Changes in clinicopathological features of primary nephrotic syndrome in children over a 10 years period: Research Paper

Haiyan Guo

First Affiliated Hospital of Anhui Medical University <https://orcid.org/0000-0002-1952-2648>

Qian Li

Shandong Provincial Hospital

Lichun Yu

Shandong Provincial Hospital

Yuan Chen

Shandong Provincial Hospital

Jing Wang

Shandong Provincial Hospital

Yue Su

Queen's University Belfast School of Medicine Dentistry and Biomedical Sciences

Shunzhen Sun (✉ ssztml@163.com)

<https://orcid.org/0000-0002-5287-5672>

Research article

Keywords: Primary nephrotic syndrome-children-clinicopathological features

Posted Date: May 20th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-29226/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

Primary nephrotic syndrome (PNS) is a common chronic disease in childhood and results in heavy illness burden. The aim of this study is to investigate the change in the clinicopathological features of children with NS worldwide.

Methods

Children with PNS were divided into two groups according to the date of admission. Group A was admitted from January 1, 2006 to December 31, 2010 and group B from January 1, 2011 to December 31, 2015. Clinical manifestations and pathological features of the children in both groups were retrospectively analyzed.

Results

This study includes 1072 patients. There were 783 cases of steroid-sensitive nephrotic syndrome (SSNS), 241 cases of steroid-resistant nephrotic syndrome (SRNS), and 48 cases of unknown steroid effects. The incidence of complications in group B was significantly higher than that in group A, especially for infections. A total of 136 (12.96%) patients underwent renal biopsy. The most common lesions were minimal change disease (44.12%). The rate of mesangial proliferative glomerulonephritis (MsPGN) significantly decreased and that of membranous nephropathy (MN) increased over the years. A total of 292 (27.24%) patients were administered immunosuppressants. The administration of Tripterygium was decreased, whereas the using of Tacrolimus increased over the years.

Conclusion

There have been changes in the incidence of complications, pathological features, and immunosuppressants in children with PNS over 10 years.

Introduction

Primary nephrotic syndrome (PNS) is one of the most common kidney diseases in children with an incidence of 2.0 to 7/100,000 and a prevalence of 16/100,000[1][2]. The incidence of PNS in East Asian children is approximately three to four times higher than that in Caucasians[3][4]. The major clinical features of PNS are proteinuria, hypoalbuminemia, hyperlipidemia, and varying degrees of edema. Glucocorticoids are the first-line drug for children with PNS[2]. However, 60–80% of children with steroid-sensitive nephrotic syndrome (SSNS) usually relapse, approximately 60% would have five-fold or more incidences of relapses[1] and approximately 10% of children with PNS relapsed into adulthood[5].

Additionally, between 7.4% and 19.6% of children have steroid-resistant nephrotic syndrome (SRNS) in Turkey[6]. Steroid-sparing immunosuppressive medications, such as calcineurin inhibitors, cytotoxic drugs, Mycophenolate Mofetil, and Rituximab are used in SRNS and steroid-dependent/frequently relapsing nephrotic syndrome (SDNS/FRNS). Minimal change disease (MCD) is the most common pathological type of PNS in children. In recent years, focal segmental glomerulosclerosis (FSGS) has gradually increased in children with PNS[1]. Most children with refractory FSGS eventually develop end-stage renal disease (ESRD). PNS is able to complicate with infection, thromboembolic disease and acute kidney injury. The mortality of PNS has been reduced from 40–0.7% because of the use of antibiotics, but infections were still the leading cause of death in children with PNS[5][7].

Besides those complications in patient, PNS would cause a huge burden for family, and society in general. A cross-sectional analysis of a hospitalization database for children with the burden of this disease in the United States showed that an estimated 48,700 hospital days were required in 2006 and 2009[8] and the total cost was 25.9 billion dollars. This consumes large amounts of social resources and property, so we need to clarify the characteristics of PNS in order to manage it better.

There are currently no published data focusing on the clinicopathological changes of PNS. To identify the changes in clinicopathological features of children with PNS worldwide, we performed a retrospective study in a single center to examine the changes in clinicopathological features of childhood NS in recent years. This study aimed to summarize the clinicopathological features of children with PNS.

