EVALUATION OF TREATMENT OUTCOMES AND PROGNOSTIC FACTORS IN MANAGING CHILDREN WITH STEROID SENSITIVE NEPHROTIC SYNDROME IN MALAYSIA

KHAIRUNNISA BINTI MOHAMAD

UNIVERSITI SAINS MALAYSIA

2025

EVALUATION OF TREATMENT OUTCOMES AND PROGNOSTIC FACTORS IN MANAGING CHILDREN WITH STEROID SENSITIVE NEPHROTIC SYNDROME IN MALAYSIA

by

KHAIRUNNISA BINTI MOHAMAD

Thesis submitted in fulfilment of the requirements
for the degree of
Master of Science

May 2025

ACKNOWLEDGEMENT

In the name of Allah, the most Gracious, the most Merciful. All praise to Allah for giving me the opportunity to explore the knowledge and continuous endurance to accomplish this degree. First and foremost, I extend my sincere gratitude to my main supervisor, Dr. Hadzliana Zainal, for her invaluable advice and guidance at every stage of this process. I am deeply thankful to my co-supervisor, Dr. Nur Arzuar Abdul Rahim, for his insightful comments and suggestions throughout the study. Additionally, I would like to acknowledge Dr. Tengku Hasnita Tengku Hussain for her invaluable contributions to the development and validation of this study.

I am very grateful to Allah for blessing me with such a supportive family. I would like to convey my appreciation to my mother, Pn. Salmiah Ishak, and my husband, Ahmad Khaidir Zuhidin for their unwavering support, prayers, and help in every way. May Allah grant both of you the greatest rewards for your sacrifice and kindness. Special heartfelt thanks to my children, Khalisah, Arsyad, and Khayra, for their unconditional love and understanding.

I would also like to thank all the staff at each study centre, particularly the pharmacists and specialists, for their invaluable contributions to patient identification. Additionally, I am immensely grateful to the staff at the Paediatric Clinic and Record Department for their indispensable assistance in record tracing throughout the data collection process. Finally, I wish to express my deepest appreciation to the Ministry of Health, Malaysia for granting study leave and providing financial support for my degree.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF ABBREVIATIONS AND SYMBOLS

+	Plus
±	Plus-minus
ACE	Angiotensin-converting enzyme
AKI	Acute kidney injury
aOR	Adjusted odds ratio
APN	Arbeitsgemeinschaft fur Paediatrische Nephrologie
ARB	Angiotensin receptor blockers
ARR	Annualised relapse rate
AUC	Area under curve
BAPN	British Association for Paediatric Nephrology
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
C3	Complement component 3
C4	Complement component 4
CI	Confidence interval
CNI	Calcineurin inhibitor
e.g.	“exempli gratia” (for example)
eGFR	Estimated glomerular filtration rate
FR/SDNS	Frequent relapse or steroid dependent nephrotic syndrome
FRNS	Frequent relapse nephrotic syndrome
FSGS	Focal segmental glomerulosclerosis
g/L	Gram per litre

HIS	Hospital information system
IFRNS	Infrequent relapse nephrotic syndrome
IgA	Immunoglobulin A
IL	Interleukin
INS	Idiopathic nephrotic syndrome
IPNA	International Pediatric Nephrology Association
ISKDC	International Study for Kidney Diseases in Children
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
kg/m^2	kilograms per square metre
MCD	Minimal change disease
mg/dL	Milligrams per decilitre
mg/kg/day	Milligrams per kilogram per day
mg/m^2	Milligrams per square metre
mg/m^2/day	Milligrams per square metre per day
mg/mg	Milligrams per milligram
mg/mmol	Milligrams per millimole
mmHg	Millimetre of mercury
MOH	Ministry of Health
NS	Nephrotic syndrome
OR	Odds ratio
PhIS	Pharmacy Information System
QOL	Quality of life
RBC/HPF	Red blood cells per high power field
RCT	Randomised control trial

SD	Standard deviation
SDNS	Steroid dependent nephrotic syndrome
SRNS	Steroid resistant nephrotic syndrome
SSA	Steroid sparing agent
SSNS	Steroid sensitive nephrotic syndrome
UPCR	Urine protein creatinine ratio
URTI	Upper respiratory tract infection
µg.h/ml	Micrograms times hour per millilitre

LIST OF APPENDICES

PENILAIAN HASIL RAWATAN DAN FAKTOR PROGNOSTIK DALAM PENGURUSAN KANAK-KANAK DENGAN SINDROM NEFROTIK SENSITIF STEROID DI MALAYSIA

ABSTRAK

Sindrom nefrotik sensitif steroid (SSNS) dalam kalangan kanak-kanak secara amnya mempunyai prognosis positif, namun ianya lebih sukar sekiranya pesakit mengalami relaps yang kerap atau sindrom nefrotik yang bergantung kepada steroid (FR/SDNS). Steroid, terutamanya prednisolone merupakan rawatan utama, manakala ejen *steroid sparing* (SSA) dikhaskan untuk mereka yang mengalami relaps yang kerap, ketoksikan steroid yang ketara, atau kebergantungan steroid yang berterusan. Walaupun protokol rawatan telah berubah dari masa ke semasa, kajian mengenai keberkesanan pengurusan SSNS dalam kalangan kanak-kanak di Malaysia masih terhad. Oleh itu, kajian ini bertujuan menilai hasil rawatan serta mengenal pasti faktor prognostik yang mempengaruhi perkembangan FR/SDNS dan keperluan terapi SSA. Kajian kohort di beberapa hospital secara retrospektif ini melibatkan 216 kanak-kanak SSNS, dengan median tempoh pemantauan selama 3.4 tahun (julat 1.0-15.0). Kajian ini mendapati 58.8% mengalami FR/SDNS, 27.3% mengalami relaps yang jarang berlaku, dan 13.9% menunjukkan remisi jangka masa panjang. Rawatan awal steroid sama ada mengikut protokol yang pendek atau panjang, tidak mempengaruhi risiko mengalami FR/SDNS (p=0.619). Namun, pesakit FR/SDNS didapati mengalami relaps pertama lebih awal (median: 4.2 bulan, julat: 1.0-37.7) serta insiden kesan sampingan steroid yang lebih tinggi (50.4%). Relaps dalam tempoh enam bulan selepas diagnosis dikaitkan dengan perkembangan FR/SDNS (*adjusted odds ratio* [aOR] 7.04, 95% *Confidence Interval* [CI] 3.53-14.02). Dalam kalangan pesakit

FR/SDNS, 42.1% kes berjaya dikawal dengan monoterapi steroid, manakala 45.5% memerlukan SSA. Keperluan SSA dikaitkan dengan relaps awal dalam tempoh kurang daripada tiga bulan selepas diagnosis FR/SDNS (*adjusted hazard ratio* [aHR]=2.26, 95% CI 1.26-4.05). Cyclophosphamide atau levamisole sebagai SSA pertama menunjukkan pengurangan kadar relaps yang ketara ($p<0.001$) dengan hasil yang setanding selepas satu tahun, manakala levamisole dan cyclosporine A didapati berkesan sebagai rawatan pilihan selepas kegagalan rawatan cyclophosphamide. Kajian ini menekankan keberkesanan yang setara antara protokol rawatan awal steroid yang pendek dan panjang serta keperluan strategi rawatan berasaskan risiko. Kajian lanjut diperlukan untuk menyiasat hasil pengenalan awal terapi SSA berdasarkan masa relaps disamping memperhalusi garis panduan dalam mengoptimumkan pengurusan penyakit SSNS dalam kalangan kanak-kanak.

