

## Evaluation of the Rationality of Appropriate Doses of Corticosteroid Drugs in Patients With Nephrotic Syndrome in Hospitals

Susan Sintia Ramdhani<sup>1</sup>, Nurhidayati Harun<sup>1</sup>, Tina Marlina<sup>1</sup>

<sup>1</sup>Pharmacy Study Program, STIKes Muhammadiyah Ciamis, West Java, Indonesia

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### Correspondence

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E-mail : [susansintiar@gmail.com](mailto:susansintiar@gmail.com)

### ABSTRACT

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Nephrotic syndrome is a kidney disease where symptoms include massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia. This nephrotic syndrome disease is more often found in cases of children than adults. The purpose of this study was to determine the accuracy of dosage in patients with nephrotic syndrome. The method used in this study is a qualitative descriptive method of obtaining data retrospectively by taking a sample population of nephrotic syndrome patients in the Outpatient Installation of the Ciamis Hospital January-July 2020 Period. Descriptive analysis includes dose accuracy based on Kidney Disease: Improving Global Outcomes (KDIGO) management which is presented in the form of tables and narratives. The results of this study indicate that the ratio between men and women is 3: 1 with age under 15 years. There were 18 cases of nephrotic syndrome that used corticosteroid therapy. The most widely used corticosteroids were methylprednisolone 61.1% (11 patients) and prednisone 38.9% (7 patients). The use of doses in 18 cases of nephrotic syndrome was declared appropriate (100%) and in accordance with management recommendations.

## INTRODUCTION

Nephrotic Syndrome (SN) is a kidney disease in which symptoms that arise include massive proteinuria, edema, hypoalbuminemia and hyperlipidemia (Manalu, 2019). This nephrotic syndrome disease has special characteristics, namely frequent relapses, frequent failures in treatment and complications arising either from co-morbidities or due to the treatment itself (Simanullang, 2020). Pathogenic abnormalities that underlie nephrosis are proteinuria, a result of increased permeability of the glomerular capillary walls. The mechanism for this increase in permeability is unknown but may be related to the loss of negatively charged glycoproteins in the capillary wall. In nephrosis status, protein loss usually exceeds 2 g/24 hours, which mainly consists of albumin (Tjiptaningrum et al, 2016).

The prevalence in Indonesia is reported as 6 per 100,000 per year in children aged less than 14 years. The ratio of boys and girls 2:1 varies up to 3:2. The incidence of nephrotic syndrome in adults is three new cases per 100,000 every year (Amalia, 2018). This nephrotic syndrome is included in the three most common kidney diseases that occur in children and is said to rank first with a percentage of 35%, followed by post-streptococcal acute glomerulonephritis (GNAPS) 26%, and urinary tract infections 23% (Avner et al., 2015).

The study group conducted by the International Study of Kidney Disease in Children (ISKDC) and according to Kidney Disease: Improving Global

Outcomes (KDIGO) (2012) recommends that in the first 4 weeks prednisone is given 60 mg/m<sup>2</sup> or 2 mg/kg every day followed by 4 weeks secondly at 40 mg/m<sup>2</sup> or 1.5 mg/kg alternately or intermittently (maximum 40 mg daily) and continued for 2-5 months with

Reduce the dose and then evaluate the progress of treatment. Nephrotic syndrome has first-line therapy, namely by using oral corticosteroids, the corticosteroids that are usually given are prednisolone or oral prednisone. In addition to corticosteroids, immunosuppressants are also indicated for nephrotic syndrome, especially for SNRS such as cyclophosphamide, cyclosporine and rituximab (Downie et al., 2017).

Based on the Regency/City Health Profile, there were new cases of nephrotic syndrome at the age of 5-14 years with a total of 395 (0.67%) in the West Java Provincial Hospital (Health Office, 2012). Cases of nephrotic syndrome that occurred in Ciamis Regency were in the 2015-2016 study which stated that the number of cases of Nephrotic Syndrome for the January-December 2015 period in the Melati Room of the Regional Public Service Agency of the Ciamis Regional General Hospital was 13 cases, then in the January-December 2015 period In May 2016 there were 3 cases of Nephrotic Syndrome (Siswadi, 2016). Based on this research background, the authors are interested in conducting research on dosage accuracy by evaluating the Rationality of Appropriate Dosage of Corticosteroid Group Drugs in Nephrotic Syndrome Patients in Hospitals.

