

An empirical study on the index system of rational drug use in children with primary nephrotic syndrome

A cross-sectional study

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Abstract

In the study's early stage, the research group had established an evaluation index system for the rational drug use of primary nephrotic syndrome in children. To assess the feasibility of the established index system, we conducted this empirical study.

The cross-sectional study was conducted by using the Hospital Information System to extract some general clinical data of hospitalized children with primary nephrotic syndrome, which included registration number, age, sex, diagnosis and medication, etc. Utilize the SPSS23.0 software and Excel 2016 to descriptively analyze information.

224 hospitalized children with primary nephrotic syndrome who met the inclusion criteria were included, ranging from 18 years old and 10 months to 11 months and 23 days, with an average age of 8.40, plus or minus 4.30 years. 148 males (66.07%) and 76 females (33.93%). The duration of hospitalization was 1–57 days, with an average hospitalization time of 10.59 days. The most common is respiratory infections, such as the bronchopneumonia, the mycoplasma pneumonia, etc. This study had successfully completed the measurement of the evaluation index system for the rational drug use of primary nephrotic syndrome in children.

All indicators are feasible, but the operability and applicability need further research and improvement.

Abbreviations: HIS = hospital information system, PNS = primary nephrotic syndrome, RDU = rational drug use, WHO = World Health Organization.

Keywords: children, empirical research, primary nephrotic syndrome, rational drug use

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1. Introduction

1.1. Background

The rational drug use (RDU) is always emphasized by the World Health Organization, especially for children.^[1] And in 2014, our research team conducted a systematic search to evaluate existing drug-related indicators and found that there was only 1 set of medication indicators developed for children, while this set of indicators was designed for children in primary health care, which was not suitable for the treatment of specific diseases.^[2] Therefore, we intended to establish sets of indicators to assess the children's RDU. By screening diseases in hospitalized children according to prevalence and burden of disease, we decided to assess the RDU of children's primary nephrotic syndrome (PNS). And based on the previous Delphi expert consultation method and the Analytic Hierarchy Process, we had established the index system of PNS in children in 2017, which included 2 primary indicators and 16 secondary indicators. In order to verify the feasibility of the index, we conducted an empirical study in 2018.

1.2. Aim

To verify the feasibility of the index which was established in 2017.

2. Methods

This was a cross-sectional study. We obtained the data from the Hospital Information System (HIS) through the information department with manual extraction. We extracted 2 years' data

from 2016 to 2017, which included registration number, age, sex, diagnosis, and medication, and so on. Then utilized the SPSS23.0 software and Excel 2016 to descriptively analyze information. The data were all from the West China Second University Hospital and LM had access to information that could identify individual participants during or after data collection.

This study was approved by the Institutional Review Board of West China Second University Hospital. But it didn't involve patient consent, because the research was a retrospective study and all data was from the HIS. Therefore, the study didn't involve any patients to participate, interfere with patients' treatment or divulges patients' private information.

2.1. Study selection

The study population were inpatients in the department of nephrology, west China Second University Hospital, during the period of January 1, 2016 and December 31, 2017. The inclusion criteria:

- (1) PNS with definite diagnosis (ICD-10);
- (2) Resident children aged 0–18 years old.

3. Results

3.1. General information

Between 2016 and 2017, a total of 224 hospitalized children with PNS were included in the study. There were 148 boys (66.07%) and 76 girls (33.96%), which the ratio of male to female children was 2:1. The youngest child was 11 months and 23 days old, while the oldest was 18 years, 10 months and 27 days old; the average age (mean \pm SD) was 8.40 ± 4.30 years old. The number of hospital days varied from 1 day to 57 days, with an average hospital time (mean \pm SD) of 10.59 ± 9.12 days. Patients' general information were summarized in Table 1.

3.2. Disease diagnosis

After PNS children were admitted to the hospital, various complications often occurred. We counted the total number of diseases on every patient according to the admission diagnosis and

Table 1

Patients' general information.

Sex	Male (n, %)	Female (n, %)	Total (n,%)
Numbers	148 (66.07%)	76 (33.96%)	224 (100%)
Age (yr)	8.45 ± 4.20	7.54 ± 4.38	8.40 ± 4.30
Hospital stay (d)	11.11 ± 9.30	9.59 ± 8.73	10.59 ± 9.12

Table 2

Changes of patients' diseases amounts.

Diseases amounts	Admission diagnosis (n,%)	Discharge diagnosis (n,%)
1–2	194 (86.61%)	79 (35.27%)
3–4	27 (12.05%)	86 (38.39%)
5–6	3 (1.34%)	47 (20.98%)
≥ 7	0	12 (5.36%)

discharge diagnosis, respectively. Details in Table 2. From the data, it can be seen that the majority of patients have increased their total number of illnesses after admission, and the change in the number of comorbidities can, to a certain extent, represent changes in the number of complications. And complications of PNS include infection (mainly respiratory infection), thrombosis and embolism complications, acute renal failure, protein and fat metabolism disorders. The most common is respiratory infections, such as the bronchopneumonia, the mycoplasma pneumonia, and so on.

