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## Effects of Corticosteroid on Henoch-Schönlein Purpura: A Systematic Review

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### Abstract

**OBJECTIVE**—No consensus exists among general pediatricians or pediatric rheumatologists regarding whether corticosteroid therapy ameliorates the acute manifestations of Henoch-Schönlein purpura or mitigates renal injury. Therefore, we sought to synthesize the reported experimental and observational data regarding corticosteroid use.

**METHODS**—We performed a meta-analysis based on a comprehensive review of the literature in the Medline database (1956 to January 2007) and the Cochrane Controlled Trials Register. On the basis of reported outcomes among patients with Henoch-Schönlein purpura who were treated at diagnosis with corticosteroids compared with patients treated with supportive care only, we calculated odds ratios for the resolution of abdominal pain, the need for surgical intervention secondary to severe pain or intussusception, the likelihood of Henoch-Schönlein purpura recurrence, and the development of transient or persistent renal disease.

**RESULTS**—Of 201 articles retrieved from the initial literature search, 15 were eligible for inclusion. Corticosteroid treatment did not reduce the median time to resolution of abdominal pain but did significantly reduce the mean resolution time and increased the odds of resolution within 24 hours. Early corticosteroid treatment significantly reduced the odds of developing persistent renal disease. In addition, although the results were not statistically significant, the prospective data suggest reduced odds of both surgical intervention and recurrence.

**CONCLUSIONS**—Corticosteroids, given early in the course of illness, seem to produce consistent benefits for several major clinically relevant Henoch-Schönlein purpura outcomes.

### Keywords

Henoch-Schönlein purpura; corticosteroids; children; meta-analytic methods; systematic reviews

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Henoch-schönlein purpura (hsp) is the most common vasculitis of childhood, affecting between 8 and 20 per 100 000 children annually and accounting for 49% of all childhood vasculitides in the United States.<sup>1,2</sup> Although typically self-limited, HSP can cause gastrointestinal hemorrhage, intussusception, and end-stage renal disease (ESRD). Renal involvement, manifested by hematuria, proteinuria, nephrotic syndrome, or renal insufficiency, may occur in 60% of children.<sup>3</sup> In 1 recent study, 54% of patients developed renal manifestations within 3 months of diagnosis, 11.6% had persistent abnormalities after 7 years, and none developed ESRD.<sup>4</sup> However, previous studies have reported that as much as 21% of children with HSP-associated nephritis develop rapidly progressive glomerulonephritis<sup>5</sup>; 15% of these children with HSP-associated rapidly progressive glomerulonephritis, which is to say 2% of all patients with HSP, may progress to have uremia or ESRD.<sup>6</sup> Furthermore, even seemingly benign HSP may have long-lasting effects: 2 studies have reported that 40% and 70% of term pregnancies of women with a history of childhood-onset HSP were complicated by hypertension, proteinuria, or preeclampsia.<sup>7,8</sup>

The goals of treating HSP are typically to (1) ameliorate acute symptoms, (2) mitigate short-term morbidity (such as abdominal complications that require surgery), and (3) prevent chronic renal insufficiency. Because HSP is characterized by leukocyte infiltration of the blood vessel walls along with immunoglobulin A deposition (with resulting vascular injury and necrosis), and because corticosteroids inhibit inflammatory processes, early treatment with corticosteroids has been postulated to be effective for all 3 therapeutic goals, but much controversy remains.<sup>9-13</sup> Although the literature is replete with retrospective studies that evaluated corticosteroid use for HSP, currently there are only 3 published prospective, placebo-controlled studies on the subject, and they vary in their conclusions regarding the utility of early corticosteroid administration.<sup>9,11,14</sup>

Through a systematic review and meta-analysis, we sought to compare and contrast the experimental and observational data regarding corticosteroid use and, where appropriate, synthesize the data for 5 main clinical questions: (1) Do corticosteroids shorten the duration of abdominal symptoms in HSP? (2) Do corticosteroids decrease the odds of surgical intervention for HSP? (3) Do corticosteroids decrease the odds of disease recurrence? (4) Do corticosteroids decrease the odds of renal disease (transient plus persistent) in HSP? and (5) Do corticosteroids decrease the odds of developing persistent renal disease in HSP?

