Long-Term Adverse Effects of Corticosteroid Therapy in Children with Nephrotic Syndrome

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Abstract

Background: Childhood nephrotic syndrome is a relapsing glomerular disorder in which corticosteroids remain central to induction of remission and treatment of subsequent relapses. Most children with steroid-sensitive nephrotic syndrome respond rapidly to prednisolone, but frequent relapses and steroid dependence can result in substantial cumulative corticosteroid exposure during critical periods of physical, endocrine, skeletal, and psychosocial development. This review examines the long-term adverse effects of corticosteroid therapy in children with nephrotic syndrome, with particular attention to impaired linear growth, obesity and altered body composition, cardiovascular and metabolic abnormalities, compromised bone health, hypothalamic-pituitary-adrenal axis suppression, ophthalmologic and dermatologic toxicity, infection, behavioral disturbances, and deterioration in health-related quality of life. Interpretation of these complications requires separation of treatment toxicity from the effects of active nephrosis, nutritional disturbances, recurrent hospitalization, chronic inflammation, and exposure to steroid-sparing immunosuppressive agents. Evidence indicates that cumulative corticosteroid exposure and persistent steroid dependence are important determinants of morbidity, although susceptibility varies considerably between children and some adverse effects improve after corticosteroid reduction or withdrawal. Contemporary treatment therefore aims not only to achieve remission but also to minimize cumulative glucocorticoid burden through appropriate treatment duration, early recognition of toxicity, and rational use of steroid-sparing therapies. Longitudinal monitoring of growth, body mass index, blood pressure, glucose metabolism, bone health, ocular complications, adrenal function, behavior, and patient-reported outcomes should form an integral part of pediatric nephrotic syndrome care.

Keywords: nephrotic syndrome, corticosteroids, growth impairment,

Introduction

Idiopathic nephrotic syndrome is among the most common glomerular diseases of childhood and is characterized clinically by nephrotic-range proteinuria, hypoalbuminemia, edema, and frequently hyperlipidemia. The majority of affected children have steroid-sensitive nephrotic syndrome (SSNS), reflecting the ability of glucocorticoids to induce complete remission of proteinuria. Current international recommendations continue to place oral prednisone or prednisolone at the center of initial therapy because of its effectiveness, familiarity, availability, and decades of clinical experience. The therapeutic success of corticosteroids transformed the prognosis of childhood nephrotic syndrome, but the same treatment created a second clinical problem: repeated or prolonged glucocorticoid exposure in children who may relapse for many years. [1]

Approximately 85–90% of children with idiopathic nephrotic syndrome achieve remission after initial glucocorticoid therapy. Relapse is common, however, and a substantial subgroup develops frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS). These children may receive repeated courses of high-dose daily prednisolone followed by alternate-day treatment, sometimes together with prolonged low-dose maintenance therapy. The resulting cumulative exposure can extend across preschool years, middle childhood, and puberty, periods during which normal growth, bone mineral accrual, metabolic programming, body composition, emotional regulation, and school development are particularly important. [2]

The adverse-effect profile of systemic glucocorticoids is broad. Obesity, Cushingoid appearance, impaired height velocity, hypertension, glucose intolerance, reduced bone formation, cataract, behavioral disturbance, infection risk, and suppression of the hypothalamic-pituitary-adrenal (HPA) axis have all been recognized in children receiving repeated steroid treatment. Modern trials have also changed the interpretation of exposure: increasing the duration of corticosteroid treatment beyond evidence-based regimens does not necessarily improve long-term relapse outcomes and can add treatment burden. This has shifted therapeutic thinking from maximizing steroid exposure to identifying the minimum exposure that reliably induces remission and controls relapse. [3]

A major difficulty in assessing long-term steroid toxicity is that children with nephrotic syndrome are not otherwise healthy corticosteroid recipients. Active nephrosis itself can affect growth, nutritional status, vitamin D metabolism, lipid concentrations, infection risk, physical activity, and psychosocial functioning. Relapse frequency is also closely linked to corticosteroid exposure, producing confounding by disease severity. A child with the highest cumulative steroid dose is often the same child with the greatest number of relapses, more clinic visits, greater school absence, and more exposure to additional immunosuppression. A clinically useful review must therefore distinguish direct glucocorticoid effects from disease-related and treatment-related coexisting factors. [4]