Materials And Methods

Study Design And Population

This was a retrospective study based on an electronic medical record system. We included children with PNS who were admitted to the Department of Pediatric Nephrology Rheumatology, Shandong Provincial Hospital Affiliated to Shandong University, from January 1, 2006 to December 31, 2015, with an onset age from 1 to 14 years. The search key words were PNS, age from 1 to 14 years. The same patient ID only counted one patient because of repeat hospitalization. Exclusion criteria were listed as follows: congenital NS and hereditary NS, or secondary NS, such as hepatitis B virus-associated nephritis and lupus nephritis.

Methods

Medical Record Collection

We collected general data (sex, age), steroid response (SRNS, SSNS), complications, renal pathological type and immunosuppressive regimen. Children who were diagnosed with PNS were divided into two groups: group A, with admission from January 1, 2006 to December 31, 2010, and group B, with

admission from January 1, 2011 to December 31, 2015. The patients in group A who were admitted to hospital for recurrence during 2011–2015 wouldn't be included in group B.

Renal Biopsy

Indications of renal biopsy were SRNS, SDNS/FRNS. After seeking consent of the guardians of children, an ultrasound-guided percutaneous renal biopsy was performed. Kidney pathologies were based on the World Health Organization WHO 1995 classification scheme for glomerular diseases[9].

Definitions

Diagnostic criteria for PNS were listed as follows: (1) proteinuria: three times a week as indicated by random or morning urine protein/creatinine (mg/mg) levels ≥ 2.0 , or 24-h urine protein quantitation ≥ 50 mg/kg; (2) hypoproteinemia with plasma albumin levels < 25 g/L; (3) hyperlipidemia defined as plasma cholesterol levels > 5.7 mmol/L; and (4) different degrees of edema.

PNS was divided into the following two types according to steroid response: (1) SSNS was defined as when patients' urinary protein turned negative within 4 weeks of prednisone treatment in sufficient amounts (2 mg/kg/d or 60 mg/m²/d). (2) SRNS was defined as when urinary protein was still positive after prednisone treatment for more than 4 weeks.

Pns Recurrence And Frequency Of Recurrence

Relapse was identified when morning urine protein changed from negative to (+++) or (++++ for 3 consecutive days, 24-h urinary protein quantitation was ≥ 50 mg/kg, or urinary protein/creatinine (mg/mg) was ≥ 2.0 . Frequent relapse was defined as relapse that occurred more than two times in the course of disease within 6 months, or relapse that occurred more than three times within 1 year.

Infections included lower respiratory tract infection, urinary tract infection, and the others that required hospitalization.

The criteria for admission were the emergence of complications and recurrence of proteinuria.

Statistical analysis

Statistical analyses were performed with SPSS software (version 22.0, IBM, NY, USA). Using the Kolmogorov-Smirnov test, continuous variables with normal distribution are presented with the mean and standard deviation (SD); the median and interquartile range (IQR) is shown when a normal distribution was not observed. Comparisons of continuous variables between the two groups were performed with Student's t-test or Mann-Whitney U test. ² tests were used to analyse percentages. Descriptive statistics

are presented as percentages and means and standard deviations. *P* values of < 0.05 were considered statistically significant.

Results

Baseline characteristics

From January 1, 2006 to December 31, 2015, 8193 inpatients were admitted to our department, of whom 2832 were diagnosed with PNS. This number accounted for 34.57% (2832/8193) of the hospitalized children in the same period. A total of 2832 hospitalizations were recorded for 1072 patients (806 boys and 266 girls), the ratio of boys to girls with PNS was 3:1. There were 372 patients in group A and 700 patients in group B. The age of onset was from 1 to 14 years (mean age 4.92 ± 2.87 years). The frequency of hospitalization varied from 1 to 17 times with a mean time of 2.75 ± 3.03 . There were 59 patients in Group A who still needed to be admitted to hospital in the period of Group B. The number of hospitalization days ranged from 1 to 65 days, with a mean of 10.41 ± 8.83 days. There were 783 cases of SSNS, 241 cases of SRNS, and 48 cases of unknown steroid effects. There were no significant differences in baseline characteristics between the two groups (Table 1).