## METHODS

### Data Sources

The published medical literature was searched by using the Cochrane Controlled Trials Register (CCTR) and Medline database. Articles written in all languages were included in the search, and translation was obtained when needed.

CCTR and Medline were searched by using the Medical Subject Headings (MeSH) terms “steroids,” “methylprednisolone,” and “dexamethasone” and the key words “Henoch” and “corticosteroids.” “Henoch” and “purpura, Schönlein-Henoch” were grouped together and joined by “or.” “Steroids,” “methylprednisolone,” “dexamethasone,” and “corticosteroids” were grouped together and joined by “or.” Both groups of terms were joined together by “and.” The only limit applied to the search was “all children: 0-18 years.”

Given the large number of studies obtained from the literature search ( $N = 201$ ), we cite in this report only the studies that were chosen for inclusion. A full list of publications is available at [www.pediatric-generalists.org/weiss.htm](http://www.pediatric-generalists.org/weiss.htm).

## Study Eligibility

Eligible studies were limited to those that examined the use of corticosteroids for the treatment of HSP; observational and randomized, controlled trials were included. An article was excluded if it (1) was a review, (2) examined therapy with a drug other than corticosteroids, (3) was a case report with fewer than 5 subjects with HSP, (4) focused on individuals older than 18 years, (5) did not discuss therapy with corticosteroids, (6) included only patients with nephritis at study onset, (7) did not assess definite outcomes, or (8) did not discuss HSP.

## Study Selection

The initial literature search of the CCTR and Medline databases yielded 201 articles in 14 languages. Titles were reviewed to screen for eligibility. If the title yielded insufficient data to determine if a study was eligible, the abstract was obtained and reviewed. Articles without sufficient information in the abstract or those without an accessible abstract were examined in full text. Interpreters who were familiar with medical language and study designs evaluated all articles written in languages other than English.

Two of the authors (Drs Weiss and Feinstein) independently screened each of the potential titles, abstracts, and articles to determine inclusion. Disagreements were resolved by discussion and consensus mediated by a third author (Dr Feudtner). Reasons for article exclusion are presented in Table 1. After all the exclusions were applied, 15 articles remained for further analysis (Table 2).

In an attempt to find all relevant articles, the reference lists of included articles were searched and yielded 2 additional articles for potential inclusion.<sup>15,16</sup> However, neither article was included because the outcomes could not be abstracted. In addition, the authors of the included articles were contacted to learn of any unpublished trials or studies.

## Data Extraction

Two authors (Drs Weiss and Feinstein) independently abstracted data from the remaining articles. Disagreements were resolved by discussion and consensus mediated by a third author (Dr Feudtner). Abstracted data from the remaining articles included information regarding the study population, existence of a control group, study limitations, and information relating to the resolution of abdominal pain, surgical intervention, recurrence, and the incidence of renal sequelae.

## Statistical Analyses

Pooled odds ratios (ORs) were obtained by using the “metan” command for Stata 9.2 (Stata Corp, College Station, TX) for each of 5 clinical outcomes: (1) resolution of abdominal pain; (2) surgical intervention for severe abdominal pain or intussusception; (3) recurrence; (4) cumulative renal abnormalities; and (5) persistent renal abnormalities. The odds of having each outcome in patients who were treated with corticosteroids was compared with patients treated with routine supportive care for both prospective and retrospective studies. Results from fixed-effects models are reported. Tests for heterogeneity were performed for each analysis as a way to evaluate to what extent the results were consistent and suitable for fixed-effect modeling. If the test for heterogeneity was significant, we did not calculate a pooled OR. The Egger test for bias was performed and funnel plots were performed for each of the clinical outcomes to evaluate for publication bias. Each of the funnel plots was symmetrical, which suggests the absence of publication bias. The Egger test for bias could only be applied to analyses with 2 or more studies.

