Adjuvant treatment with Yupingfeng formula for primary nephrotic syndrome in children
A PRISMA systematic review and meta-analysis of randomized controlled trials
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Abstract
Background: Yupingfeng formula (YPFF) has been prescribed as adjuvant treatment for pediatric patients with primary nephrotic syndrome (PNS) in China for years. However, the efficacy and adverse effects of these formulations are controversial. A systematic review and meta-analysis of randomized controlled trials (RCTs) were performed to evaluate the benefits and harms of YPFF in treating PNS in children.

Methods: The MEDLINE, EMBASE, Cochrane Library, CNKI, VIP, WanFang, and CBM databases were searched for RCTs comparing therapies with and without YPFF for PNS from inception to May 13, 2017. Relative risk (RR) and 95% confidence intervals (CI) were expressed for dichotomous outcomes, and weighted mean difference (WMD) with 95% CI for continuous outcomes. Cochrane collaboration tool was used to evaluate the risk of bias of methodologies.

Results: Eight studies with 538 participants were identified. Treatment with YPFF significantly increased serum levels of IgA (WMD, 0.48, 95% CI, 0.40–0.56, P < .001), IgG (WMD, 3.36, 95% CI, 2.61–4.12, P < .001), CD4+ T-lymphocytes (WMD, 3.35, 95% CI, 2.26–4.43, P < .001), but decreased the level of CD8+ T-lymphocytes (WMD, −3.38, 95% CI −5.48 to −1.28, P = .002). YPFF also increased the rates of complete remission (RR: 1.35, 95% CI, 1.09–1.67, P = .005), and decreased the rates of relapse (RR: 0.57, 95% CI, 0.45–0.71, P < .001), and infection (RR: 0.72, 95% CI 0.62–0.83, P < .001). There was no significant difference in the level of IgM between the groups (WMD, 0.12, 95% CI −0.11–0.35, P = .322).

Conclusions: YPFF could improve total remission rate and decrease the frequency of relapse and infection rate. The beneficial influence of YPFF may be associated with its immunomodulatory effects. More high-quality studies with larger sample sizes are needed to further identify its efficacy and safety.

Abbreviations: 95% CI = 95% confidence intervals, CKD = chronic kidney diseases, ESRD = end-stage renal diseases, LMWH = low molecular weight heparin, MeSH = medical subject headings, PNS = primary nephrotic syndrome, RCTs = randomized controlled trials, RR = relative risk, TCM = traditional Chinese medicine, WMD = weighted mean difference, YPFF = Yupingfeng formula.

Keywords: children, meta-analysis, primary nephrotic syndrome, Yupingfeng formula

1. Introduction
Primary nephrotic syndrome (PNS) is a common disease in children, and accounts for about 90% of childhood nephrotic syndrome.[1] The pathological mechanism is still unclear, which is supposed to be associated with immune disorders.[1–4] Pediatric patients mostly need steroids to achieve remission. However, 76% to 93% of them relapse after steroid therapy, 45% to 50% of which are frequent relapse or steroid-dependent.[5,6] In addition, infections are always the “hot potato” because of the application of steroids and the trigger of relapses. It is important to prevent or reduce the infection in children with PNS.

Yupingfeng formula (YPFF) is a traditional Chinese medicine (TCM), the history of which can be traced back to Yuan Dynasty. YPFF consists of Radix astragali, Atractylodes macrocephala, and Radix saposhnikoviae in a proportion of 3:1:1 by weight of dried plants and has been widely used to treat immunocompromised patients.[7,8] Besides, YPFF has been used for infection prevention like recurrent respiratory tract infections.[9,10] Accumulating evidence has proven the immunomodulatory and anti-inflammatory activity of YPFF. YPFF attenuates the inflammatory responses through inhibiting the NLRP3 inflammasome[11] and influencing the levels of inflammatory cytokines.[12] Besides, YPFF exerts immune regulation by impacting the balance of Th17 cells and Treg cells[12] and upregulating the proportion of CD4+/CD8+ and NK cells’ activity.[13] Therefore, YPFF has been used to treat PNS for years in China.[14] However,
no previous meta-analysis was carried out to evaluate the effects of YPFF on PNS in children. Therefore, we performed this systematic review and meta-analysis to assess the clinical efficacy and immunomodulatory effects of YPFF in children with PNS using the available randomized controlled trials (RCTs).

