; both concluded that addition of these agents did not improve outcomes. In relapsing nephrotic syndrome, there were few data with only 648 evaluated patients. Four studies examined the benefit of daily prednisone to prevent relapse during infection while the remaining nine studies examined a variety of different regimens aimed at maintain-

ing remission. There were no studies examining the use of long-term low-dose alternate-day prednisone in FRNS, although this regimen is commonly used and is recommended in guidelines. Adverse effects were poorly reported in general. In particular, few studies reported on psychological disturbances with prednisone and none reported on quality of life.

Implications for practice

- Children in their initial episode of SSNS should be treated with prednisone for 2 or 3 months since RCTs of high methodological quality show no benefit of extending prednisone duration beyond 3 months.
- In children with frequently relapsing SSNS, administering low-dose daily prednisone for 5–7 days at the onset of infection reduces the risk of infection-related relapse.

Clinical perspective

Corticosteroids remain the first treatment for children presenting with idiopathic nephrotic syndrome and to induce remission in relapses of SSNS. New data from well-designed RCTs, which showed no benefit of continuing prednisone in the initial episode of SSNS beyond 2 or 3 months, have resulted in a change to the conclusions of the systematic review. There are additional data supporting giving low-dose daily prednisone at the onset of an infection to reduce the risk of relapse so this management strategy may be considered in children with frequently relapsing disease.

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