## RESULTS

### Do Corticosteroids Shorten the Duration of Abdominal Symptoms in HSP?

Although there is no consensus regarding the indication for corticosteroid use in HSP, anecdotally, abdominal pain is the most common reason that corticosteroids are prescribed. Huber et al<sup>11</sup> and Ronkainen et al<sup>9</sup> prospectively evaluated the effect of corticosteroids on abdominal pain duration by using 14-day symptom diaries. Huber et al<sup>11</sup> used 2 mg/kg per day of corticosteroids for 1 week, with weaning over week 2, whereas Ronkainen et al<sup>9</sup> used 1 mg/kg per day of corticosteroids for 2 weeks, with weaning over weeks 3 and 4 (Table 2). Using median values of total abdominal pain duration, Huber et al did not find any difference between the treatment and control groups ( $P = .8$ ) (Fig 1A). In contrast, Ronkainen et al found a mean reduction of 1.2 days of pain in patients who were treated with corticosteroids ( $P = .03$ ) (Fig 1A). Three retrospective studies reported on such effects within the first 24 hours after corticosteroid administration.<sup>17-19</sup> However, after analysis, there was evidence of heterogeneity among the included studies ( $P = .015$ ). A likely source of heterogeneity was the timing of corticosteroid administration in relation to disease onset. In the study by Reinehr et al<sup>18</sup> 31 of 57 patients received corticosteroids >21 days after the onset of HSP, whereas in the other 2 studies the treatment group received corticosteroids within several days of diagnosis. Analysis excluding the study by Reinehr et al showed a statistically significant positive corticosteroid effect, and there was no significant heterogeneity (OR: 5.42; 95% confidence interval [CI]: 1.60–18.29;  $P = .476$ ) (Fig 1B).

A study by Chao et al<sup>20</sup> looked at a unique group of patients with HSP who had hepatobiliary involvement. Involvement was defined by elevated liver transaminase levels and abnormal abdominal ultrasound results. Of those treated with corticosteroids, 90% with hepatic involvement, 100% with cholecystitis, and 100% with gallbladder sludge recovered within 7 days. In contrast, in the untreated group, 25% with hepatic involvement, none of those with cholecystitis, and only 50% with gallbladder sludge had resolution within 7 days. All patients in both groups, however, had resolution of symptoms by 14 days.

### Do Corticosteroids Decrease the Incidence of Surgical Intervention for HSP?

Only 3 studies (1 randomized, controlled trial and 2 observational trials) reported intussusception, a rare and potentially life-threatening abdominal complication during the acute phase of HSP.<sup>11,18,19</sup> Huber et al<sup>11</sup> provided the only prospective study that reported incidence of intussusception; the risk of intussusception was reduced, but not to a significant degree, in the group that received corticosteroids (OR: 0.16; 95% CI: 0.01–3.62). The 2 retrospective studies together suggest a protective effect of corticosteroid exposure (OR: 0.75; 95% CI: 0.13–4.46) (Fig 2). There was no evidence of heterogeneity between the studies ( $P = .39$ ).

### Does Early Treatment With Corticosteroids Decrease the Odds of HSP Recurrence?

Recurrences affect up to one third of children with HSP.<sup>13,21</sup> Many of these children require additional hospital admissions and pharmacotherapy. The 2 prospective studies with recurrence data suggest a protective effect of corticosteroids (OR: 0.32; 95% CI: 0.07–1.49), and there was no significant heterogeneity ( $P = .70$ ) (Fig 3).<sup>11,14</sup> The 5 retrospective observational studies that examined HSP recurrence exhibited heterogeneity ( $P < .01$ ), so a pooled OR is not reported.<sup>11,13,14,20-23</sup> The ORs and 95% CIs are reported for each study (Fig 3). No evidence of publication bias was found (Egger test:  $P = .55$ ).