EVALUATION OF TREATMENT OUTCOMES AND PROGNOSTIC FACTORS IN MANAGING CHILDREN WITH STEROID SENSITIVE NEPHROTIC SYNDROME IN MALAYSIA

ABSTRACT

Steroid sensitive nephrotic syndrome (SSNS) in children generally has a positive prognosis, yet a subset experiences frequent relapses or steroid dependent nephrotic syndrome (FR/SDNS), posing management challenges. Steroids, mainly prednisolone, are the first-line treatment, with steroid sparing agents (SSAs) reserved for ongoing relapses, steroid toxicity, or persistent steroid dependency. Despite evolving treatment protocols, studies on SSNS management outcomes in Malaysian children remain limited. Therefore, this study aimed to assess treatment outcomes and identify prognostic factors influencing FR/SDNS development and the need for SSA. This retrospective multicentre cohort study followed 216 children with SSNS for a median of 3.4 years (range 1.0–15.0). Among them, 58.8% developed FR/SDNS, 27.3% had infrequent relapses, and 13.9% achieved sustained remission. The initial steroid protocol, either short or prolonged, did not influence FR/SDNS risk (p=0.619). However, FR/SDNS patients experienced earlier first relapses (median: 4.2 months, range: 1.0-37.7) and a higher incidence of steroid-related adverse effects (50.4%). A relapse within six months of diagnosis was strongly associated with FR/SDNS development (adjusted odds ratio [aOR] 7.04, 95% CI 3.53-14.02). Among FR/SDNS cases, 42.1% were managed with steroid monotherapy, while 45.5% required SSAs. The need for SSA was linked to an early relapse of less than three months post-FR/SDNS diagnosis (adjusted hazard ratio [aHR] 2.26, 95% CI 1.26-4.05). Cyclophosphamide or levamisole as the first SSA significantly reduced relapse rates

($p<0.001$) with comparable one-year outcomes, while levamisole and cyclosporine A were effective for post-cyclophosphamide treatment failures. This study underscores the comparable efficacy of short and prolonged initial steroid protocols and the need for risk-stratified treatment strategies. Future research should investigate the early introduction of SSA therapy based on relapse timing and further refine SSNS management approaches.

CHAPTER 1

INTRODUCTION

1.1 Overview of Nephrotic Syndrome

Nephrotic syndrome (NS), a disease characterised today as a clinical syndrome of severe proteinuria, hypoalbuminemia, and oedema (International Pediatric Nephrology Association [IPNA], 2023) was not a well-documented condition in the past, although general oedema has been described in literature since the time of Hippocrates (Pal and Kaskel, 2016). Consequently, the condition was treated as a disease with unclear organ sources until Theodore Zwinger of Basel described general oedema as a kidney ailment in 1722 (Pal and Kaskel, 2016). However, the concept of NS as a disease was only established in 1830 (Pal and Kaskel, 2016).

Children with NS often present clinically with initial periorbital swelling, which may progress to involve the abdomen and lower extremities. In childhood NS cases, oedema typically manifests bilaterally, symmetrically, and shows pitting upon pressure. In severe cases, oedema may become generalised and worsen, necessitating intervention (IPNA, 2023). Additional clinical indicators may include frothy or foamy urine and a history of antecedent upper respiratory tract infections (URTI) (Noone et al., 2018).

Complications frequently encountered at the time of NS diagnosis or during relapse encompass infections, acute kidney injury (AKI), and hyperlipidaemia (Noone et al., 2018). Less commonly observed complications include hypovolemic crisis and thromboembolism. Early signs of spontaneous bacterial peritonitis may include abdominal pain and fever. More serious symptoms, like neurological signs or irritability along with headaches, could be the signs of cerebral venous sinus

thrombosis (Noone et al., 2018). Additionally, other types of infections, haematuria, and hyperglycaemia may also be evident during hospitalisation (Welegerima et al., 2021).

1.1.1 Diagnosis of nephrotic syndrome in children

The diagnosis of NS is made based on clinical characteristics of nephrotic-range proteinuria, defined as urine protein creatinine ratio (UPCR) of at least 200 mg/mmol (2 mg/mg) in a spot urine, or at least 1000 mg/m^2 per day in a 24 h urine sample corresponding to 3+ (300–1000 mg/dL) or 4+ (≥ 1000 mg/dL) by urine dipstick, and either hypoalbuminemia (serum albumin of < 30 g/L) or oedema, if the serum albumin level is not available (IPNA, 2023). Children presented with macroscopic haematuria should be investigated for complement C3 and C4 levels, antinuclear and anti-streptococcal antibodies, and antineutrophilic cytoplasmic antibodies to rule out autoimmune disease and post-streptococcal glomerulonephritis (IPNA, 2023).

1.1.2 Aetiology of childhood nephrotic syndrome

Childhood NS can be classified based on its aetiology into three main types namely primary, secondary, and congenital. Primary NS, commonly referred to as idiopathic nephrotic syndrome (INS), represents the most frequently encountered form (Noone et al., 2018). The precise aetiology of INS remains elusive, with no specific underlying medical condition or trigger identified. However, current understanding suggests that INS may arise from a complex interplay of genetic predisposition, environmental factors, and immune system dysfunction (Hussain et al., 2013). In contrast, secondary childhood NS arises due to an underlying medical condition or trigger, including autoimmune diseases, infections, and certain medications. Meanwhile, congenital NS is a rare variant of childhood NS that manifests from birth,

stemming from genetic mutations resulting in abnormal kidney development and function, or, more rarely, triggered by infection (Noone et al., 2018).