The research gap is particularly relevant to long-term pediatric outcomes. Much of the published literature consists of cross-sectional cohorts, retrospective studies, relatively small prospective series, or studies in heterogeneous disease phenotypes. Data on final adult height, recovery of the HPA axis, fracture outcomes, long-term cardiometabolic risk, and the independent effect of cumulative steroid exposure on health-related quality of life remain less complete than short-term remission data. The aim of this review is to integrate current evidence on the long-term adverse consequences of corticosteroid therapy in children with nephrotic syndrome, examine their mechanisms and clinical determinants, and outline a practical strategy for toxicity reduction and surveillance.

Corticosteroid Exposure in Childhood Nephrotic Syndrome

Glucocorticoids exert anti-inflammatory and immunomodulatory effects through cytoplasmic glucocorticoid receptors that subsequently regulate transcription of numerous genes. Their therapeutic activity includes suppression of cytokine signaling and lymphocyte function, while nonimmune actions influence carbohydrate, protein, lipid, bone, cardiovascular, and neuroendocrine physiology. These effects explain why the same drug can rapidly induce remission while simultaneously producing multisystem toxicity when exposure is intense, repeated, or prolonged. Children may be particularly susceptible because treatment is delivered while organs and endocrine systems are still developing. [5]

Current treatment has moved toward limiting unnecessary steroid exposure. The 2025 KDIGO guideline supports defined courses for the first episode and subsequent relapses and recommends glucocorticoid-sparing therapy in children with FRNS who develop serious steroid-related adverse effects and in children with SDNS. The clinical importance of this recommendation extends beyond preventing visible Cushingoid features. It recognizes cumulative glucocorticoid toxicity as a treatment outcome in its own right and supports modifying therapy before potentially persistent growth, skeletal, metabolic, ocular, or psychosocial consequences become established. [1]

Nutritional management also interacts with treatment toxicity. Increased appetite during prednisolone treatment can increase energy intake, while sodium intake may worsen edema and blood pressure. Calcium and vitamin D intake may be inadequate at the same time that glucocorticoids impair bone

formation. Dietary assessment in children with nephrotic syndrome has therefore become part of supportive management rather than an ancillary issue. Strategies directed at steroid toxicity should incorporate nutrition, physical activity, and family education rather than relying only on pharmacologic changes. [6]

Biological Basis of Long-Term Glucocorticoid Toxicity

Synthetic glucocorticoids diffuse through the cell membrane and bind cytoplasmic glucocorticoid receptors, after which receptor complexes interact with glucocorticoid-response elements and other transcription factors. These genomic actions modify inflammatory pathways but also affect gluconeogenesis, protein catabolism, adipocyte differentiation, osteoblast function, vascular responsiveness, and central nervous system signaling. Rapid non-genomic effects also occur. Toxicity is therefore not attributable to a single mechanism; it represents the integrated result of receptor activation across multiple tissues. [5]

Growth impairment is linked to effects at several levels of the growth hormone–insulin-like growth factor-1 (GH–IGF-1) axis and the growth plate. Glucocorticoids can suppress pulsatile growth hormone secretion, reduce tissue responsiveness to IGF-1, inhibit chondrocyte proliferation, interfere with collagen synthesis, and increase protein catabolism. At the growth plate, reduced proliferation and matrix production limit longitudinal bone growth. These actions can become clinically important even without an overt endocrine deficiency because circulating hormone concentrations may not accurately reflect reduced tissue activity. [7]

Skeletal toxicity develops through suppression of osteoblast differentiation and function, enhanced apoptosis of osteoblasts and osteocytes, altered calcium handling, and, particularly during early exposure, changes in bone resorption. In growing children, the effect is more complex than adult glucocorticoid osteoporosis because treatment coincides with expected skeletal expansion and accumulation of peak bone mass. Nephrotic urinary losses of vitamin D-binding protein and abnormalities in vitamin D status may act in parallel with glucocorticoid toxicity, so reductions in bone density cannot always be assigned entirely to steroid treatment. [8]