### Do Corticosteroids Decrease the Likelihood of Developing Cumulative Renal Abnormalities With HSP?

Eight studies have reported data on cumulative (transient or persistent) renal abnormalities during the year after diagnosis.<sup>9-14,17,24</sup> Heterogeneity was present among both the prospective and retrospective studies ( $P = .03$  and  $P < .01$ , respectively), so pooled ORs are not reported. Instead, the individual ORs and 95% CIs of each study, prospective and retrospective, are shown (Fig 4). No evidence of publication bias was found (Egger test:  $P = .59$  and  $.66$  for the prospective and retrospective studies, respectively).

### Do Corticosteroids Decrease the Likelihood of Developing Persistent Renal Abnormalities?

In the 3 prospective studies, early corticosteroid treatment significantly reduced the odds of developing persistent renal disease (OR: 0.43; 95% CI: 0.19–0.96) (Fig 5A).<sup>8,10,13</sup> There was no evidence of marked heterogeneity among the studies ( $P = .341$ ). In addition, no evidence of publication bias was found (Egger test:  $P = .99$ ). The retrospective study by Saulsbury<sup>12</sup> did not show a statistically significant difference in renal outcome between the exposed and unexposed patients (OR: 1.25; 95% CI: 0.29–5.37) (Fig 5B).

### Sensitivity Analyses

**Does the Dose of Corticosteroid Matter?**—We investigated if the corticosteroid dose affects the likelihood of developing persistent renal disease by using unrestricted and restricted regression models and the likelihood-ratio test. The doses and duration of treatment for each study are listed in Table 2. Two studies were excluded from this analysis because corticosteroid dose was not reported.<sup>20,23</sup> The result of the likelihood-ratio test was statistically insignificant ( $P = .07$ ), which suggests but fails to identify a significant dose-response effect.

### What Future Study Would Reverse the Findings of This Meta-analysis?

Sensitivity analyses were performed to determine what sample size and magnitude of effect of a future hypothetical study would be required to reverse the findings, from the prospective studies, regarding the benefit of corticosteroid to decrease persistent renal disease presented in this meta-analysis. We conducted sensitivity analyses with hypothetical sample sizes of 200 and 400 patients and assuming an incidence of 5% and 20% persistent renal involvement in the control group (Fig 6). If the baseline risk of renal involvement in controls is 5%, a new study with 200 patients would need an effect size greater than an OR of 3.0 for the pooled OR to reach 1.0. A study with 400 patients would need an effect size greater than an OR of 2.25 for the new pooled OR to reach 1.0; for the new pooled OR to be statistically significant, the effect size would need to be larger than 3 (Fig 6A). If the baseline risk of renal involvement in controls is 20%, the OR of a new study with 200 patients would need to be  $>1.75$  to raise the pooled OR to 1.0 and  $>3.0$  to achieve significance. A new study with 400 patients would need an OR of  $>1.4$  to raise the pooled OR to 1.0 and  $>2.25$  to achieve statistical significance (Fig 6B).

## DISCUSSION

This systematic review and data summary of 15 eligible articles suggests that early treatment of corticosteroids for children with HSP is associated with statistically significant increased odds of abdominal pain resolution within 24 hours and reduced odds of persistent renal disease. In addition, although the analyses lacked sufficient statistical precision, the likelihood of surgical intervention and of HSP recurrence may also be reduced. Overall, across all analyses, the pattern of effect is in the direction favoring the use of corticosteroids; none of the analyses indicated harm.