Table 1
Baseline characteristics of children with PNS

Characteristics	Group A N = 372	Group B N = 700	Total	P Value
Age of onset	5.08 ± 2.84	4.83 ± 2.88	4.92 ± 2.87	0.165
Number of hospitalizations	2.95 ± 3.19	2.65 ± 2.93	2.75 ± 3.03	0.12
Gender				0.18
male	289	517	806	
female	83	183	266	
Steroid effect				0.06
SSNS	258	525	783	
SRNS	91	150	241	
Unknown	23	25	48	

Pathological Manifestations

A total of 136 patients underwent biopsy, accounting for 12.69% in 1072 patients. Unfortunately, considering the potential risks and complications, almost half of the parents declined this special

operation.

The most common pathological type was MCD (n = 60, 44.12%), followed by mesangial proliferative glomerulonephritis (MsPGN) (n = 31, 22.79%), FSGS (n = 19, 13.97%), membranous nephropathy (MN) (n = 15, 11.03%), membranoproliferative glomerulonephritis (MPGN) (n = 6, 4.41%), IgM nephropathy (n = 4, 2.94%), and focal proliferative glomerulonephritis (FGN) (n = 1, 0.73%). The rates of MsPGN and MN were significantly different ($p < 0.01$, $p = 0.04$) between the two groups; the rate of MsPGN decreased over 10 years, while that of MN increased. Two patients underwent a repeated renal biopsy; one patient with stage II–III membranous nephropathy progressed to membranous nephropathy and one patient progressed from MCD to FSGS. (Table 2).

Table 2
Complications,pathological type and immunosuppressive agents of children with PNS

	Group A	Group B	Total	P Value
Total complications	139	373	512	<0.01
Infections	125	324	449	<0.01
AKI	15	21	36	0.38
Adrenal crisis	8	13	21	0.82
Thromboembolism	2	5	7	1
intussusception	0	3	3	0.56
Reversible posterior leukoencephalopathy	0	1	1	0.54
hypertension	10	14	24	0.52
Secondary hypothyroidism	1	2	3	1
Pathological type				
MCD	23	37	60	0.30
MsPGN	25	6	31	<0.01
FSGS	7	12	19	0.62
MN	3	12	15	0.04
MPGN	1	5	6	0.23
IgMN	0	4	4	0.13
FGN	1	0	1	0.44
Immunosuppressive agents				
Single immunosuppressive agent	67	135	202	0.62
Combined immunosuppressive agent	35	55	90	0.42
CTX	85	143	228	0.39
CsA	22	20	42	0.02
TAC	2	37	39	<0.01
MMF	11	38	49	0.07
tripterygium	12	4	16	0.01
LEF	0	4	4	0.30

The main pathological types of SSNS were MCD and MsPGN, and those of SRNS were mainly MCD, MsPGN, and FSGS. The associations between pathological type and clinical classification and steroid response are shown in Table 3.

Table 3
Comparison of pathological type in A.B group (composition ratio%)

	Group A	Group B	Total	P Value
MCD	23(38.33)	37(48.68)	60(44.12)	0.30
MsPGN	25(41.67)	6(7.89)	31(22.79)	<0.01
FSGS	7(11.67)	12(15.79)	19(13.97)	0.62
MN	3(5.00)	12(15.79)	15(11.03)	0.04
MPGN	1(1.67)	5(6.58)	6(4.41)	0.23
IgMN	0(0.00)	4(5.26)	4(2.94)	0.13
FGN	1(1.67)	0(0.00)	1(0.73)	0.44
Total	60(100)	76(100)	136(100)	0.02

Complications

A total of 512 patients with PNS had complications. More patients had complications in group B (373/700) than did those in group A (139/373) ($p=0.001$). A total of 449 patients had infectious complications, including acute upper respiratory infection, bronchial pneumonia, urinary tract infection, skin infection; 36 had acute renal insufficiency, 21 had adrenal crisis, 24 had hypertension, 7 had thromboembolism, 3 had intussusception, 3 had secondary hypothyroidism and 1 had reversible posterior leukoencephalopathy. The incidence of infection in group B was significantly higher($p=0.001$) than that in group A, with no significant difference in other types of complications between these two groups (Table 4).