2. Methods
This meta-analysis was conducted according to the recommendations of the PRISMA[15] guidelines.

2.1. Protocol and registration
A protocol has been registered for this systematic review and meta-analysis in PROSPERO (CRD42017071260).

2.2. Search strategy
XS and XZ comprehensively searched the MEDLINE, EMBASE, Cochrane Library, CNKI, VIP, WanFang, and CBM databases independently from inception to May 13, 2017. We conducted searches by using medical subject headings (MeSH) terms for MEDLINE, EMTREE terms for EMBASE, and text words without language restrictions. The detailed search strategy is shown in S1 Protocol. In addition, we checked the references of published studies to further identify relevant studies.

2.3. Study selection
The titles and abstracts of all records were screened independently by 2 investigators (XS and XZ) for relevance and the full text of relevant studies was identified for eligibility by the same 2 investigators. Any discrepancy was resolved by discussion with a third reviewer (JD).

Studies were included if they met the following criteria: study design: RCTs; study population: children with diagnosis of PNS; intervention: YPFF plus other drugs versus other drugs (such as prednisone and low molecular weight heparin); outcome measures: the primary outcomes were complete remission, partial remission, urinary protein excretion, plasma albumin, relapse, the serum immunoglobulin levels (IgA, IgG or IgM) or T-lymphocytes subtype (CD4+, CD8+), and complications of PNS. The second outcomes were mortality, total cholesterol, triglycerides, edema remission, the duration of remission, adverse effects, the number, and proportion of patients developing hypertension, chronic kidney diseases (CKD) or end-stage renal diseases (ESRD); and the follow-up duration was no less than 3 months. We excluded studies with insufficient data or irrelevant topics. No experiment on humans or animals was performed, so that the ethical approval was not necessary.

2.4. Data extraction and quality assessment
Detailed information was extracted from all included studies and entered into a standardized extraction form by 2 reviewers (XS and XZ) independently. The extracted data contained: the first author, year of publication, country, sample size, age of children, gender, YPFF interventions and controls, diagnosis, follow-up duration, and outcome measures. We collected incomplete data by contacting with the first or the corresponding author by e-mail. Disagreements were settled by an independent adjudicator (JD).

We assessed the risk of bias according to the Cochrane Risk of Bias tool without masking the trial name.[16,17] Two reviewers (XS and XZ) respectively labeled each trial with “low,” “unclear,” or “high” risk of bias on following domains: random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. If at least 1 key domain was judged to be at high risk for a trial, it would be considered as at high risk of bias overall. If all key domains were judged to be low risk for a trial, it would be considered as at low risk of bias, otherwise it would be considered as at unclear risk of bias.[18]

2.5. Statistical methods
Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes and weighted mean differences (WMDs) with 95% CIs for continuous outcomes.

Statistical heterogeneity was evaluated using the I² statistic and the Cochrane Q statistic. Data were analyzed with a fixed-effect model if I² < 50% or P > .10, otherwise random-effects model was used if I² < 50% or P > .10. Pre-defined subgroup analysis was performed when the heterogeneity was high, and sensitivity analysis was conducted to explore potential sources of heterogeneity by omitting each trial in turn. All statistical analyses were performed using Review Manager 5.0 and STATA software, version 12.0 (StataCorp, College Station, TX). If studies were less than 3, then we provided a qualitative description.

3. Results
3.1. Search flow and description of included studies
A total of 1387 studies were yielded in the initial literature search. Eight studies eligible for inclusion criteria were included (Fig. 1). In total, 538 children with PNS were identified in this meta-analysis. All of the studies were conducted in China and published in Chinese. Treatment duration varied from 12 weeks to 1 year. Serum immunoglobulin levels were measured before and after treatment. Patients in the control group were treated with conventional Western medical treatment, while those in experimental group received YPFF in addition to Western medicine. YPFF involved in these studies were all by herbal particle.