3.3. Treatment and medication

According to the calculation formula of the established index system, the extracted data were sorted, classified and counted, and the measured data of the index system were obtained. The empirical results were shown in Table 3.

4. Discussion

4.1. Feasibility analysis of indicator system

This study had successfully completed the measurement of the evaluation index system for the RDU of PNS in children. All indicators were feasible, but some indicators needed to be

Table 3

the empirical results of rational drug use in children with primary nephrotic syndrome.

First-rank indicators	Second-rank indicators	Results
1. Drug selection	1.1 Proportion of antibiotic use	60.27%
	1.2 Proportion of ACEI/ARB use in non-hypertensive children	5.67%
	1.3 Proportion of albumin use	6.45%
	1.4 Proportion of immune enhancers use	14.81%
	1.5 Proportion of calcium phosphatase inhibitors use	100.00%
	1.6 Proportion of calcium supplements	10.50%
	1.7 Proportion of prednisone is preferred for children with hormone therapy	25.93%
	1.8 Proportion of hormone shock treatment in initial treatment	0.00%
	1.9 Proportion of CTX in children with hormone-sensitive frequency recurrence using immunosuppressive agents	62.50%
	1.10 Proportion of anticoagulant preventive measures (limited measures: warfarin, dipyridamole, clopidogrel, aspirin, and low molecular weight heparin)	32.42%
2. Drug usage and dosage	2.1 Proportion of initial treatment of hormones > 60 mg/d	48.15%
	2.2 Proportion of intravenous drug use in children with diuretics	9.68%
	2.3 Proportion of intravenous CTX in children using CTX	87.50%
	2.4 Proportion of ACEI/ARB combined with diuretics	8.82%
	2.5 Initial treatment (3 days before admission), proportion of diuretics used	80.65%
	2.6 Proportion of blood concentration monitoring in patients who use calcineurin inhibitor (CNI) drugs	10.00%

ACEI=angiotensin converting enzyme inhibitors, ARB=Angiotensin II receptor antagonists, CNI=calcineurin inhibitor, CTX=cyclophosphamide.

extracted by manual from the HIS, which had reduced the operability of the index system. In addition, because there were many complications in children with PNS, drug combine-use were complex. While the index system doesn't involve the RDU of complications, which will lead to the reduction of the index applicability. The indicator did not provide a standard value to measure the empirical findings, but provided a data reference for horizontal comparisons between indicators or between different hospitals. And the research team will further study the indicator standard values in the next step.

4.2. Result analysis

The indicator system included 2 first-level indicators and 16 second-level indicators. "Drug selection" and "Usage and dosage" were primary indicators; and among the secondary indicators: 3 items (25%) were used to evaluate hormone use, and 5 items (25%) were used to evaluate the use of immunomodulators, 8 items (50%) were used to assess the use of symptomatic treatments.

It is well known that infection is the main cause of PNS recurrence and a key factor affecting the treatment and prognosis of children with kidney disease. The proportion of antibiotics used was 60.27% (item 1.1), which reflected the incidence of infection in children to some extent. However, most of the clinical PNS complicated infections are concealed and easy to miss diagnosis, so the possibility of higher infection rate is not ruled out. If the ratio is too high, it means the frequency of antibiotic use is too high and may warn us whether rational the antibiotic use is or whether there are many nosocomial infection. Then, the clinical pharmacist should conduct prescription check to help doctors use antibiotics rationally. Besides, studies have shown that the incidence of nosocomial infections increases significantly after 20 days of admission, and the general length of hospital stay is preferably controlled within 20 days.^[3] So, minimizing the length of hospital stay and reducing the chance of contact with pathogenic bacteria are both good ways for children with PNS. While, the ratio cannot help us judge the specific details of the antibiotics use.

Item 1.2 was 5.67%, which was from the Japanese guideline (2013). In this guideline, RAS inhibitors were recommended to reduce urinary protein for patients with both nephrotic syndrome and hypertension. While whether RAS inhibitors could effectively reduce urinary protein levels in patients with nephrotic syndrome without hypertension was unclear.^[10] So, the lower the ratio, the better.

Proportion of albumin use is 6.45% (item 1.3), which is low and I prefer to regard it as a reasonable ratio, because I think the use of albumin may aggravate edema and proteinuria and further decline in renal function. Although Rajmohan and other studies have also confirmed that the combined use of albumin can enhance the sodium excretion of furosemide.^[4] However, albumin is expensive and may cause serious complications such as blood-borne infections and anaphylactic shock. And its use does not achieve the expected effect of improving hypoproteinemia, but will cause "protein overload kidney disease". If the more the amount of human albumin infused, the longer it will take to achieve complete remission, and the increased risk of refractory nephropathy will be greatly increased. When the daily infusion of albumin exceeds 20g, the damage to the kidneys is particularly prominent.