Table 4
Relationships between pathological type and clinical classification and steroid response

	Pathological type							Total
	MCD	MsPGN	FSGS	MN	MPGN	IgMN	FGN	
SSNS	30	13	1	1	1	2	0	48
SRNS	30	18	18	14	5	2	1	88

Treatment

We designed a treatment regimen according to the Chinese Medical Association guidelines[10][11] combined with clinical and pathological manifestations. Steroids were the first line therapy for all patients. Moreover, patients with steroid resistance or frequent relapse are given the second line therapy in addition to steroid, based on treatment guidelines - immunosuppressive agents.

A total of 292 (27.24%) patients used immunosuppressive agents. Among these patients, 202 (69.18%) used a single immunosuppressive agent and 90 (30.82%) used two or more immunosuppressive agents in succession. The drug which was most frequently used was Cyclophosphamide (CTX) 228(78.08%), followed by Cyclosporine A(CsA) 42(14.38%), Tacrolimus (TAC) 39(13.36%), Mycophenolate mofetil (MMF) 49(16.78%), Tripterygium 16(5.48%), Leflunomide (LEF) 4(1.37%). The administration of CsA and Tripterygium decreased ($p = 0.02$ $p = 0.01$), and the use of TAC gradually increased over time($p \leq 0.001$). (Table 5)

Table 5
Comparison of immunosuppressive agents in A and B groups
(composition ratio%)

	Group A n = 102	Group B n = 190	Total n = 292	P Value
CTX	85(83.33)	143(75.26)	228(78.08)	0.39
CsA	22(21.57)	20(10.53)	42(14.38)	0.02
TAC	2(1.96)	37(19.47)	39(13.36)	≤ 0.01
MMF	11(10.78)	38(20)	49(16.78)	0.07
Tripterygium	12(11.76)	4(2.10)	16(5.48)	0.01
Leflunomide	0(0)	4(2.10)	4(1.37)	0.30

Discussion

Our study showed that there were some clinicopathological changes of PNS in children over 10 years (2006–2015). Children with PNS accounted for 34.57% of all hospitalized children in the Department of Pediatric Nephrology Rheumatology over the 10-year period. In 1982, children with PNS in some provinces and cities in China accounted for 21% of all hospitalized children and this rate was 31% in 1992[12]. This finding suggests that hospitalization for PNS had increased over these years. In this study, the group B was twice the size of group A, which may have been a result from the economic development and convenient public transportation. In our study, the ratio of boys to girls with PNS was 3:1 and the subjects were mainly pre-school children, which was consistent with domestic and international studies[12][13]. Because of disease relapse or infused cyclophosphamide, the number of hospitalizations

fluctuated between 1 and 17 times, and 59 patients in Group A still needed to be admitted to hospital in the period of Group B. The days of hospitalization varied from 1 to 65 days with a mean length of 10.41 ± 8.83 days. This hospital stay was longer than the mean length of stay in Gipson DS' study (5 ± 0.1 days)[8].

In our study, there was no significant difference in the response to glucocorticoids between the two groups. Dincel et al[14] found that 88.3% of children with PNS were SSNS and 11.7% of patients were SRNS, which was in accordance with our findings. Another study showed that approximately 10% of patients with PNS had SRNS, and SRNS pathology was predominantly FSGS[13]. Even though our study did not show any difference in the rate of SRNS, the proportion of SRNS was higher than that in Dincel et al's study[14], and slightly higher than that (10–20%) previously reported in China[11]. This suggested an increasing trend of SRNS in recent years. There were 48 patients with an unknown steroid response because we were unable to follow them up.

MCD, MsPGN, and FSGS are the most common pathological types of PNS in children[14][15][1]. Our findings further supported this conclusion. In our study, the rate of MsPGN gradually decreased in recent years, while that of MN increased. The specific etiology of this finding is unclear. One reason for the decrease in the percentage of MsPGN is due to the increasing tendency of MPGN or MN. In addition, a multicenter study in China[16] showed that an increased incidence of idiopathic membranous nephropathy (IMN) was associated with an increase in Particulate Matter 2.5(PM2.5) in the environment. How the mechanisms of exposure to PM2.5 increase the risk of MN remains to be elucidated. Furthermore, a previous study in our center[17] indicated that the incidence of children with FSGS and MN showed an upward trend in the past 20 years. Especially in the latest 5 years, the incidence of FSGS and MN in renal pathological types has significantly increased. However, other results[18] demonstrated that the main pathology of PNS in children was FSGS, which may have been related to hospitals receiving difficult referral cases. On the other hand, in our study, there were two children with FSGS and recurrent disease who had repeated renal biopsies, including one with pathological findings of MN (II–III), which progressed to MN (III) and FSGS. The other child showed a change from minimal changes to FSGS, and the pathological findings were more severe than the former ones. For those repeatedly refractory patients, repeated renal biopsy can assess the severity of disease, predict the outcome and adjust the treatment regimen timely.