Genetic predisposition in INS differs from genetic mutations in congenital NS in terms of inheritance pattern, disease mechanism, and the timing of disease onset. Idiopathic nephrotic syndrome was traditionally considered a polygenic disorder, where multiple genetic variations contribute to an individual's susceptibility (Lane et al., 2019). These variations, often linked to immune regulation, interact with environmental and immunological factors, influencing disease onset (Lane et al., 2019). However, recent genomic studies suggested that a subset of INS cases may be monogenic, where a single gene mutation is sufficient to cause the severe form of the disease (Gbadegesin et al., 2021).

Meanwhile, congenital NS is a monogenic disorder caused by pathogenic mutations in genes essential for kidney function (Wang and Mao, 2016). These genetic mutations lead to severe, early-onset proteinuria, which usually presents at birth or within the first three months of life, establishing congenital NS as a hereditary disorder with a direct genetic cause (Lane et al., 2019). Approximately 80% of affected children have genetic forms of the disease, with most being resistant to standard therapies (Lane et al., 2019). Despite these genetic complexities, this study specifically focuses on investigating childhood INS.

1.1.3 Pathophysiology of idiopathic nephrotic syndrome

The pathophysiology of INS revolves around the complex dysfunction of the glomerular filtration barrier, a highly specialised part of the kidneys responsible for regulating blood filtration and allowing only specific molecules to pass from the blood into the urine (see Figure 1.1). It is built up of three main layers of endothelial cells

lining the inner glomerular capillaries, glomerular basement membrane, and glomerular visceral epithelial cells known as podocytes (Van Den Berg and Weening, 2004). Podocytes are specialised endothelial cells covering the outer side of glomerular capillaries, with extension shapes called foot processes connected by a unique cell junction known as the slit diaphragm. An advanced actin cytoskeleton secures normal podocyte function, mainly localised within the foot process (Downie et al., 2017).

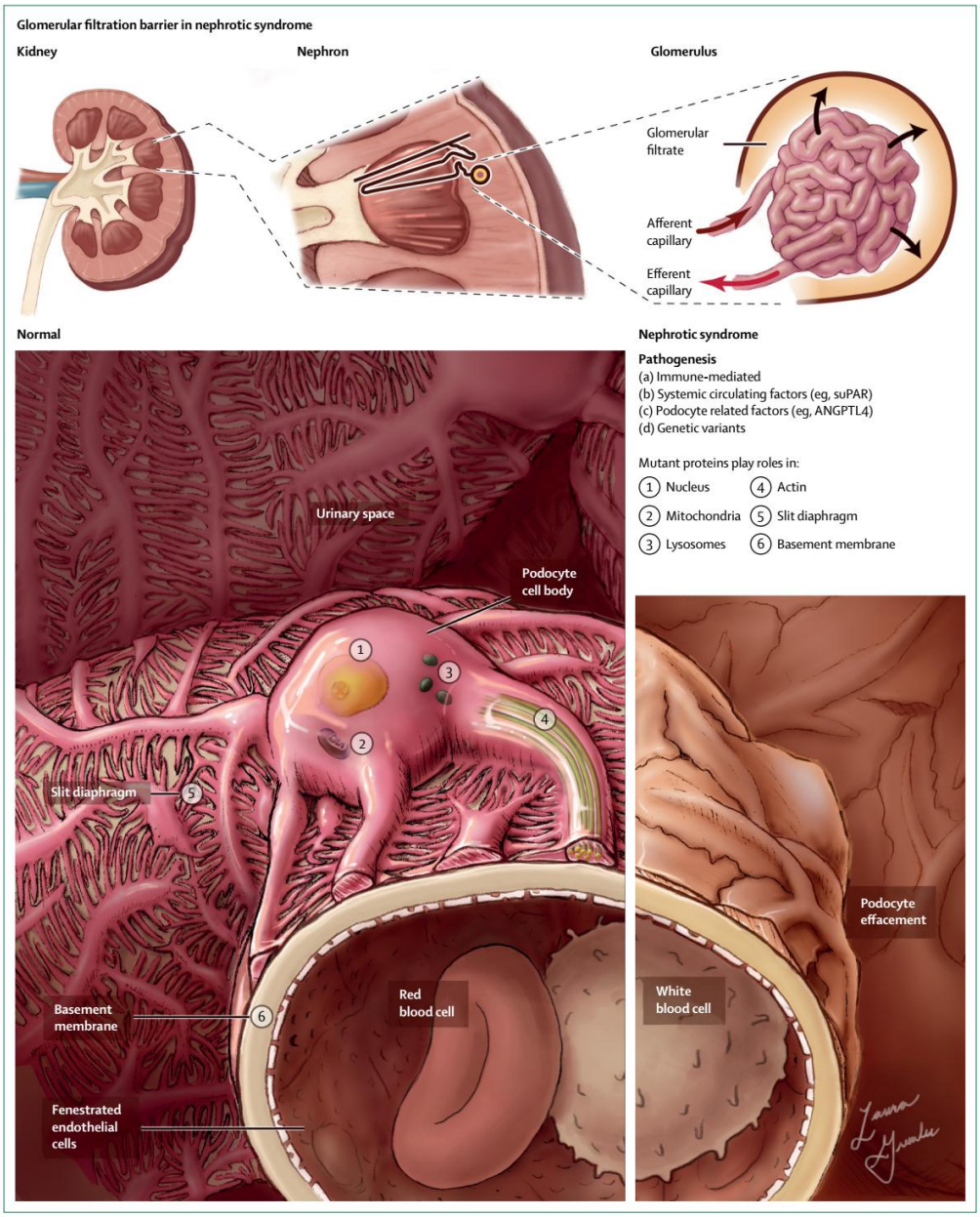

Figure 1.1 The glomerular filtration barrier and pathophysiology of idiopathic nephrotic syndrome. Figure adopted from Noone et al., (2018)

In INS, the flattening or effacement of podocyte foot processes indicates barrier dysfunction, allowing macromolecules like proteins and blood cells to leak into the urine (Noone et al., 2018). Although the precise mechanisms underlying the INS pathogenesis are not fully understood, current evidence suggests that immune dysregulation, possibly derived from T and/or B cells, releases circulating glomerular permeability factors, altering the glomerular filtration barrier and causing podocyte injuries (Colucci et al., 2022).

1.1.4 Incidence of childhood idiopathic nephrotic syndrome

The incidence of childhood INS in Malaysia is not well documented in the available literature. Globally, the incidence was reported at 2.92 new cases per 100,000 children per year, with the Southeast and East Asia region reporting a higher incidence of 6.11 cases (Veltkamp et al., 2021). Western countries documented a notably lower incidence compared to non-Western regions, with rates of 2.18 versus 6.07 cases per 100,000 children, respectively (Veltkamp et al., 2021). Childhood INS is one of the most common glomerular diseases in children, alongside acute poststreptococcal glomerulonephritis. However, based on its incidence, it is considered relatively rare compared to other common paediatric diseases(Veltkamp et al., 2021).