This review emphasizes the necessity for a more complete understanding of the ways in which corticosteroids impact the course of HSP, in both the acute and chronic settings. Corticosteroids were first postulated to benefit children with HSP in the 1950s and are effective in the treatment of other vasculitides in children and adults.<sup>25</sup> Corticosteroids are the cornerstone of treatment for the majority of juvenile vasculitides including systemic lupus erythematosus, Wegener granulomatosis, polyarteritis nodosa, and Takayasu arteritis. By contrast, corticosteroid treatment is controversial for use for Kawasaki disease, another acute childhood vasculitis with potential morbidity and mortality; 1 recent report found no effect of corticosteroid,<sup>26</sup> whereas others have heralded the beneficial effects of corticosteroids.<sup>27,28</sup> Given this information should corticosteroid be given to children who present to the hospital with new-onset HSP? A rigorous answer to this question would have substantial clinical implications. Despite the widespread use of corticosteroids for vasculitides, there is no consensus yet among physicians as to whether corticosteroids should be given for HSP and, if so, for what indications.

There are several important potential limitations of the evidence we present. First, the definition of renal involvement differed among the studies, which means that different dimensions or degrees of HSP severity were potentially captured. For example, among the 3 prospective studies, the definition of proteinuria ranged from 200 to 400 mg/L, and the definition of hematuria ranged from 5 to 10 red blood cells per high-powered field. Second, the dosing regimens and mode of delivery for corticosteroids were not the same in each study (Table 2). When corticosteroid therapy was stratified by high- versus low-dose steroids for each of the clinical outcomes, there were no statistical differences between the 2 groups (data not shown). Although various doses of corticosteroids or the method of delivery (oral versus intravenous) may affect the size of the risk reduction, these changes in dose or route are unlikely to reverse the direction of effects. Third, the studies did not uniformly classify HSP cases as incident or recurrent. Therefore, the potential exists to inappropriately group severe recurrence with milder recurrence such as rash alone. Likewise, given uncertainty about loss to follow-up, particularly in the corticosteroid-treated group, the protective effect of corticosteroids is likely to be an underestimate.

Two other limitations should be kept in mind when interpreting these data. First, our ability to draw robust conclusions was hampered by the limited number of prospective studies and small numbers of patients within the studies, which often resulted in imprecise measures of treatment effects. Although the effect of corticosteroid on several of the outcomes did achieve statistically significant evidence of benefit, the failure to demonstrate benefit regarding other outcomes and the failure to show a significant dose-response effect may reflect either the still relatively underpowered nature of the combined existing studies or a true absence of impact. Second, the effects noted in the retrospective observational studies probably include some degree of confounding by indication, whereby patients with greater disease severity were more likely to receive corticosteroids. Given that most of the retrospective studies nevertheless continued to show a benefit, the results across all studies are more reassuring.

These caveats notwithstanding, our findings suggest that the potential benefit of corticosteroid administration early in the course of HSP may be more prominent than previously suggested for both acute (pain, surgical intervention) and chronic (recurrence, renal disease) complications of disease. If corticosteroid therapy is truly as effective as this meta-analysis suggests, then broader use of corticosteroid would likely decrease prolonged hospitalization, the risk of surgery, or chronic renal disease and may, by extension, prove beneficial even for those seemingly benign cases in female patients who later develop complications during pregnancy. As demonstrated by the sensitivity analyses, our findings regarding the potential benefit of corticosteroid to reduce chronic renal disease are robust; to

reverse our findings, not only would the sample size need to be greater than any published study on HSP to date, but it also would have to show an OR of harm from corticosteroid administration  $>2.25$ , which is unlikely. Better-designed retrospective studies with standardization of corticosteroid exposure by accounting for the probability that any patient would receive corticosteroids and larger prospective, randomized, controlled trials are needed to assess all clinically relevant outcomes. Knowledge from such studies is essential for guiding our interventions early in the course of HSP and improving patient outcomes for both children and adults.