3.2. Characteristics of the trials included
The number of patients included in the studies varied from 50 to 86, with a total of 538 patients in the 8 studies. The proportion of males was 67.3%. The age of the patients ranged from 2 to 14.4 years, with a mean age of 5.65 years. Seven studies mentioned the follow-up duration of the disease: from 12 weeks to 2 years. Among the 8 studies, the inclusion and exclusion criteria were defined in 3 studies, and 7 studies reported the termination and completion. Seven studies reported interventions with YPFF plus prednisone therapy versus prednisone alone. Only 1 study used YPFF plus low molecular weight heparin (LMWH) versus LMWH. The doses of YPFF used ranged from 5 to 10 g 3 times a day according to age. Detailed description of included studies was shown in Table 1. A variety of outcome measures were reported. The evaluation of the outcomes was performed at the end of the treatment.

3.3. Methodological quality
The risk of bias assessment was shown in Figure 2. All studies mentioned randomization, but only 6 studies had a detailed
description of random sequence generation. None of the studies
described allocation concealment or blinding of patients. Seven
studies mentioned follow-up; and one of these described the drop-
out or withdrawal information. Seven of the studies included
reported that characteristics of subjects in different groups have
similar baseline (age, sex, race, and disease course).

3.4. Remission

Three studies\cite{19,20,21} evaluated the rate of complete remission. As
shown in Figure 3, compared with the conventional therapy,
treatment with YPFF significantly improved the complete
remission rate (RR: 1.35; 95% CI: 1.09–1.67; $P = .005$; $I^2$: 0.0%).

3.5. Relapse

Five studies\cite{4,7,19,22,23} reported the data of relapse. Treatment with
YPFF decreased the rate of relapse (RR: 0.57; 95% CI: 0.45–
0.71; $P < .001$; $I^2$: 0.0%) compared with conventional treatment
(Fig. 4).

3.6. Infection

Five studies\cite{4,7,19,22,23} assessed the rate of infection. Treatment
with YPFF decreased the risk of infection (RR: 0.72; 95% CI: 0.62
to 0.83; $P < 0.001$; $I^2$: 0.0%) compared with conventional
treatment (Fig. 5).

3.7. Changes of immunoglobulin levels

Seven studies\cite{4,7,19,21,24} evaluated the changes of serum IgG and
IgA level and 4 studies\cite{7,19,21,24} of IgM level. A total of 267
patients were involved in the YPFF treatment groups, and 271 in
the control group. As shown in Figures 6 A and B, treatment with
YPFF significantly increased serum IgG level (WMD: 3.36; 95%
CI: 2.61–4.12; $P < .001$; $I^2$: 75.4%) and IgA level (WMD: 0.48;
95% CI: 0.40–0.56; $P < .001$; $I^2$: 78.8%) compared to control
Four studies reported the changes of T-lymphocytes subtype. Changes of T-lymphocytes subtype between with and without YPFF treatment group (Fig. 6C).

| Author [References] | YPF group | Control group | Treatment duration | Follow-up duration | Outcome interesting |
|---------------------|-----------|---------------|--------------------|-------------------|--------------------|
| Xiang M[4]          | YPF particle + Prednisone | Prednisone | 1 year | 1 year | 1 + 2 + 3 + 4 + 9 + 10 + 11 + 12 + 14 + 15 |
| Chen L[19]          | YPF particle + Prednisone | Prednisone | 1 year | 1 year | 6 + 7 + 8 + 10 + 11 + 13 + 14 |
| Lin N[4]            | YPF particle + Prednisone | Prednisone | 1 year | 1 year | 3 + 4 + 5 + 6 + 7 + 8 + 9 + 10 + 13 + 14 |
| Wei R[7]            | YPF particle + Prednisone | Prednisone | 12 weeks | 6 months | 9 + 10 + 11 + 12 + 13 + 14 |
| Xu et al[17]        | YPF particle + Prednisone | LMWH + ACH | 12 weeks | 12 weeks | 1 + 12 |
| Shi et al[27]       | YPF particle + Prednisone | Prednisone | 9 months | 9 months | 6 + 7 + 8 + 9 + 10 + 11 |
| Li XY[16]           | YPF particle + Prednisone | Prednisone | 16 weeks | 4 months | 1 + 5 + 6 + 7 + 8 + 9 + 10 + 11 + 12 + 13 |

ACH = adrenocortical hormone. C = control group. E = experimental group. LMWH = Low Molecular Weight Heparin. NP = Not provided. YPF = Yupingfeng.