1.1.5 Classification of childhood idiopathic nephrotic syndrome

Idiopathic nephrotic syndrome is typically classified either based on the response to the initial steroid or the underlying histopathology. Basically, INS is characterised as either steroid sensitive nephrotic syndrome (SSNS) or steroid resistant nephrotic syndrome (SRNS) according to the response to steroid therapy at the time of diagnosis (Noone et al., 2018). The pattern of subsequent relapse is used to further classify SSNS children either as infrequent relapse nephrotic syndrome (IFRNS),

frequent relapse nephrotic syndrome (FRNS), or steroid dependent nephrotic syndrome (SDNS) (Noone et al., 2018).

The IPNA defines key terms related to INS, as outlined in Table 1.1. In its latest guidelines, the definition of FRNS has been revised from ≥2 relapses within six months of the initial episode or ≥4 relapses within any 12 months to ≥2 relapses within six months of the initial episode or ≥3 relapses within any 12 months (IPNA, 2023). Similarly, the definition of infrequent relapse has been updated from <4 relapses within any 12 months to <3 relapses within 12 months (IPNA, 2023).

A renal biopsy confirms the underlying histopathology of childhood INS. The most common lesions found are minimal change, also known as minimal change disease (MCD), or focal segmental glomerulosclerosis (FSGS). With little podocyte alterations, the glomeruli in MCD seem normal or almost normal under the microscope, whereas FSGS might exhibit some localised scarring in certain parts of the glomeruli (Noone et al., 2018).

However, since renal biopsy is an invasive and potentially risky procedure, it is not recommended as a routine in children above one year of age at disease onset with typical features of INS since most of these children exhibit MCD (IPNA, 2023). Furthermore, the prognosis of childhood INS is best determined by steroid responsiveness rather than histopathology (Webb et al., 1996). A biopsy is recommended only in children with two or more concerning clinical or biochemical parameters or in those who are not responding to steroids (Gulati et al., 2002). Therefore, patients with atypical clinical features, including macroscopic haematuria, AKI not related to hypovolemia, sustained hypertension, arthritis and/or rash, or

abnormal biochemicals such as low C3 levels, and those with SRNS should be biopsied (IPNA, 2023).

Table 1.1 Definition of terms in childhood idiopathic nephrotic syndrome

Terms	Definition
Remission	UPCR (based on first morning void or 24 h urine sample) ≤ 20 mg/mmol (0.2 mg/mg) or <100 mg/m^2 per day, respectively, or Negative or trace dipstick on ≥3 consecutive days
Relapse	UPCR ≥ 200 mg/mmol (≥ 2 mg/mg), or Urine dipstick ≥3 + (≥ 300 mg/dL) on a spot urine sample on 3 consecutive days, with or without the reappearance of oedema in a child who had previously achieved complete remission
Steroid sensitive nephrotic syndrome	Complete remission is achieved within 4 weeks of treatment with prednisolone at standard dose
Late response steroid sensitive nephrotic syndrome	Complete remission between 4 and 6 weeks of prednisolone therapy
Steroid resistant nephrotic syndrome	Lack of complete remission at 4 weeks of therapy with the same standard prednisolone treatment
Infrequent relapse nephrotic syndrome	< 2 relapses in the 6 months following remission of the initial episode, or < 3 relapses in any subsequent 12-month period (revised definition)
Frequent relapses nephrotic syndrome	≥2 relapses within 6 months of the initial episode, or ≥ 3 relapses within any 12 months (revised definition)
Steroid dependent nephrotic syndrome	Steroid sensitive nephrotic syndrome who experienced 2 consecutive relapses during recommended prednisolone therapy for the first presentation or relapse, or within 14 days of its discontinuation

UPCR, Urine protein-creatinine ratio

Biopsy also can be considered in patients more than 12 years of age on a case-by-case basis, in patients with persistent microscopic haematuria of more than 30 RBC/HPF of freshly voided urine, especially in populations with a high incidence of glomerular diseases such as IgA nephropathy in East Asia (IPNA, 2023).

1.2 Management of childhood idiopathic nephrotic syndrome

The primary goal of treatment at the initial diagnosis of INS is to achieve remission, marked by the resolution of proteinuria, and to sustain remission over the long term (IPNA, 2023; Kidney Disease: Improving Global Outcomes [KDIGO], 2021). Steroids are the first-line treatment for childhood INS, with over 90% of children initially responding, thereby being classified as SSNS. However, despite this initial response, approximately 70-80% of these children experience relapses, and 19-60% progress to frequent relapse or steroid dependent nephrotic syndrome (FR/SDNS) (Carter et al., 2020; Dossier et al., 2019; Nakanishi et al., 2013; Sinha et al., 2012; Welegerima et al., 2021).

Factors such as younger age at diagnosis, male gender, delayed time to initial remission, and shorter duration of remission after diagnosis are associated with progression to FR/SDNS (Andersen et al., 2010; Sinha et al., 2012; Vivarelli et al., 2010; Yap et al., 2001). Additionally, a review by Chanchlani and Parekh (2016) suggests that genetic and environmental factors may influence the incidence and treatment response in childhood INS, which can vary by ethnicity.

In recent years, the duration of initial steroid treatment at INS diagnosis has been modified based on evidence favouring shorter therapy over prolonged treatment (Hahn et al., 2015). Figure 1.2 illustrates the treatment approach for INS, as outlined in the 2023 IPNA clinical practice recommendations for diagnosing and managing children with SSNS (IPNA, 2023). The highlighted parts represent the pathway examined in this study.

Following the initial induction therapy of 4 to 6 weeks of steroids, children are categorized as having either SSNS or SRNS (IPNA, 2023; KDIGO, 2021). In some

SSNS children, no further relapse occurs after the initial remission, while the rest may undergo occasional or frequent relapses. In FR/SDNS cases, initial management may involve the use of prolonged low-dose steroids before considering the implementation of steroid sparing agent (SSA). If a child continues to experience relapses or encounters steroid toxicity, switching to another type of SSA is a feasible option until control is achieved. In cases where relapse remains uncontrolled, a combination of different SSA may be administered, although the evidence supporting this approach is currently lacking (IPNA, 2023).