## Acknowledgments

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## Abbreviations

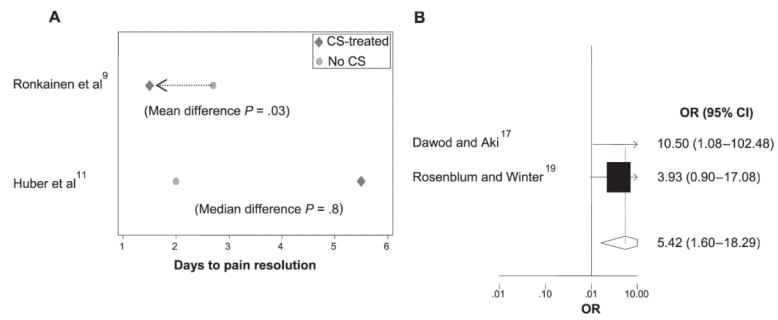
<b>HSP</b>	Henoch-Schönlein purpura
<b>ESRD</b>	end-stage renal disease
<b>CCTR</b>	Cochrane Controlled Trials Register
<b>OR</b>	odds ratio
<b>CI</b>	confidence interval

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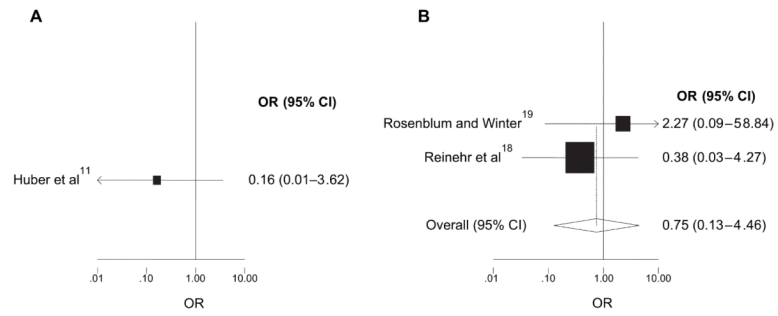
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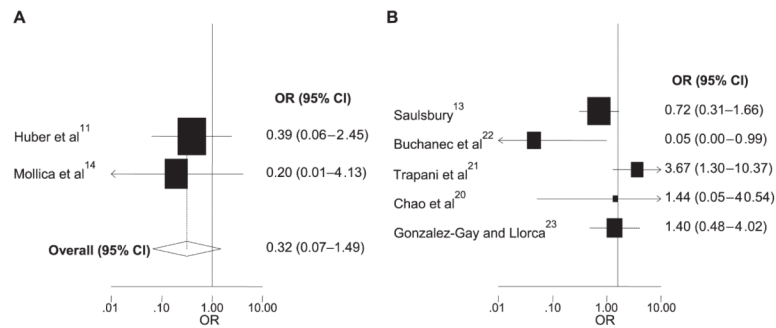




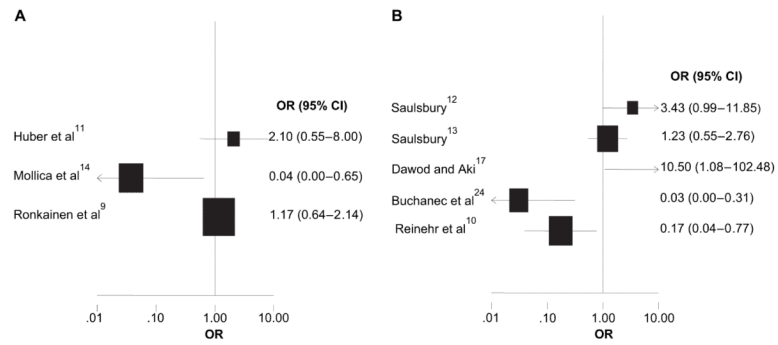
**FIGURE 1.** Corticosteroid (CS) treatment of HSP and resolution of abdominal pain. A, Prospective: time to resolution of abdominal pain (days) reported in means and medians. B, Retrospective: ORs (95% CIs) of abdominal pain resolution within 24 hours of corticosteroid administration. The box size is proportional to the inverse of the magnitude of the variance.