## METHOD

This research is a descriptive retrospective study using secondary data in the form of patient medical records. The object of the study was the medical record data of patients with a diagnosis of nephrotic syndrome at Outpatient Hospital Ciamis Hospital in the period January-July 2020. This research was conducted in the Medical Record Installation section at Ciamis Hospital from April 30 to May 5 2021. The sampling technique used in this study i.e. total sampling. The inclusion criteria in this study were all patient medical record data

with a diagnosis of nephrotic syndrome, patients undergoing therapy using corticosteroid class drugs, non-obese nephrotic syndrome patients (<90kg body weight). While the exclusion criteria in this study were patients with acute or chronic renal failure, other chronic diseases such as chronic hypertension, tuberculosis, malignancy, and severe malnutrition as well as patients who died during treatment.

Appropriate medical record data were used for the study of 18 patients. The data that has been collected will be analyzed statistically descriptive in the form of frequency and distribution to describe the use of corticosteroid class of drugs related to the correct dose adjusted for management recommendations in Kidney Disease: Improving Global Outcomes (KDIGO). Then tabulating the dose calculation and the percentage of suitability is processed using Microsoft Excel format.

## RESULTS AND DISCUSSION

Nephrotic syndrome is classified as a disease that doesn't appear often, but this disease requires high vigilance, especially in children. The side effects caused by

nephrotic syndrome will be more severe if not treated early. Nephrotic syndrome can occur in any intrinsic or systemic renal disease affecting the glomerulus. The most common sign of nephrotic syndrome is an increase in body fluids including periorbital edema

which is more visible in the morning (Andriyani et al., 2021). Edema is the predominant clinical condition of the syndrome which occurs with varying degrees of severity, ranging from moderate to localized edema on specific body sites (face, legs, abdomen, genitals) to massive generalized edema (Pasini et al., 2017).

In the 18 cases of nephrotic syndrome studied, the initial symptoms were edema, proteinuria, and hypoalbuminemia. Where most of the patient's first complaints are physically the most prominent, namely edema, in which edema is a symptom characterized by swelling caused by fluid accumulation. Usually patients who come with symptoms of edema or swelling starting from the moon face to swelling all over the body.

### Characteristics of Nephrotic Syndrome Patients Based on Age

The incidence of nephrotic syndrome is reported to occur in children under 16 years. The age of the patients with nephrotic syndrome studied was mostly under the age of 15 in 11 patients (61.1%) (table 1).

One of the factors that can predict response to therapy and renal outcome is the SN genetic variant. There are several genetic mutations in genes that play a role in the occurrence of severe nephrotic syndrome, namely NPHS1, NPHS2, ACTN4, CD2AP, WT1, TRPC6, LAMB2. Happening

mutations in these genes result in changes in the glomerulus, which can cause severe proteinuria (Hjorten et al., 2016).

**Table 1. Nephrotic syndrome patients by age**

Age	Frequency (n=18)	Percentage (%)
2-15	11	61,1%
16-30	7	38,9%
Total	18	100%

Factors that can cause nephrotic syndrome include genetic factors that allow it to occur at the age of 2-15 years and it can also occur due to basic immunological disorders or disturbances of cellular immunity and lifestyle which may influence each other in the occurrence of the syndrome nephrotic. At the age of 5-15 years this is included in the process of social development, which since entering school age, intellectual, social, and emotional development are factors that influence a child's perception of psychosocial and quality of life (Suryanagara et al., 2016).

### Characteristics of Nephrotic

### Syndrome Patients Based on Gender

From several studies say that gender affects the occurrence of nephrotic syndrome, which occurs more often in men than women. In 18 cases of nephrotic syndrome, most of them occurred in males with a percentage of 72.2% compared to 27.8% in females (table 2).

The results of the study showed that based on gender, the majority of nephrotic syndrome patients were male with a ratio of around 70% more male than female. This shows that the results of this study are the same as previous studies.

**Table 2. Patients with nephrotic syndrome by sex**

Gender	Frequency (n=18)	Percentage (%)
Man	13	72,2%
Woman	5	27,8%
Total	18	100%

In the male sex, it is known that hormonal factors have a large enough contribution. In men, the hormone testosterone, which is almost 100% in blood plasma bound to protein, in nephrotic syndrome, there is damage to glomerular filtration which causes protein to escape in the urine. So that in men it is likely to have a higher incidence (Nugroho, 2016). However, the relationship between nephrotic syndrome and hormones is still

unclear, because the effect of the hormones estrogen and progesterone on the progress of glomerular damage is unknown (Nurhasnah et al., 2018).

### Urine Protein Levels in Nephrotic Syndrome Patients

Edema that occurs in patients is theoretically related to the level of protein contained in the urine, during urination, patients with nephrotic syndrome

experience protein excretion with special characteristics of dark and frothy urine. This proteinuria examination, which is often called a urinal examination, can be used as a diagnosis of nephrotic syndrome.

Proteinuria +4 has the highest number of patients with nephrotic syndrome, with a total of 8 people (44.5%).