Glucocorticoids also increase hepatic glucose production and promote peripheral insulin resistance while stimulating appetite and favoring central adiposity. Mineralocorticoid-like effects, increased vascular reactivity, weight gain, sodium exposure, and the renal disease itself may contribute to elevated blood pressure. Repeated treatment can consequently produce a cluster of obesity, hypertension, dyslipidemia, and impaired glucose regulation that warrants assessment as an interconnected cardiometabolic phenotype rather than as unrelated laboratory abnormalities. [5]

Linear Growth and Final Height

Linear growth is one of the most clinically important long-term concerns because reduced height velocity may be subtle during individual treatment courses yet become substantial after years of relapsing disease. Emma and colleagues followed children with severe steroid-responsive nephrotic syndrome for an average of almost 12 years. During the prepubertal period, patients lost height standard deviation score, and corticosteroid exposure was the major predictor of unfavorable growth. Partial catch-up occurred after prednisone withdrawal, but children with early disease onset and those continuing treatment around the pubertal years were at greater risk of height loss. [9]

The relationship with cumulative dose has been confirmed in other cohorts. Valavi and colleagues studied 97 prepubertal children and found that mean height Z-score declined after prednisolone exposure; the reduction was greater among children with higher cumulative doses and four or more relapses. This finding is particularly relevant clinically because it links growth impairment not simply to a diagnosis of nephrotic syndrome but to the intensity of repeated treatment. The same study also found reduction in predicted growth potential relative to pretreatment target height. [10]

Long-term growth data are not completely uniform. Donatti and Koch examined adults with childhood-onset steroid-responsive idiopathic nephrotic syndrome and found that mean final height Z-score did not significantly differ from the initial height Z-score. Final stature correlated most strongly with initial and target height rather than cumulative prednisone exposure. These findings indicate that some children

achieve adequate catch-up growth and that temporary slowing of height velocity does not inevitably translate into permanent adult short stature. [11]

Earlier longitudinal work similarly shows heterogeneity. In a pediatric cohort of 85 steroid-responsive patients, growth trajectories were influenced by treatment and clinical characteristics, while another long-term study from Iran demonstrated adverse relationships between sustained glucocorticoid exposure and linear growth. These differences across studies probably reflect variation in relapse frequency, age at disease onset, steroid regimen, duration of follow-up, pubertal timing, nutritional status, and use of steroid-sparing drugs. A single cumulative-dose threshold is therefore unlikely to predict growth outcome equally in all children. [12]

Puberty deserves special attention. Normal pubertal growth depends on coordinated sex steroid, GH, and IGF-1 activity. Continuing substantial glucocorticoid exposure during this period can reduce the magnitude or alter the timing of the pubertal growth spurt. Clinical follow-up should therefore move beyond measuring height alone. Height velocity, height-for-age Z-score, relation to mid-parental target height, Tanner stage, and evidence of delayed puberty provide a more informative picture. A flattening growth curve during repeated steroid courses should be treated as a clinically relevant toxicity signal rather than accepted as an unavoidable feature of nephrotic syndrome. [13]

Growth can also be influenced by disease activity. Before widespread steroid therapy, children with persistent nephrosis could experience poor growth because of urinary protein loss, reduced appetite, chronic illness, infection, altered thyroid hormone transport, micronutrient loss, and intestinal edema. Modern patients may experience a combination of active disease and iatrogenic suppression. This distinction is important when interpreting short stature in SRNS, where persistent proteinuria and chronic kidney disease may contribute independently, compared with a child in prolonged remission whose main ongoing exposure is corticosteroid therapy. [14]

The most recent prospective evidence reinforces the need for longitudinal rather than single-point assessment. In a large childhood nephrotic syndrome cohort, obesity and short stature were studied from diagnosis through follow-up, allowing timing and disease phenotype to be incorporated into risk assessment. Such designs are valuable because they differentiate abnormalities present near diagnosis from those emerging during years of treatment. The clinical aim should not be limited to detecting height below −2 SD; a progressive decline in an individual child's height Z-score may represent meaningful treatment toxicity before the conventional short-stature threshold is reached. [15]