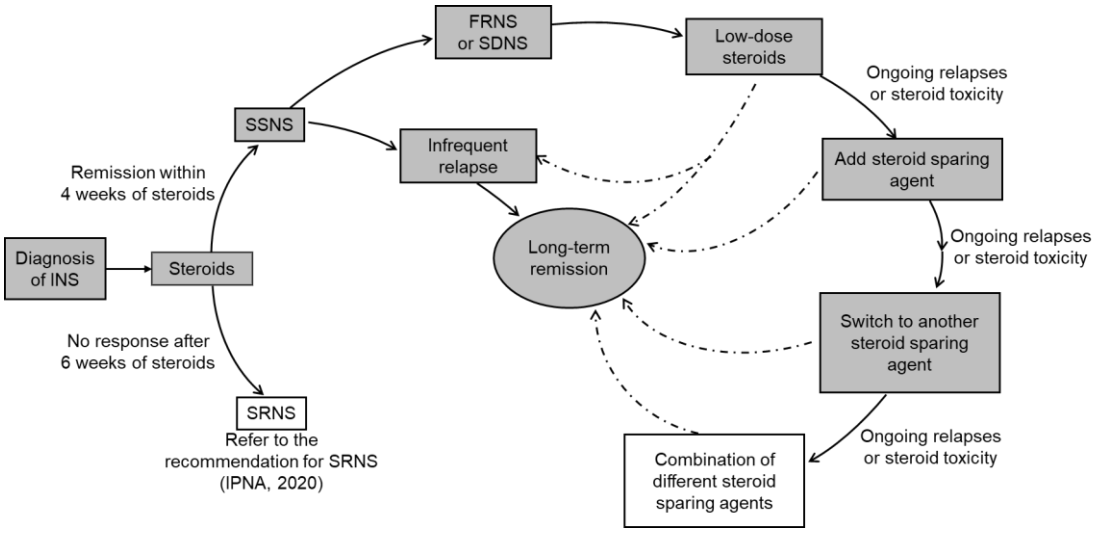

Figure 1.2 Treatment algorithm for childhood idiopathic nephrotic syndrome. Figure adapted from Noone et al., (2018). FRNS, Frequent relapse nephrotic syndrome, INS, Idiopathic nephrotic syndrome, SDNS, Steroid dependent nephrotic syndrome, SSNS, Steroid sensitive nephrotic syndrome, SRNS, Steroid resistant nephrotic syndrome

Although initial steroid treatments effectively induce remission in most children (Carter et al., 2020; Dossier et al., 2019), relapse remains a significant issue that has yet to be fully resolved. Over several decades, global relapse rates have only decreased from 87% to 66% (Veltkamp et al., 2021), indicating a need for further

improvement. The high relapse rate, particularly in cases of FR/SDNS, increases the risk of steroid toxicity and long-term complications (Bharati et al., 2023).

1.2.1 Long-term outcomes of steroids treatment for steroid sensitive nephrotic syndrome

Over the years, treatment protocols for childhood NS have evolved, focusing largely on the duration of initial steroid treatment at disease onset. There is a concern regarding the long-term prognosis of childhood NS following the transition from prolonged to shorter treatment durations, especially the risk of relapse (Ma et al., 2009; Mishra et al., 2012). Although a meta-analysis demonstrated that the duration of initial treatment did not influence the risk of relapse or the proportion of children developing frequent relapses (Hahn et al., 2020), the incidence of FR/SDNS has been reported with considerable variation across different studies (Carter et al., 2020; Dossier et al., 2019; Sinha et al., 2012).

Long-term steroid treatment, particularly in children with FR/SDNS, increases their risk of steroid toxicity (Bharati et al., 2023). Commonly reported adverse effects include weight gain, growth retardation, and cushingoid features, with an increased risk of infections, especially in those on extended therapy (Aljebab et al., 2017). Additionally, these children are at higher risk for other complications such as low bone density, hypertension, hyperglycaemia, and ocular issues (Bharati et al., 2023; Lee et al., 2020). These risks underscore the importance of vigilant monitoring and careful consideration in the use of steroids.

1.2.2 Role of steroid sparing agents in steroid sensitive nephrotic syndrome

Children diagnosed with frequent relapse or steroid dependency typically experience years of relapsing-remitting disease that necessitates long-term steroid therapy. The emergence of second-line treatment with SSA has provided new avenues

for managing relapse in these children. Previously, SSA therapy was promptly initiated in FR/SDNS children suffering from steroid toxicity, while others continued with long-term prednisolone therapy to manage the frequent relapses (Paediatric Protocol for Malaysian Hospitals, 2019). However, recent guidelines recommend initiating either low-dose prednisolone or SSA therapy at the diagnosis of FRNS (IPNA, 2023). Children starting with low-dose prednisolone can be transitioned to SSA if the relapse remains uncontrolled (experiences ongoing relapses or significant adverse effects) or develops steroid dependency (IPNA, 2023). However, the optimal sequencing for introducing different types of SSA remains unclear due to limited conclusive evidence (Larkins et al., 2020).

1.3 Problem Statement

In Malaysia, treatment protocols for childhood NS have shifted from a prolonged 6-month initial steroid regimen to a shorter 3-month initial regimen in 2019, following the release of the 4th edition Paediatric Protocol for Malaysian Hospitals (Paediatric Protocol for Malaysian Hospitals, 2019). Despite the widespread use of steroids as the primary treatment, there is a notable lack of studies evaluating the outcomes of this therapy in managing SSNS among children in Malaysia. This scarcity of local data represents a significant gap in understanding the effectiveness of previous and current treatment protocols, particularly concerning the long-term development of FR/SDNS. Additionally, earlier studies have not thoroughly examined the outcomes of steroid treatment in children with FR/SDNS (Elzouki and Jaiswal, 1988; Srivastava et al., 1992). It is also unclear how long children with ongoing relapses should be treated with multiple steroid courses before introducing a second-line treatment.

Addressing this knowledge gap is crucial, especially in light of global efforts to identify the most effective treatment strategies.

Researchers have linked various factors, including demographic, clinical characteristics, and treatment outcomes post-diagnosis to the long-term prognosis among children with SSNS (Andersen et al., 2010; Dakshayani et al., 2018; Sinha et al., 2012; Vivarelli et al., 2010; Yap et al., 2001). These studies aimed to identify children at higher risk of progressing to FR/SDNS for closer monitoring and possibly treatment modalities. However, previous findings have been inconclusive, and differences in study populations make it challenging to apply these results to the local context (Chanchlani and Parekh, 2016). Therefore, examining associated factors among Malaysian children may provide a more tailored approach to identifying relevant predictors within the Malaysian healthcare setting.