As many as 8 people (88%) were included in the category of massive proteinuria (table 3).

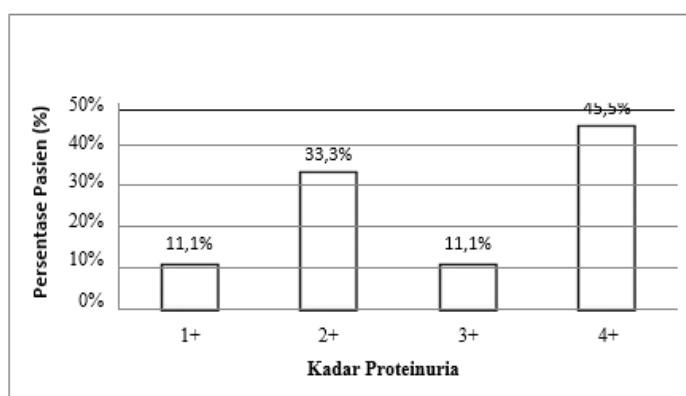
**Table 3. Patients with nephrotic syndrome according to urine examination**

Urine Proteins	Frequency (n=18)	Percentage (%)
+1	2	11,1%
+2	6	33,3%
+3	2	11,1%
+4	8	44,5%
Total	18	100%

Normally in every healthy human being, approximately 150 mg of protein is excreted into the urine every day (Jumaydha et al., 2016). This proteinuria is thought to result from increased permeability of the glomerular capillary walls. The mechanism for this increase in permeability is unknown, but it may be related to the loss of the negative charge of glycoproteins in the capillary walls and result in albuminuria (Andriyani et al., 2021).

Routine urine examination using the dipstick method which is a semi-quantitative urine examination (Tjiptaningrum et al, 2016).

The graph above shows that the urine examination results of nephrotic syndrome patients show more patients with +4 proteinuria (graph 1). The condition of a patient with +4 proteinuria in which the urine is very cloudy and the turbidity is condensed due to excretion of urine with too much protein. Several possible factors occurred because at the time of the urinal examination, which was already in a state of massive proteinuria, the symptoms caused were not very clear and the patient's cost factor resulted in delays in prevention and supporting examinations



**Figure 1. Graph of urine examination results of patients with nephrotic syndrome**

### Use of Corticosteroids in Patients with Nephrotic Syndrome

Patients with nephrotic syndrome have the main therapy using immunosuppressants, especially corticosteroids. These corticosteroids remain the standard first-line treatment of nephrotic syndrome to achieve full remission (Welegerima et al., 2021).

In this study, based on the patient's response to corticosteroids, more patients with nephrotic syndrome who often experience relapses (SNRS) were found during treatment using corticosteroids. The most widely used corticosteroids were methylprednisolone (61.1%) and prednisone (38.9%) (table 4).

**Table 4. Patients with nephrotic syndrome according to the use of corticosteroid drugs**

Corticosteroids used	Frequency (n=18)	Percentage (%)
Prednisone	7	38,9%
Methylprednisolone	11	61,1%
Total	18	100%

Prednisone is used as the first line of treatment for patients with nephrotic syndrome. Therapeutic response and side effects vary depending on the individual patient. It is said that this prednisone has no glucocorticoid effect but can work after being converted to the active metabolite of hydroxylated prednisolone, and its plasma concentration may be higher than that of the parent drug. This occurrence depends on the severity of the disease and the pharmacokinetic factors of the drug. According to one study which stated that the volume of distribution and plasma clearance of prednisone increased during the acute phase of nephrotic syndrome but decreased when clinical improvement of the disease was obtained (Muryawan et al., 2017).

As for other corticosteroids, namely methylprednisolone, it is sometimes used for first-line therapy for steroid-sensitive nephrotic syndrome (SSNS) (Pasini et al., 2017). Methylprednisolone has indications for inducing diuresis or for reducing symptomatic proteinuria in

idiopathic nephrotic syndrome. Methylprednisolone also reduces

binding of immunoglobulins to cell surface receptors and inhibiting the synthesis and/or release of interleukins, resulting in a decrease in T-cell blastogenesis and a decrease in the expansion of the primary immune response (Dexa Medica, 2020). Therefore, long-term treatment is necessary to prevent recurrence.

In this study the factors that led to the use of methylprednisolone were more than prednisone because patients with nephrotic syndrome required pulse therapy of methylprednisolone by tapering off in patients with steroid sensitive nephrotic syndrome (SSNS). The other influencing factor is the availability of drugs.

### Use of drug combinations in patients with nephrotic syndrome

In addition to using a single corticosteroid therapy, a combination of

drugs can be used to get better therapeutic results. This drug combination is needed because it has a greater therapeutic effect than if the drug is used alone.