1. complete remission; 2. partial remission; 3. urinary protein excretion; 4. plasma albumin; 5. CD3+; 6. CD4+; 7. CD8+; 8. CD4+/CD8+; 9. IgG; 10. IgA; 11. IgM; 12. no remission; 13. relapse; 14. infection; 15. cholesterol.

3.8. Changes of T-lymphocytes subtype

Four studies reported the changes of T-lymphocytes subtype. As shown in Figures 7 A and B, treatment with YPFF increased CD4+ counts (WMD: 3.35; 95% CI: 2.26–4.43; P < .001; I² = 0.0%) in a fixed effect model but decreased CD8+ counts (WMD: -3.38; 95% CI: -5.48 to -1.28; P = .002; I² = 86.7%) in a random effect model.

3.9. Changes of urinary protein excretion and plasma albumin

There were two studies analyzed the data of urinary protein excretion and plasma albumin. Both of the studies showed significant difference between YPFF group and control study.

3.10. Changes of cholesterol

One study reported the changes of cholesterol. There was significant difference between with and without YPFF treatment group.

3.11. Adverse events

Three studies reported the safety as outcome measures, and no adverse events was mentioned.

3.12. Subgroup analysis and sensitivity analysis on the changes of T-lymphocytes subtype and immunoglobulin level

As summarized in Table 2, subgroup analysis was conducted based on the forms of YPFF (particles vs powder), treatment duration of YPFF (≥ 6 months vs < 6 months) and follow-up period (≥ 6 months vs < 6 months). However, the source of heterogeneity was not identified. Sensitivity analysis showed that pooled result changed little after changing to fixed-effects or random-effects models, or after removing anyone study. The details of subgroup analysis and sensitivity analysis were shown in S1–S4 Fig and S5–S6 Fig of the supplementary materials, http://links.lww.com/MD/C351, respectively.

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis to evaluate the efficacy of YPFF in treating PNS in children. In this systematic review, 8 studies involving 538 participants were included: 267 versus 271 between experimental and control group. Treatment with YPFF significantly increased serum levels of IgA, IgG, CD4+ T-lymphocytes, but decreased the level of CD8+ T-lymphocytes. YPFF also increased the rates of complete remission and decreased the rates of relapse, no remission, and infection. There was so significant difference in the level of IgM between the groups. Two studies referred urinary protein excretion and plasma albumin, and both reported significant difference between YPFF group and control study.

One study mentioned cholesterol and reported no significant difference between experimental and control group. We performed a subgroup and sensitivity analysis but didn’t find the source of heterogeneity. However, the result remains stable after excluding any one study.

The pathogenesis of PNS has not been fully clarified, which is supposed to be associated with immunologic dysfunction. Children with PNS are susceptible to infection, which in return hinder the pharmacological actions of steroids and lead to relapse. Consequently, immunoregulation and infection prevention is of vital importance in treating children with PNS.

YPFF consist of Radix astragali, Atractylodes macrocephala, and Radix saposhnikoviae is suitable for Lung and Spleen Qi deficiency. Zhou et al reported that YPFF can enhance the body immunity. Xu et al verified that YPFF could improve the...
serum level of IgA, IgG, and the intestinal level of sIgA. YPFF acts on the intestinal mucosa and then further influences systemic immune function. T cells of children with recurrent respiratory tract infection increased markedly after treating with YPFF.

Despite benefits of YPFF above, the potential adverse effects of YPFF should be payed attention to. In this systematic review and meta-analysis, none of the included studies reported any adverse events so that YPFF seemed to be safe and well tolerable for children with PNS. However, the adverse effects of YPFF need attention as only three studies reported safety as outcome.