Although the guidelines outline the indications for SSA therapy, the decision to start SSA or continue with low-dose prednisolone at the early stages of FRNS remains uncertain. Previous studies have explored predictors for SSA use but did not focus on the specific needs of children with FR/SDNS (Harambat et al., 2013; Vivarelli et al., 2010). Given that SSA treatment is mainly reserved for those who have progressed to FR/SDNS (IPNA, 2023), it is essential to investigate factors that specifically predict the need for SSA therapy in this subgroup. This could help ensure the timely initiation of SSA therapy and improve relapse management.

The limited number of clinical trials comparing SSAs has created uncertainty about the best SSA for managing FR/SDNS in children (Larkins et al., 2020). As a result, SSA selection often depends on historical, institutional, or physician preferences rather than solid scientific evidence (McKay et al., 2022). In Malaysia,

cyclophosphamide has traditionally been recommended as the first SSA, though levamisole has recently emerged as an alternative (Paediatric Protocol for Malaysian Hospitals, 2019). However, there is still limited evidence on the outcomes associated with these choices. Researching the effectiveness and safety of these agents would provide valuable insights into improving current treatment practices.

1.4 Study Objectives

1.4.1 General objective

To evaluate the treatment outcomes and determine the prognostic factors in managing children with SSNS.

1.4.2 Specific objectives

1) To evaluate the outcomes of steroid treatment in children with SSNS
2) To determine the risk factors for frequent relapses and steroid dependency in children with SSNS
3) To determine the factors associated with the requirement of SSA among children with FR/SDNS
4) To evaluate the outcomes of SSA treatment among children with FR/SDNS.

1.5 Significance of Study

The motivation for this research arises from the need to enhance relapse control in children with SSNS, particularly those experiencing frequent relapse and steroid dependence. High relapse rates and the emergence of steroid toxicity highlight the need for a comprehensive evaluation of current treatment protocols as well as the identification of factors that predict disease prognosis and guide treatment modalities.

Performing such an evaluation is crucial for optimising therapeutic approaches, minimising adverse effects, and improving patient outcomes. By identifying predictive factors, healthcare providers can implement more personalised and effective treatment plans, ensuring better long-term health and quality of life (QOL) for children with SSNS. Additionally, understanding these factors can contribute to developing more refined clinical guidelines and inform future research, eventually enhancing the overall management of SSNS.

Furthermore, the scarcity of localised studies in Malaysia emphasises the importance of this research in providing context-specific insights to inform clinical practice. The aim is to contribute valuable knowledge to global efforts in optimising clinical practices and improving long-term outcomes for children with SSNS.

CHAPTER 2

LITERATURE REVIEW

2.1 Steroids for Treatment of Childhood Idiopathic Nephrotic Syndrome

Steroids or glucocorticoids, mainly prednisolone, have emerged as a key component in the management of childhood INS. Its mechanism of action involves immunosuppression through the activation of glucocorticoid receptors expressed in immune cells and podocytes (Colucci et al., 2018; Zhao et al., 2018). Figure 2.1 illustrates the mechanism of action of steroids in treating childhood INS, highlighting the key pathways involved in their immunosuppressive and anti-inflammatory effects via glucocorticoid receptors. These anti-inflammatory properties play a crucial role in modulating the immune response and preserving podocyte integrity, ultimately contributing to the reduction of proteinuria (Zhao et al., 2018).

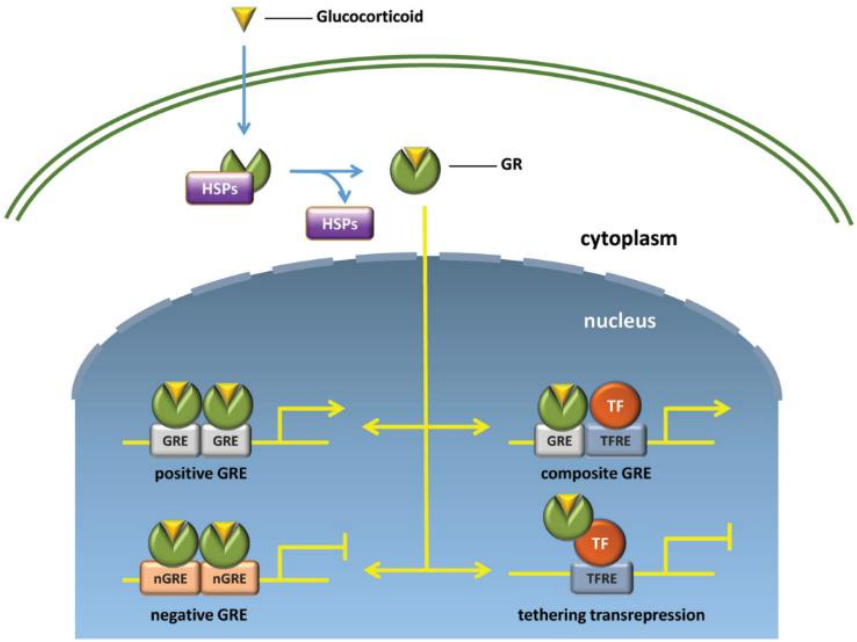

Figure 2.1 Molecular mechanism of glucocorticoid receptor (GR) signalling pathway. Glucocorticoids (GCs) diffuse into the cytosol and bind to GR, causing dissociation from chaperone proteins (HSPs) and translocation to the nucleus. There, GR forms dimers and regulates gene transcription, either activating or repressing target genes. Adopted from Zhao et al., (2018). TF, Transcription factor, GRE, Glucocorticoid response element, nGRE, Negative glucocorticoid response element, TFRE, Transcription factor response element.

2.1.1 History and evolution of steroids for treatment of childhood idiopathic nephrotic syndrome

The use of steroids in the treatment of INS dates to the early 1950s when Arneil and Wilson from Glasgow initially employed injections of cortisone and adrenocorticotropic hormone (Pal and Kaskel, 2016). As soon as prednisolone or prednisone became available as oral steroids, the main role was taken over. The International Study for Kidney Diseases in Children (ISKDC) in 1965 established a standard prednisolone regimen that has become fundamental for the treatment of INS (Pal and Kaskel, 2016). The introduction of steroid therapy has significantly reduced the mortality rate to 3% among children with NS (Report of the ISKDC, 1984).

2.1.1(a) Treatment for initial episode of childhood idiopathic nephrotic syndrome

The earliest prednisolone regimen recommended by ISKDC involved daily oral administration of prednisolone at a dosage of 60 mg/m^2/day for four weeks followed by intermittent prednisolone at 40 mg/m^2 for 3 out of 7 days per week for four weeks as initial treatment (ISKDC, 1979). However, in 1981, the APN suggested replacing intermittent dosing with alternate-day prednisolone at 40 mg/m² for four weeks, due to unsatisfactory outcomes related to relapse rates (APN, 1981).