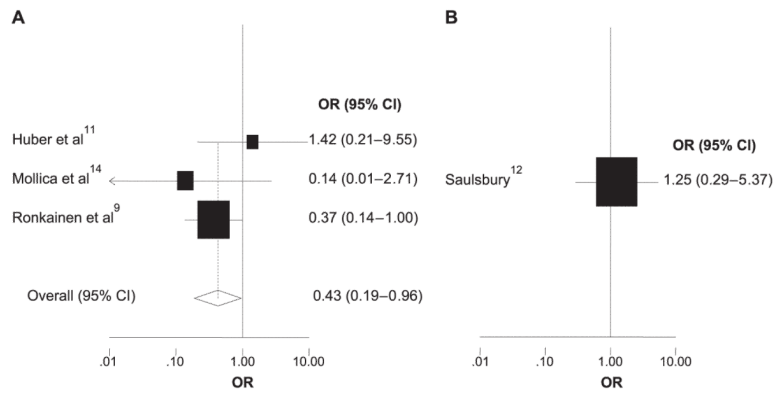
**FIGURE 2.** Corticosteroid treatment and odds of surgery. Shown are the ORs (95% CIs) of subsequent surgical intervention for severe abdominal pain and/or intussusception. A, Prospective; B, retrospective. The box size in B is proportional to the inverse of the magnitude of the variance.



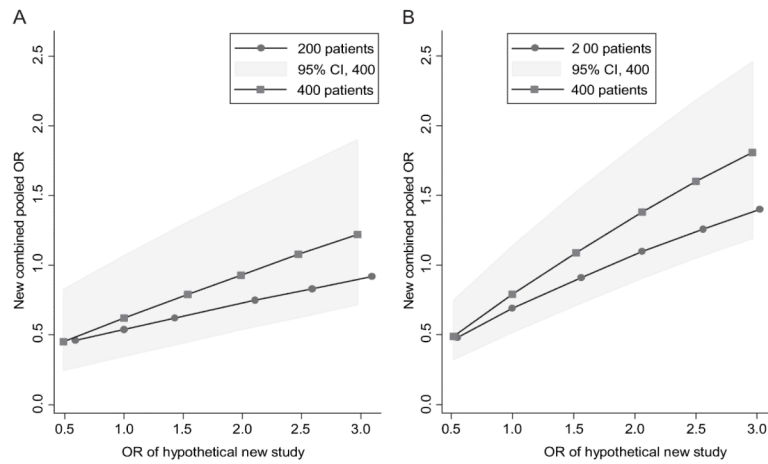
**FIGURE 3.** Corticosteroid treatment of HSP and odds of recurrence. Shown are the ORs (95% CIs) of HSP recurrence. A, Prospective; B, retrospective. The box sizes are proportional to the inverse of the magnitude of the variance. No overall OR is displayed in B because of the heterogeneity of the studies.



**FIGURE 4.** Corticosteroid treatment and odds of cumulative incidence of renal disease. Shown are the ORs (95% CIs) of patients with HSP with cumulative (transient or persistent) renal involvement if treated early with corticosteroids. A, Prospective; B, retrospective. The box sizes are proportional to the inverse of the magnitude of the variance. No overall OR is displayed because of the heterogeneity of the studies.



**FIGURE 5.** Corticosteroid treatment and odds of persistent renal disease. Shown are the ORs (95% CIs) of persistent renal involvement after HSP diagnosis. A, Prospective; B, retrospective. An end point of 1 year was used for the Huber et al<sup>11</sup> and Mollica et al<sup>14</sup> studies and 6 months for the Ronkainen et al<sup>9</sup> study. The box size in A is proportional to the inverse of the magnitude of the variance.



**FIGURE 6.** Sensitivity analysis of effect size of future hypothetical studies for likelihood of persistent renal involvement. Shown are the new combined pooled OR versus OR of a hypothetical new study with sample sizes of 200 and 400. The prevalence of persistent renal involvement in the control group was calculated at either 5% (A) or 20% (B).