In our study, 512 (47.76%) children with PNS had complications in hospital. In particular, the incidence of infections was significantly higher in group B than in group A. However, there were no significant differences in other types of complications between the groups. Some previous studies have shown that 60% of patients[19][8] have at least one complication, and 14–16% of patients have at least one serious complication in the course of PNS. Historically, infections were the leading cause of mortality in children with PNS, and even now, infection is the leading cause of morbidity in children with PNS[20][2]. Infections are due to urinary loss of immunoglobulins and complement, impaired lymphocytic function. The reason for higher incidence of infection in group B in our finding was not clear, but it may be related to more air pollution. Song et al[21] have shown that the hospitalization rate of children with pneumonia was

positively correlated with levels of the air pollution marker PM 2.5, and ambient PM 2.5 contributed as much as 33.1% (95% confidence interval: 22.6%, 42.4%) to total acute lower respiratory infection (< 5 years) deaths in China. Therefore, we speculated that the increase in hospitalization is due to the rising rate of infection.

Glucocorticoids are still the first-line regimen for children with PNS. However, for SRNS or FRNS, the option of immunosuppressants has changed over recent years. The proportion of CsA and Triptolide administered was decreased, while the proportion of TAC used was increased in our study. The reasons for this finding were related with the recommendation of TAC in the treatment guidelines in China and some other countries. However, CsA and Triptolide have severe side effects. In addition, the administration of immunosuppressive drugs improves the remission rate of refractory PNS. A previous report[19] showed that 51% of patients with PNS received two or more immunosuppressive agents. For children with SRNS, Trautmann A et.al showed that using enhanced immunosuppressive agents had a good effect[13]. CTX was the most used immunosuppressant[22], and our study confirmed it. Several case series suggest that TAC is effective for FRNS or SDNS[2]. Moreover, TAC was superior to MMF in maintaining remission of SRNS[23]. Reports[24][25] found that Adalimumab and Rituximab can help patients to achieve a long-term remission period, improve quality of life, and reduce the hospitalization rate. However, Adalimumab and Rituximab are not widely used because of high costs. However, using immunosuppressive drugs also increased the rate of infection in children with PNS. Therefore, when using immunosuppressive agents, clinicians need to consider the advantages and disadvantages of these agents.

Our study also has some limitations. Primarily, this was a retrospective, single-center study. Future studies need to include other medical centers to identify changes in the clinicopathological features of PNS. In addition, the biopsy reports were not reported by the same pathologist because the study lasted 10 years.

In conclusion, our study showed the rate of complications has significantly increased with mainly infectious complications. The rate of MsPGN has decreased in recent years, while that of MN increased. Glucocorticoids are still the first-line treatment for children with PNS. However, due to the choice of immunosuppressive agents, the use of Tacrolimus in children increased whereas Tripterygium decreased. This study was a part of a series of studies which aim to further examine clinicopathological features and complications of children with PNS.

Abbreviations

PNS:Primary nephrotic syndrome; SRNS:Steroid-resistant nephrotic syndrome; SSNS:Steroid-sensitive nephrotic syndrome; SDNS/FRNS:Steroid-dependent/frequently relapsing nephrotic syndrome; MCD:Minimal change disease; MsPGN:Mesangial proliferative glomerulonephritis; MN:Membranous nephropathy; FSGS:Focal segmental glomerulosclerosis; MPGN:Membranoproliferative

glomerulonephritis; ESRD:End-stage renal disease; CTX:Cyclophosphamide; CsA:Cyclosporine A; TAC:Tacrolimus; MMF:Mycophenolate mofetil; LEF:Leflunomide.