Obesity, Cushingoid Appearance, and Body Composition

Weight gain is among the most visible adverse effects of repeated glucocorticoid treatment. Increased appetite, high caloric intake, reduced physical activity during relapses, fluid retention, and glucocorticoid-driven redistribution of adipose tissue can produce increased BMI and characteristic central adiposity. Facial rounding and Cushingoid appearance may be distressing even when BMI remains below the obesity threshold because body-image changes can be rapid and socially conspicuous. These effects are particularly relevant in school-age children and adolescents, in whom appearance can affect self-esteem and peer interaction. [16]

Long-term cohorts indicate that obesity does not affect all patients equally. Among adolescents and young adults with childhood-onset nephrotic syndrome, Bharati and colleagues reported obesity in 22.7% of a cohort enriched for FRNS and SDNS, alongside growth failure, low bone mineral density, hypertension, and increased carotid intima-media thickness. The clustering of these abnormalities suggests that repeated treatment and persistent disease activity can produce a long-term phenotype extending beyond temporary steroid-related weight gain. [17]

Importantly, weight may improve when disease activity and steroid exposure decrease. Long-term follow-up into adulthood has shown relatively normal BMI in some cohorts of patients who had childhood SSNS, illustrating the potential reversibility of treatment-related changes. Families can therefore be counseled that steroid-related weight gain is not necessarily permanent, while still taking current obesity seriously because childhood adiposity can impair physical activity, increase blood pressure, aggravate insulin resistance, and worsen psychosocial well-being. [18]

Cardiometabolic Effects

Glucocorticoids alter glucose metabolism through increased hepatic gluconeogenesis, impaired peripheral glucose uptake, and insulin resistance. Clinically overt diabetes is uncommon in most pediatric nephrotic cohorts, but impaired fasting glucose, hyperinsulinemia, or increased HbA1c can occur, particularly in children with high cumulative exposure, obesity, family predisposition, or concurrent calcineurin inhibitor treatment. Monitoring should therefore be risk based, with greater attention given to children who gain substantial weight or require prolonged immunosuppression. [19]

Hypertension is similarly multifactorial. Steroid-associated fluid and sodium retention, weight gain, enhanced vascular responsiveness, calcineurin inhibitor use, renal parenchymal abnormalities, and active nephrosis may all contribute. Blood pressure should be interpreted using age-, sex-, and height-specific pediatric standards rather than adult thresholds. Repeated normal measurements are important because hypertension can be episodic during high-dose treatment and may later become sustained in children with ongoing metabolic or renal risk. [17]

Dyslipidemia is intrinsic to active nephrotic syndrome because hepatic lipoprotein production increases while catabolism of several lipoprotein particles is altered. Steroid-induced weight gain and insulin resistance can add a secondary metabolic component, particularly during remission when severe nephrosis-related lipid abnormalities would otherwise be expected to improve. Persistent dyslipidemia in a child in stable remission should therefore prompt assessment of obesity, diet, treatment exposure, and other cardiovascular risk factors rather than being attributed automatically to previous nephrosis. [20]

Mechanistically, nephrotic dyslipidemia includes increased cholesterol and triglyceride-rich lipoproteins and alterations in lipoprotein-processing enzymes and receptors. Chronic exposure may contribute to endothelial dysfunction and cardiovascular risk, although the long-term clinical consequences in children with SSNS remain incompletely defined. The presence of increased carotid intima-media thickness in some long-term cohorts supports continued cardiovascular surveillance in heavily treated patients, particularly when obesity and hypertension coexist. [21]

Bone and Mineral Health

Bone health represents an interaction between the underlying nephrotic state and glucocorticoid therapy. Urinary loss of vitamin D-binding protein can lower total 25-hydroxyvitamin D concentrations during active proteinuria, while reduced activity, dietary limitations, delayed puberty, and recurrent inflammation may further compromise bone acquisition. At the same time, glucocorticoids directly suppress osteoblast activity and longitudinal skeletal growth. This combination can impair both bone density and bone quality during the years in which peak bone mass is normally being accumulated. [22]

Vitamin D insufficiency may be present even before substantial corticosteroid exposure. In a prospective study at diagnosis, Nielsen and colleagues found insufficient vitamin D status in the large majority of children studied, with vitamin D concentrations associated with serum albumin. This finding is important because it prevents an overly simple attribution of all mineral abnormalities to glucocorticoids. Active urinary protein loss itself can create a biochemical environment that increases skeletal vulnerability before treatment-related effects accumulate. [23]