No guidelines recommended to use immune enhancers, while all guidelines referred that immunization in children with NS would decline, especially after using hormones. So we self-made item 1.4 to observe the frequency of immune enhancers use, and

the result was 14.81%, which was not high. Although a low score doesn't represent RDU, a high score could bring us some warnings—too much abuse.

Proportion of calcium phosphatase inhibitors (CNI) use was 100.00% (item 1.5), which was in agreement with the Canadian Nephrology Society guideline (CNS 2014). The guideline referred: tacrolimus (calmodulin inhibitor) is recommended as the first choice in the second-line regimen.^[5] But on the other hand, all the children using CNI were only 8 in this research, so it might give us little information. Therefore, we need a larger sample size to validate the indicator.

Although PNS are manifested in the kidney, they have certain effects on other systems of the body. PNS generally uses glucocorticoids and immunosuppressive agents as the main treatment methods. There are many reports in the literature that the bone metabolism of children is abnormal during hormone therapy;^[6] other reports indicate that PNS itself is for adults or children. Bone metabolism can have certain effects.^[7,8] Therefore, children with PNS may have short stature, glucocorticoid-related osteoporosis, fractures and other complications. It is known from the literature that in the course of treatment with glucocorticosteroids, an appropriate amount of vitamin D and calcium supplementation can effectively alleviate the above-mentioned adverse reactions;^[9] the Japanese guideline (2013) suggested that nephrotic syndrome is a risk factor for decreases in bone mineral density and compression fractures.^[10] In this study, the result was only 10.5% (item 1.6), which was low. Therefore, we conducted a small scale investigate and the reasons were mainly 2 points: 1 was the calcium used as an over-the-counter drug and patients could buy it outside; the other was some parents had prepared enough calcium tablets for children at home, so they had no necessity to buy calcium again.

The KDIGO guidelines recommended the prednisone for PNS,^[11] but in the investigation, the ratio was only 25.93% (item 1.7). Reasons were as followed: Methylprednisolone or hydrocortisone were often used. Although the effect of both were the same as prednisone, methylprednisolone had a slight increase in anti-inflammatory effect due to methyl substitution, and the sodium retention effect was significantly reduced, the effect of hydrocortisone was 1.25 times that of cortisone.^[12]

Item 1.8 was a negative indicator and item 1.9 was a positive indicator, item 1.10 was also a negative indicator and made by the group.

Hormone therapy for first-onset nephrotic syndrome requires adequate and adequate course of treatment. A sufficient amount and sufficient course of treatment are the key to initial treatment, which can reduce the recurrence rate of 1–2 years after onset. According to the experts' suggestion, we set a max dosage, and the proportion is 48.15%, which is a little high. Therefore, we need to pay attention to the RDU. The guideline suggested use diuretics by intravenous administration but proportion is only 9.68%,^[9] we thought this is not the best way to RDU (item 2.2). The guideline (China 2010) suggested item 2.3 and the result is 87.50%, which is good.

We self-made the item 2.4 and result was 8.82%, which was good. We considered that diuretic drugs combined with antihypertensive drugs, the effect was enhanced, but easy to cause severe hypotension, the combination of angiotensin converting enzyme inhibitors and Angiotensin II receptor antagonists isn't advocated currently. Although the combination of the 2 drugs can better reduce urinary protein, the risk of

doubling creatinine and dialysis is greater. In 2008, the American Heart Association (ACC) published the world's largest ONTARGET study, although the study's population is inconsistent with ours, the results can be referred to. It reported that in patients with high cardiovascular risk, the combination of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists was not superior to a single drug, but the adverse reactions (kidney damage, blood potassium greater than 5.5mmol/L) were significantly increased.^[13]

We estimated the initial treatment (3 days before admission) and 80.65% patients had received diuretics therapy (in item 2.5). The ratio is high and not good, because experts think when children with PNS have high edema, they often use diuretics to diuresis, but the effect is not ideal, and sometimes there are complications. If the kidney function of the children is sensitive to hormones, hormone will be the best diuretic. Generally, diuresis begins 1 to 10 days after taking the hormone.

In item 2.6, we recommend patients should be monitored for CNI blood concentration, but only 10% of patients have completed, indicating that the RDU of CNI is worth strengthening.

5. Application and Disadvantages

At present, there is no criterion for the numerical indicators of results. Only based on the results of the same indicators in different hospitals, a horizontal comparison can be made to provide reference and warning for the rational use of hospitalized children in hospitals. Other hand, some indicators were limited to a certain population not all PNS children and not all indicators were positive or negative indicators, such as item 1.2, the lower and the better, to some extent, it may not be convenient. So, further research is in need and we are in progress.

6. Conclusion

All indicators are feasible, but the operability and applicability need further research and improvement.

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Author contributions

ML, LLZ and LNZ conceived the study. ML and LNZ developed the initial indicators, ML collected and analysed the data and drafted and revised the manuscript, and LLZ and LNZ read and approved the final manuscript. All members revised the indicators.

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