Declarations

Availability of data and material

This was a retrospective study based on an electronic medical record system. We included children with PNS who were admitted to the Department of Pediatric Nephrology Rheumatology, Shandong Provincial Hospital Affiliated to Shandong University, from January 1, 2006 to December 31, 2015, with an onset age from 1 to 14 years. The search key words were PNS, age from 1 to 14 years. The same patient ID only counted one patient because of repeat hospitalization.

Ethics approval and consent to participate

This study was approved by the Medical Ethics committee of Shandong Provincial Hospital affiliated Shandong University and all participants consent to join this study.

Consent for publication

All authors approved the final version of the manuscript for publication.

Competing interests

No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Ethical Review of Medical Research on Human Being

(NO. 2018-053)

Project Name	Changes in clinicopathological features of primary nephrotic syndrome in children over 10 years		
Funding	Natural Science Foundation of Shandong Province(2015HM009) and key research and development project of Shandong Province (2017GSF218005).		
Department	Department of Pediatric Nephrology Rheumatology, Shandong Provincial Hospital Affiliated to Shandong University		
First Author	Hai-yan Guo	Professional Title	postgraduate
Corresponding Author	Shu-zhen Sun	Professional Title	Ph. D., Professor
Reviewing Documents	Ethical review		
Review Result	☒ agree	Agree	
	☐ agree after revision		
	☐ disagree(project terminated or suspended)		
Comments	<p>Informed consent has been provided. The subjects' rights and interests are protected well in the whole process. The research hereby is approved by the Medical Ethics Committee of Shandong Provincial Hospital affiliated to Shandong University.</p> <div style="text-align: center;"> </div>		

Funding

This study was supported by grants from the Natural Science Foundation of Shandong Province (CN) (2015HM009), key research and development project of Shandong Province (2017GSF218005). We thank all study participants and members who assisted with this analysis.

Authors' contributions

Haiyan Guo was a major contributor in writing the manuscript. Shunzhen Sun analysed and interpreted the patient data and revised the final manuscript. Qian Li and Chen Yuan performed the kidney biopsy, and interpreted the patient data. Jing Wang Yue Su and Lichun Yu analysed data and interpreted the patient's clinical data and contributed to writing the manuscript. All authors read and approved the final manuscript.

Acknowledgment

We thank Zhen Junhui, PhD, from Shandong University for providing the pathological data.

References

1. Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet*. 2003;362:629–39.
2. 10.1016/S0140-6736(18)30536-1
Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. *Lancet* [Internet]. Elsevier Ltd; 2018;392:61–74. Available from: [http://dx.doi.org/10.1016/S0140-6736\(18\)30536-1](http://dx.doi.org/10.1016/S0140-6736(18)30536-1).
3. Sato M, Ishikura K, Ando T, Kikunaga K, Terano C, Hamada R, et al. Prognosis and acute complications at the first onset of idiopathic nephrotic syndrome in children: a nationwide survey in Japan (JP-SHINE study). *Nephrol Dial Transplant*. 2019;1–7.
4. Kikunaga K, Ishikura K, Terano C, Sato M, Komaki F, Hamasaki Y, et al. High incidence of idiopathic nephrotic syndrome in East Asian children: a nationwide survey in Japan (JP-SHINE study). *Clin Exp Nephrol*. Springer Japan; 2016;1–7.
5. Metz DK, Kausman JY. Childhood nephrotic syndrome in the 21st century: What's new? *J Paediatr Child Health*. 2015;51:497–504.
6. Özlü SG, Demircin G, Tökmeci N, Çaltık Yılmaz A, Aydoğdu Ö, Bülbül M, et al. Long-term prognosis of idiopathic nephrotic syndrome in children. *Ren Fail*. 2015;37:672–7.
7. Heron M. Deaths: Leading causes for 2015. *Natl Vital Stat Reports*. 2017;66.
8. 10.1053/j.ajkd.2012.12.025
Gipson DS, Messer KL, Tran CL, Herreshoff EG, Samuel JP, Massengill SF, et al. Inpatient health care utilization in the united states among children, adolescents, and young adults with nephrotic syndrome. *Am J Kidney Dis* [Internet]. Elsevier Inc.; 2013;61:910–7. Available from: <http://dx.doi.org/10.1053/j.ajkd.2012.12.025>.
9. Churg J, Bernstein JGR. Renal disease-classification and atlas of glomerular disease. *Ann Intern Med*. 1995;123:80.
10. Nephrology, CS of PPB of the. Diagnosis and Treatment of Common Kidney Disease Evidence-based Guide (a) - Steroid -sensitive, relapse-dependent nephrotic syndrome diagnosis and treatment guidelines (Trial). *Chinese J Pediatr*. 2009;47:167–70.