Longitudinal observations during corticosteroid treatment have documented reduction in total-body bone mineral density Z-score together with declining vitamin D concentrations. Pańczyk-Tomaszewska and colleagues observed significant deterioration over one year despite vitamin D supplementation in their cohort, indicating that children with repeated nephrotic relapses may require individualized assessment rather than uniform assumptions about skeletal protection. [24]

Abnormalities can persist into remission. Cetin and colleagues reported lower vitamin D concentrations and reduced bone-density indices among children with SSNS who had been off glucocorticoids for at least six months. Bone mineral density in growing children must be interpreted carefully because short stature itself influences areal DXA measurements. Z-scores adjusted appropriately for age, sex, and body size are preferable to adult T-scores, and fracture history may provide clinically meaningful information not captured by densitometry alone. [25]

HPA-Axis Suppression and Adrenal Insufficiency

Repeated systemic glucocorticoids suppress endogenous corticotropin-releasing hormone and ACTH secretion and can produce adrenal cortical atrophy. Suppression may persist after treatment is stopped, creating risk during febrile illness, surgery, severe vomiting, or other physiological stress. Clinical recognition is difficult because fatigue, poor appetite, weakness, abdominal symptoms, and hypotension are nonspecific, while a child may appear entirely well between stress episodes. [26]

In children with nephrotic syndrome, biochemical suppression can be frequent. Abu Bakar and colleagues studied children several weeks after corticosteroid discontinuation and found HPA-axis suppression on low-dose Synacthen testing in approximately one third despite normal early morning cortisol levels. Steroid dependence increased risk. These findings show that apparent clinical recovery after tapering does not guarantee immediate normalization of adrenal reserve. [27]

More recent studies continue to report substantial rates of abnormal adrenal testing, although prevalence varies widely according to the test used, cortisol threshold, treatment schedule, and timing after steroid withdrawal. This heterogeneity argues against indiscriminate testing of every child but supports heightened suspicion in heavily exposed patients, particularly those receiving prolonged alternate-day treatment or repeated high-dose courses. Families of children with documented suppression require clear instructions about stress dosing and urgent assessment during significant illness.

Ophthalmologic and Dermatologic Toxicity

Posterior subcapsular cataract is a recognized complication of chronic systemic glucocorticoid exposure. Risk appears related to cumulative treatment and individual susceptibility, and affected children may be asymptomatic in the early stages. Glucocorticoid-associated elevation of intraocular pressure is less frequently reported in pediatric nephrotic syndrome but remains biologically plausible and clinically important. Long-term cohorts of FRNS have documented cataracts among treatment-associated morbidities. [28]

Skin and soft-tissue changes include acne, striae, easy bruising, impaired wound healing, facial rounding, and occasionally increased susceptibility to superficial infection. Although these effects are rarely life threatening, their psychological significance should not be underestimated, particularly in adolescents. A narrow definition of steroid toxicity based only on laboratory abnormalities misses treatment effects that may determine adherence, body image, school participation, and willingness to continue therapy. [29]

Infection and Immune Consequences

Children with nephrotic syndrome are already susceptible to infection because urinary losses of immunoglobulins and complement factors, edema, and active disease can impair host defenses. Systemic glucocorticoids add dose-dependent immunosuppression by altering leukocyte trafficking and cellular immune responses. Attribution again requires caution: serious infections may occur because of active nephrosis, steroid therapy, other immunosuppressants, or a combination of all three. [30]

In a 20-year experience evaluating febrile admissions of children with nephrotic syndrome, serious bacterial infection occurred in 14.6% of admissions, with pneumonia, bacteremia/sepsis, and urinary tract infection among the most frequent diagnoses. Active nephrosis was associated with greater risk. These findings support prompt assessment of fever and attention to immunization, but they also show why infection in nephrotic syndrome should not automatically be labeled a steroid adverse effect. [31]

Neurobehavioral and Psychiatric Effects

Behavioral toxicity may occur rapidly during high-dose treatment and can recur with subsequent courses. Reported manifestations include irritability, aggression, emotional lability, anxiety, depressive symptoms, hyperactivity, poor concentration, and sleep disturbance. These symptoms can affect parent-child relationships and school functioning even when renal disease is responding well. Because the child may behave normally between courses, families sometimes recognize the association with prednisolone before clinicians do. [32]