In response to the persistent issue of high relapse rates, numerous trials have been conducted to explore alternative prednisolone regimens aimed at prolonging remission and reducing subsequent relapses. One such trial tested a shorter prednisolone course consisting of two weeks of daily dosing followed by two weeks of alternate-day dosing (APN, 1988). However, this regimen resulted in shorter remission durations and higher relapse rates in the long run, leading to its abandonment.

Consequently, further research into longer courses has been conducted in response to the drawbacks of shorter prednisolone regimens. Notably, an earlier study by Ksiek and Wyszyska (1995) has shown that a prolonged 6-month prednisolone course effectively reduces the relapse rate without introducing additional risks of adverse effects, compared to the standard 2-month regimen. This finding has been agreed upon by research conducted by Anand et al., (2013) and Mishra et al. (2012), which similarly demonstrated favourable outcomes with prolonged prednisolone regimens. These collective insights underscore the potential benefits of extended prednisolone courses in optimising treatment outcomes for children with INS and have served as a basis for changes in the treatment guidelines at that time.

However, concerns about the increased risk of steroid toxicities began to emerge after Bagga et al. (1999) conducted a study on a 16-week prednisolone course. Despite reporting a remission rate similar to the standard ISKDC regimen, the study noted a greater incidence of steroid toxicities. Prolonging the daily administration of prednisolone in the study increased the risk of steroid toxicity due to higher cumulative doses. Meanwhile, another study by Hiraoka et al. (2003) found no significant difference in cumulative sustained remission rates when comparing the standard 2-month regimen to a prolonged 6-month prednisolone course. However, subgroup analysis in the study revealed that children younger than four years at disease onset may benefit from the prolonged regimen. These conflicting findings have encouraged further investigation into the outcomes of prolonged versus standard initial regimens.

Subsequent studies have suggested that extending the initial course of prednisolone treatment from three to six months may not significantly impact the disease course in children with INS (Sinha et al., 2015; Teeninga et al., 2013).

Yoshikawa et al. (2015) found that a 2-month initial prednisolone regimen is not inferior to 6-month therapy concerning the occurrence of FRNS. Additionally, according to Webb et al. (2019) in the PREDnisolone in NephrOtic Syndrome Randomised Clinical Trial (PREDNOS RCT), there have been no demonstrated clinical benefits associated with administering prednisolone beyond 8 weeks.

A recent meta-analysis examining current clinical trials found no benefit in extending prednisolone treatment beyond two or three months in the initial treatment of SSNS (Hahn et al., 2020). These findings underscore the importance of balancing treatment duration with the risk of steroid toxicity in improving outcomes for children with INS. While the current recommendation for initial treatment with prednisolone is typically set at 8 to 12 weeks (IPNA, 2023; KDIGO, 2021), the relapse rate following the first episode of INS has been less than satisfactory (Veltkamp et al., 2021).

Similar to Paul et al.'s (2014) findings suggesting no clear benefit of the 12-week regimen over the standard 8-week regimen, a more recent study by Lucchetti et al., (2023) also concluded that both regimens result in similar outcomes at 24 months. However, a meta-analysis by Schijvens et al. (2021) concluded that an 8-week regimen may not achieve comparable outcomes in terms of time to first relapse and relapse rate as a 12-week regimen. The disagreement could be attributed to the higher cumulative dose associated with longer treatment durations.

Interestingly, a retrospective study by Baek et al. (2015) revealed that patients who responded earlier within the first week of the initial treatment showed similar outcomes, regardless of whether they were on an 8-week or a 12-week regimen. Therefore, they proposed adjusting the treatment duration based on the time to initial response. This study has sparked further research into modifying treatment protocols

for the initial diagnosis. However, subsequent prospective studies by Pasini et al. (2021) and Tang et al. (2022) did not identify any significant difference in relapse rates after adjusting the treatment regimen based on time to remission.

Another recently published non-randomised comparator study examined the impact of a response-adjusted protocol in children achieving remission within 8 days. They compared an 8-week course of tapering doses of prednisolone to the standard 24-week regimen. The study reported significantly lower mean cumulative steroid doses and no relapses during the faster tapering period. Most importantly, the development of FR/SDNS, proportions of relapse-free patients, and adverse effects were similar between the groups (Zion et al., 2022). These findings may shed light on the benefits of adjusted regimens among early responders and potentially reduce the risk of steroid toxicity associated with prolonged treatment.

Given the lack of collinearity among previous studies, determining the optimal duration and benefits of prednisolone treatment for the first episode of INS in children remains challenging. However, results from robust clinical trials have indicated that prolonging initial treatment does not necessarily improve patient outcomes. The response-adjusted prednisolone regimen presents a novel approach worthy of further exploration in future clinical trials. Therefore, while the optimal initial treatment regimen for INS in children remains uncertain, current evidence indicates that a treatment duration of 8 to 12 weeks for initial steroid therapy may be appropriate for childhood INS (IPNA, 2023; KDIGO, 2021). This recommendation is practiced for the initial treatment of childhood INS in Malaysian treatment protocol (Paediatric Protocol for Malaysian Hospitals, 2019).

2.1.1(b) Treatment for subsequent relapse in childhood idiopathic nephrotic syndrome

A standard prednisolone dose of 60 mg/m^2/day (or 2 mg/kg/day) has been used to induce remission during relapse, defined as resolved of proteinuria for three consecutive days, followed by maintenance of 40 mg/m^2 (or 1.5 mg/kg) on alternate days for another four weeks (IPNA, 2023; KDIGO, 2021). However, despite the success in managing occasional relapses, concerns have arisen regarding the increased risk of steroid toxicities among those experiencing multiple relapses due to repeated steroid exposure (Aljebab et al., 2017). Optimising the treatment regimen for subsequent relapses is essential to balance efficacy and safety. This sub-subtopic will focus on the evolution of steroid regimens for treating relapses that occur after the initial diagnosis among IFRNS children, excluding children classified as FR/SDNS, as defined in Subsection 1.1.5.

Several small-scale studies have investigated an alternative strategy for administering lower doses of prednisolone to mitigate steroid toxicity in children experiencing disease relapses (Borovitz et al., 2020; Mantan et al., 2022; Raja et al., 2017; Sheikh et al., 2021). Initial findings indicated that a lower prednisolone dose of 1 mg/kg/day induces remission without affecting the relapse rate, as reported by Raja et al. (2017) and Borovitz et al. (2020). Furthermore, a trial conducted by Sheikh et al. (2021) also demonstrated that a low dose of prednisolone (1 mg/kg/day) was non-inferior to the standard dose (2 mg/kg/day). The proportion of children achieving remission, the number of subsequent relapses, and the mean cumulative steroid doses during the follow-up period in both groups were comparable. However, children in the low-dose group showed a tendency towards a higher rate of subsequent relapses, and the development of FR/SDNS, warranting further investigation.