11. Nephrology CS. of PB of. Guidelines for the diagnosis and treatment of common kidney disease in children (Trial) (III) - Guidelines for the diagnosis and treatment of steroid-resistant nephrotic syndrome. *Chinese J Pediatr.* 2010;48:72–5.
12. Y Z iang, Shen K. *Zhu Futang Practice of Pediatrics.* 2014.
13. Trautmann A, Schnaidt S, Lipska-ZiŁtkiewicz BS, Bodria M, Ozaltin F, Emma F, et al. Long-term outcome of steroid-resistant nephrotic syndrome in children. *J Am Soc Nephrol.* 2017;28:3055–65.
14. Dinçel N, Yilmaz E, Kaplan Bulut I, Hacikara Ş, Mir S. The long-term outlook to final outcome and steroid treatment results in children with idiopathic nephrotic syndrome. *Ren Fail.* 2015;37:1267–72.
15. Chang JW, Tsai HL, Yang LY, Chen TJ. Epidemiology and predictors of end-stage renal disease in Taiwanese children with idiopathic nephrotic syndrome. *J Epidemiol.* 2012;22:517–22.
16. Xu X, Wang G, Chen N, Lu T, Nie S, Xu G, et al. Long-term exposure to air pollution and increased risk of membranous nephropathy in China. *J Am Soc Nephrol.* 2016;27:3739–46.
17. Liu SW, Sun SZ, Li Q, Zhou AH, Yao XJWL. Clinical and pathological analysis of 753 children with renal diseases. *Chinese J Pediatr.* 2017;32:526–30.
18. Guan N, Ding J, Yang JY, Xiao HJ, Yao YLJ. Clinical characteristics and prognosis analysis of children with idiopathic nephrotic syndrome with different responses to steroid therapy from a single center in 20 Years. *Chin J Appl Clin Pediatr.* 2014;29:1291–4.
19. Wang CS, Yan J, Palmer R, Bost J, Wolf MF, Greenbaum LA. Childhood Nephrotic Syndrome Management and Outcome: A Single Center Retrospective Analysis. *Int J Nephrol.* 2017;2017.
20. 10.1016/j.pcl.2018.08.006
Wang C, Greenbaum LA. Nephrotic Syndrome. *Pediatr Clin North Am* [Internet]. Elsevier Inc; 2019;66:73–85. Available from: <https://doi.org/10.1016/j.pcl.2018.08.006>.
21. 10.1016/j.envpol.2017.01.060
Song C, He J, Wu L, Jin T, Chen X, Li R, et al. Health burden attributable to ambient PM2.5 in China. *Environ Pollut* [Internet]. Elsevier Ltd; 2017;223:575–86. Available from: <http://dx.doi.org/10.1016/j.envpol.2017.01.060>.
22. Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *Cochrane Database Syst Rev.* 2019;2019.
23. 10.1016/j.kint.2017.01.019
Sinha A, Gupta A, Kalaivani M, Hari P, Dinda AK, Bagga A. Mycophenolate mofetil is inferior to tacrolimus in sustaining remission in children with idiopathic steroid-resistant nephrotic syndrome. *Kidney Int* [Internet]. Elsevier Inc; 2017;92:248–57. Available from: <http://dx.doi.org/10.1016/j.kint.2017.01.019>.
24. Ravani P, Bonanni A, Ghiggeri GM. Randomised controlled trial comparing ofatumumab to rituximab in children with steroid-dependent and calcineurin inhibitor-dependent idiopathic nephrotic syndrome: Study protocol. *BMJ Open.* 2017;7.
25. Nagano C, Sako M, Kamei K, Ishikura K, Nakamura H, Nakanishi K, et al. Study protocol: Multicenter double-blind, randomized, placebo-controlled trial of rituximab for the treatment of childhood-onset

early-stage uncomplicated frequently relapsing or steroid-dependent nephrotic syndrome (JSKDC10 trial). BMC Nephrol BMC Nephrology. 2019;20:1–10.