Soliday and colleagues prospectively evaluated children with steroid-sensitive nephrotic syndrome during relapse and observed clinically significant increases in anxious/depressive and aggressive

behavior during higher-dose prednisone therapy. Prednisone dose was a strong predictor of abnormal behavior. The study was small, but its repeated-measures design demonstrated the temporal relationship between corticosteroid exposure and behavioral deterioration within individual children. [33]

Hall and colleagues subsequently reported increased total behavioral scores after four weeks of steroid treatment, particularly involving aggression and poor attention. Larger observational work has also associated cumulative prednisolone exposure with behavioral abnormalities, especially in children with frequent relapses or steroid dependence. These data support asking about behavior and sleep routinely rather than waiting for severe psychiatric symptoms to emerge. [34]

Behavioral outcomes remain influenced by more than medication. Chronic illness, recurrent edema, appearance changes, school absence, parental anxiety, restrictions on activities, and uncertainty regarding relapse can all alter psychosocial functioning. A child with severe behavioral difficulty should therefore receive a broad assessment that considers timing relative to steroid dose, family environment, disease activity, sleep, and pre-existing neurodevelopmental or psychiatric vulnerability. [35]

Health-Related Quality of Life

Health-related quality of life (HRQoL) integrates physical functioning with emotional, social, and school experiences and is particularly useful in a disorder in which conventional laboratory outcomes may not represent the child's daily burden. The Pediatric Quality of Life Inventory (PedsQL) has been widely used in nephrotic syndrome and includes physical, emotional, social, and school domains. Patient self-report is preferred when developmentally feasible, while parent proxy-report provides complementary information, particularly in younger children. [36]

The relationship between medications and HRQoL has been examined longitudinally. Khullar and colleagues followed 295 children and found lower adjusted HRQoL among those exposed to steroids and steroid-sparing agents compared with periods without medication exposure. Steroids were particularly associated with lower functioning scores, while steroid-sparing treatment was associated with fatigue-related differences. The findings illustrate a critical point: reducing prednisone exposure does not automatically eliminate treatment burden because alternative agents have their own adverse-effect profiles and are often prescribed to patients with more severe disease. [37]

Data from Egyptian children are especially relevant to the clinical context of the present review. Eid and colleagues found that children with idiopathic nephrotic syndrome had lower HRQoL than healthy controls and that longer disease duration, more relapses, higher cumulative steroid exposure, and a greater number of medications were associated with poorer quality-of-life scores. Steroid-resistant patients had particularly low scores, again showing the combined contribution of disease phenotype and treatment burden. [38]

The Midwest Pediatric Nephrology Consortium similarly demonstrated that disease duration influences quality of life. Children and adolescents with nephrotic syndrome can experience persistent limitations even when conventional renal outcomes are favorable. These findings argue for inclusion of patient-reported outcomes in routine follow-up and clinical research rather than defining successful treatment solely as remission of proteinuria. [39]

PROMIS instruments have also been studied in nephrotic syndrome. Children with active disease reported more anxiety, pain interference, fatigue, and mobility limitation than children with inactive disease. The ability of these measures to discriminate active from inactive nephrosis demonstrates that patient-reported outcomes capture clinically meaningful disease activity that may not be represented by laboratory testing alone. [40]

Studies from different geographic settings show variation in absolute HRQoL values but broadly support a measurable burden. In South India, children with nephrotic syndrome had higher total PedsQL scores than children with several other chronic diseases but continued to show school-related difficulties. This finding is useful because “better than another chronic illness” should not be interpreted as normal functioning. It also indicates that the choice of comparison group strongly affects how quality-of-life results are described. [41]

Sudanese data demonstrated lower overall PedsQL scores than healthy controls, with school functioning

among the most affected domains. Iranian and other cohorts have similarly identified impaired HRQoL associated with nephrotic syndrome and its complications. Geographic, cultural, educational, socioeconomic, and health-system differences make direct comparison of raw scores difficult, but the consistency of impaired school and psychosocial functioning supports a broad approach to survivorship care. [42]