**TABLE 1**  
**Reasons for Exclusion of Articles**

	<i>n</i>
Initial set: total	201
Excluded: total <sup>a</sup>	186
Review articles <sup>2,29-57</sup>	30
Case reports with <5 cases <sup>3,58-113</sup>	79
Therapy with drug(s) other than corticosteroids <sup>114-184</sup>	54
Focus on patients >18 y old <sup>185-189</sup>	4
No corticosteroid therapy <sup>190</sup>	1
Nephritis at onset in all patients <sup>5,191-200</sup>	11
No extractable outcomes <sup>201-206</sup>	6
Not an HSP study <sup>207</sup>	1
Final set: total	15

<sup>a</sup>The references cited (29–207) are available at [www.pediatric-generalists.org/Weiss/All-Citations-for-HSP-Systematic-Review.pdf](http://www.pediatric-generalists.org/Weiss/All-Citations-for-HSP-Systematic-Review.pdf).

TABLE 2

## Summary of Included Articles and Corticosteroid Use

Author	Sample Size	Study Design	Corticosteroid Dose	Initiation of Treatment From Time of Diagnosis	
			Dose, mg/kg per d	Duration	
Ronkainen et al <sup>9</sup> (2006)	171	Prospective, randomized, placebo-controlled	1	2 wk, weaning over 2 wk	At diagnosis
Huberet al <sup>1</sup> (2004)	40	Prospective, randomized, placebo-controlled	2	1 wk, weaning over 1 wk	At diagnosis
Mollica et al <sup>14</sup> (1992)	168	Prospective, randomized, placebo-controlled	1	2 wk	At diagnosis
Trapani et al <sup>21</sup> (2005)	150	Retrospective	1–2	Mean of 13.7 d (range: 7–32)	Not stated
Gonzalez-Gay and Llorca <sup>23</sup> (2005)	78	Retrospective	Not stated		Not stated
Reinehr et al <sup>18</sup> (2000)	101	Retrospective	2 <sup>a</sup>	1 wk	<3 wk (46%), >3 wk (54%)
Reinehr et al <sup>10</sup> (2000)	171	Retrospective	2 <sup>a</sup>	1 wk	<3 wk (15%), >3 wk (85%)
Chao et al <sup>20</sup> (2000)	20	Retrospective	Not stated	Range: 3–7 d	Not stated
Saulsbury <sup>13</sup> (1999)	100	Retrospective	1.6 <sup>b</sup>	Mean: 8.9 d (range: 5–28 d)	Mean: 8.5 d (range: 1–40 d)
Temmel et al <sup>16</sup> (1993)	86	Retrospective	2	1 wk, weaning over 1 wk	At diagnosis (30%), at onset of abdominal pain (70%)
Saulsbury <sup>12</sup> (1993)	69	Retrospective	1.7 <sup>c</sup>	Mean: 8 d (range: 5–10 d)	Mean: 5 d (range: 1–19 d)
Dawood and Ak <sup>17</sup> (1990)	40	Retrospective	1–2	Mean: 7 d (range: 3–30 d)	Not stated
Buchanec et al <sup>22</sup> (1988)	39	Retrospective	1–2.5	10 d, weaning over 1–2 wk	At diagnosis
Buchanec et al <sup>15</sup> (1987)	33	Retrospective	1–2.5	10 d, weaning over 1–2 wk	At diagnosis
Rosenblum and Winter <sup>19</sup> (1987)	43	Retrospective	1–2	Not stated	<1 wk (75%), <12 d (96%)

Shown is a summary of the 15 included articles' study design, corticosteroid dose, duration of treatment, and timing of treatment in respect to diagnosis.

<sup>a</sup>Dose was increased to 3 to 5 mg/kg per day if abdominal pain was present for >24 hours.

<sup>b</sup>Mean dose: 1.6 mg/kg per day (range: 1.2–2.0 mg/kg per day).

<sup>c</sup>Mean dose: 1.7 mg/kg per day (range: 1.3–2.1 mg/kg per day).