Besides, combined pharmacological activities of medicinal plants may exert adverse effect. Consequently, the safety of YPFF needs to be further investigated.

The methodological quality of included trials was shown in Fig. 2. The baseline characteristics were similar to ensure the reliability of the research. However, there were several flaws in the quality of the included studies. Although most studies provided random sequence generation, none of the trials mentioned allocation concealment so the selection bias could not be excluded. Besides, a few studies mentioned blinding, which may lead to performance and detection bias.

Figure 2. The risk of bias assessment with the Cochrane tool. A, Risk of bias graph. B, Risk of bias summary.
Figure 3. Effect of Yupingfeng on rate of complete remission compared with control group.

Figure 4. Effect of Yupingfeng on rate of relapse compared with control group.

Figure 5. Effect of Yupingfeng on rate of infection compared with control group.
There were several potential limitations in our meta-analysis. First, some linguistic biases may exist due to language limitations, though a systematically search strategies was used to minimize publication bias. Second, the sample size of included studies was relatively small. Further large-scale studies were still needed. Finally, most RCTs involved in the meta-analysis had limitations such as the lack of detailed methodology and suboptimal quality of the study design. Consequently, well-designed, large-scale RCTs were needed to further explore the effects of YPFF for PNS.

5. Conclusions
YPFF could improve total remission rate and decrease the frequency of relapse, no remission and infection rate. The beneficial influence of YPFF may be associated with its
Table 2
Subgroup analyses on the changes of immunoglobulin level.

| Subgroups          | Number of trials | Pooled WMD | 95% confidence interval | Heterogeneity between trials |
|--------------------|------------------|------------|--------------------------|-----------------------------|
| **1. IgA**         |                  |            |                          |                             |
| Treatment duration |                  |            |                          |                             |
| ≥6 months          | 4                | 0.55       | 0.47 to 0.63             | \( P < 0.001; \hat{\eta} = 67.6\% \) |
| <6 months          | 2                | 0.28       | 0.10 to 0.46             | \( P = 0.003; \hat{\eta} = 0.0\% \) |
| Follow-up period   |                  |            |                          |                             |
| ≥6 months          | 5                | 0.52       | 0.43 to 0.60             | \( P < 0.001; \hat{\eta} = 72.5\% \) |
| <6 months          | 1                | 0.25       | -0.08 to 0.56            | -                           |
| Forms of Yupingfeng |                  |            |                          |                             |
| particles          | 5                | 0.44       | 0.30 to 0.58             | \( P < 0.001; \hat{\eta} = 77.2\% \) |
| powder             | 2                | 0.48       | 0.38 to 0.58             | \( P < 0.001; \hat{\eta} = 84.3\% \) |
| **2. IgG**         |                  |            |                          |                             |
| Treatment duration |                  |            |                          |                             |
| ≥6 months          | 4                | 3.46       | 2.99 to 3.93             | \( P < 0.001; \hat{\eta} = 0.0\% \) |
| <6 months          | 2                | 2.48       | 0.21 to 4.75             | \( P = 0.032; \hat{\eta} = 87.1\% \) |
| Follow-up period   |                  |            |                          |                             |
| ≥6 months          | 5                | 3.49       | 3.06 to 3.92             | \( P < 0.001; \hat{\eta} = 0.0\% \) |
| <6 months          | 1                | 1.29       | 0.02 to 2.56             | -                           |
| Forms of Yupingfeng |                  |            |                          |                             |
| particles          | 5                | 2.92       | 2.16 to 3.69             | \( P < 0.001; \hat{\eta} = 58.7\% \) |
| powder             | 2                | 3.36       | 2.61 to 4.12             | \( P < 0.001; \hat{\eta} = 70.0\% \) |
immunomodulatory effects. More high-quality studies with larger sample sizes are needed to further identify its efficacy and safety.

Acknowledgements

The authors would like to thank all the participants in the study. This study was funded by Application of Yupingfeng in Childhood Renal Diseases.

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