Another study by Mantan et al. (2022) showed comparable outcomes in children treated with either a lower prednisolone dose of 1 mg/kg alternate days or the standard maintenance dosage of 1.5 mg/kg alternate days after achieving remission at relapse. However, due to the study's short duration and focus on children with infrequent relapses, further verification is necessary in children with FR/SDNS.

A shorter duration of maintenance therapy may be a viable alternative for children with IFRNS. Although a 2-week regimen failed to demonstrate noninferiority to the standard 4-week regimen in a study by Kainth et al. (2021), it showed comparable time to relapse and a similar proportion of children developing FR/SDNS within one year. Further insights are expected from the RESTERN trial, which aims to clarify the effectiveness of 2-week versus 4-week prednisolone maintenance therapy for treating INS relapse (Schijvens et al., 2017). Furthermore, the extended duration of the maintenance course following remission induction did not prevent further relapses, as shown by Gargiulo et al. (2021). As a result, they concluded that a tapering schedule of a 4-week prednisolone regimen at relapse is deemed unnecessary.

Despite efforts to standardise treatment regimens, a wide variability persists in the dosage and duration of maintenance prednisolone at relapse. Recent studies have highlighted the potential benefits of lower-dose prednisolone at induction and shorter maintenance courses for children with infrequent relapses. However, further validation is deemed crucial to develop the most accurate strategies for the best treatment of relapses among children with SSNS. Therefore, current IPNA guidelines recommend a standard 4-week maintenance therapy during relapse without further tapering (IPNA, 2023), a recommendation also practiced in Malaysia for treating IFRNS (Paediatric Protocol for Malaysian Hospitals, 2019).

2.1.1(c) Treatment for children diagnosed with frequent relapses or steroid dependent nephrotic syndrome

The main objective of INS treatment is to maintain remission while minimising adverse effects. Therefore, the prolongation of low-dose prednisolone therapy has been fundamental for the treatment of FR/SDNS (APN, 1981). In typical clinical practice, these challenging forms of SSNS are managed with a protocol involving standard prednisolone during relapse followed by a tapering regimen, with maintenance achieved through low alternate-day doses (≤0.5 mg/kg/48h) for six months in FRNS, or potentially longer in SDNS cases (Paediatric Protocols for Malaysian Hospitals, 2019).

However, a study conducted by Yadav et al. (2019) demonstrated enhanced treatment outcomes in terms of relapse rates and sustained remission in children with FRNS when given daily low-dose prednisolone (0.2-0.3 mg/kg/day) rather than the traditional long-standing alternate-day regimen. As a result, the updated IPNA guideline now includes both alternate-day and daily prednisolone as treatment options for maintenance therapy during relapse (IPNA, 2023). Nevertheless, the daily dosage has not yet been incorporated into the Malaysian treatment protocol and is not currently practiced.

2.1.1(d) Variation in prednisolone dosing in children with idiopathic nephrotic syndrome

Despite the long-standing use of prednisolone for treating childhood INS, recent studies have actively investigated its dosing (Basu et al., 2020; Schijvens et al., 2017; Weerasooriya et al., 2023). Dosing based on weight at 2 mg/kg/day has emerged as an alternative to the standard approach of administering prednisolone at 60 mg/m^2/day, which is based on body surface area (BSA). Feber et al. (2009) highlighted the potential for underdosing with weight-based prednisolone, particularly in small

children weighing ≤ 30 kg. An example of dose calculations for a child weighing 20 kg and measuring 110 cm in height (BSA = 0.78 m^2) is provided below, using the weight-based and BSA-based methods.

- Weight-based, 2 mg/kg/day: 2 mg x 20 kg = 40 mg/kg/day
- BSA-based, 60 mg/m^2/day: 60 mg x 0.78 m^2 = 46.8 mg/m^2/day

The weight-based method results in a dose approximately 15% lower than the BSA-based method. While this discrepancy did not significantly impact the initial treatment response, it did increase the risk of frequent relapses, as noted by Saadeh et al. (2011). Conversely, Raman et al. (2016) and Basu et al. (2020) concluded that BSA-based and weight-based prednisolone dosing are equally effective in inducing and maintaining remission. Moreover, Basu et al. (2020) suggested that weight-based dosing may be more advantageous due to fewer adverse effects, likely attributable to the administration of a lower cumulative prednisolone dose.

Besides that, the administration of prednisolone as a single daily dose or in divided doses has been questioned to affect the outcomes of treatment in INS children. Initially, the recommended prednisolone regimen by the ISKDC and the Arbeitsgemeinschaft fur Paediatrische Nephrologie (APN) involved divided daily doses (APN, 1981; Report of the ISKDC, 1979). However, a shift towards a single daily dose, typically administered in the morning, has gained preference due to perceived benefits such as reduced adverse effects, minimised suppression of the adrenocortical axis, and improved compliance (Ekka et al., 1997). Nevertheless, the study also found that both dosing approaches were equivalent in their ability to induce remission (Ekka et al., 1997).

A recent study by Weerasooriya et al. (2023) compared the outcomes of a split-dose versus a single daily dose of prednisolone. They found that administering two-thirds of the dose in the morning and one-third in the evening resulted in faster remission with comparable adverse effects. However, this effect was significant only in children younger than 5 or older than 10 years, while no significant difference in time for remission was observed in those aged 5 to 10 years. Additionally, variations in the baseline use of second-line agents among participants may limit the generalisability of the findings (Weerasooriya et al., 2023).

In summary, dosing based on weight and BSA has led to acceptable outcomes across different studies. Both single- and divided-dose prednisolone regimens are widely used globally, suggesting that both approaches may be equally effective. Nevertheless, using divided doses may offer practical benefits, particularly for paediatric patients, by potentially reducing the amount of medication required per dose, thus minimising pill burden or liquid volume.

2.1.2 Effectiveness of steroid treatment in children with steroid sensitive nephrotic syndrome

Response to initial steroid treatment has been used as a benchmark to foresee the prognosis of childhood INS (Vivarelli et al., 2010). It is characterised by significant reductions in proteinuria, improvements in serum albumin levels, and the resolution of oedema. Children with SSNS exhibit a favourable response to initial steroid therapy, with remission achieved between one and two weeks (Dakshayani et al., 2018; Welegerima et al., 2021). A delayed response, however, has been associated with a higher risk of relapses and FRNS (Balaji et al., 2017; Vivarelli et al., 2010; Yap et al., 2001). The time interval between remission and the first relapse ranged from 3 to 8