Family functioning should also be considered. Childhood nephrotic syndrome requires urine monitoring, medication administration, repeated medical visits, dietary adjustments, recognition of relapse, and decisions about infection exposure. Family stress may influence both child-reported and parent-proxy HRQoL. Prospective work during the COVID-19 pandemic further illustrated the interaction between external stressors, family functioning, and quality of life in families managing childhood nephrotic syndrome. [43]

Distinguishing Steroid Toxicity From Disease Burden

Causal attribution is one of the central methodological problems in this field. Frequent relapse drives cumulative steroid exposure, while frequent relapse itself increases edema, dietary restriction, hospitalization, missed school, infection risk, psychological distress, and laboratory abnormalities. Children with severe courses are also more likely to receive calcineurin inhibitors, cyclophosphamide, mycophenolate mofetil, levamisole, or rituximab. Cross-sectional associations between cumulative prednisone and an adverse outcome can therefore reflect both drug toxicity and greater underlying disease burden.

This issue is especially important for growth, bone mineral density, dyslipidemia, and HRQoL. Persistent proteinuria can compromise nutrition and vitamin D status independently of steroids; calcineurin inhibitors can affect blood pressure and glucose metabolism; and chronic disease itself can impair psychosocial functioning. Stronger future studies should treat cumulative prednisolone exposure as a time-varying variable and simultaneously model relapse activity, remission duration, other immunosuppressive exposure, puberty, nutritional status, and socioeconomic determinants.

Steroid-Sparing Therapy as a Toxicity-Reduction Strategy

The purpose of steroid-sparing treatment in FRNS and SDNS is not merely to reduce the number of relapses. It is also to reduce cumulative glucocorticoid toxicity while maintaining remission. Available agents include levamisole, cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil, and rituximab. Selection depends on disease phenotype, previous treatment, adverse-effect priorities, adherence, monitoring requirements, fertility considerations, availability, and family preference. Current guidelines specifically support moving to steroid-sparing therapy when serious glucocorticoid toxicity develops. [44]

Shortening steroid exposure when supported by evidence is another strategy. In a randomized trial of treatment for relapse, Kainth and colleagues compared two versus four weeks of alternate-day prednisolone after remission. The shorter regimen substantially reduced cumulative corticosteroid exposure, although the prespecified statistical criterion for noninferiority was not established. Studies such as this are important because cumulative dose reduction should be pursued through evidence-based regimens rather than arbitrary undertreatment that increases relapse risk. [45]

Rituximab has changed management of complicated FRNS and SDNS. In the randomized placebo-controlled trial by Iijima and colleagues, rituximab significantly prolonged the relapse-free period in heavily affected children. Its role illustrates the balance required in modern nephrotic syndrome treatment: replacing repeated prednisone exposure may reduce steroid-specific toxicity but introduces infusion reactions, B-cell depletion, infection considerations, and cost. Steroid minimization is therefore not equivalent to treatment minimization; it is a shift toward a different risk-benefit profile. [46]

Other steroid-sparing therapies have established roles, but each has characteristic toxicities. Calcineurin inhibitors can cause nephrotoxicity, hypertension, cosmetic effects, or glucose disturbances; cyclophosphamide has gonadal and hematologic risks; mycophenolate commonly causes gastrointestinal and hematologic adverse effects; and levamisole requires blood-count monitoring because neutropenia can occur. Choosing among these therapies should therefore be individualized

rather than based only on which agent produces the greatest steroid reduction. [47]

Monitoring and Prevention of Long-Term Toxicity

Monitoring should begin when corticosteroids are initiated rather than after visible toxicity has developed. Height and weight should be plotted serially using appropriate growth standards, with calculation of BMI and height Z-scores. Height velocity is particularly informative in growing children. Blood pressure should be measured with an appropriately sized cuff and interpreted using pediatric percentiles. Pubertal development should be assessed in older children, particularly when height velocity falls or prolonged treatment extends into adolescence. [1]