**Table 5. Patients with nephrotic syndrome according to drug combinations**

<b>Drug Combination</b>	<b>Frequency (n=18)</b>	<b>Percentage (%)</b>
Single corticosteroid	2	11,1%
Corticosteroids + Vitamins	7	38,9%
Corticosteroids + Vitamins + ACE	3	16,7%
Corticosteroids + Vitamins + Antibiotics	2	11,1%
Corticosteroids + Vitamins + Diuretics	4	22,2%
<b>Total</b>	<b>18</b>	<b>100%</b>

The drug combination most often used in nephrotic syndrome patients was corticosteroids + vitamin D (38.9%) (table 5). Apart from corticosteroids, another drug given to patients in this study was furosemide. The administration of this diuretic class of drugs aims to increase urine production and reduce symptoms of edema in patients. There are also patients who use combination drugs with spironolactone works by lowering blood pressure and also reducing fluid accumulation in the body in patients with nephrotic syndrome (Prabu, 2015). Administration of Angiotensin converting enzyme (ACE) inhibitors in some patients using the drug captopril. Aims to reduce proteinuria by lowering blood pressure, reducing intra-glomerular pressure and reducing the risk of progression of kidney disorders in patients with secondary nephrotic syndrome (Mughtar et al., 2015). Long-term use of corticosteroids can also increase the risk of infection. Therefore, for the purpose of preventing and treating infection, antibiotics are given to patients (Dewi, 2019). Giving vitamins containing aquamin calcium and vitamin D3 is used to help meet the needs

of calcium and vitamin D, because if a nephrotic syndrome patient takes long-term steroid class drugs it has side effects in the form of growth disorders, osteoporosis. So it is minimized effectively by consuming vitamins (Sinta, 2020).

#### **Rationality of Dosage in Patients with Nephrotic Syndrome**

Rationale or accuracy of drug dosage within the range of therapeutic doses, in terms of daily use dose based on the patient's special conditions (Kartika Untari et al., 2018). Factors that affect the dose include age, body weight and physiological state.

In this study the criteria for the right dose were based on the suitability of the dose of 1x-1 day of drinking with the calculation of the dose according to the interval of corticosteroid therapy. Full dose prednisone has a maximum dose of 80 mg/day. Then methylprednisolone has the maximum dose 60 mg/day, while for the use of pulse methylprednisolone it has a maximum dose of 1000 mg/day in patients with steroid-resistant nephrotic

syndrome (Trihono et al., 2012).

Processing of data from medical

records of patients with nephrotic syndrome which was taken resulted in 100% correct dose (table 6).

**Table 6. Patients with nephrotic syndrome according to the right dose**

Category	Frequency (n=18)	Frequency (n=18)
Correct Dosage	18	100%
Incorrect Dosage	-	-
Total	18	100%

Nephrotic syndrome is a condition that requires gradual treatment and cannot be given immediately in full. The dosage must also be adjusted according to the patient's condition. In the 18 cases studied, many patients were in the tapering off phase. Because the data on nephrotic syndrome patients obtained were not fully treated from the start, it is possible that nephrotic syndrome patients are in the tapering off stage which causes drug administration to not be completely the same as the initial dose given. During this tapering off period, the patient is given the lowest dose of drug to achieve remission. Calculation of the dose is more accurate using the patient's body weight, but in this study there were limitations in the medical records where not all patient data resumes included body weight.

After analyzing the patient dose, the results showed that of the 18 cases experienced the right dose (100%). The patient was stated to be on the right dose because the dose given was appropriate and did not exceed the maximum dose stated in the recommendations for the management of nephrotic syndrome.

There are some limitations in this research. First, the collection of data obtained from retrospective secondary data from medical records, not all of the data was collected at the start of treatment. Second, this study has a small sample size

or not many. Third, this study did not evaluate all factors that might be predictive of nephrotic syndrome due to study limitations. Based on some of these weaknesses, further research is needed with a larger number of samples and sufficient time to get better research results.

## CONCLUSIONS AND RECOMMENDATIONS

In this study found as many as 18 cases of nephrotic syndrome patients who used corticosteroid therapy. The most widely used corticosteroids were methylprednisolone 61.1% (11 patients) and prednisone 38.9% (7 patients). The dosage used in 18 cases of nephrotic syndrome was stated to be the correct dose (100%) according to the recommendations for the management of Kidney Disease: Improving Global Outcomes (KDIGO). This nephrotic syndrome requires early treatment to get therapy so as to minimize its severity.

## SUGGESTION

It is necessary to carry out further research on nephrotic syndrome starting from the proper use of drugs from various aspects in detail with the 4T (right indication, right patient, right drug, right dose). (Ramdhani et al., 2022)



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