Metabolic surveillance should be adapted to risk. Children with rapid weight gain, obesity, prolonged high-dose therapy, hypertension, acanthosis, family history of diabetes, or calcineurin inhibitor exposure merit assessment of fasting glucose or HbA1c and lipid profile. Nutritional counseling should address excessive energy intake and sodium while maintaining adequate protein, calcium, vitamin D, and overall dietary quality. The objective is not restrictive dieting during childhood but prevention of avoidable steroid-associated weight gain and metabolic deterioration. [48]

Bone surveillance begins with clinical assessment: fracture history, back pain, physical activity, diet, vitamin D risk, pubertal progression, and cumulative steroid exposure. Serum 25-hydroxyvitamin D can be useful, particularly in children with repeated relapses or persistent proteinuria. DXA is not required routinely for every steroid-treated child but can be considered when there is substantial cumulative exposure, recurrent fractures, marked growth impairment, delayed puberty, or additional skeletal risk factors. Interpretation should follow pediatric principles. [18]

Behavior, sleep, school attendance, and emotional functioning should be discussed at visits during and after high-dose courses. Families can be warned prospectively that irritability, aggression, mood symptoms, and sleep changes may occur, which often helps them recognize a medication relationship and seek assistance early. Severe depression, suicidality, psychosis, or dangerous aggression requires urgent specialist evaluation rather than simple reassurance that symptoms are steroid related. [49]

Ophthalmologic review is reasonable in children receiving prolonged or repeated corticosteroid treatment, particularly when exposure is substantial or visual symptoms develop. Adrenal suppression should be considered during tapering and after cessation in heavily exposed children. Any child with known adrenal insufficiency requires a written stress-dose plan. Infection prevention includes appropriate vaccination, prompt evaluation of significant fever, and individualized decisions regarding live vaccines during immunosuppressive treatment.

The overall approach is best framed as cumulative-toxicity surveillance. A child's height trajectory, BMI, blood pressure, metabolic profile, bone status, ocular health, behavior, school functioning, and HRQoL should be considered together. A collection of modest abnormalities may justify therapeutic modification even when none individually meets a severe toxicity threshold. This approach aligns treatment decisions with the developmental priorities of childhood rather than concentrating exclusively on urinary protein remission.

Long-Term Outcomes and Remaining Evidence Gaps

Long-term prognosis of SSNS is generally favorable with respect to kidney function, but a subset of children continues to relapse into adolescence or adulthood. Historical and modern cohorts show that the burden of treatment is heterogeneous: some patients recover normal growth and have little adult morbidity, while those with prolonged FRNS or SDNS can accumulate skeletal, metabolic, ocular, and growth complications. This variability makes prediction for an individual child difficult and highlights the need to identify early markers of high cumulative treatment burden. [50]

Several research priorities remain. Studies should report cumulative glucocorticoid exposure using standardized prednisone-equivalent metrics, distinguish daily from alternate-day exposure, and record timing relative to puberty. Prospective cohorts should evaluate body composition rather than BMI alone, vertebral fractures rather than bone density alone, and dynamic adrenal function when clinically indicated. Final adult height and peak bone mass require follow-up beyond traditional pediatric study periods.

Patient-reported outcomes should also be integrated into comparative treatment trials. A regimen that achieves similar relapse control with better growth, body image, school attendance, behavior, fatigue, and family functioning may provide an important benefit even if proteinuria outcomes are identical. Conversely, a steroid-sparing agent that reduces prednisone exposure but substantially worsens another aspect of quality of life cannot be considered automatically superior. Treatment evaluation should therefore combine disease control, cumulative steroid dose, treatment-specific toxicity, and patient-reported well-being.

Conclusion

Corticosteroids remain highly effective and indispensable in the treatment of steroid-sensitive nephrotic syndrome, but recurrent and prolonged exposure can produce clinically important effects on growth, body composition, cardiovascular and glucose metabolism, bone health, adrenal function, ocular health, behavior, and quality of life. The greatest burden occurs in children with frequent relapses and steroid dependence, in whom disease severity and treatment toxicity are closely intertwined. Modern care should therefore aim for sustained remission with the lowest effective cumulative glucocorticoid exposure, early introduction of appropriate steroid-sparing therapy when toxicity or dependence develops, and structured longitudinal surveillance extending beyond laboratory evidence of renal remission. Protecting normal growth, development, psychological health, and participation in childhood activities is a central therapeutic outcome rather than a secondary consideration.

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